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Original Article

Insulin Resistance in Patients with Cirrhosis and Portal Hypertension

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Insulin Resistance in Patients with Cirrhosis and Portal Hypertension

Authors: Eva Erice[1,2,*], Elba Llop[1,3], Annalisa Berzigotti[1,2], Juan G. Abraldes[1,2], Ignacio Conget[4], Susana Seijo[1], Enric Reverter[1], Agustin Albillos[2,5], Jaume Bosch[1,2], Juan Carlos García-Pagán[1,2]

Affiliation: *[1]Hepatic Hemodynamic Laboratory, Liver Unit. Hospital Clínic, Institut d´Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona; [2]Centro de Investigación Biomédica en red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [3] Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain.; [4] Endocrinology and Diabetes Unit. Hospital Clínic, (IDIBAPS), Barcelona, Spain; [5] Gastroenterology Unit. Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), University of Alcalá. Madrid, Spain.*

Author Contributions: E Erice and JC García-Pagán were involved into study concept and design, acquisition, analysis and interpretation of data, drafting of the manuscript and statistical analysis. E Llop, A Berzigotti, S Seijo, A Albillos and E Reverter were involved into acquisition of data, I Conget collaborated into interpretation of data and J. G-Abraldes and J Bosch participated in the critical revision of the manuscript for important intellectual content.

Addresses of authors: Eva Erice: evaerice@terra.es , Elba Llop: elballop@hotmail.com , Annalisa Berzigotti: ABERZIGO@clinic.ub.es, J.Gonzalez-Abraldes: JGON@clinic.ub.es , Ignacio Conget: ICONGET@clinic.ub.es , Susana Seijo: susanaseijo@hotmail.com , Agustin Albillos: aalbillosm@meditex.es; Jaume Bosch: JBOSCH@clinic.ub.es

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Contact Information: Juan Carlos García-Pagán. Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic, Villarroel 170, Barcelona 08036, Spain.

*E-mail:*JCGARCIA@clinic.ub.es. *Telephone: +3493227 1713; fax: (34)93 22 79 856.*

ABSTRACT

***Background*:** Insulin Resistance (IR) is involved in the pathogenesis of endothelial dysfunction and is also present in patients with cirrhosis. Intrahepatic endothelial dysfunction plays a major role, increasing hepatic vascular resistance and promoting portal hypertension (PH). In addition, beta-adrenergic agonists and insulin share several intracellular signalling pathways. Thus, IR may influence the response to beta-blockers.

Aims: This study aimed at evaluating the relationship between IR and hepatic hemodynamics in patients with cirrhosis and with the portal pressure response to acute beta-blockade.

Patients and Methods: 49 patients with cirrhosis and PH were included. Hepatic and systemic hemodynamics were measured and IR was estimated by using the updated *homeostasis model assessment* (HOMA-2) index. Patients with HOMA-2 >2.4 were considered IR. In patients with hepatic venous pressure gradient (HVPG) >10 mmHg (clinically significant portal hypertension: CSPH) hemodynamic measurements were performed again 20 minutes after i.v. propranolol.

***Results*:** Mean HOMA-2 index was 3 ± 1.4. 57% of patients had IR. A weak correlation between HOMA-2 index and HVPG was observed. 86% of patients had CSPH. HOMA-2 index was an independent predictor of CSPH. However, in patients with CSPH the correlation between HOMA-2 index and HVPG was lost. HVPG but not IR predicted the presence of oesophageal varices. Response to propranolol was not different between patients with or without IR.

***Conclusion*:** In non-diabetic patients with cirrhosis, HOMA-2 index is directly associated with the presence of CSPH and indirectly with varices, but does allow neither grading HVPG nor predicting its response to propranolol.

81 **247 words**

82 ***Key Words:*** endothelial dysfunction, insuling signalling, portal pressure, beta-blockade,

83 HOMA index.

INTRODUCTION

Portal hypertension (PH) is a serious consequence of cirrhosis that results in life-threatening complications with increased morbidity and mortality (3; 4; 22). In cirrhosis, enhanced hepatic resistance to portal blood inflow is the primary factor in the pathophysiology of PH. Secondly, an increased portal blood inflow contributes to the maintenance and worsening of PH despite the development of portosystemic collaterals. Insufficient nitric oxide (NO) bioavailability in sinusoidal endothelial cells, a condition known as endothelial dysfunction, is considered a major pathogenic factor to increase hepatic vascular tone (27) and has shown to be secondary to several different posttranslational alterations in the regulation of hepatic endothelial NO synthase (eNOS).

In addition to its metabolic action on glucose uptake, insulin also stimulates endothelial NO production, by activating the phosphatidylinositol 3-kinase and serine-threonine kinase (PI3K/Akt) signalling pathway (50). As a consequence, insulin resistance (IR) have been shown to result in impaired PI3K/Akt signalling pathway, causing a decrease in NO production with the ensuing development of endothelial dysfunction (41) in several cardiovascular disorders, such as arterial hypertension, diabetes and atherosclerosis (12; 36; 44).

