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Association of insulin resistance surrogates with disease severity and adverse outcomes in chronic thromboembolic pulmonary hypertension: a multicenter cohort study

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Abstract

Background Chronic thromboembolic pulmonary hypertension (CTEPH) is a severely progressive disease that leads to right heart failure and death. Previous studies have shown that diabetes and insulin resistance (IR) are closely related to pulmonary hypertension, but the role of IR in patients with CTEPH remains unexplored. In this study, we investigated the relationship between four insulin resistance indices and disease severity, hemodynamic parameters, and adverse outcomes in patients with CTEPH.

Methods We conducted a multicenter, retrospective cohort study involving 516 patients diagnosed with CTEPH between January 2013 and December 2022. The metabolic score for IR (METS-IR), triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio, triglyceride and glucose (TyG) index, and triglyceride-glucose-body mass (TyG-BMI) index were used to quantify IR levels in patients with CTEPH. The primary endpoint events were clinical worsening. Multivariable Cox regression, restricted cubic splines, and receiver operating characteristic analyses were used to evaluate the predictive value of surrogates for IR.

Results Compared with in low to intermediate-low risk patients, the METS-IR (36.2 ± 6.7 vs. 37.7 ± 8.7, $p = 0.038$) and TyG-BMI index (204.0 ± 36.2 vs. 212.6 ± 46.5, $p = 0.022$) were significantly increased in high to intermediate-high risk patients. METS-IR correlated with markers of disease severity, such as World Health Organization functional class, 6-minute walk distance, and N-terminal pro-brain natriuretic peptide levels. During a mean of 2.5 years' follow-up, 110 participants experienced all-cause death or worsening condition. METS-IR independently predicted clinical worsening

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(hazard ratio: 1.27; 95% confidence interval 1.06–1.53 per 1.0-standard deviation increment, $p = 0.009$) after fully adjusting for covariates. Adding METS-IR to the COMPERA 2.0 risk score significantly improved its predictive ability, reclassification and discrimination ability.

Conclusions METS-IR is an independent predictor of clinical worsening in patients with CTEPH. It offers a convenient marker for assessing disease severity and long-term outcomes in clinical risk assessment.

Keywords Insulin resistance, Chronic thromboembolic pulmonary hypertension, Metabolic score for insulin resistance, Severity, Prognosis

Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is the fourth subtype of pulmonary hypertension, triggered by the organization of thrombi, which leads to narrowing or occlusion of the pulmonary arteries, altered blood flow dynamics, and structural remodeling of the pulmonary microvascular bed. This cascade of events results in a progressive increase in pulmonary arterial pressure, ultimately leading to right heart failure and death [1]. The pathogenesis of CTEPH is multifactorial [2]. Although pulmonary embolism and concomitant lower-extremity varicosities are recognized as potential risk factors, up to 25% of patients with CTEPH do not report a history of pulmonary embolism [3]. Notably, a registry study conducted in Japan, which included patients with CTEPH who underwent balloon pulmonary angioplasty (BPA), found that this proportion exceeded 80% [4]. Thus, it is evident that the risk factors for CTEPH remain unclear. Consequently, proactive identification of critical factors associated with CTEPH is essential for accurately evaluating disease severity and predicting clinical outcomes in affected patients.

Insulin resistance (IR) refers to the reduced sensitivity of target organs or tissues to insulin, resulting in impaired glucose uptake and utilization [2]. Individuals with IR frequently exhibit metabolic dysfunctions such as hypertension and dyslipidemia, which are strongly linked to adverse cardiovascular disease outcomes [5]. Although glucose-clamp techniques offer an objective IR assessment, their high cost, complexity, and invasiveness hinder their broad implementation [6]. Alternative indices, including the triglycerides and glucose (TyG) index, triglyceride glucose-body mass index (TyG-BMI) index, triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio, and metabolic score for insulin resistance (METS-IR), have been validated as effective, accessible surrogates for IR [7–10]. Furthermore, increasing evidence suggests that these insulin-independent surrogate markers are independent and significant predictors of cardiovascular diseases, such as stroke, atherosclerosis, and heart failure [11–13].

However, the ability of these surrogates to predict disease severity and long-term adverse outcomes in patients with CTEPH has not yet been reported. Therefore, we conducted a multicenter retrospective cohort study to investigate the relationship between various surrogates for IR and the functional status, ultrasound parameters, hemodynamic indices, and adverse outcomes in patients with CTEPH. Additionally, we assessed whether incorporating surrogates for IR into existing risk stratification tools could offer enhanced predictive power. These findings have significant implications for clinicians in the early identification and management of patients with high-risk CTEPH.

Methods

Study design and population

This multicenter retrospective cohort study included 565 consecutive patients with CTEPH who were diagnosed or treated at three level-3 hospitals in China between January 2013 and December 2022. The diagnosis of CTEPH was based on current guidelines and necessary pulmonary hemodynamic examinations [1, 14, 15]. Specific features are as follows: the hemodynamic characteristics are consistent with the diagnosis of precapillary pulmonary hypertension; mismatch on ventilation/perfusion scintigraphy with at least one large perfusion defect in one segment or in two subsegments; or evidence of pulmonary vascular lesions on computed tomography and/or magnetic resonance imaging or pulmonary angiography. These data were collected after at least 3 months of effective anticoagulation. The baseline assessment included data acquired at the time of CTEPH diagnosis for incident cases (diagnosed after January 1, 2013) and data obtained at the most recent visit for previously treated patients (diagnosed before January 1, 2013). The date of diagnosis was defined as the date of the first right heart catheterization (RHC) that met the hemodynamic criteria for CTEPH. After excluding missing or confusing data, 516 participants were included in the statistical analyses (Supplementary Figure S1). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients.

Measurements and definitions

Clinical data were collected via an electronic medical record system by three independent reviewers, including

demographics, comorbidities, pulmonary hypertension (PH)-specific medications, history of balloon pulmonary angioplasty or pulmonary endarterectomy (PEA), World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, and parameters derived from echocardiography and invasive pulmonary hemodynamics. Three independent reviewers were blinded to the clinical outcomes of the study participants at the time of data collection. Fasting peripheral venous blood samples were obtained before RHC to collect laboratory data, including fasting plasma glucose (FPG), triglyceride (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Standardized spreadsheets were used to organize and record retrospective data.

Diabetes mellitus (DM) was defined as a previous diagnosis of any type of diabetes, use of DM-approved treatment, fasting blood glucose levels ≥ 126 mg/dL (7.0 mmol/L) documented on two different days, blood glucose levels ≥ 200 mg/dL (11.1 mmol/L) at the 120-min time-point of an oral glucose tolerance test, or a hemoglobin A1c (HbA1c) level ≥ 6.5%. Furthermore, in a patient presenting with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) was considered diagnostic [16]. Hypertension was defined by a self-reported physician diagnosis, recent use of antihypertensive medication, or a blood pressure reading of ≥ 140/90 mmHg [17]. The METS-IR was calculated using the following formula: METS-IR = ln (2 × FPG + TG) × BMI / ln (HDL-C) [7]. The formulas used to calculate the other three IR indices [8, 18, 19] are provided in Supplementary Table S1.

