

Prognostic significance of insulin resistance in pulmonary hypertension

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Abstract

Aims The relationship between insulin resistance (IR) and glucose intolerance with pulmonary hypertension (PH) has been suggested in recent investigations. In the present study, we aimed to show the prevalence of IR and its correlation with haemodynamic variables as well as its prognostic significance in this group of patients.

Methods and results Among 100 new and returning patients with PH, scheduled for right heart catheterization (RHC), 59 non-diabetic patients were enrolled. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to assess IR. The study population were followed up for a median (interquartile range) of 48 (23–48) months for all-cause mortalities. Most of the study population [mean (standard deviation) age of 45.9 (17.3)] were classified as class I of PH classification (47.5%). Overall, 27% of our study population had IR considering the Iranian cut points of HOMA-IR. The prevalence of IR in non-diabetic, non-metabolic syndrome patients with precapillary PH (PAH) was 34.2%, which was higher than the prevalence of IR in non-diabetic, non-metabolic syndrome Iranian population (24.1%). There was no difference between IR and insulin sensitive (IS) groups regarding demographic and clinical findings, 6 min walk test, and laboratory and haemodynamic data in univariable and multivariable analyses. The mortality rate in the follow-up period was 44.1%. The survival of patient with IR was slightly lower than IS patients; however, IR was not an independent predictor of death.

Conclusions The glucose metabolism is dysregulated in patients with PH, and IR may increase the risk of adverse events among these patients.

Keywords Pulmonary hypertension; Insulin resistance; Glucose intolerance

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Introduction

Pulmonary arterial hypertension (PAH) is a disease of pulmonary vascular bed in which the remodelling, vasoconstriction, and increased thrombotic state in pulmonary vasculature lead to a progressive increase in pulmonary vascular resistance, right ventricular failure, and death.¹

The pathophysiological mechanisms involved in the development and progression of PAH are complex and the role

of many genetic and environmental factors have been suggested.^{2,3}

One of the recent advances in describing the pathophysiology of PAH is the presence of an association between insulin resistance (IR) and PAH.^{4–11}

Our previous study⁶ indicated that the incidence of glucose intolerance and IR could be higher in patients with PAH. However, our study population was only composed of patients with class I of PAH. In addition, we did not directly assess IR

and used triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) ratio (TG/HDL-C) as a surrogate of IR in our study population.

The homeostasis model assessment-estimated insulin resistance (HOMA-IR), developed by Matthews *et al.*, is a convenient method for estimation of IR and has been widely used in clinical and epidemiological researches.^{12,13}

In the present study, we aimed to assess HOMA-IR in patients with pulmonary hypertension (PH) in all PH classes [without a history of diabetes mellitus (DM)] and its prognostic significance in this group of patients.

Methods

Patient selection

The study population was selected among patients scheduled for right heart catheterization (RHC) between March 2015 and March 2016 for evaluation of PH for the first time or at follow-up according to the following inclusion/exclusion criteria.

Inclusion criteria:

- 1- Presence of PH based on updated clinical classification of PH; a mean of pulmonary artery pressure (PAP) \geq 25 mmHg in RHC
- 2- Age \geq 18 years

Exclusion criteria:

- 1- Established DM
- 2- Under treatment for hyperlipidaemia
- 3- Presence of glucose intolerance [glycosylated haemoglobin (HbA1c) $>$ 6%] or high blood sugar in favour of undiagnosed DM [fasting blood sugar (FBS) $>$ 126 mg/dL or 2 h plasma glucose \geq 200 mg/dL] in laboratory evaluations preceded RHC
- 4- A history of prednisolone intake or other corticosteroids
- 5- Decompensated right ventricular failure and/or overt fluid overload
- 6- Inability to perform 6 min walk test (6MWT)
- 7- Isolated postcapillary PH

Patients' evaluation and follow-up

Clinical history and a thorough physical examination were obtained from all the patients. The New York Heart Association (NYHA) functional class of all study population was assessed by the same investigator.