IR has been described in several liver disorders (9; 14; 32; 39) where it may have important clinical consequences. Thus, it has been suggested that IR has a negative impact on the response rates to interferon-based therapy in chronic HCV infection (19) and that IR could be a predictor of the presence of PH in patients with NAFLD (16). Furthermore, a recent published clinical study has suggested that IR is able to independently predict the presence of gastroesophageal varices in cirrhosis (11). The authors attributed this effect to a possible pathophysiological link between IR and PH.

IR could contribute to either impairment of the sinusoidal endothelial dysfunction or increment of peripheral vascular resistance in liver cirrhosis. Therefore, a possible effect of IR on the hepatic vasculature promoting an increase in intrahepatic resistance may be counteracted by a potential effect of IR increasing splanchnic resistance and reducing portal blood flow, with a resulting unpredicted effect on portal pressure. Unfortunately, up to now, there is no study evaluating the relationship between IR and hepatic and systemic hemodynamics in liver cirrhosis.

The current pharmacological therapy for portal hypertension is non-selective beta-adrenergic blockers (5). Several factors influence the HVPG response to beta-blockers, such as the degree of liver failure, dose of beta-blockers, extent of portal-systemic collaterals and varices or beta-2 adrenoceptor gene polymorphisms (1; 2; 8; 15; 17; 47). IR could represent another component in this multifactorial phenomenon. Vascular relaxation in response to beta-2 adrenoceptor agonists involves two components (24; 49): one endothelium-independent, mediated by the activation of the cyclic AMP dependent-protein kinase A (PKA) pathway in vascular smooth muscle cells; and another endothelium-dependent, mediated by the activation of the PI3K/Akt signalling pathway that leads to NO release. As mentioned, this pathway is shared with insulin signalling (13; 34). A possible down-regulation of this pathway by IR could interfere with the beta-adrenergic signalling. Hence, it is plausible that IR may represent an additional factor influencing the hemodynamic response to propranolol in patients with cirrhosis.

The main aim of this study was to investigate the potential relationship between IR and hepatic and systemic hemodynamics in patients with cirrhosis. As secondary endpoints, the value of IR predicting the presence of clinical significant portal hypertension (CSPH: defined as an hepatic venous pressure gradient (HVPG) > 10mmHg) and

gastroesophageal varices, as well as the influence of IR on the hemodynamic response to acute beta-adrenergic blockade will be assessed

PATIENTS AND METHODS

Patients

The study was performed in 49 out of 267 patients with cirrhosis, referred from May 2008 to February 2010 to the Hepatic Hemodynamic Laboratory for the evaluation of PH (Figure a). All patients were diagnosed with cirrhosis at the clinic based on biological, ultrasonographic or histological criteria. The extensive exclusion criteria were: absence of portal hypertension (HVPG < 6 mmHg); pregnancy or lactation; cardiac, renal or respiratory failure; hepatocellular carcinoma; portal vein thrombosis; previous surgical or transjugular portosystemic shunt; presence of infection or acute decompensation in the prior two weeks; prescription of hypolipemiant, antihypertensive, corticosteroid, bronchodilatador, vasoactive or hypoglycemic agents within one month. Patients with established diabetes or metabolic syndrome (defined by the International Diabetes Federation) were excluded to discard their probable direct effect on the IR component derived from liver cirrhosis.

The study was performed according to the principles of the Declaration of Helsinki. The Ethics Research Committee of the Hospital Clinic of Barcelona approved the protocol in May 2008. Informed written consent to participate in the study was obtained for every patient.

Methods

Hemodynamic studies

After fasting overnight, patients were transferred to the Hepatic Hemodynamic Laboratory. In brief, a venous introducer was placed in the internal jugular vein by the

Seldinger technique under local anaesthesia. Under fluoroscopy a Swan-Ganz catheter (Edwards Laboratory, Los Angeles, CA) was advanced into the pulmonary artery for measurement of cardiopulmonary pressures and cardiac output (CO) by thermal dilution. Subsequently, a 7F balloon-tipped catheter (Edwards Lifesciences Fogarty 7F, Los Angeles, CA) was guided into the main right hepatic vein to measure wedged and free hepatic venous pressure, as described by previous authors to obtain hepatic pressures (6; 21). Mean arterial pressure (MAP, mmHg) was measured every 5 minutes by a non-invasive automatic sphygmomanometer and the heart rate was derived from continuous electrocardiogram monitoring.

In the subgroup of patients with CSPH, a solution of indocyanine green (Pulsion Medical Systems, Munich, Germany) was infused intravenously at a constant rate of 0.2 mg/min, preceded by a priming dose of 5 mg. After an equilibration period of at least 40 minutes, 4 separates sets of simultaneous samples of peripheral and hepatic venous blood were obtained for the measurement of hepatic blood flow (HBF, mL /min) by the Fick principle, as previously described (26; 37). In these patients, after baseline measurements, intravenous propranolol (0.15 mg/kg) was administered over 10 minutes and hepatic and cardiopulmonary pressures, CO and HBF were assessed again after 20 minutes.

All measurements were taken by triplicate and permanent tracings were obtained in a multichannel recorder (Mac-Lab/Specials Lab, General Electric Medical System).