Patients were classified as low-, intermediate-low-, intermediate-high-, or high-risk using the 4-strata COMPERA 2.0 risk score [20–22] (Supplementary Table S2). For each parameter in the prediction model (WHO-FC, NT-proBNP levels and 6MWD), a score of 1–4 points was assigned. The individual risk score was determined by summing the total points and dividing by the number of variables, with decimal values rounded to the nearest integer.

Endpoints and follow-up

Clinical worsening, the primary outcome of this study, was defined as the first occurrence of any of the following events: all-cause death, lung transplantation, unplanned PH-related hospitalization, or re-hospitalization due to heart failure. Follow-up data were collected through outpatient clinical visits, hospital readmissions, or telephone interviews with patients or their relatives after discharge. Three participating centers used the same follow-up protocol. Patients were followed up every 3–6 months. Endpoints were adjudicated by an independent committee.

Statistical analysis

Continuous variables are presented as the mean ± standard deviation or median [25th–75th percentile]. Categorical variables were presented as counts (percentages). Group comparisons were performed using an independent-sample t-test, Mann–Whitney U-test, chi-squared test, or Fisher's exact test, as appropriate. Correlations between the IR indices and identified markers of disease severity were examined using Spearman correlation coefficients. One-way analysis of variance was conducted to compare the insulin resistance indices across the different risk strata. Restricted cubic spline curves were used to assess the relationship between the IR indices and clinical worsening on a continuous scale.

The four IR indices were standardized (Z-score) and incorporated into unadjusted or adjusted models to evaluate the influence of a 1.0-standard deviation (SD) increase in the indices on clinical worsening. Univariable Cox regression analysis identified risk factors for clinical worsening, and factors with $p < 0.05$ or clinical significance were included in the multivariable Cox regression model. To control for potential confounders, Model 1 was adjusted for age, sex, and ethnicity. Model 2 included adjustments from Model 1 plus DM, WHO-FC, 6MWD, ln(NT-proBNP), PH-specific medications, BPA, and PEA. Model 3 was further adjusted for venous oxygen saturation (S_VO_2), cardiac index, and PVR based on Model 2. The variance inflation factor (VIF) method was used to test for collinearity, with no clear evidence of multicollinearity observed (VIF < 5 for all variables). Subgroup analyses stratified by sex, age, body mass index (BMI), and DM were performed. The p-values for the interaction effects were calculated by introducing a multiplicative term.

The area under the curve (AUC) of the receiver operating characteristic (ROC) curves were employed to assess the predictive power of each of the four IR indices and the COMPERA 2.0 risk score for primary endpoint, respectively. To assess the incremental predictive performance of clinical worsening after introducing four IR indices (as continuous variables) to the COMPERA 2.0 risk score, various measures were used including the calculation of C statistic, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI). The C statistic was calculated to represent the performance of each model using "Survival" R package. Both the continuous NRI and IDI were calculated using "survIDINRI" R package. Statistical significance was set at $p < 0.05$ (two-sided), while data analysis was performed using R-studio (version 4.4.2).

Results

Baseline characteristics

A total of 516 patients with CTEPH were enrolled, with a median age of 57.0 years [48.0–65.0], 48.1% females, and 96.9% Han Chinese. During the median follow-up period of 24.93 months, 110 patients (21.3%) experienced clinical worsening. The baseline characteristics of the participants with and without clinical worsening are presented in Table 1. Patients with clinical worsening had a higher proportion of WHO-FC class III to IV, a more restricted 6MWD, and higher NT-proBNP levels than patients without clinical deterioration. Additionally, they had higher rates of diabetes and pericardial effusion, larger right ventricular end-diastolic diameter (RVED), smaller left ventricular end-diastolic diameter (LVED), higher pulmonary vascular resistance (PVR), lower cardiac output, and reduced mixed S_VO_2. Most patients received anticoagulants, and approximately 74.0% were given targeted therapy during their initial hospitalization. The remaining patients declined treatment because of financial constraints or intolerance. Patients with clinical worsening had significantly higher METS-IR score, while no differences were observed in the TyG index, TyG-BMI index, or TG/HDL-C ratio between groups.

Relationship between IR indices and severity of CTEPH

The four IR indices were associated with different indicators of CTEPH severity, as shown in Table 2. For example, METS-IR was positively correlated with WHO-FC, NT-proBNP, RVED, pericardial effusion, mean pulmonary arterial pressure, and pulmonary vascular resistance and negatively correlated with 6MWD and LVED. However, no correlation was observed between METS-IR and S_VO_2 (r = -0.058, p = 0.186), cardiac index (r = – 0.028, p = 0.532), and right atrial pressure (r = 0.049, p = 0.266).

Figure 1 illustrates the levels and distribution of the four indices across COMPERA 2.0 risk categories, specifically comparing low-to-intermediate-low-risk versus intermediate-high-to-high-risk groups. The TyG-BMI index (low to intermediate-low risk: mean ± SD, 204.0 ± 36.2; high to intermediate-high risk: 212.6 ± 46.5, p = 0.022) and METS-IR (low to intermediate-low risk: mean ± SD, 36.2 ± 6.7; high to intermediate-high risk: 37.7 ± 8.7, p = 0.038) both showed significant increases as the COMPERA 2.0 risk score escalated. As a sensitivity analysis, the relationship between the four IR indices and the abbreviated European Society of Cardiology (ESC) 3-strata risk stratification was explored (details of the scoring methods are presented in Supplementary Table S3). The results showed that METS-IR was able to distinguish among low-risk, intermediate -risk and high-risk patients (Supplementary Figure S2).

Association between IR indices and adverse outcome of CTEPH

The four IR indices were defined as continuous variables, with the median acting as the reference point. Restricted cubic spline regression was used to fit the unadjusted Cox proportional hazards model. Unadjusted spline plots revealed a nonlinear relationship between the four indices and the hazard ratio (HR) for clinical worsening (Fig. 2). To further evaluate the predictive value of the IR indices for primary endpoint events, we established three Cox regression models evaluating the effect of a 1.0-SD increment in each index (Table 3). After fully adjusting for covariates in Model 3, only METS-IR (HR 1.273, 95%CI: 1.063–1.525 per 1.0-SD increment; p = 0.009) independently predicted clinical worsening, including all-cause death, lung transplantation, unplanned PH-related hospitalization, and re-hospitalization due to heart failure. No collinearity was detected in the multivariate Cox regression analysis. Subgroup analyses stratified by age, sex, BMI, and DM status identified interaction factors (Fig. 3), particularly between DM subgroups and the impact of METS-IR on adverse outcomes (p for interaction = 0.049). Considering the correlation between HbA1c and prognosis of CTEPH [23], we further adjusted it in sensitivity analysis, and the results were consistent with the main conclusions (Supplementary Table S4).