Body weight of the study population was measured with the subject wearing a hospital gown and their height was measured without shoes. Waist circumference was measured midway between the iliac crest and the lower rib margin.

Body mass index (BMI) was calculated by the weight divided by the square of the height.

The 6MWT was performed according to the protocol of Guyatt *et al.*¹⁴

All the blood analyses were performed at our laboratory on the day of RHC. Blood samples were collected from all study population after 12 h of overnight fasting. FBS was measured using enzymatic colorimetric method with glucose oxidase. HbA1c was assayed using high performance liquid chromatography (HPLC) by standardized laboratory protocol using a method certified by the National Glycohemoglobin Standardization Program. Fasting insulin was assayed by radioimmunoassay (Immunotech, Prague, Czech Republic) with a sensitivity of 0.5 μ U/mL.

HOMA-IR was calculated by the following formula:

Fasting insulin (U/L) \times FBS (mg/dL)/405, as described by Matthews *et al.*^{12,13}

Total cholesterol was measured using enzymatic colorimetric method with cholesterol esterase and cholesterol oxidase. HDL-C was measured after precipitation of the apolipoprotein B-containing lipoproteins with phosphotungstic acid. Serum TG level was measured using an enzymatic colorimetric method with glycerol phosphate oxidase.

Patients were defined to have IR or insulin sensitivity (IS) based on the HOMA-IR. The proposed value of HOMA-IR for distinction between IS and IR was considered according to what described in an Iranian study by Esteghamati *et al.*¹² Accordingly, the HOMA-IR \geq 1.775 was considered as IR in non-diabetic people. The cut point of HOMA-IR for IR in those who have metabolic syndrome features is 4.325.

As our previous study,⁶ we also checked the ratio of TG/HDL-C. We defined an individual as IS when TG/HDL-C ratio was $<$ 2.0 and IR when TG/HDL-C ratio was $>$ 3.0.

We also defined the metabolic syndrome in our study population according to the International Diabetes Federation (IDF).¹⁵

According to IDF definition, a person defined as having metabolic syndrome should have central obesity plus any two of the following: (i) fasting plasma glucose \geq 100 mg/dL (or diabetes); (ii) TG \geq 150 mg/dL; (iii) HDL $<$ 40 mg/dL for men and $<$ 50 mg/dL for women; and (iv) systolic blood pressure \geq 130 mmHg or diastolic blood pressure \geq 85 mmHg.

The central obesity, based on cut-off points of the Iranian population, is defined as waist circumference $>$ 90 cm in males and females.¹⁵

Using HOMA-IR cut-off, the prevalence of IR in those without and with IDF defined-metabolic syndrome is considered 24.1% and 42.5%, respectively, in Iranian population.¹²

Right heart catheterization was performed by standard method in all patients in catheterization laboratory. The following variables were measured for each patient: mean right atrial pressure (RAP); systolic and end-diastolic right ventricu-

lar pressure; systolic, diastolic, and mean PAP; pulmonary capillary wedge pressure (PCWP); and mixed venous oxygen saturation and cardiac output (CO) by the Fick method. The cardiac index (CI) was calculated by dividing CO to body surface area (BSA). The European Society of Cardiology 2015 guideline in diagnosis and management of PH was considered to define the presence of PH and determine the haemodynamic category (precapillary vs. postcapillary) as well as the PH World Health Organization (WHO) group of each patient.¹

All selected patients were followed up until the end of 2019 for all causes of death by reviewing the hospital records or by contacting them on the phone.

This study was approved by the research and ethics committee of Rajaie Cardiovascular Medical and Research Center, and written informed consent was obtained from all patients.

Mortality risk assessment

For the mortality risk assessment of study participant, the simplified risk assessment tool as described by Boucly *et al.* was used.¹⁶

Four variables, namely, NYHA functional class, 6MWT distance, RAP, and CI, were considered for this risk stratification. The study participants were divided into low and high risk according to these criteria. The patients were categorized as low risk if they had three to four of four low-risk criteria.