Portal pressure was estimated from HVPG (mmHg) as the difference between wedged (WHVP) and free hepatic venous pressure (FHVP). Cardiac index (CI, L/min/m^2) was calculated as CO/ body surface area and systemic vascular resistance index (SVRI, dyne*seg*m^2 /cm^5) as (MAP - RAP) x 80/ CI (RAP, right atrial pressure). Patients exhibiting a decrease in HVPG ≥10% from baseline after iv propranolol administration,

were defined as "hemodynamic responders" (31; 48). In patients with ascites, the body mass index, BMI, (kg/m^2), was calculated using a correction factor of 4 kg to estimate the real weight. It represents the mean of evacuated litres in large-volume paracentesis (18; 40) .

Evaluation of insulin resistance

IR was estimated from fasting plasma glucose and insulin levels by using the updated *homeostasis model assessment* (HOMA-2) index (35) and it was calculated using the HOMA-2 calculator, which is downloadable from The Oxford Centre for Diabetes, Endocrinology and Metabolism web site *(www.dtu.ox.ac.uk)*. HOMA is an index that estimates steady state beta cell function (%B) and insulin sensitivity (%S). It has been previously validated in healthy populations, non-insulin treated type 2 patients and people with metabolic syndrome. Several studies suggest that HOMA index could be an useful tool to identify subjects with insulin resistance at risk of developing cardiovascular diseases (10; 29).

Eighty-two healthy normoweight subjects (50 males and 32 females, age ranging between 28 and 48 years) without family history of *diabetes mellitus* were chosen to define the normal value of the HOMA-2 index in our area. The upper 75-percentile value of the HOMA-2 index was 2.4. Patients with HOMA-2 index above this value were considered to have IR.

In the subgroup of patients with CSPH, the C-peptide-to-insulin molar ratio in peripheral venous blood was used to estimate indirectly insulin metabolism, as assessed previously(30; 35). In normal conditions, insulin and C-peptide are secreted into the portal vein in a 1:1 molar ratio. The liver mainly clears endogenous insulin, whereas C-peptide is cleared by the kidney in a lower metabolic clearance rate than insulin. As a

consequence, the C-peptide-to-insulin molar ratio in peripheral venous blood is higher than 1.0 (7) . Plasma free insulin and C-peptide were measured by radioimmunoassay. In addition, blood samples from peripheral and hepatic veins were obtained to measure NO products (NO_x: NO_2^- ,NO^-_3) by chemiluminescence (Nitric Oxide Analyzer, NOA 280; Sievers Instruments, Boulder, CO) and von Willebrand factor (Ag vWF) by enzyme linked immunosorbent assay system as a marker of endothelial dysfunction.

Statistics

Statistics analyses were performed using SPSS 16.0 statistical package (SPSS Inc. Chicago, IL). All results are expressed as mean ± standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. U Mann-Whitney was used to perform comparisons between groups for continuous variables and Fisher test, test and linear-by-linear test for categorical variables. Correlation was performed by Rho´s Spearman coefficient. Statistical significance was established as $P < 0.05$. Multivariable logistic regression models were constructed to look for independent predictors of varices, CSPH and IR.

RESULTS

Clinical and hemodynamic characteristics of patients with cirrhosis with and without IR

The baseline clinical and laboratory characteristics of the 49 patients included are shown in Table 1. Mean age was 57 years and 55% were male. The most frequent aetiology of cirrhosis was HCV infection (51%) and active alcoholism was present in 8 patients. Mean Child-Pugh score was 7 ± 2.1. The mean HOMA-2 index was 3 ± 1.4. Thirty of the 49 patients (61%) had a HOMA-2 index above the cut-off value defining IR (>2.4) with a mean value of 4 (ranging from 2.5 to 6). As shown in Table 1, patients with IR had higher BMI, bilirubin, Child-Pugh and MELD scores, cardiac index, HVPG and significantly lower systemic vascular resistance, platelets count and prothrombin time than those without. Multivariate logistic regression analysis disclosed prothrombin time as the only independent predictor for the presence of IR.

IR, HVPG and CSPH

A weak but significant correlation between HOMA-2 index and HVPG was observed (Figure b1; $r^2 = 0.19$, p=.02). Thirty-eight of the 49 patients included (86%) had CSPH (Table 2). Correlation between HOMA-2 index and HVPG was lost when only patients with CSPH were considered ($r^2= 0.02$, p= 0.29; Figure b2).

As shown in Table 2, patients with CSPH had significantly higher HOMA-2 index, more ascites, presence of oesophageal varices and worse hepatocellular function than patients without CSPH. Multivariate analysis disclosed high HOMA-2 index and low prothrombin time as the only independent predictors for the presence of CSPH.

In the subgroup of 38 patients with CSPH (mean HVPG: 17.5±5 mmHg; range: 10 to 31.5), 27 patients were IR (71%) and 11 patients were not (29%). As shown in Table 3, prothrombin time, insulin, C-peptide and SVRI were significantly different in patients

with IR without significant differences in hepatic or peripheral NOx or vWF A g levels. However, no significant differences in HVPG were observed (HVPG; 18±5 vs. 16 ±4.5 mmHg, p= .39). Multivariate analysis also disclosed prothrombin time in addition to body mass index as independent predictors for the presence of IR in the subgroup of patients with CSPH. Interestingly, a significant inverse association between HOMA-2 and the C-peptide-to-insulin molar ratio (a surrogate of portal systemic shunting) was observed (r= -0.35, p= .04) (Figure c).

