Research Article

Diagnostic Utility of Pan-Immune-Inflammation Value (PIV) in Predicting Insulin Resistance: Results from the National Health and Nutrition Examination Survey (NHANES) 2017–2020

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Article Info

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Keywords

PIV, pan-immune-inflammation value, insulin resistance, inflammation, diabetes, metabolic syndrome.

Abstract

Background

Insulin resistance (IR), a hallmark feature of diabetes and metabolic syndrome, is characterized by chronic low-grade inflammation. Pan-immune-inflammation value (PIV), an emerging immune cell count-based inflammatory index, is the global quantifier of systemic inflammation. This study analyses the levels of PIV and its association with various markers of IR.

Materials and Methods

This retrospective, cross-sectional study was done using the Center for Disease Control-National Health and Nutritional Examination Survey (CDC-NHANES) pre-pandemic data from 2017–2020. Data from 4620 survey participants was included after screening. Homeostasis model assessments of insulin resistance (HOMA-IR) and beta-cell function (HOMA-B), triglyceride glucose (TyG) index, visceral adiposity index (VAI), and lipid accumulation product (LAP) were used as markers of IR. Multiple logistic regression and trend analysis were done to determine the associations, and receiver operator characteristic curve (ROC) analysis was done to estimate the diagnostic utility of PIV to predict IR.

Results

PIV levels were significantly higher in obesity, diabetes, and metabolic syndrome. HOMA-IR, HOMA-B, LAP, VAI, and TyG levels were found to be higher in those with higher PIV (i.e., quartiles 4 and 3). Regression and trend analysis showed that the odds ratio for IR increased with PIV. However, ROC indicated that the diagnostic utility of PIV to predict IR is low compared to the other surrogate markers.

Conclusions

PIV levels differed significantly based on glycemic status, BMI, and metabolic syndrome status. PIV showed a significant positive association with IR. However, the ability of PIV to predict IR is not optimal compared to other surrogate markers.

Introduction

Insulin resistance (IR) is the major hallmark feature of type 2 diabetes mellitus (DM) and metabolic syndrome. IR is a complex metabolic defect leading to a decreased response toward insulin, impaired regulation of blood glucose levels, and other adverse events [1]. IR is recognized as a chronic low-grade inflammation state affecting various tissues, mainly adipose tissue, liver, and skeletal muscle [2]. Adipose tissue-derived cytokines (i.e.,) adipokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), adipokines (leptin, adiponectin, and resistin), monocyte chemoattractant protein-1 (MCP-1), and nuclear factor kappa-B (NFκB) are widely reported to promote low-grade inflammation, which could play a central role in IR [3,4].

IR can be determined to an extent by various biochemical and anthropometric indices. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) and Beta-cell Function (HOMA-B) are widely used markers of IR [5]. Triglyceride glucose (TyG) index, visceral adiposity index (VAI), and lipid accumulation product (LAP) are other surrogate markers of IR [6,7]. The associations between inflammatory markers and markers of insulin resistance have been studied extensively. High-sensitivity C-reactive protein (hs-CRP), a widely used marker of systemic inflammation, showed a significant positive association with insulin resistance as measured by HOMA-IR [8], and high CRP could independently predict IR in the future [9]. Estimation of serum CRP is usually done in those with inflammation and infection. The accumulating evidence regarding the pathogenesis of the disease and advancements in diagnostic assays have led to the development of various biomarkers of inflammation, such as IL-6, IL-1 beta, and TNF-alpha.

In this regard, several blood cell count-based inflammatory biomarkers have gained importance in cancer. Pan-immune-inflammation value (PIV), a relatively new biomarker of inflammation derived using the counts of neutrophils, lymphocytes, platelets, and monocytes, was a better prognostic marker in cancer. As it encompasses all major immune cells, PIV is considered the global quantifier of the cellular compartment of systemic inflammation [10]. The PIV values predicted mortality in ST-elevation myocardial infarction (STEMI) [11], end-stage renal disease (ESRD) [12], and hepatic steatosis [13]. However, PIV levels in patients with diabetes mellitus and metabolic syndrome and their association with IR have not been addressed.