The predictive value and incremental performance of four IR indices for clinical worsening

The ROC analysis was used to determine the optimal cut-off value of four indices for predicting clinical worsening. The optimal cut-off value for TyG index, TyG-BMI index, TG/HDL-C ratio and METS-IR were 8.06, 253.63, 4.04, and 47.47. The METS-IR performed better than TyG index (ΔAUC = 0.034, p =0.006) and TyG-BMI index (ΔAUC = 0.054, p <0.001) in predicting clinical worsening, while its predictive performance is similar to TG/HDL-C ratio.

ROC curves were constructed to explore the predictive ability of the COMPERA 2.0 risk stratification model, and the COMPERA 2.0 model plus each of the four IR indices for clinical worsening (Fig. 4). Adding METS-IR significantly improved the C-statistics of the COMPERA 2.0 risk score (0.677 vs. 0.627, p = 0.028). Moreover, including METS-IR significantly enhanced both reclassification and discrimination beyond COMPERA 2.0 risk stratification (Table 4). Unfortunately, the results showed no significant incremental predictive ability of TyG index, TyG-BMI index, and TG/HDL-C ratio to the COMPERA 2.0 risk score (p > 0.05).

Table 1 Baseline characteristics

Variables	Overall (*n* = 516)	Non-CW (*n* = 406)	CW (*n* = 110)	*P*-value
Demographics				
Age, years	57.00 [48.00, 65.00]	57.00 [48.00, 64.00]	58.00 [48.00, 65.00]	0.640
Female, n (%)	248 (48.06)	196 (48.28)	52 (47.27)	0.852
Han ethnicity, n (%)	500 (96.90)	395 (97.29)	105 (95.45)	0.324
BMI, kg/m^2	24.02 [21.72, 26.53]	23.92 [21.67, 26.23]	24.03 [21.97, 28.58]	0.210
Current smoking, n (%)	160 (31.01)	128 (31.53)	32 (29.09)	0.624
Alcohol intake, n (%)	130 (25.19)	101 (24.88)	29 (26.36)	0.750
Clinical evaluation and comorbidities				
WHO-FC, n (%)				0.003
I or II	248 (48.06)	209 (51.48)	39 (35.45)	
III or IV	268 (51.94)	197 (48.52)	71 (64.55)	
6MWD, m	375.00 [316.00, 429.00]	384.00 [321.00, 438.00]	356.00 [268.00, 400.00]	< 0.001
History of PTE, n (%)	328 (63.57)	259 (63.79)	69 (62.73)	0.837
Diabetes mellitus, n (%)	141 (27.33)	95 (23.40)	46 (41.82)	< 0.001
Arterial hypertension, n (%)	147 (28.49)	112 (27.59)	35 (31.82)	0.383
Coronary heart disease, n (%)	46 (8.91)	37 (9.11)	9 (8.18)	0.761
OSA, n (%)	168 (32.56)	137 (33.74)	31 (28.18)	0.269
Laboratory data				
NT-proBNP, pg/mL	1038.00 [222.00, 2219.80]	836.60 [169.00, 1982.00]	1487.00 [762.00, 3128.00]	< 0.001
Albumin, g/L	42.07 ± 4.75	42.27 ± 4.68	41.33 ± 4.92	0.066
ALT, IU/L	22.00 [15.00, 34.00]	22.00 [15.00, 34.00]	22.00 [15.00, 35.00]	0.875
AST, IU/L	27.00 [22.00, 34.00]	27.00 [22.00, 33.00]	28.00 [21.00, 36.00]	0.357
Triglyceride, mmol/L	1.17 [0.88, 1.57]	1.19 [0.89, 1.64]	1.11 [0.86, 1.51]	0.225
Cholesterol, mmol/L	4.31 [3.65, 5.05]	4.39 [3.74, 5.15]	4.00 [3.34, 4.78]	0.001
HDL-C, mmol/L	1.17 [0.97, 1.46]	1.19 [0.99, 1.47]	1.08 [0.86, 1.34]	< 0.001
LDL-C, mmol/L	2.64 [2.12, 3.30]	2.68 [2.17, 3.33]	2.43 [2.00, 3.20]	0.041
FPG, mmol/L	5.17 [4.69, 5.74]	5.19 [4.71, 5.73]	5.10 [4.62, 5.80]	0.317
Serum creatinine, umol/L	83.78 [71.10, 96.00]	82.78 [70.99, 94.44]	85.58 [72.65, 98.00]	0.087
Blood urea nitrogen, mmol/L	6.30 [5.20, 7.62]	6.24 [5.15, 7.60]	6.30 [5.27, 7.82]	0.235
Echocardiography				
Pericardial effusion, n (%)	104 (20.16)	73 (17.98)	31 (28.18)	0.018
LAD, mm	34.00 [30.00, 37.00]	34.00 [30.00, 37.00]	33.00 [31.00, 38.00]	0.482
LVED, mm	41.00 [36.00, 46.00]	41.00 [37.00, 46.00]	39.00 [35.00, 44.00]	0.014
LVEF, %	65.00 [60.00, 68.00]	65.00 [60.00, 68.00]	64.00 [60.00, 67.00]	0.544
RVED, mm	33.00 [28.00, 38.00]	32.00 [28.00, 37.00]	36.00 [30.00, 41.00]	< 0.001
TRV, m/s	4.30 [3.80, 4.80]	4.30 [3.80, 4.80]	4.30 [3.90, 4.80]	0.258
sPAP, mmHg	83.02 ± 25.36	82.04 ± 25.77	86.63 ± 23.44	0.093
Pulmonary hemodynamics				
S_VO_2, %	67.90 [62.55, 72.45]	68.30 [63.25, 72.95]	66.20 [61.05, 70.70]	0.008
mRAP, mmHg	7.00 [4.00, 9.00]	6.00 [4.00, 9.00]	7.00 [4.00, 12.00]	0.009
mPAP, mmHg	47.00 [39.00, 56.00]	46.00 [38.00, 56.00]	50.00 [39.00, 62.00]	0.050
PAWP, mmHg	10.00 [8.00, 12.00]	10.00 [7.00, 12.00]	10.00 [8.00, 12.00]	0.534
Cardiac index, L/min/m^2	2.78 [2.24, 3.23]	2.80 [2.29, 3.25]	2.49 [2.12, 3.16]	0.019
PVR, wood units	9.38 [5.89, 12.80]	8.94 [5.72, 12.33]	11.06 [6.71, 14.49]	0.003
Treatment				
Anticoagulant, n (%)	499 (96.71)	393 (96.80)	106 (96.36)	0.821
PH-specific therapy, n (%)	382 (74.03)	308 (75.86)	74 (67.27)	0.068
PH combination therapy, n (%)	77 (14.92)	57 (14.04)	20 (18.18)	0.279
BPA or PEA, n (%)	373 (72.29)	306 (75.37)	67 (60.91)	0.003
Insulin resistance indices				
TyG index	8.53 ± 0.54	8.55 ± 0.54	8.47 ± 0.54	0.202
TyG-BMI index	208.84 ± 42.46	207.86 ± 41.86	212.48 ± 44.41	0.312

Table 1 (continued)