IR and Esophageal Varices

As shown in Table 4, patients with EV had a significantly higher MELD score, HOMA-2 index, cardiac index, HVPG and presence of CSPH and a significantly lower prothrombin time and SVRI than patients without EV. However, multivariate analysis disclosed that only HVPG independently predict the presence of oesophageal varices, either evaluated as continuous variable or categorized in CSPH vs non-CSPH.

Acute HVPG response to propranolol

In the CSPH group (n=38), acute propranolol administration produced a significant reduction in HVPG (-15%, p= .00) (Table 5). No significant correlation was found between HOMA-2 index and reduction in HVPG (r=-0.054, p= .6). There were no statistically significant differences in the hemodynamic response to acute iv propranolol in patients with or without IR (-15%±10.5 *vs* -15%±11.5, p= .39) (Table 5). The percentage of "hemodynamic responders" was similar in both groups (IR group 65% *vs* without-IR: 64% p=NS).

DISCUSSION

Insulin is known to regulate glucose metabolism and NO production by activating endothelial NO synthase(50). Reduced secretion of NO, as a consequence of IR, is responsible for endothelial dysfunction in several cardiovascular diseases and is associated with severity of disease (12; 36; 44). IR is very frequent in chronic liver disorders and has been associated with the development of hyperglycaemia, hepatic steatosis and enhanced structural damage favouring the occurrence of cirrhosis (32). Nevertheless, up to now, the prevalence of IR in patients with cirrhosis and the real impact on the pathophysiology of PH has not been adequately evaluated. A recent published clinical study has suggested that the presence of IR, assessed by the HOMA index, could play a role *per se* in the pathogenesis of PH in patients with cirrhosis with mild hepatocellullar insufficiency (Child-Pugh A) (11). Authors from this study suggest that a HOMA value equal o higher than 3.5 combined with a low platelet count/ spleen diameter ratio could identify those patients with cirrhosis and oesophageal varices. These two parameters have been validated positively in another independent cohort of 340 patients with cirrhosis. Moreover, there was a positive correlation with the HOMA score and worsening of the hepatic function. (33). However, these affirmations have not been accompanied by a hepatic hemodynamic study.

The cohort of patients included in the current study was selected in order to obtain a homogeneous group and avoid possible confounding factors, which may influence the HOMA-2 index (by altering insulin and glucose levels), such as stress situations, metabolic syndrome or medically treated diabetes, and its interpretation in cirrhosis. The present study confirms that IR, assessed by HOMA-2 index, is a very frequent phenomenon in patients with cirrhosis and PH. Indeed, IR was found in more than 60% of our patients, a figure that increased to more than 70% if only patients with CSPH

were considered. A weak but significant correlation between HOMA-2 index and HVPG was observed. In addition, HOMA-2 index together with prothrombin time were the only independent predictors for the presence of CSPH. These findings suggest that IR may play a role in the progression of the chronic liver disease at the earlier stages, as it has already been suggested in patients with NAFLD (16), where the presence of IR was associated with the presence of mild PH (in that study all patients had HVPG < 10 mmHg). Interestingly our data, including patients with more severe PH, shows that once CSPH has developed, the correlation between HOMA-2 index and HVPG is lost. These results suggest that, once CSPH has developed, further increments of HOMA-2 index may reflect hyperinsulinism secondary to two different mechanisms: either beta-pancreatic hypersecretory state, as suggested by the moderately higher C-peptide levels in patients with IR, or reduction of insulin clearance as a consequence of portal-systemic shunting, as suggested by the observed inverse correlation between HOMA-2 index and C-peptide-to-insulin molar ratio. Indeed, it has been previously shown (7) that in patients with portal-systemic collateral circulation, the hepatic first pass clearance of insulin decreases and as a consequence, C-peptide-to-insulin molar ratio decreases while HOMA-2 index increases. Lack of correlation between HOMA-2 index and NO and Ag vWF levels, as indicators of endothelial dysfunction, does not support a role for IR in the pathophysiology of PH either. These results are consistent with the findings of a previous study (20), which did not find a correlation between peripheral vein insulin concentration and portal pressure in a group of patients with alcoholic cirrhosis and PH.

Overall, from a pathophysiological point of view, the results of our study suggest that IR might have a role in the initial steps contributing to the development of CSPH. But once CSPH has developed, increments of HOMA-2 index may be more a consequence

of the unpredictable development of portal-collateral circulation that a cause for the worsening of the severity of PH.

Additionally, our study confirms previous observations demonstrating that oesophageal varices (EV) are more frequent in patients with IR than in those without. However, multivariate analysis disclosed HVPG, either as a continuous variable or categorized as CSPH vs non-CSPH, as the only significant variable predicting the presence of gastroesophageal varices. These results clearly demonstrate that an increased HVPG above 10 mmHg, and not IR, is the pathophysiological factor linked to the presence of EV. However, these results strongly suggest that IR may be used as a non-invasive marker of CSPH, an issue that requires confirmation.