Hence, this study was done to determine the levels of PIV in those with diabetes and metabolic syndrome. The association of PIV with various markers of IR was also explored in this study.

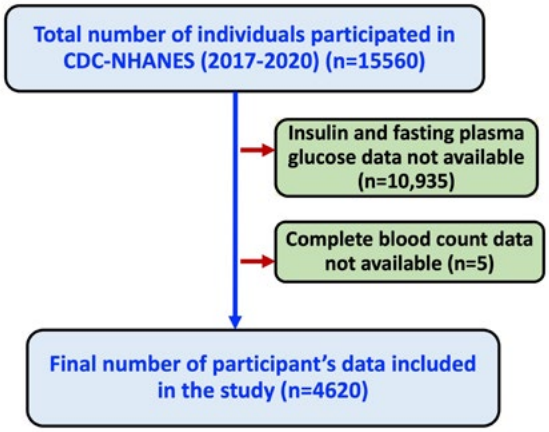
Methods

Data source

The study is done using the data obtained from the Center for Disease Control's (CDC) National Health and Nutritional Examination Survey (NHANES) pre-pandemic data from 2017–2020. The survey was approved by the National Center for Health Statistics (NCHS) Ethics Review Board (ERB) (Protocol #2018-01, Continuation of Protocol #2011-17, effective October 26, 2017). The survey was carried out in compliance with the Declaration of Helsinki. The participants were interviewed, and subsequent physical examination and laboratory investigations were done at the mobile examination center (MEC) after obtaining informed consent [14]. This completely de-identified data is available in the public domain; hence, subsequent approval from the NCHS ERB and institutional review board is exempted for this study.

Among the participants who participated in the survey (n = 15560), only those with data on complete blood count (CBC), fasting plasma insulin, and glucose were included in the study (n = 4620) (Figure 1). The methodology used for CBC, fasting plasma insulin, glucose, and lipid profile were discussed in detail [14].

Figure 1: Flow chart to describe the retrieval of data



CDC - Center for Disease Control, NHANES - National Health and Nutrition Examination Survey

Formulas used for calculating PIV, HOMA-IR, HOMA-B, LAP, TyG and VAI

PIV is calculated using the formula [10]:

$$PIV = \frac{\text{Neutrophils (1000 cells per μL)} * \text{Platelets (1000 cells per μL)} * \text{Monocytes (1000 cells per μL)}}{\text{Lymphocytes (1000 cells per μL)}}$$

Homeostatic model assessment of insulin resistance (HOMA-IR) and - beta cell function (HOMA-B) [5] is calculated by

$$HOMA\text{-}IR = \frac{\text{Fasting insulin (μU/mL)} * \text{Fasting plasma glucose (mg/dL)}}{405}$$

$$\text{HOMA-B}=\frac{20*\text{Fasting insulin }(\mu U/mL)}{\text{Fasting plasma glucose (mg/dL)}-63}$$

Visceral adiposity index (VAI) [6] is calculated by:

$$\text{VAI (men)}=\frac{\text{Waist circumference (in cm)}}{(39.68+(1.88*\text{BMI}))}*\left(\frac{\text{Triglycerides(in mg/dL)}*0.012229}{1.03}\right)*\left(\frac{1.31}{\text{HDL-C(in mg/dL)}*0.02586}\right)$$

$$\text{VAI (women)}=\frac{\text{Waist circumference (in cm)}}{(39.58+(1.88*\text{BMI}))}*\left(\frac{\text{Triglycerides(in mg/dL)}*0.012229}{0.81}\right)*\left(\frac{1.51}{\text{HDL-C(in mg/dL)}*0.02586}\right)$$

Lipid accumulation product (LAP) [6] is calculated as follows:

LAP(men)=(Waist circumference(in cm)-65)*(Triglycerides (in mg/dL)*0.012229)

LAP(women)=(Waist circumference (in cm) 58) * (Triglycerides(in mg/dL)*0.012229)

Triglyceride glucose (TyG) [7] is calculated by:

$$\text{TyG}=\text{Ln}\left(\frac{\text{Fasting plasma glucose (mg/dL)}*\text{Triglycerides (mg/dL)}}{2}\right)$$

Criteria for Metabolic Syndrome, BMI, Prediabetes, and Diabetes Mellitus.