Low-risk criteria:

- 1- NYHA class I–II
- 2- 6MWT distance > 440 m
- 3- RAP < 8 mmHg
- 4- CI ≥ 2.5 L/min/m²

Study endpoints

The primary endpoint of the study was to determine the prevalence of IR in patients with PH and its different subgroups.

The secondary endpoint was the prevalence and the predictors of all causes of mortality and its relationship with IR.

Statistical analysis

IBM SPSS Statistics 19 (IBM SPSS Statistics for Windows, Version 19.0, Armonk, NY, USA: IBM Corp.) was used for all statistical analyses. The normality of distribution for all variables was verified by the one-sample Kolmogorov–Smirnov test. Categorical variables were reported as number (percentage), and quantitative variables were expressed as mean (standard deviation) or median (interquartile range, IQR) as appropriate. The Student's *t*-test, χ^2 test, and Mann–Whitney test were used for comparisons and associations, as

appropriate. Relationships were assessed using the Pearson or Spearman correlation coefficient depending on their distribution. *P* value < 0.05 was considered significant.

Results

Among 100 new and returning patients with PH scheduled for RHC between 2015 and 2016, a total of 59 patients (54.2% female) were enrolled according to our inclusion/exclusion criteria.

Table 1 depicts clinical, laboratory, and haemodynamic characteristics of all study participants, IR, and IS subgroups.

The mean (standard deviation) of age was 45.9 (17.3) years. The majority of patients had NYHA class of II and III and considering the WHO PH classification, 47.5% were in class I (PAH), 28.8% class II (PH due to left heart), 5.1% class III (PH due to lung diseases), 16.9% class IV (chronic thromboembolic PH), and 1.7% class V (multifactorial PH including patients with haemolytic anaemias).

Regarding the haemodynamic classification of PH, 42 (71.2%) and 17 (28.8%) patients had precapillary PH and combined postcapillary PH, respectively.

The aetiological diagnoses in patients with class I of PH were idiopathic PAH and Eisenmenger syndrome in 11 and 17 patients, respectively. Ten (35%) patients had been evaluated as naïve PH and the rest of them were on specific PH therapy including phosphodiesterase 5-inhibitors (PDE5-I) and/or bosentan.

The most common aetiology for the patients in WHO PH group of II was dilated (ischaemic or non-ischaemic) cardiomyopathy.

Insulin resistance

As shown in *Table 1*, 16 (27.1%) patients had criteria of IR. Except one case who had combined postcapillary PH, and the rest of IR patients were in precapillary PH group. So we decided to analyse the significance of IR only in patients with precapillary PH.

Table 2 depicts the comparison of clinical, laboratory, and haemodynamic characteristics of IR and IS patients with precapillary PH (PAH).

Among 42 patients with precapillary PH, 4 patients showed the criteria of metabolic syndrome. As the patients with high fasting glucose level were excluded before enrolment, these 4 patients had central obesity plus a history of systemic hypertension or TG ≥ 150 mg/dL or HDL < 40 mg/dL for men and <50 mg/dL for women.

Thirteen of the remaining 38 patients had the criterion of IR, which means that the prevalence of IR (34.2%) in non-diabetic, non-metabolic syndrome PAH patients might be higher than Iranian general population.

Table 1 Clinical, laboratory, and haemodynamic characteristics of all study participants, insulin resistance, and insulin sensitive subgroups, *n* = 59