Our study also shows that IR does not influence the hemodynamic response to acute i.v. propranolol administration. The effect of propranolol administration on HVPG and systemic hemodynamics was similar for patients with or without IR and no cut-off value of HOMA-2 was identified to predict the response to i.v. propranolol.

In conclusion, non-diabetic patients diagnosed with liver cirrhosis and CSPH have increased HOMA-2 index. This increment is probably due more to the development of portal-collateral circulation than an impairment of PH secondary to endothelial intrahepatic dysfunction by IR. However, HOMA-2 index may have potential for the non-invasive prediction of CSPH and as a consequence of gastroesophageal varices.

STATEMENT OF INTERESTS

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Potential competing interests: Nothing to report.

Figure Legends

Figure a.- Flow chart showing the exclusion criteria for patients in the study.

Abbreviations: HVPG: hepatic venous pressure gradient, HCC hepatocellular carcinoma

Figure b.- Relation between HOMA-2 index and HVPG in the 49 patients (b1) and in the subgroup of 38 patients with CSPH (b2)

Abbreviations: HOMA-2 index:homeostasis model assessment -2 index, HVPG: hepatic venous pressure gradient.

Figure c.- Relation between C-peptide-to-insulin molar ratio and HOMA-2 index.

Abbreviations: HOMA-2 index: homeostasis model assessment-2 index.

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	Study population (n= 49)	Non-IR group (n=19)	IR group (n=30)	*P**
Gender	27 / 22	11 / 8	16 / 14	.77
Age (y)	57 (10)	56 (9)	58 (10.6)	.31
Active alcoholism (%)	16	21	13	.7
BMI (kg/m²)	25.6 (5.7)	24 (2)	27 (4.6)	.03
Aetiology (n)	Alcohol (15) HCV (25) HBV (6) Other (3)	Alcohol (4) HCV (11) HBV (3) Other (1)	Alcohol (11) HCV (14) HBV (3) Other (2)	.83
Ascites (n)	16	5	11	.65
Varices (n)	28	8	20	.16
Bilirubin (mg/ dL)	2.1 (2.1)	1.3 (1.1)	2.5 (2.4)	.05
Albumin (g/ L)	32 (6)	33 (6.5)	32 (5.5)	.52
Platelets (x10⁹/L)	103 (46)	117 (49)	94 (43)	.06
Prothrombin time (%)	67 (20)	77 (15)	60 (19)	.003
Child-Pugh Class (A/ B/C)	28 / 12/ 9	14 / 3 / 2	14 / 9 / 7	.08
Child-Pugh Score	7 (2.1)	6 (1.6)	7.5 (2.3)	.05
MELD score	12.5 (5.2)	10 (3)	14 (5.6)	.01
HOMA-2 index	3 (1.4)	1.6 (0.6)	3.9 (1)	.00
Glucose (mmol/ L)	5.6 (1)	5 .3 (1)	5.8 (1)	.07
Insulin (pmol/ L)	144.5 (68.8)	81.8 (27.5)	191.5 (55)	.00
MAP (mmHg)	92 (14)	94 (13.2)	90 (14.7)	.4
CI (L/min/m²)	3.7 (1.3)	3.1 (0.6)	4.02 (1.3)	.02
SVRI (dyne*sec*m²/cm⁵)	3091 (7317)	2376 (553)	1881.6 (885)	.008
HVPG (mmHg)	15.5 (6)	13 (5)	17 (5.5)	.002
CSPH (%)	77.6	58	90	.014

Table 1.- **Baseline clinical and hemodynamic characteristics of the 49 patients included**

Continuous variables are expressed by mean /(SD). P* non-IR vs IR group. *Abbreviations:* BMI: body mass index, HOMA-2 index: homeostasis model assessment-2 index, hepatic/ peripheral NOx: hepatic /peripheral nitric oxide, hepatic/ peripheral vWF Ag: hepatic/peripheral von Willebrand factor antigen.

	HVPG < 10 (n=11)	HVPG ≥10 (n=38)	*P**
Gender (M/W)	5/ 6	22 / 16	.5
Age (y)	56 (12.4)	58 (9.5)	.5
Active alcoholism (%)	0	21	.17
Aetiology (n)	Alcohol (0) HCV (8) HBV (3)	Alcohol (15) HCV (17) HBV (3) Other (3)	.17
Ascites (n)	0	16	.009
Varices (n)	0	28	.00
Bilirubin (mg/dL)	0.8 (0.2)	2.5 (2.2)	.00
Albumin (g/ L)	36 (3.7)	31 (5.4)	.017
Platelets (x10^9)	108 (46)	102 (51)	.2
Esplenomegaly (%)	55%	79	.2
Prothrombin time (%)	85 (9.5)	62 (18.2)	.00
Child-Pugh Class (A/ B/C)	11/ 0 / 0	17 / 12 / 9	.04
Child-Pugh Score	5 (1)	7 (2)	.004
MELD score	7.6 (1.1)	13.4 (5.1)	.00
HOMA-2 index	1.85 (1.2)	3.4 (1.3)	.001
Glucose (mmol/ L)	5.2 (0.7)	5.7 (1.1)	.15
Insulin (pmol/ L)	91.5 (58.2)	160 (64.4)	.003
MAP (mmHg)	97 (16.3)	90 (13.7)	.038
CI (L/min/m^2)	2.4 (1.5)	4 (1.2)	.00
SVRI (dyne*sec*m^2/cm^5)	2,800 (750)	1,892.6 (651)	.00
HVPG (mmHg)	8 (1)	17.5 (5)	.00