The metabolic syndrome is diagnosed based on the American Heart Association-National Heart Lung Blood Institute (AHA-NHLBI) guidelines [15]. BMI values are used to diagnose overweight, obesity, and underweight based on CDC guidelines [16]. The participants are categorized into normoglycemia, prediabetes, and diabetes based on the American Diabetes Association 2023 guidelines [17].

Statistical analysis

All statistical analyses were performed using the R programming language, version 4.3.1. The parameters were checked for their distribution by the Shapiro-Wilk test, and appropriate statistical tests were conducted. The data across the quartiles were analyzed using the Kruskal-Wallis test with post-hoc Bonferroni correction. Receiver operator characteristic (ROC) curves were plotted for PIV and other surrogate measures of insulin resistance to predict metabolic syndrome. The ROC curve is plotted using the "pROC" R package, which calculates the sensitivity, specificity, and optimal cut-off value of Youden's index [18]. The diagnosis of metabolic syndrome is done by the R package "MetabolicSyndrome" [19].

Results

The baseline characteristics of the participants included in the study are represented in Table 1.

Table 1: Baseline characteristics of the participants.

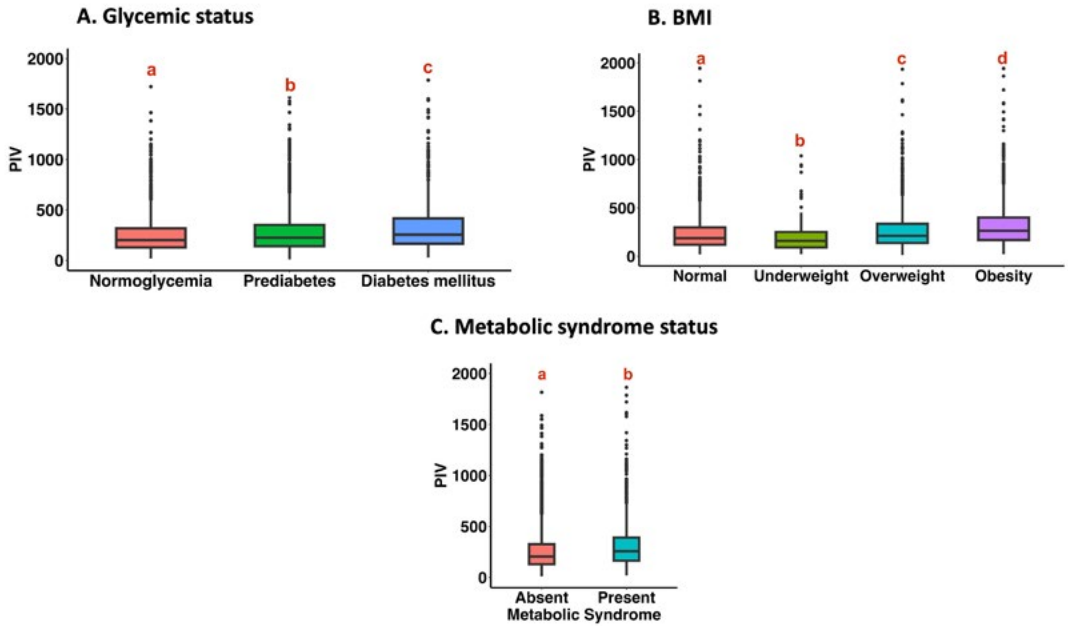
Parameter	
Number of participants	4620
Age in years	46 (27-62)
Gender (%)	
Male	2251 (49)
Female	2369 (51)
BMI status (based on CDC guidelines)	
Underweight	141 (3.1)
Normal	1276 (28.1)
Overweight	1370 (30.2)
Obesity	1753 (38.6)