Variables	All study participants <i>N</i> = 59	Insulin resistance <i>N</i> = 16	Insulin sensitive <i>N</i> = 43	<i>P</i> value ^a
Sex (female), number (%)	32 (54.9)	9 (57)	23 (53)	0.02
Age, years, mean (SD)	45.9 (17.3)	46.2 (19.9)	45.8 (16.5)	0.1
Body mass index, kg/m ² , mean (SD)	23.9 (4.9)	24.3 (5.8)	23.8 (4.6)	0.01
Waist circumference, cm, mean (SD)	83.8 (17.6)	84.7 (17)	82 (16)	0.4
History of hypertension, number (%)	10 (17)	2 (12.5)	8 (18.6)	0.5
Central obesity, number (%)	22 (37)	5 (31.2)	17 (39.5)	0.5
Metabolic syndrome, number (%)	6 (10.2)	2 (12.5)	4 (9.3)	0.7
Pulmonary hypertension class, number (%)				
Class I	28 (47.5)	11 (69)	17 (39.5)	0.05 ^b
Class II	17 (28.8)	1 (6.3)	16 (37.2)	
Class III	3 (5.1)	1 (6.3)	2 (4.7)	
Class IV	10 (16.9)	3 (19)	7 (16.3)	
Class V	1 (1.7)	0	1 (2.3)	
Pulmonary hypertension haemodynamic type				0.02
Precapillary	42 (71.2)	15 (25.4)	27 (45.7)	
Combined postcapillary	17 (28.8)	1 (1.7)	16 (27.1)	
NYHA functional class				0.5
I	1 (1.6)	0	1 (2.3)	
II	26 (44)	8 (50)	18 (42)	
III	29 (49.1)	8 (50)	21 (49)	
IV	3 (0.5)	0	3 (7)	
6MWT, m, median (IQR)	330 (290–400)	375 (300–403)	330 (280–390)	0.3
FBS, mg/dL, mean (SD)	91.7 (10.7)	91.7 (10.4)	91.7 (10.9)	0.9
TG, mg/dL, mean (SD)	111 (42)	124 (50)	106 (38)	0.1
HDL, mg/dL, mean (SD)	39 (10)	38 (9.5)	40 (10)	0.6
Total cholesterol, mg/dL, mean (SD)	145 (41)	152 (42)	143 (41)	0.4
HbA1c, %, median (IQR)	5.0 (4.9–5.8)	5.02 (4.9–5.8)	5.2 (4.9–5.2)	0.9
TG/HDL, mg/dL, mean (SD)	2.8 (1.07)	3.2 (1.3)	2.7 (0.9)	0.1
Insulin level, mIU/L, median (IQR)	42.9 (20.9–104.9)	142 (117–207)	31 (20–51)	<0.0001
HOMA-IR, median (IQR)	0.8 (0.4–1.9)	2.5 (2.2–3.7)	0.6 (0.4–1)	<0.0001
Cardiac index, L/min/m ² , mean (SD)	2.4 (0.6)	2.6 (0.6)	2.3 (0.6)	0.3
Right atrial pressure, mmHg, median (IQR)	10 (8–14)	8.5 (7–13)	11 (8–16)	0.1
Mean pulmonary artery pressure, mmHg, median (IQR)	40 (30–50)	33 (27–51)	42 (36–50)	0.2
High-risk criteria, number (%)	49 (83.1)	13 (81.3)	36 (83.7)	0.8
Mortality rate, number (%)	26 (44.1)	7 (43.8)	19 (44.2)	0.9

6MWT, 6 min walk test; FBS, fasting blood sugar; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IQR, interquartile range; NYHA, New York Heart Association; SD, standard deviation; TG, triglyceride.

^aThe comparison is between insulin sensitivity and insulin resistance.

^bComparison between the different pulmonary hypertension groups by Fisher's exact test.

As shown in *Table 2*, there was no statistically significant difference between the groups of IR and IS in terms of demographic, clinical, BMI, features of metabolic syndrome, and haemodynamic data.

The central obesity was observed in 30% of PAH group and according to the IDF, four (9.5%) of them fulfilled the criteria for the metabolic syndrome in which 50% had IR.