Table 2.- **Clinical and hemodynamic characteristics of the patients with and without CSPH**
Continuous variables are expressed by mean /(SD). P* HVPG <10 vs HVPG ≥10 group. *Abbreviations:* EV: esophageal varices, HOMA-2 index: homeostasis model assessment-2 index, MAP: mean arterial pressure, CI: cardiac index, SVRI: systemic vascular resistance index, HVPG: hepatic venous pressure gradient

	Non-IR group (n=11)	IR group (n=27)	*P**
Age (y)	58 (8.5)	58 (10)	.59
Active alcoholism (%)	36	15	.19
BMI (kg/m²)	24 (2.3)	27 (5)	.01
Aetiology (n)	Alcohol (4) HCV (5) HBV (1) Other (1)	Alcohol (11) HCV (11) HBV (3) Other (2)	.96
Ascites (%)	45	41	.95
Varices (%)	70	70	1.0
Bilirubin (mg/ dL)	1.7 (1.4)	2.8 (2.4)	.28
Albumin (g/ L)	31 (7)	32 (5.6)	.54
Protrombin time (%)	73 (18)	58 (17)	.02
Child-Pugh Class (A/ B/C)	6 / 3 / 2	11 / 9 / 7	.45
MELD score	11 (3.3)	14 (5.5)	.1
HOMA-2 index	1.9 (0.4)	3.8 (1.0)	.00
Glucose (mmol/ L)	5 (1.1)	5.9 (1.2)	.28
Insulin (pmol/ L)	90.3 (18)	187.5 (54.2)	.00
C-peptide (nmol/ L)	0.9 (0.5)	1.4 (0.5)	.01
C-peptide/ Insulin	10.3 (4.5) (n=10)	8 (2.9) (n=25)	.09
Hepatic NO_x (µmol/ L)	25.1 (19.3)	21.8 (9.1)	.77
Peripheral NO_x ((µmol/ L)	24.36 (15.9)	24.24 (11.2)	.67
Hepatic vWF Ag (U/ dL)	152 (27.2)	140 (32)	.21
Peripheral vWF Ag (U/ dL)	135 (28.1)	139 (37)	.77
MAP (mmHg)	95 (14.5)	90 (13.5)	.27
CI (L/ min/ m²)	3.4 (0.6)	4.2 (1.3)	.07
SVRI (dyne*sec*m²/ cm⁵)	2,205 (575)	1,765 (647)	.05
HVPG (mmHg)	16 (4.5)	18 (5)	.39
HBF (L/ min)	1.04 (0.3) (n=9)	0.92 (0.5) (n=21)	.14

Table 3.- **Baseline clinical and hemodynamic characteristics of the 38 patients with CSPH**

Continuous variables are expressed by mean /(SD). P* non-IR vs IR group. *Abbreviations:* BMI: body mass index, HOMA-2 index: homeostasis model assessment-2 index, hepatic/ peripheral NOx: hepatic /peripheral nitric oxide, hepatic/ peripheral vWF Ag: hepatic/peripheral von Willebrand factor antigen.