Glycemic status (based on ADA criteria, 2023)	
Normoglycemia	1593 (34.5)
Prediabetes	2270 (49.1)
Diabetes mellitus	757 (16.4)
Metabolic Syndrome status (based on AHA-NHLBI criteria, 2005)	
Yes	1616 (35)
No	3004 (64)
Pan - immune inflammation index value (PIV)	221.9 (139.6-352.1)
CRP, mg/L	1.7 (0.7-4.2)
Fasting plasma glucose, mg/dL	102 (95-112)
HbA1C, %	5.5 (5.3-5.9)
Fasting plasma insulin, µU/L	10.2 (6.3-16.6)
Markers of insulin resistance	
HOMA-IR	2.6 (1.6-4.6)
HOMA-B	4.9 (3.1-8)
VAI	1.36 (0.83-2.22)
TyG	9.22 (8.85-9.76)
LAP	39.88 (20.37-69.31)

The continuous data are represented by the median (interquartile range). The categorical data (gender, BMI status, glycemic status, and metabolic syndrome status) are represented in numbers (percentages). Homeostatic model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-B), visceral adiposity index (VAI), triglyceride-glycemic index (TyG), and lipid accumulation product (LAP) are shown as makers of insulin resistance.

PIV values differ significantly based on glycemic status, as they were higher in those with diabetes and pre- diabetes compared to those with normoglycemia (Figure 2A). The increase in PIV values paralleled BMI, as it was found to be higher in those with overweight and obesity and lower in those with underweight (Figure 2B). PIV levels were significantly higher in those with metabolic syndrome. (Figure 2C)

Figure 2: Comparison of PIV values based on Glycemic status, BMI and Metabolic Syndrome status



The pan-immune-inflammation values (PIV) were compared based on the glycemic status (A), body mass index, BMI (B), and metabolic syndrome status (C). The box and whisker plots showing dissimilar alphabets are significantly different from one another ($p<0.05$). THe Kruskal-Wallis test iwth post hoc Bonferroni correction was done (A, B), and the Mann-Whitney U test was dont (C).

The data was categorized into quartiles using PIV values, and baseline characteristics were analyzed across the quartiles (Table 2). The age of the participants was significantly higher in Q3 and Q4 (i.e., in those with higher PIV values). The gender distribution was similar across the quartiles. The glycemic status was significantly different across the quartiles, with significantly higher number of diabetics in Q3 and Q4. The metabolic syndrome status was significantly different across the quartiles, with significantly higher number of metabolic syndrome participants in Q3 and Q4 (Table 2).