As HOMA-IR had a non-normal distribution, Spearman's rank correlation was used to show whether there was any correlation between HOMA-IR and TG/HDL ratio. We could not find any correlation between these two variables (Spearman's rho = 0.2, *P* value = 0.1); however, the TG/HDL ratio was higher in IR group and all the patients with metabolic syndrome features had a TG/HDL ratio more than 3. On the other hand, despite the fact that the difference was not statistically significant, both serum insulin levels [median (IQR) = 76 (25–149) mIU/L in those with TG/HDL > 3 vs. 56 (20–110) mIU/L in those with TG/HDL < 3, *P* = 0.5] and HOMA-IR [median

(IQR) = 1.4 (0.5–2.8) in those with TG/HDL > 3 vs. 1 (0.4–1.9) in those with TG/HDL < 3, *P* = 0.5] were higher in those with a TG/HDL ratio more than 3.

There was also no statistically significant correlation between fasting insulin, HOMA-IR, and BMI or 6MWT distance.

Study outcomes

Mortality risk assessment

Considering the simplified mortality risk assessment tool, 49 of 59 patients could be categorized as elevated risk.

In precapillary PH group, 33 of 42 patients were categorized as elevated risk.

There was no difference between IR and IS groups in terms of the risk category (*P* = 0.8). However, although the HOMA-IR level was not different in elevated risk and low-risk groups [the median (IQR) of HOMA-IR in elevated

Table 2 Comparison of clinical, laboratory, and haemodynamic characteristics of insulin resistance and insulin sensitive patients with precapillary pulmonary hypertension (PAH), $n = 42$

Variables	All patients with precapillary PH $N = 42$	Insulin resistance $N = 15$	Insulin sensitive $N = 27$	P value
Sex (female), number (%)	25 (59.5)	9 (59)	16 (60)	0.9
Age, years, mean (SD)	45.9 (17.3)	46.3 (20.6)	42.6 (16)	0.5
Body mass index, kg/m^2 , mean (SD)	23.9 (4.9)	24.2 (6)	23.1 (4.4)	0.4
Waist circumference, cm, mean (SD)	81 (17)	80 (18)	81 (16)	0.8
History of hypertension, number (%)	5 (11.9)	1 (6.7)	4 (14.8)	0.4
Central obesity, number (%)	12 (30)	4 (27)	8 (29)	0.8
Metabolic syndrome, number (%)	4 (9.5)	2 (13.3)	2 (7.4)	0.5
NYHA class				0.6
I	1 (2.4)	0	1 (3.7)	
II	24 (57.1)	8 (53)	16 (59)	
III	17 (40.5)	7 (47)	10 (37)	
IV	0	0	0	
6MWT, m, median (IQR)	330 (290–400)	390 (300–405)	380 (310–410)	0.8
FBS, mg/dL , mean (SD)	91.7 (10.7)	92 (9.7)	89 (9.4)	0.5
TG, mg/dL , mean (SD)	113.7 (41)	128 (50)	105 (33)	0.09
HDL, mg/dL , mean (SD)	40 (10)	39 (9.5)	41 (11)	0.6
Total cholesterol, mg/dL , mean (SD)	146 (38)	156 (40)	141 (37)	0.2
HbA1c, %, median (IQR)	5.0 (4.9–5.8)	5.0 (4.9–5.8)	5.1 (4.8–5.9)	0.5
TG/HDL, mg/dL , mean (SD)	2.8 (1.07)	3.3 (1.3)	2.7 (0.9)	0.09
Insulin level, mIU/L , median (IQR)	42.9 (20.9–104.9)	148.8 (121–239)	31.3 (21–60)	<0.0001
HOMA-IR, median (IQR)	0.8 (0.4–1.9)	3.2 (2.4–3.7)	0.6 (0.1–1.1)	<0.0001
Cardiac index, $\text{L}/\text{min}/\text{m}^2$, mean (SD)	2.4 (0.6)	2.6 (0.5)	2.5 (0.5)	0.6
Right atrial pressure, mmHg , median (IQR)	10 (8–14)	8 (7–13)	10 (8–12)	0.6
Mean pulmonary artery pressure, mmHg , median (IQR)	40 (30–50)	34 (27–52)	45 (30–55)	0.4
High-risk criteria, number (%)	33 (78.6)	12 (80)	21 (78)	0.8
Mortality rate, number (%)	14 (33.3)	7 (47)	7 (26)	0.1