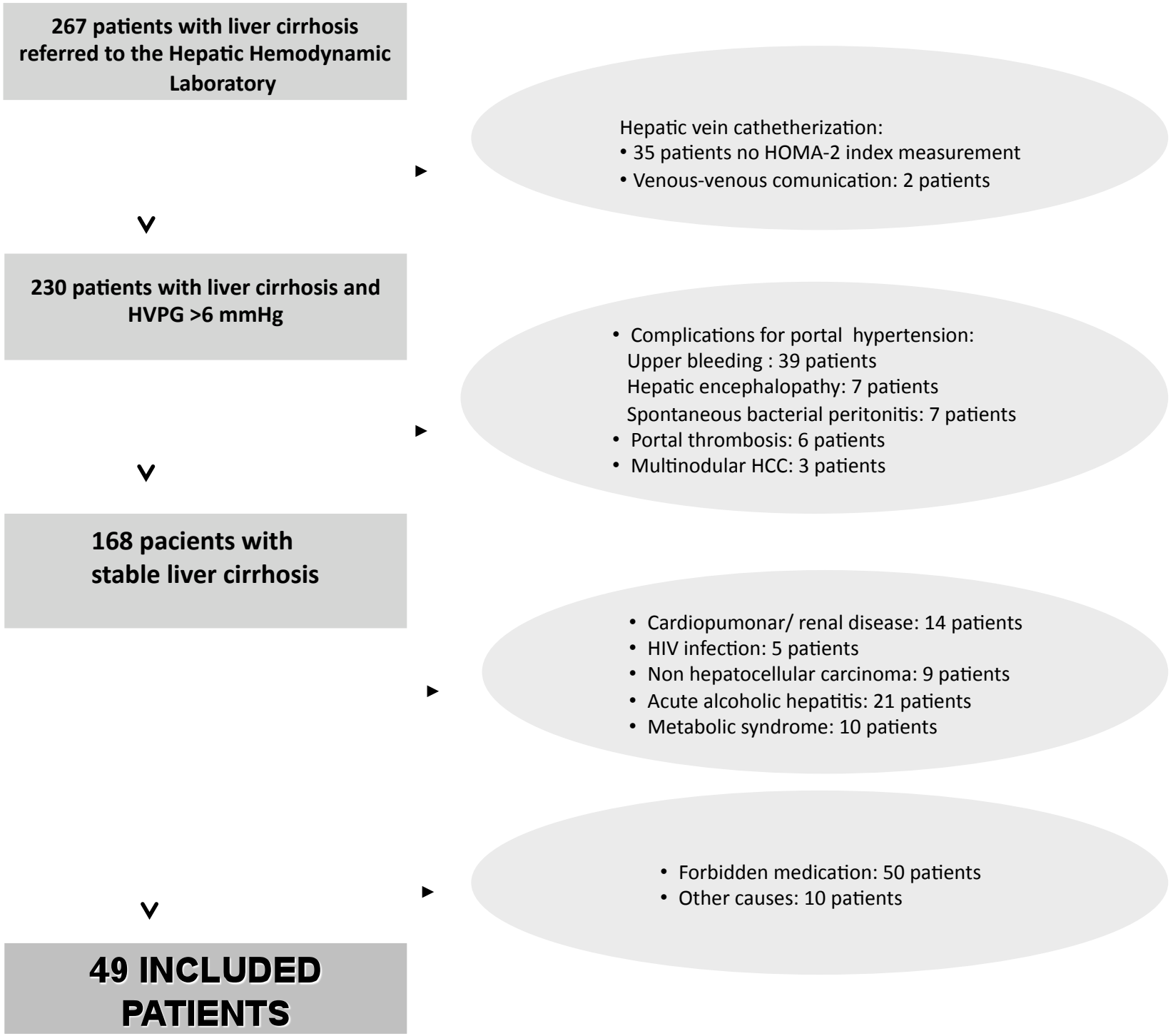
	EV (n=27)	No EV (n=22)	*P**
Age (y)	58 (9.3)	56 (10.8)	.28
Active alcoholism (%)	18.5	13.6	.71
Bilirubin (mg/ dL)	2.4 (2.2)	1.8 (2)	.06
Albumin (g/ L)	32 (6.4)	34 (5.4)	.07
Protrombin time (%)	62 (18.2)	73 (19)	.04
Platelets (10^9)	105 (55)	101 (33)	.2
Child-Pugh Class (A/ B/C)	12 / 9 / 6	16 / 3 / 3	.1
Child-Pugh Score	7 (2.1)	6.5 (2)	.09
MELD score	13.4 (4.7)	11.2 (5.6)	.04
HOMA-2 index	3.4 (1.3)	2.5 (1.4)	.02
Glucose (mmol/ L)	5 .6 (1)	5.6 (1.2)	.75
Insulin (pmol/ L)	163.4 (62)	121.3 (71)	.016
MAP (mmHg)	89 (11)	97 (17)	.12
CI ($L/min/m^2$)	4 (1.2)	3.3 (1.4)	.016
SVRI ($dyne*sec*m^2/cm^5$)	1778 (547)	2469 (961)	.005
HVPG (mmHg)	17.5 (5)	13 (6)	.005
CSPH (>10 mmHg)(%)	96.3	54.5	.001

Table 4.- **Clinical and hemodynamic characteristics of the patients with or without gastroesophageal varices** Continuous variables are expressed by mean /(SD). P* yes EV vs no EV group. *Abbreviations:* EV: oesophageal varices, HOMA-2 index: homeostasis model assessment-2 index, MAP: mean arterial pressure, CI: cardiac index, SVRI: systemic vascular resistance index, HVPG: hepatic venous pressure gradient

	Study population (n=38 patients)				Non-IR group (n= 11 patients)				IR group (n=27 patients)				P*
	Baseline	**After iv Propranol**	**% Change**	P	**Baseline**	**After iv Propranol**	**% Change**	P	**Baseline**	**After iv Propranol**	**% Change**	P	
HR (beat/min)	76 (12)	60 (9)	-19.8 (13)	.00	72 (11)	59 (8)	-18 (5)	.00	77 (13)	62 (10)	-19 (9)	.00	.25
CI (L/ min/ m²)	4 (1.2)	3 (0.8)	-19 (12.7)	.00	3.4 (0.6)	2.7 (0.5)	-19 (11)	.01	4.2 (1.3)	3.2 (1)	-19 (13.5)	.00	.07
HVPG (mmHg)	17.5 (5)	15 (4.5)	-15 (10.5)	.00	16 (4.5)	13.5 (3.5)	-15 (11.5)	.01	18 (5)	15.5(5)	-15 (10.5)	.00	.39
HBF (L/ min)	0.95 (0.5)	0.76 (0.4)	-16 (19)	.00	1.04 (0.3) (n=9)	0.83 (0.3)	-16 (20.5)	.07	0.92 (0.5) (n=21)	0.74 (0.50)	-16.5 .9)	.00	.14