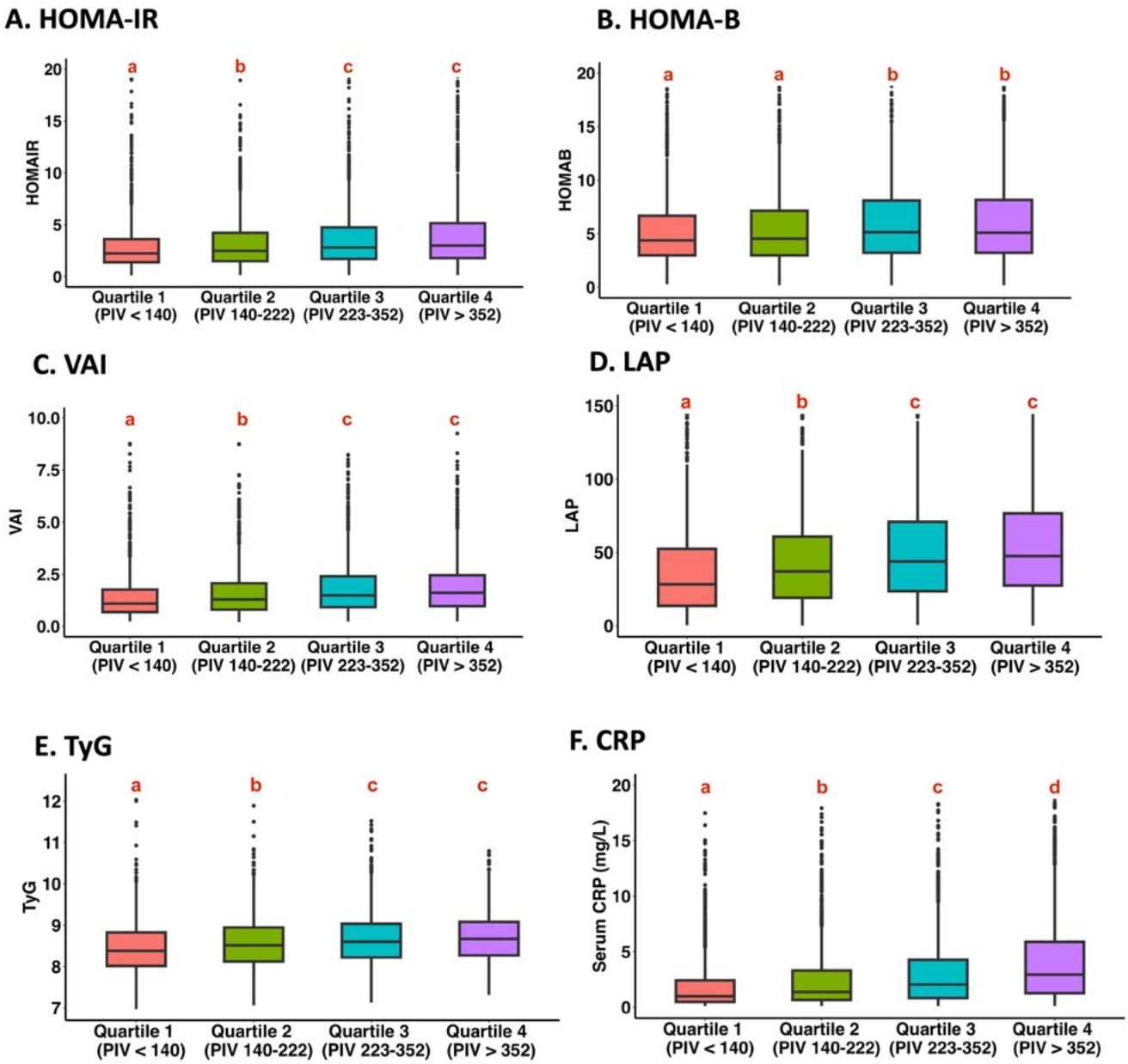
Table 1: Comparison of baseline characteristics across the PIV Quartiles

Parameter	Quartile 1, Q1 (PIV < 140)	Quartile 2, Q2 (PIV 140-222)	Quartile 3, Q3 (PIV 223-352)	Quartile 4, Q4 (PIV > 352)	P value
No of participants	1155	1155	1155	1155	-
Age in years	43[a] (24-60)	45[a] (27-60)	46[b] (28-63)	51[c] (31-67)	<0.0001
Gender (%)					
Male **Female**	556 (49) 589 (51)	589 (51) 566 (49)	548 (47) 566 (49)	548 (47) 607 (53)	0.268
Glycemic status (based on ADA criteria)					
Normoglycemia **Prediabetes** **Diabetes mellitus**	458 (40) 558 (48) 139 (12)	428 (37) 555 (48) 172 (15)	378 (33) 582 (50) 195 (17)	329 (28) 575 (50) 251 (22)	<0.0001
Metabolic Syndrome status (based on AHA-NHLBI criteria)					
Yes **No**	301 (26) 854 (74)	355 (31) 800 (69)	466 (40) 689 (60)	494 (43) 661 (57)	<0.0001

The data were categorized based on pan-immune-inflammation values (PIV) into quartiles (Q1, Q2, Q3, and Q4). The categorical data (gender, glycemic status, metabolic syndrome status) were represented as numbers (percentages) and compared across the quartiles using the Chi-Square test. Age was expressed as median and interquartile range (IQR), and the Kruskal-Wallis test with post hoc Bonferroni correction was done. Quartile with dissimilar alphabet in their superscript denote that age in that quartile were significantly different from the other.

The markers of insulin resistance and inflammation were compared across the PIV quartiles (Figure 3). There was a significant difference in the levels of these markers across the quartiles (Kruskal-Wallis test, $p < 0.0001$). The HOMA-IR, VAI, LAP, and TyG values trended upward as PIV increased (i.e., from Q1 to Q4). The values were higher in Q2, Q3, and Q4 compared to Q1. However, the values were not different between Q4 and Q3. (Figure 3A, 3C-3E). The HOMA-B values were higher in Q3 and Q4 compared to Q1 and Q2. The HOMA-B values were not different between Q1 vs. Q2 and Q3 vs. Q4 (Figure 3B). Serum CRP values were increased in parallel with the PIV values from Q1 to Q4 (Figure 3F).