Variables	Overall (*n* = 516)	Non-CW (*n* = 406)	CW (*n* = 110)	*P*-value
TG/HDL-C ratio	2.92 ± 2.49	2.85 ± 2.41	3.18 ± 2.73	0.211
METS-IR	37.01 ± 7.94	36.47 ± 7.60	38.97 ± 8.81	0.003
Follow-up time, months	24.93 [12.16, 44.36]	24.73 [12.16, 42.50]	26.50 [13.27, 51.7]	0.113

Data are presented as mean ± standard deviation, median [25th–75th percentile] or number (percentage)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BPA, balloon pulmonary angioplasty; CW, Clinical worsening; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LAD, left atrium dimension; LDL-C, low-density lipoprotein cholesterol; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; METS-IR, metabolic score for insulin resistance; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; 6MWD, 6-min walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; OSA, obstructive sleep apnea; PAWP, pulmonary arterial wedge pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PTE, pulmonary thromboembolism; PVR, pulmonary vascular resistance; RVED, right ventricular end-diastolic diameter; sPAP, systolic pulmonary arterial pressure; SVO2, mixed venous oxygen saturation; TG/HDH-C, triglyceride to high-density lipoprotein cholesterol ratio; TRV, tricuspid regurgitation velocity; TyG, Triglyceride and glucose; TyG-BMI, triglyceride-glucose-body mass index;WHO-FC, World Health Organization functional class.

Table 2 Correlation analysis between insulin resistance indices with established markers of CTEPH severity

Variables	TyG index		TyG-BMI index		TG/HDL-C ratio		METS-IR	
	Coefficient (*r*)	*P* value	Coefficient (*r*)	*P* value	Coefficient (*r*)	*P* value	Coefficient (*r*)	*P* value
WHO-FC	0.183	< 0.001	0.197	< 0.001	0.075	0.089	0.122	0.006
6MWD	− 0.112	0.011	− 0.226	< 0.001	− 0.083	0.060	− 0.170	< 0.001
ln (NT-proBNP)	0.255	< 0.001	0.373	< 0.001	0.093	0.034	0.237	< 0.001
Echocardiography								
RVED	0.207	< 0.001	0.191	< 0.001	0.061	0.163	0.100	0.024
LVED	− 0.089	0.043	− 0.349	< 0.001	-0.040	0.367	− 0.252	< 0.001
TRV	0.069	0.119	0.210	< 0.001	0.029	0.508	0.179	< 0.001
sPAP	0.074	0.094	0.217	< 0.001	0.024	0.582	0.175	< 0.001
Pericardial effusion	0.205	< 0.001	0.192	< 0.001	0.102	0.020	0.110	0.012
Pulmonary hemodynamics								
S_vO_2	− 0.123	0.005	− 0.147	0.001	− 0.003	0.953	-0.058	0.186
mPAP	0.185	< 0.001	0.271	< 0.001	0.050	0.255	0.196	< 0.001
PAWP	− 0.053	0.228	0.088	0.047	− 0.033	0.454	0.101	0.021
PVR	0.138	0.002	0.310	< 0.001	0.036	0.417	0.226	< 0.001
Cardiac index	0.076	0.083	0.056	0.203	0.002	0.969	− 0.028	0.532
mRAP	− 0.138	0.002	− 0.006	0.887	− 0.058	0.190	0.049	0.266

CTEPH, chronic thromboembolic pulmonary hypertension; LAD, left atrium dimension; LVED, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; METS-IR, metabolic score for insulin resistance; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; 6MWD, 6-min walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RVED, right ventricular end-diastolic diameter; sPAP, systolic pulmonary arterial pressure; S_vO_2, mixed venous oxygen saturation; TG/HDH-C, triglyceride to high-density lipoprotein cholesterol ratio; TRV, tricuspid regurgitation velocity; TyG, Triglyceride and glucose; TyG-BMI, triglyceride-glucose-body mass index; WHO-FC, World Health Organization functional class

Discussion

To the best of our knowledge, this is the first study to compare the relationships of surrogate markers for IR with disease severity and adverse outcomes in patients with CTEPH. This study provides novel clinical evidence for the risk stratification of patients with CTEPH. Our results demonstrate that various surrogate markers of IR exhibit positive correlations with several clinical parameters, including WHO-FC, NT-proBNP, RVED, tricuspid regurgitation velocity, systolic pulmonary arterial pressure, mPAP, pulmonary vascular resistance, mean right atrial pressure, and pericardial effusion. Conversely, these IR surrogates are negatively correlated with 6MWD, LVED, and pulmonary artery wedge pressure. Additionally, levels of TyG-BMI and METS-IR were significantly elevated in patients with intermediate to high-risk CTEPH. After adjusting for potential confounders, METS-IR was identified as an independent predictor of mortality, lung transplantation, and rehospitalization due to heart failure in this cohort. Notably, among all the IR surrogates, only METS-IR significantly enhanced the predictive capability of the COMPERA 2.0 risk stratification tool for adverse outcomes. Therefore, surrogates for IR, particularly METS-IR, may serve as indicators for assessing disease severity and prognosis in patients with CTEPH. Additionally, METS-IR could complement the COMPERA 2.0 risk stratification framework in predicting adverse outcomes.

Although methods such as the pancreatic suppression test, hyperinsulinemic-euglycemic clamp technique, and minimal model approximation of glucose metabolism are effective and accurate for directly assessing IR, they