6MWT, 6 min walk test; FBS, fasting blood sugar; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IQR, interquartile range; NYHA, New York Heart Association; PH, pulmonary hypertension; SD, standard deviation; TG, triglyceride.

risk and low-risk groups was 0.9 (0.5–2) vs. 0.8 (0.4–1.9), respectively, $P = 0.8$], the TG/HDL ratio was significantly higher in elevated risk group (3.05 ± 0.15 vs. 2.1 ± 0.18 mg/dL in elevated risk and low-risk groups, respectively, $P = 0.01$).

Patient follow-up

There was no missed follow-up and we could find the destiny of all patients.

The mortality rate during a median (IQR) follow-up period of 48 (23–48) months was 44.1%. Nine patients (five precapillary) died within a year after the RHC. The survival rate was much better in patients with precapillary PH [48 (28.5–48) months] than combined postcapillary PH [24 (18–48) months] ($P = 0.002$).

Survival analysis in patients with precapillary pulmonary hypertension

As mentioned above and because of the low prevalence of IR in patients with combined postcapillary PH, the prognostic importance of IR in patients with precapillary PH was separately analysed.

At the end of the follow-up period, the mortality rate in this group of patients was 33.3%. There were 14 deaths in precapillary group, in which 6 of them was in class I and the rest were in other classes of PH.

The median (IQR) of survival in IR and IS patients was 48 (20–48) and 48 (36–48) months, respectively ($P = 0.1$).

Although the survival was not statistically different between the two IR and IS groups, the Kaplan–Meier curve of survival analysis showed less life span in IR patients (Figure 1).

Table 3 depicts univariate and multivariate analyses for predictors of mortality in patients with precapillary PH.

Mortality was correlated with older age, male gender [9 (64.3%) males vs. 5 (35.7%) females], lower BMI, and the class of PH in univariate analyses.

People with lower 6MWT and higher HOMA-IR had higher, but not statistically significant, mortality rate.

The multivariable analysis showed that age, male sex, BMI, and CI are independent predictors of mortality.

The IR was not correlated with all-cause mortality in univariate and multivariate analyses.

Discussion

In the present study, we evaluated the prevalence of IR in patients with PH in all PH classes by HOMA-IR method; a more robust and validated index for IR showed that IR is more prevalent in those with isolated precapillary PH or PAH.

More than one-third of patients with PAH had IR in this study, which was higher than the prevalence of IR in the Iranian general population. Surprisingly, although we could show a trend towards higher mortality rate in patients with IR, despite a relatively high prevalence of IR, a significant difference in PAH aetiology, NYHA functional classification, 6MWT distance, and haemodynamic findings was not found between IS and IR PAH groups. The IR in our study population was also independent of age, sex, BMI, and features of metabolic syndrome including the TG/HDL ratio.

The subgroup analyses showed a lower prevalence of IR in combined pre–postcapillary group. Although the small num-

ber of patients in this group can be a possible explanation for this finding, a different pathophysiologic pathway rather than those related to the IR may be suggested for vascular remodelling and adding a precapillary component to a postcapillary PH.

Furthermore, IR was more prevalent in those with precapillary PH, suggesting the involvement of IR in chronic inflammatory pathways responsible for pan arteritis in precapillary PH.

Among recent advances in the underlying pathogenesis of PH, one of the most interesting aspects of research is the apparent association between PAH and IR. The main aim of these investigations would be finding the potential for novel therapeutic targets.^{4–6,8–10,17–20}

The recent investigations have shown that different classes of PH may have similar structural and functional changes in vascular bed.^{3,17,21–24} These findings, as well as favourable clinical response to pulmonary vasodilator therapies in PH classes rather than PAH, suggest a common pathophysiologic feature. Therefore, IR as a common finding in different types of PH may contribute to similar pulmonary vascular abnormalities.