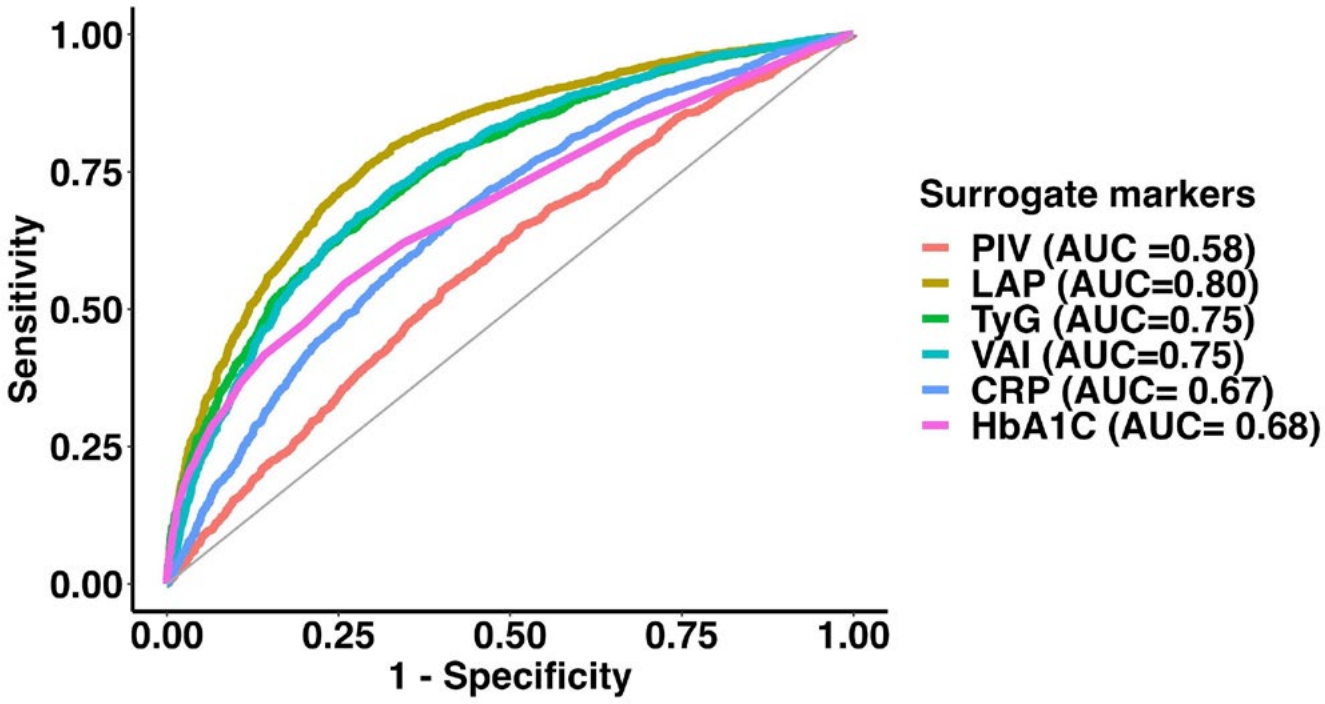
Figure 3: Comparison of surrogate markers of insulin resistance and inflammation across the PIV quartiles



The data were categorized based on pan-immune-inflammation values (PIV) into quartiles (Q1, Q2, Q3 and Q4). The markers of insulin resistance and inflammation were compared across the quartiles using the Kruskal- Wallis test and Mann Whitney U test with post hoc Bonferroni correction to do pairwaise comparisons. The box and whisker plots showing dissimial alphabets are significantly different from one another ($p<0.05$). Homeostatic model assessment of insulin resistance, HOMA-IR (A) and beta cell function, HOMA-B (B), visceral adiposity index, VAI (C), lipd accumulation product, LAP (D), triglyceride-glycemic index, and TyG (E) were shown as markers of insulin resistance. C-reactive protein, CRP (F), was shown as a marker of inflammation.