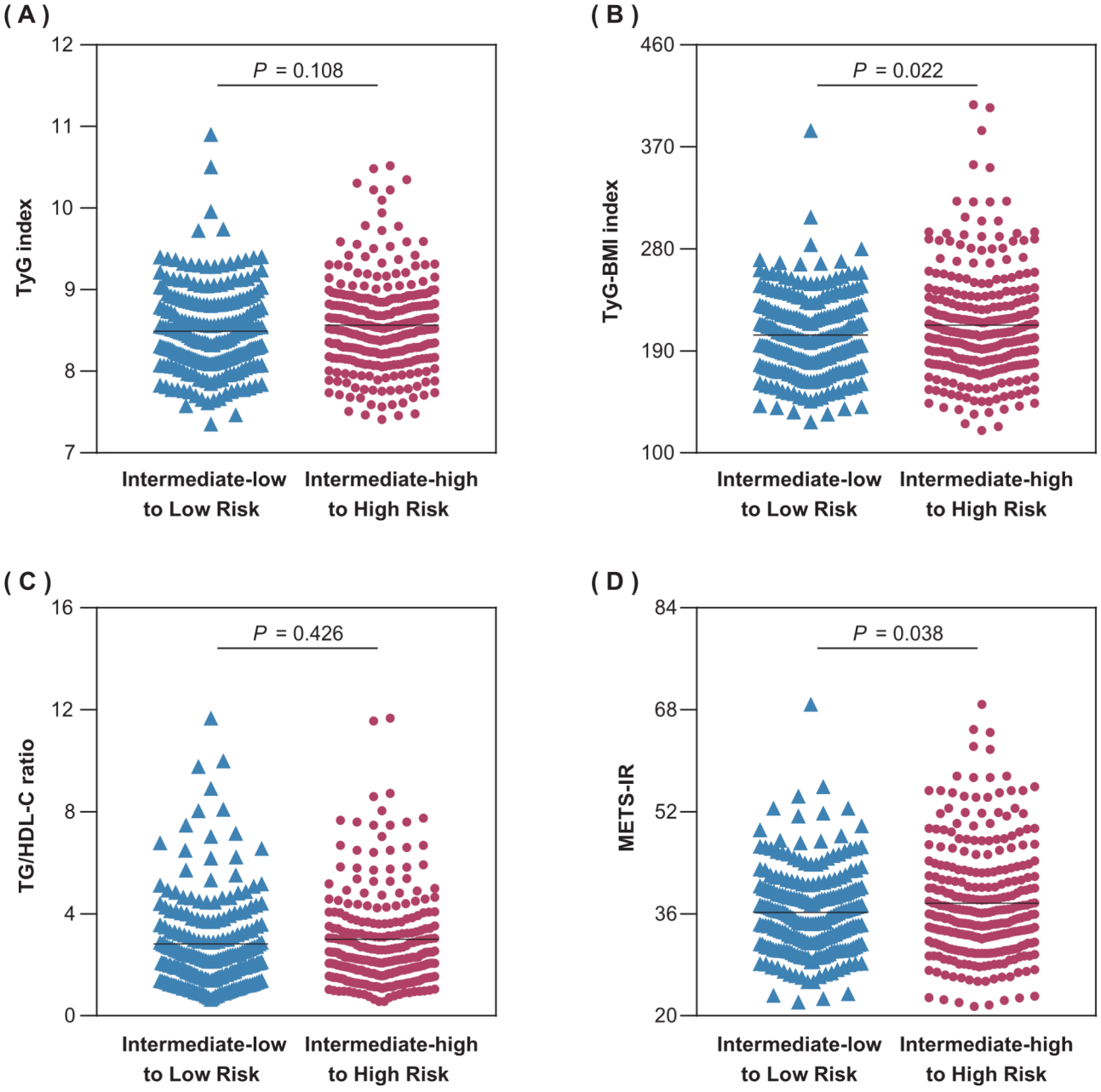

Fig. 1 Association between insulin resistance indices and the COMPERA 2.0 risk score. Scatterplots of the relationship between risk stratification and TyG index (**A**), TyG-BMI index (**B**), TG/HDL-C ratio (**C**) and METS-IR (**D**). Abbreviations: METS-IR, metabolic score for insulin resistance; TG/HDH-C, triglyceride to high-density lipoprotein cholesterol ratio; TyG, Triglyceride and glucose; TyG-BMI, triglyceride glucose-body mass index

are complex, invasive, and costly, making them difficult to apply in epidemiological and clinical research [24–26]. In 1985, Matthews et al. proposed the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) as an indirect method for evaluating IR, which simplified the process by utilizing only fasting glucose and insulin levels [27]. However, due to the complexity of measuring fasting insulin levels and the lack of standardized methods, alternative insulin-independent markers for assessing IR have been proposed, such as the TyG index, TyG-BMI index, TG/HDL-C ratio, and METS-IR. These markers have not only been validated as effective and widely accepted surrogates for assessing IR, but they also serve as important independent predictors of cardiovascular diseases, including stroke, atherosclerosis, and heart failure. Tatebe et al. [28] reported a positive correlation between the HOMA-IR and mPAP in patients with CTEPH following BPA, with IR showing improvement post-procedure. Our preliminary findings indicate that IR correlates with disease severity and long-term

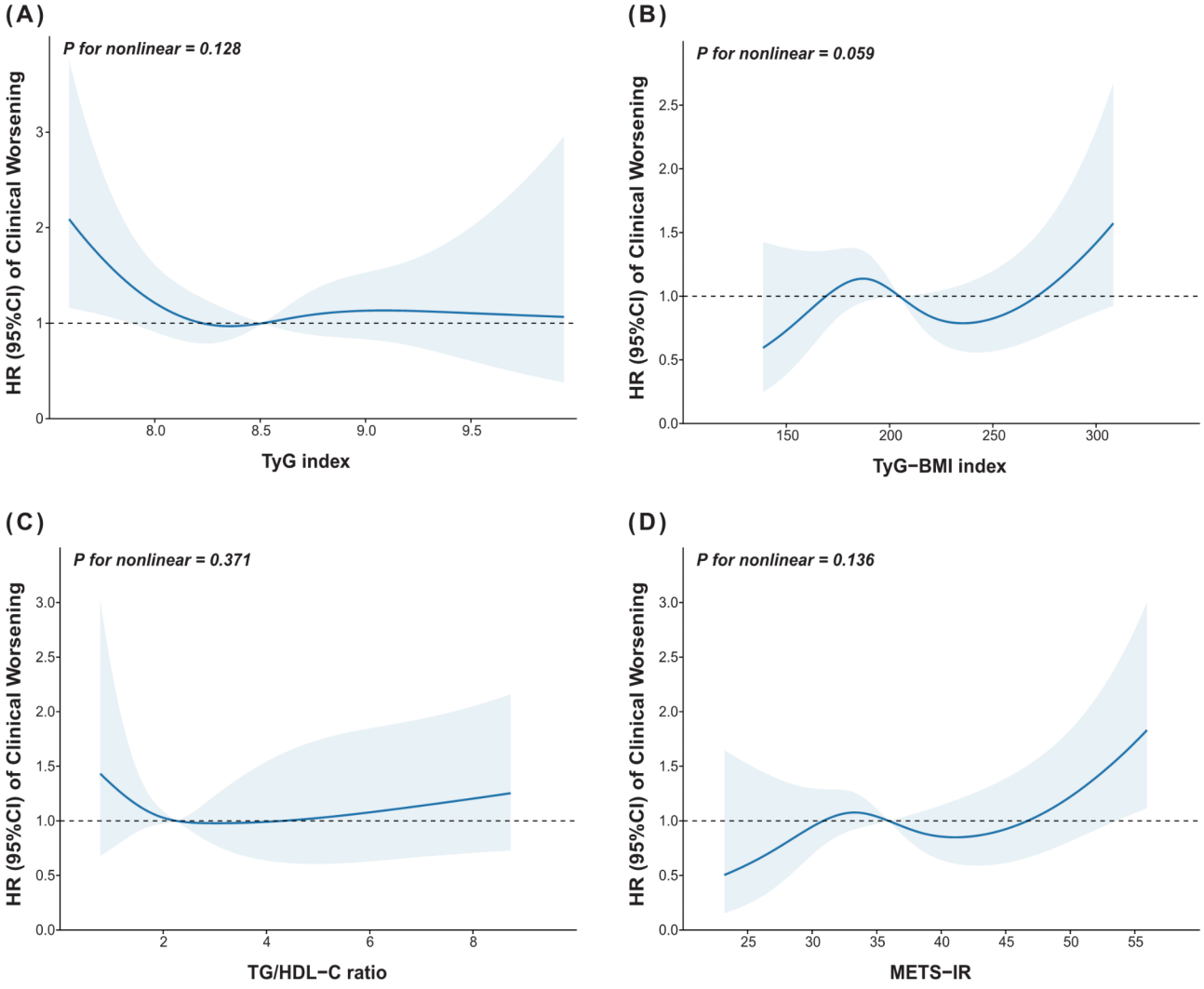

Fig. 2 Restricted cubic spline curves for clinical worsening according to the insulin resistance indices. Insulin resistance indices as continuous variables fitted an unadjusted Cox regression model using restricted cubic spline regression. CI, confidence interval; HR, hazard ratio; METS-IR, metabolic score for insulin resistance; TG/HDH-C, triglyceride to high-density lipoprotein cholesterol ratio; TyG, Triglyceride and glucose; TyG-BMI, triglyceride glucose-body mass index