Animal models and clinical studies suggest that a variety of chemokines and pro-inflammatory and inflammatory cytokines including receptor for advanced glycation end products (RAGE), interleukin-6 (IL-6), interleukin (IL-8), tumour necrotizing factor-alpha (TNF-α), chemokine CXC ligand10, 13 (CXCL), interferon-γ-induced protein 10 (IP-10), peroxisome proliferator-activated receptor-gamma (PPAR-γ), and adiponectin contribute directly to endothelial dysfunction, ongoing inflammation, and proliferation of pulmonary artery smooth muscle cell. Many of these pro-inflammatory and anti-inflammatory cytokines and chemokines have been known to induce failure of pancreatic beta cells and be

Figure 1 The Kaplan–Meier curve of survival analysis in patients with insulin resistance compared with insulin sensitive patients.

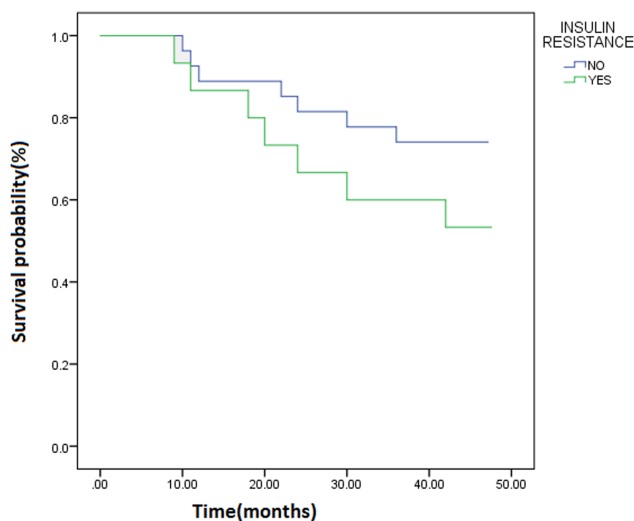


Table 3 Univariate and multivariate analyses for predictors of mortality in patients with precapillary pulmonary hypertension, *n* = 42

Characteristics	Univariate analysis			Multivariate analysis		
	Beta	<i>P</i> value	OR (95% CI)	Beta	<i>P</i> value	OR (95% CI)
Age, years	0.094	0.001	1.1 (1.03–1.16)	0.15	0.005	1.1 (1.04–1.4)
Sex, male	–1.5	0.03	0.2 (0.06–0.87)	–3.3	0.03	0.04 (0.002–0.8)
Body mass index, kg/m ²	0.18	0.03	1.2 (1.02–1.4)	0.35	0.02	1.4 (1.05–1.9)
NYHA class	0.64	0.3	1.9 (0.5–6.5)			
Pulmonary hypertension class	0.5	0.04	1.6 (1.01–2.6)			
6MWT, m	–0.008	0.07	0.98 (0.99–1.001)			
FBS, mg/dL	–0.01	0.7	0.99 (0.92–1.05)			
HbA1c	0.19	0.7	0.8 (0.3–2.4)			
TG/HDL, mg/dL	0.23	0.4	1.2 (0.7–2.2)			
Insulin level, mIU/L	0.008	0.08	1 (0.99–1.02)			
HOMA-IR	0.4	0.07	1.5 (0.9–2.4)			
IR, yes	0.9	0.1	2.5 (0.7–9.5)			
Cardiac index, L/min/m ²	–0.4	0.4	0.6 (0.2–2.2)	2.5	0.04	11.7 (1.02–133.9)
Right atrial pressure, mmHg	0.05	0.5	1 (0.9–1.2)			
Mean pulmonary artery pressure, mmHg	0.002	0.9	1 (0.9–1.03)			
High-risk criteria	0.6	0.4	2 (0.35–11)			

6MWT, 6 min walk test; CI, confidence interval; FBS, fasting blood sugar; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IR, insulin resistance; NYHA, New York Heart Association; OR, odds ratio; TG, triglyceride.