ROC curves were plotted for PIV and other surrogate measures to predict insulin resistance. HOMA-IR was used to categorize the participants into insulin-resistant (cut-off > 2.73) and non-insulin-resistant (cut-off < 2.73) [20]. LAP performed better with an AUC of 0.80 among the surrogate markers, followed by VAI (AUC =0.75), TyG (0.75), CRP (0.67), and HbA1C (0.68). The AUC of PIV is 0.58, suggesting it is not useful as a marker to predict insulin resistance (Figure 4).

Figure 4: ROC of PIV and other surrogate markers to predict insulin resistance



Receiver operator characteristic curve, ROC was constructed to predict the diagnostic utility of pan-immune-inflammation value, PIV and other surrogate markers to predict insuling resistance. Homeostatic model assessment of insulin resistance, HOMA-IR was used to cateogrize insulin resistance i.e. thode with HOMIR cutoff < 2.73 were non-insulin resistant and those with > 2.73 were insulin resistant. Predictive ability of Visceral adiposity index (VAI), lipid accumulation product (LAP), triglyceride-glycemic indic (TyG), C-reactive protein (CRP), HbAIC were also studied.

Multiple logistic regression was carried out with four models to analyze the association between PIV and IR. The effect of the model can be interpreted as an increase in PIV leading to a corresponding increase in IR. In model 1 (i.e., the unadjusted model), the incidence of IR increased by 0.08% with one unit increase in the variance of PIV, and the OR (95% CI) were 1.0008 (1, 1.001). The results of models 2 (age and gender adjusted), 3 (age, gender, and BMI adjusted), and 4 (age, gender, BMI, diabetes, and prediabetes adjusted) were similar, indicating that the strategy used for adjustment was sufficient. Collectively, PIV was independently positively associated with the occurrence of IR. However, the association was weak, as suggested by the OR (Table 3). Further, to ensure the stability of the results across various ranges of PIV, the trend test was carried out across PIV quartiles. The PIV was transformed into a categorical variable by grouping it into four levels as quartiles. Q1 was taken as the reference; the incidence of VAI and IR represented a monotonically increasing trend in all models (all P for trend < 0.001) (Table 3). This aligns with the finding that the HOMA-IR values trended upward as PIV increased (i.e., from Q1 to Q4) (Figure 3). The OR was higher as the PIV value increased (i.e., in Q2-Q4) in all models, suggesting the significant positive association of elevated PIV values with IR (Table 3).

Table 3: Multiple logistic regression model to determine the association between PIV and insulin resistance.

Viariable	n (%)	Model 1		Model 2		Model 3		Model 4	
		OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
PIV	4620	1.0008 (1-1.001)	<0.0001	1.0008 (1 – 1.001)	<0.0001	1.0004 (1.0001 – 1.0007)	<0.0001	1.0003 (1 -1.0006)	0.014
PIV Quartiles									
Quartile 1	1155	1 *(Ref)*	<0.0001	1 *(Ref)*	<0.0001	1 *(Ref)*		1 *(Ref)*	
Quartile 2	1155	1.34 (1.13-1.59)	<0.0001	1.33 (1.13-1.58)	<0.0001	1.12 (0.93-1.35)	0.233	1.14 (0.93-1.4)	0.186
Quartile 3	1155	1.82 (1.55-2.15)	<0.0001	1.8 (1.52-2.12)	<0.0001	1.31 (1.08-1.51)	0.004	1.66 (1.36-1.11)	0.002
Quartile 4	1155	2.01 (1.78-2.49)	<0.0001	2.05 (1.74-2.42)	<0.0001	1.38 (1.14-1.67)	<0.001	1.68 (1.37-1.11)	0.002
P for trend	4620	1.76 (0.57-1.98)	<0.0001	1.73 (1.54-1.95)	<0.0001	1.29 (1.12-1.47)	<0.001	1.28 (1.11-1.48)	<0.001

Model 1 – unadjusted, model 2 – adjusted for age and gender, model 3 - adjusted for age, gender and BMI, model 4 - adjusted for age, gender, body mass index, diabetes, and pre-diabetes. Homeostatic model assessment of insulin resistance, HOMA-IR was used to categorize insulin resistance (HOMA-IR cut-off < 2.73 – non-insulin-resistant and > 2.73 – insulin-resistant).