Table 3 Association between insulin resistance indices and clinical worsening

	TyG index		TyG-BMI index		TG/HDL-C ratio		METS-IR	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted	0.883 (0.719, 1.086)	0.238	1.134 (0.941, 1.366)	0.188	1.063 (0.891, 1.268)	0.500	1.228 (1.033, 1.460)	0.020
Model 1	0.851 (0.687, 1.054)	0.140	1.140 (0.941, 1.380)	0.181	1.071 (0.897, 1.278)	0.450	1.249 (1.049, 1.486)	0.013
Model 2	0.889 (0.724, 1.092)	0.261	1.195 (0.983, 1.453)	0.074	1.085 (0.904, 1.302)	0.382	1.260 (1.055, 1.504)	0.011
Model 3	0.890 (0.726, 1.091)	0.263	1.222 (0.998, 1.496)	0.053	1.063 (0.885, 1.276)	0.515	1.273 (1.063, 1.525)	0.009

Model 1: Adjusted for age, sex and ethnicity

Model 2: Adjusted for variables from Model 1 plus diabetes mellitus, WHO-FC, 6MWD, ln (NT-proBNP), PH-specific treatment, BPA and PEA

Model 3: Adjusted for variables from Model 2 plus S_vO_2, cardiac index and PVR

BPA, balloon pulmonary angioplasty; CI, confidence interval; HR, hazard ratio; ln, logarithmically transformed; NT-proBNP, N-terminal pro-brain natriuretic peptide; METS-IR, metabolic score for insulin resistance; 6MWD, 6-min walk distance; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; S_vO_2, mixed venous oxygen saturation; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; TyG, triglyceride and glucose; TyG-BMI, triglyceride-glucose-body mass index; WHO-FC, World Health Organization functional class

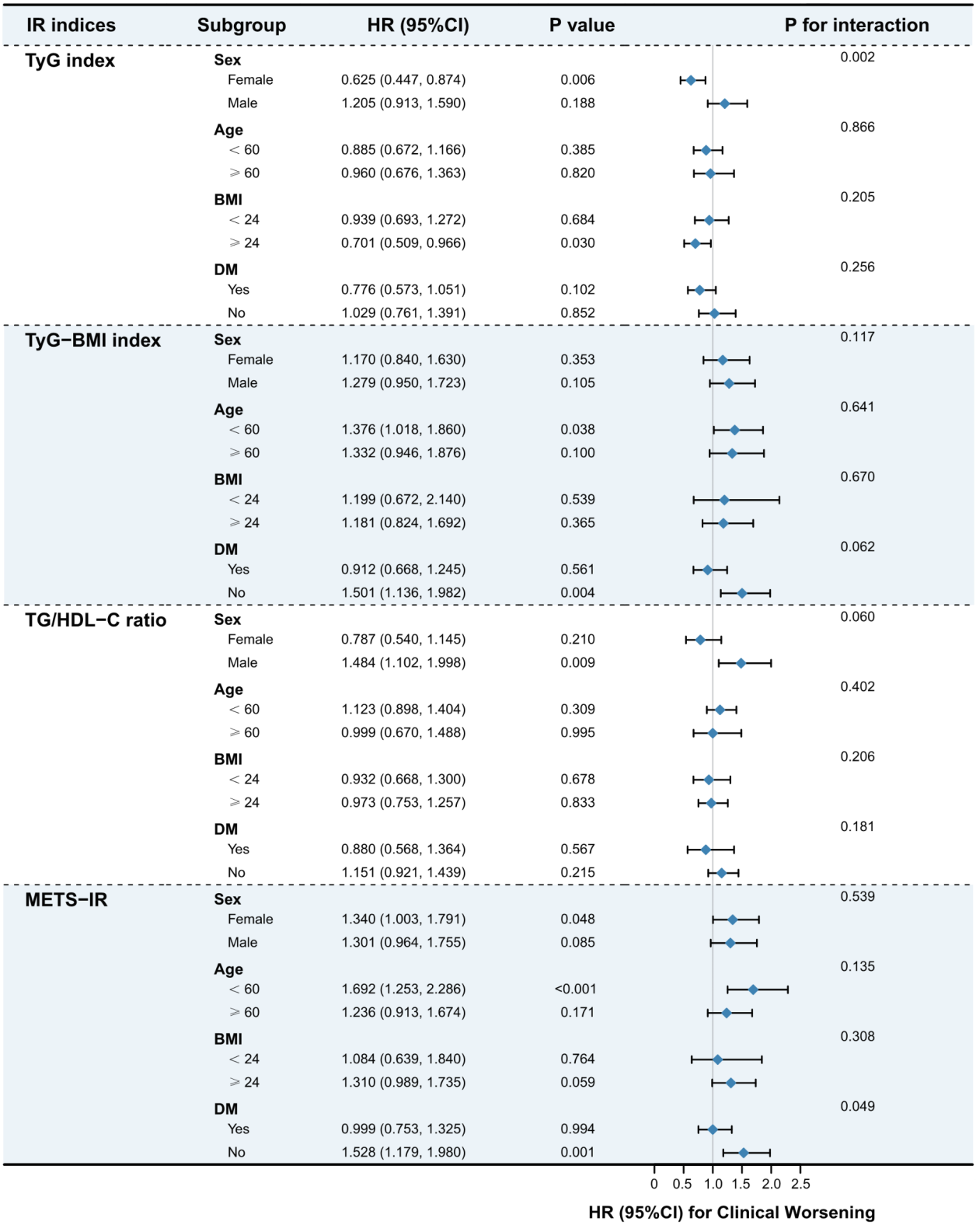

Fig. 3 (See legend on next page.)