involved in IR process in many clinical conditions including obesity.^{2–4,8–10,19,20,22–32} Mitochondrial dysfunction is an emerging concept, which has been suggested as a major pathogenic mechanism in both IR and PH.^{33,34}

Although many clinical investigations have shown the correlation between IR and PH, there are some limitations for these studies. First of all, most of them have considered the indirect evidences of IR such as TG/HDL ratio and HbA1c, which makes the results less conclusive because of the high prevalence of features of the metabolic syndrome in the general population.^{5,6,11}

On the other hand, the data regarding the accuracy of TG/HDL ratio in assessment of IR have been conflicting in different studies and study groups, and a strong and significant relationship could not be found in many studies such as our present study.^{35–37}

To overcome the problems regarding indirect measures for IR, Heresi *et al.*¹⁹ assessed metabolic phenotyping of patients with IPAH by measuring plasma insulin and glucose and estimated IR by two validated indices of IR (the Stumvoll index³⁸ and HOMA-IR). They also assessed pancreatic beta cell function in this group of patients.

They compared 14 patients with IPAH with 14 healthy subjects matched for sex, age, blood pressure, and BMI and showed a distinct pattern of metabolic abnormalities in patients with IPAH similar to those with type 2 DM suggesting an abnormal pancreatic beta cell function.¹⁹

Association between insulin resistance and prognostic factors of pulmonary hypertension

There are conflicting data regarding the correlation between IR and PH prognostic factors and/or adverse outcomes.

Although in the current study, the patients with IR had less survival, like previous studies, no correlation between IR and clinical, 6MWT distance, haemodynamics, prognostic factors, as well as the risk of mortality was found.

However, a significant number of our study population (78.5% of patients in precapillary PH group) were categorized as high risk for mortality, which would be an explanation for lack of relationship between IR and the risk of mortality.

In a study by Zamanian *et al.*, patients with IR had worse 6 month event-free survival but no relationship was found between IR and NYHA class, 6MWT distance, and haemodynamic measures.⁵

In a cohort by Pugh *et al.*, there was no difference between IR and IS patients in terms of survival and other PH-related variables including NYHA class, 6MWT distance, and haemodynamic measures.¹¹ However, the same study group showed significant improvement in haemodynamic measures of PH including mean PAP and PVR after 20% weight reduction fol-

lowing bariatric surgery in an obese female with IPAH, which was associated with a significant decrease in IR (2.6 to 1.2) as measured by the HOMA-IR.¹⁸

There were also no significant associations between the IR and NYHA class, echocardiography data, and haemodynamics variables in the Heresi *et al.* study. Albeit, this study group could show a modest correlation between IS and 6MWT distance ($r = 0.55$, $P = 0.05$). No death was reported during the following period (26 months) in this study. They have also found no correlation between IR and increased risk of hospitalization as well.¹⁹

Study strength and limitations

The careful selection of patients among all PH classes, excluding the patients with high HbA1c level, using the Iranian cut points of HOMA-IR for interpretation and a relatively prolonged follow-up period (40 months) were the strength of the study.

One of the most important limitations of our study and similar studies would be using surrogates for IR including the TG/HDL ratio and HOMA-IR.

The hyperinsulinaemic–euglycaemic clamp technique^{39,40} is the gold standard method for assessing IS, but this method is a difficult and expensive procedure.

In conclusion, all of these clinical and basic investigations including our study suggest that the glucose metabolism is dysregulated in patient with PH and IR may be considerably prevalent in this group of patients independent of the metabolic syndrome features. The IR is involved in inflammatory process responsible for development and progression of PH and may increase the risk of adverse events among these patients.

There are many published and ongoing clinical trials targeting IR in the medical therapies of PH^{18,41,42}; however, further studies using more precise methods for defining IR are needed to clarify the prognostic significance of this finding in this group of patients.

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Conflict of interest

None declared.

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