Discussion

Insulin resistance seen in diabetes and metabolic syndrome is regarded as a chronic inflammatory state [3], predisposing to impaired glucose tolerance, dyslipidemia, and hypertension [21]. PIV was significantly higher in those with diabetes, prediabetes, and metabolic syndrome. The studies have reported that increased levels of PIV seen in hypertensive [22] and NSTEMI patients [11] are associated with all-cause mortality. Hence, further prospective studies are required to study whether elevated levels of PIV seen in those with diabetes and metabolic syndrome are associated with all-cause mortality.

The interaction between insulin resistance, low-grade inflammation, and obesity has been well-elucidated in previous studies. In this study, it was found that PIV increased with BMI, and its levels were found to be significantly higher in those with overweight and obesity. Serum CRP increased in parallel with the PIV values in this study. This finding was expected, as PIV is considered a marker for inflammation. A previous study has shown that serum CRP levels are positively correlated with PIV values in patients with carcinoma [23].

In this study, there was a significant difference in the levels of surrogate markers of IR when the data was analyzed based on quartiles of PIV. The HOMA-IR, CRP, and lipid-based surrogate markers of IR (VAI, LAP, and TyG) trended upwards as PIV increased, i.e., from Q1 to Q4, suggesting the relationship between insulin resistance and inflammation (Figure 2). There are studies that have shown a positive association between elevated CRP and HOMA-IR [24,25].

ROC curve analysis showed that LAP, VAI, and TyG performed as better markers to predict insulin resistance. It has been reported in a previous study that lipid-based surrogate markers of IR can aid in identifying insulin resistance in prediabetes and diabetes [26]. However, PIV and CRP levels lacked predictive utility as markers of insulin resistance (Figure 4). The multiple logistic regression analysis of the unadjusted and adjusted models showed a weak positive association between IR and PIV. There was an increasing trend in the odds ratio for the association of PIV and IR as the PIV increased from Q1 to Q4 (Table 3).

Various complete blood count (CBC)-derived inflammatory indices such as neutrophil-lymphocyte ratio (NLR) [27], platelet-lymphocyte ratio (PLR) [28], monocyte-lymphocyte ratio (MLR) [29], and systemic immune-inflammation index (SII) [30] have been used in estimating chronic low-grade inflammation in insulin resistance. The role of PIV has been well-elucidated in cancer as a biomarker to determine prognosis and survival outcomes [10]. This study addresses the utility and association of PIV with insulin resistance in U.S. adults.

Limitation

The retrospective cross-sectional study design of this study

allows us to determine the associations. Hence, large-scale prospective studies can confirm the predictive role of PIV in insulin resistance.

Conclusion

PIV levels differed significantly based on BMI, glycemic status, and metabolic syndrome. The proportion of participants with diabetes and metabolic syndrome was higher in those with higher PIV values (i.e., quartiles 3 and 4). The participants with higher PIV values had increased levels of HOMA-IR, VAI, TyG, and LAP compared to those with lower PIV values, suggesting an association of PIV with insulin resistance. Multiple logistic regression and a trend analysis showed that the odds ratio for insulin resistance increases as the PIV value increases. However, the ROC analysis revealed a poor AUC, indicating a low diagnostic utility of PIV as a marker of insulin resistance. Hence, large- scale longitudinal studies are needed to ascertain the role of PIV as a marker for IR.

Author contributions

Ramasamy J: conceptualized and designed the study, acquired the data, analyzed data, interpreted results, and wrote the manuscript; Murugiah V: interpretation of data, drafting the manuscript; Balasubramaniam G and Dhanapalan A: analyzed data, drafting the manuscript.

Ethics Approval

The survey was approved by National Center for Health Statistics (NCHS) Ethics Review Board (ERB) (Protocol #2018-01, Continuation of Protocol #2011-17, effective through October 26, 2017). The survey was carried out in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

Disclosures

Conflict of interests

The author does not have any conflict of interest to disclose in this study.

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Data availability

This data is in the public domain and is available online.

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