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Fig. 3 Subgroup and interaction analyses of the association between insulin resistance indices and primary endpoint events. Each subgroup was adjusted for age, sex, ethnicity, DM, WHO-FC, 6MWD, ln (NT-proBNP), PH-specific treatment, BPA, PEA, S_VO_2, Cardiac index and PVR. Hazard ratios are presented as per 1.0-SD increase in the insulin resistance indices for clinical worsening. Abbreviations: BMI, body mass index; BPA, balloon pulmonary angioplasty; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; ln, logarithmically transformed; NT-proBNP, N-terminal pro-brain natriuretic peptide; METS-IR, metabolic score for insulin resistance; 6MWD, 6-min walk distance; PEA, pulmonary endarterectomy; PH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; S_VO_2, mixed venous oxygen saturation; TG/HDL-C, triglyceride to high-density lipoprotein cholesterol ratio; TyG, triglyceride and glucose; TyG-BMI, triglyceride glucose-body mass index; WHO-FC, World Health Organization functional class

prognosis in idiopathic pulmonary arterial hypertension (IPAH), with surrogates such as TyG-BMI and METS-IR acting as independent predictors of clinical deterioration [19]. Moreover, METS-IR provides additional prognostic insights beyond existing guideline-based risk stratification.

Similar findings were observed in populations with congestive heart failure and obesity [29, 30]. However, studies on IR in PH and venous thromboembolism are limited. Bosnjic et al. observed that the HOMA-IR was higher in the PE group than in the non-PE group [31]. Zare et al. [32] used HOMA-IR to assess IR in 100 patients with PH and found that 27% of the patients with PH had IR. However, there were no significant differences in 6MWD, laboratory indices, or hemodynamic parameters between the IR and non-IR groups. During a median follow-up of 48 months, the survival rate of patients with IR was slightly lower than that of patients without IR, although IR was not an independent predictor of mortality. Our team previously evaluated and compared different non-insulin-based indices for IPAH and found that TyG-BMI and METS-IR could independently predict clinical worsening events, with METS-IR providing an incremental predictive performance beyond European Society of Cardiology risk stratification [19]. Tatebe et al. [28] conducted a study involving 55 patients with CTEPH after BPA and found a positive correlation between HOMA-IR and mPAP. After BPA treatment, the HOMA-IR scores significantly decreased, indicating an improvement in IR. However, these studies had small sample sizes, mostly focused on patients with PH or pulmonary arterial hypertension (the first group), and evaluated only single surrogates for IR without comparing different IR indices concerning CTEPH. Given the high heterogeneity of PH and the diversity of non-insulin-based surrogates for IR, we initiated the current study to systematically compare the relationships between various IR markers and CTEPH disease severity and prognosis and to explore whether these indices provide additional predictive value for existing risk stratification tools.

The pathophysiological relationship between CTEPH and IR may be partly attributed to the shared risk factors between the two conditions. Additionally, systemic effects in patients with CTEPH may play a role. Studies have shown that patients with CTEPH exhibit reduced glycolysis in pulmonary arterial endothelial cells, with decreased mRNA levels of glycolytic enzymes such as hexokinase-2 and phosphofructokinase-1, and downregulation of lactate dehydrogenase subunit A protein expression [33]. Khirfan et al. [34] conducted a study involving 90 patients with CTEPH and found that compared to healthy controls, patients with CTEPH had lower HDL-C levels, and an increase in HDL-C in patients with CTEPH was associated with improved right ventricular dilation and reduced PVR after PEA. Single-cell sequencing of post-PEA pathological tissues revealed lipid metabolic reprogramming in macrophages, which may be linked to the persistence and insolubility of thrombi in pulmonary arteries and the progression of PH [35]. Changes in glucose and lipid metabolisms are often associated with obesity. An analysis by Chiu et al. [36] based on the UK National Cohort showed that despite similar hemodynamics, patients with CTEPH with a BMI > 50 kg/m^2 had the highest rates of NYHA class III/IV and the lowest five-year survival rates. We hypothesized that because METS-IR integrates factors related to blood glucose, lipid metabolism, and obesity, it demonstrates strong correlations with disease severity and has an excellent predictive ability for adverse outcomes in our cohort. Furthermore, the METS-IR offers additional predictive value when incorporated into existing risk stratification tools.

Second, systemic inflammation is a potential factor associated with IR in patients with CTEPH. Quarck et al. [37] described the pathological features of pulmonary vascular lesions in 52 patients with CTEPH after PEA and found significant elevations in C-reactive protein, interleukin-10, monocyte chemotactic protein-1, macrophage inflammatory protein-1α, and matrix metalloproteinase-9. Enhanced systemic inflammation parallels local inflammatory cell infiltration in major pulmonary arteries in advanced stages of CTEPH [37]. On the other hand, oxidative stress and inflammation are key factors in the progression of IR and the development of type 2 diabetes mellitus (T2DM) [38]. In the pathology of IR, unresolved inflammation combined with a "glycolipotoxic" environment in the pancreatic islets promotes infiltration of immune cells, which leads to dysfunction of insulin-secreting β-cells and, eventually, cell death [39]. In patients with CTEPH, particularly during periods of severe disease, evidence of systemic inflammation is present, which may contribute to the progression of IR. This exacerbates inflammation and oxidative stress, creating a vicious cycle.

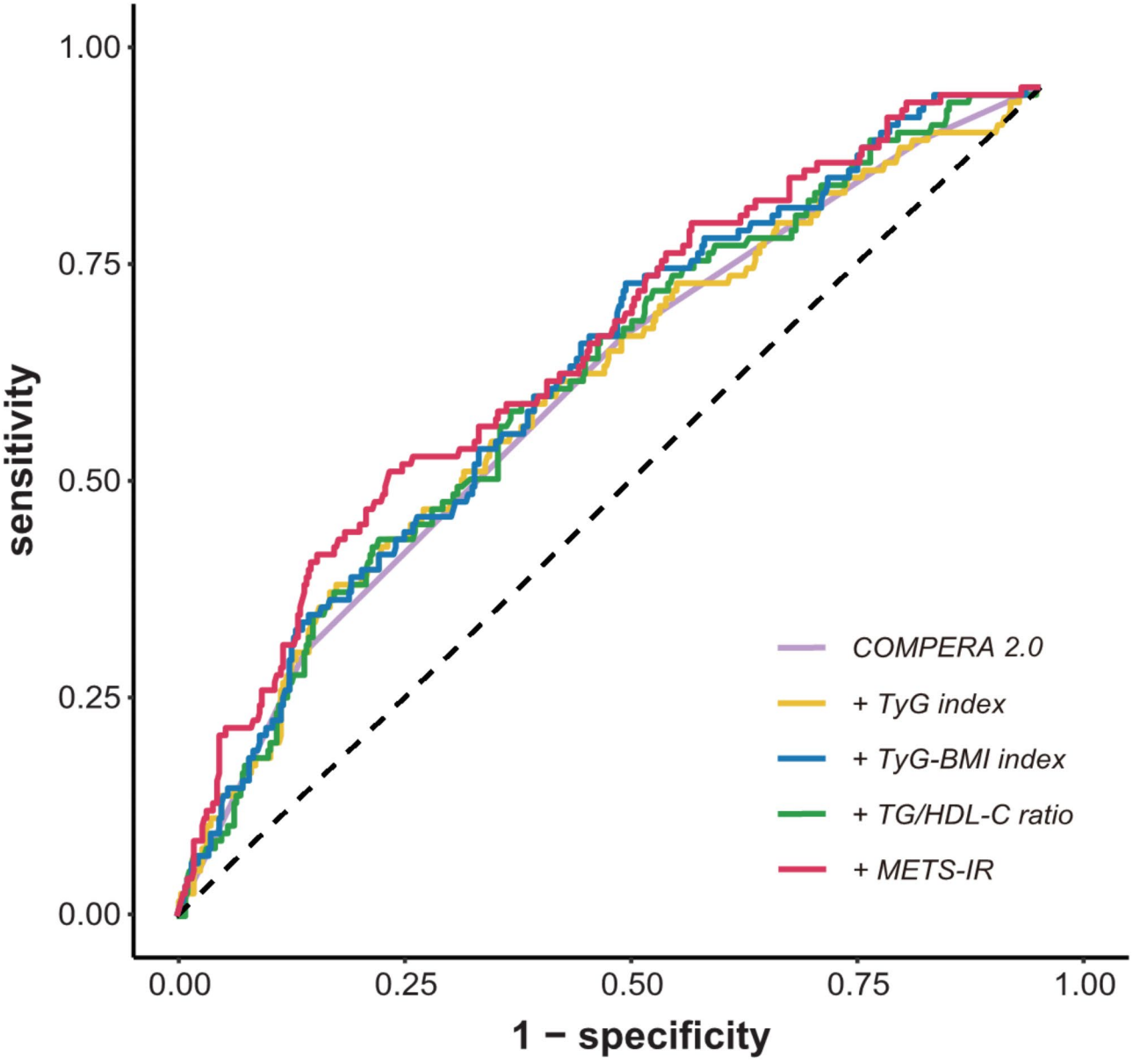

Fig. 4 ROC curves of insulin resistance indices as a marker to predict clinical worsening based on COMPERA 2.0 risk score. Abbreviations: METS-IR, metabolic score for insulin resistance; ROC, receiver operator characteristic; TG/HDH-C, triglyceride to high-density lipoprotein cholesterol ratio; TyG, Triglyceride and glucose; TyG-BMI, triglyceride glucose-body mass index

Table 4 Improvement in discrimination and risk reclassification for clinical worsening after adding insulin resistance indices

Model	C-statistic (95% CI)	*P* value	NRI (95% CI)	*P* value	IDI (95% CI)	*P* value
COMPERA 2.0	0.627 (0.565, 0.690)	Ref.	Ref.		Ref.	
+TyG index	0.631 (0.566, 0.691)	0.669	0.019 (-0.192, 0.229)	0.863	0.001 (-0.001, 0.002)	0.420
+TyG-BMI index	0.650 (0.603, 0.698)	0.151	0.103 (-0.106, 0.311)	0.335	0.009 (-0.002, 0.020)	0.120
+TG/HDL-C ratio	0.641 (0.576, 0.691)	0.297	0.097 (-0.105, 0.298)	0.346	0.003 (-0.005, 0.011)	0.455
+METS-IR	0.677 (0.609, 0.728)	0.028	0.264 (0.057, 0.471)	0.013	0.031 (0.012, 0.051)	0.002

CI, confidence interval; IDI, integrated discrimination improvement; METS-IR, metabolic score for insulin resistance; NRI, net reclassification improvement; TG/HDH-C, triglyceride to high-density lipoprotein cholesterol ratio; TyG, Triglyceride and glucose; TyG-BMI, triglyceride-glucose-body mass index

Additionally, physical inactivity and psychological symptoms may help explain the relationship between CTEPH and IR. A study by Hamburg et al. found that even short-term bed rest significantly increased the insulin response to glucose loading, as well as total cholesterol and triglyceride levels in healthy subjects [40]. Notably, patients with CTEPH are at risk of developing IR, and symptoms of anxiety and depression are commonly observed. Those with psychological issues often experience more severe disease progression [41, 42]. This further emphasizes the importance of early identification, management, rehabilitation under professional guidance, and attention to patients' mental health. These factors are interconnected, thus contributing to the development of IR, which may act as a risk factor or disease modifier for CTEPH, rather than merely a metabolic epiphenomenon.

This study has several limitations. First, its retrospective design inherently limits the ability to establish causal relationships. However, to the best of our knowledge, this is the largest study to date investigating the comparative value of different IR surrogates in patients with CTEPH. Second, we did not collect dynamic data on blood glucose, lipid levels, or BMI, which may have provided a more comprehensive assessment of IR over time. Future studies incorporating serial measurements of these metabolic parameters could offer additional insights into the temporal dynamics of IR in CTEPH. Third, the study covers a prolonged period during which significant advancements have been made in the treatment of CTEPH, including the approval of soluble guanylate cyclase stimulators and improvements in surgical techniques such as BPA. Although we adjusted for both pharmacological and interventional treatments, residual confounding due to evolving management strategies cannot be ruled out. Fourth, we utilized non-insulin-based IR indices rather than direct insulin measurements. While these indices have been validated in multiple studies as reliable proxies for IR, their limitations should be acknowledged. Future research should aim to incorporate direct insulin measurements and additional potential confounders to enhance the robustness of findings.

Conclusions

The METS-IR independently predicts clinical worsening events in patients with CTEPH. Incorporating METS-IR into the existing risk stratification tools provides additional predictive value. METS-IR may serve as a reliable and convenient indicator for assessing disease severity and estimating long-term outcomes in patients with CTEPH.

Abbreviations

AUC	Area under the curve
BMI	Body mass index
BPA	Balloon pulmonary angioplasty
CTEPH	Chronic thromboembolic pulmonary hypertension
DM	Diabetes mellitus
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic model assessment for insulin resistance
HR	Hazard ratio
IDI	Integrated discrimination improvement
IPAH	Idiopathic pulmonary arterial hypertension
IR	Insulin resistance
LDL-C	Llow-density lipoprotein cholesterol
LVED	Left ventricular end-diastolic diameter
METS-IR	Mmetabolic score for insulin resistance
mPAP	Mean pulmonary arterial pressure
6MWD	6-min walk distance
NRI	Net reclassification improvement
NT-proBNP	N-terminal pro-brain natriuretic peptide
PEA	Pulmonary endarterectomy
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
ROC	Receiver operator characteristic
RVED	Right ventricular end-diastolic diameter
SD	Standard deviation
S_VO_2	Mixed venous oxygen saturation
TG	Triglyceride
TG/HDL-C ratio	Triglyceride to high-density lipoprotein cholesterol ratio
TyG index	Triglyceride and glucose index
TyG-BMI index	Triglyceride-glucose-body mass index
VIF	Variance inflation factor
WHO-FC	World Health Organization functional class

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Author contributions

ZL, YG and QL contributed to the conception of the study. LG, SZ and SL performed the data analyses and drafted the manuscript. ZZ, QZ and TY contributed to analysis and manuscript preparation. ML, PL, AD, YW and QW contributed to data collection. All authors critically reviewed the manuscript for intellectual content and had final responsibility for the decision to submit for publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was revised and approved by the local ethics committee. Written informed consent was obtained from all patients.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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