Table 5.- **Mean hemodynamic response to iv. propranolol administration**

P* Comparative of response of non-IR group vs IR-group. Results are expressed by mean (SD).
Abbreviations: HR: heart rate, CI: cardiac index, HVPG: hepatic venous pressure gradient, HBF: hepatc blood flow, iv propranolol: intravenous administration of propranolol


267 patients with liver cirrhosis referred to the Hepatic Hemodynamic Laboratory
Hepatic vein catheterization:
• 35 patients no HOMA-2 index measurement
• Venous-venous comunication: 2 patients
230 patients with liver cirrhosis and HVPG >6 mmHg
• Complications for portal hypertension:
Upper bleeding : 39 patients
Hepatic encephalopathy: 7 patients
Spontaneous bacterial peritonitis: 7 patients
• Portal thrombosis: 6 patients
• Multinodular HCC: 3 patients
168 pacients with stable liver cirrhosis
• Cardiopumonar/ renal disease: 14 patients
• HIV infection: 5 patients
• Non hepatocellular carcinoma: 9 patients
• Acute alcoholic hepatitis: 21 patients
• Metabolic syndrome: 10 patients
• Forbidden medication: 50 patients
• Other causes: 10 patients
49 INCLUDED PATIENTS

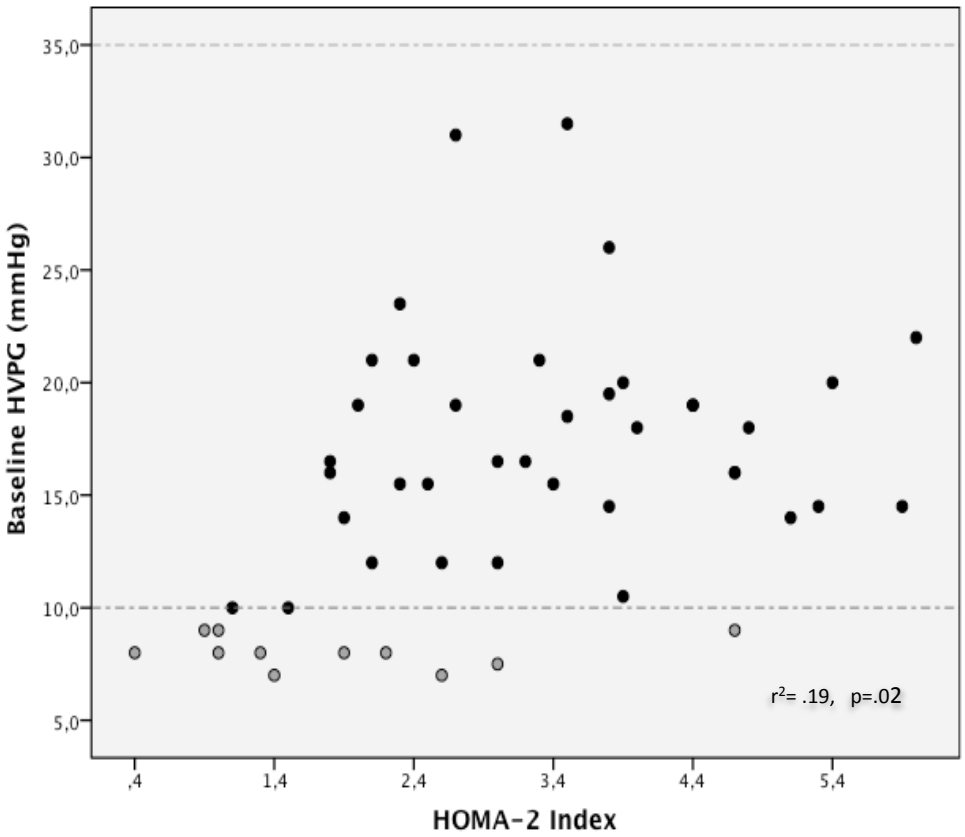


Figure b1

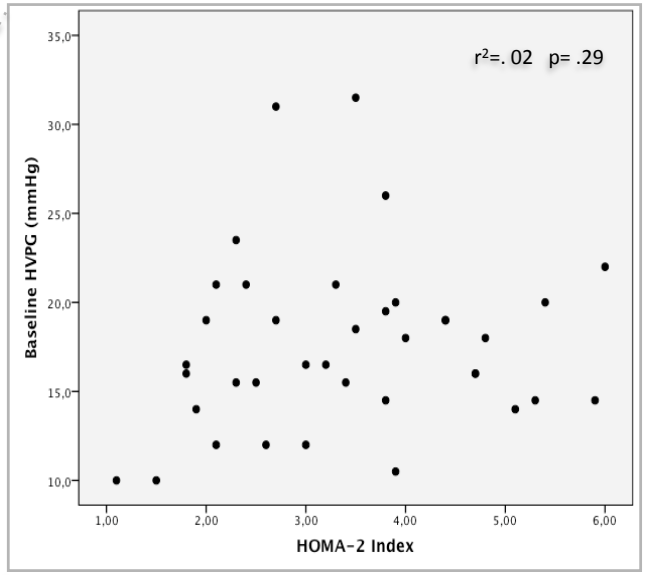
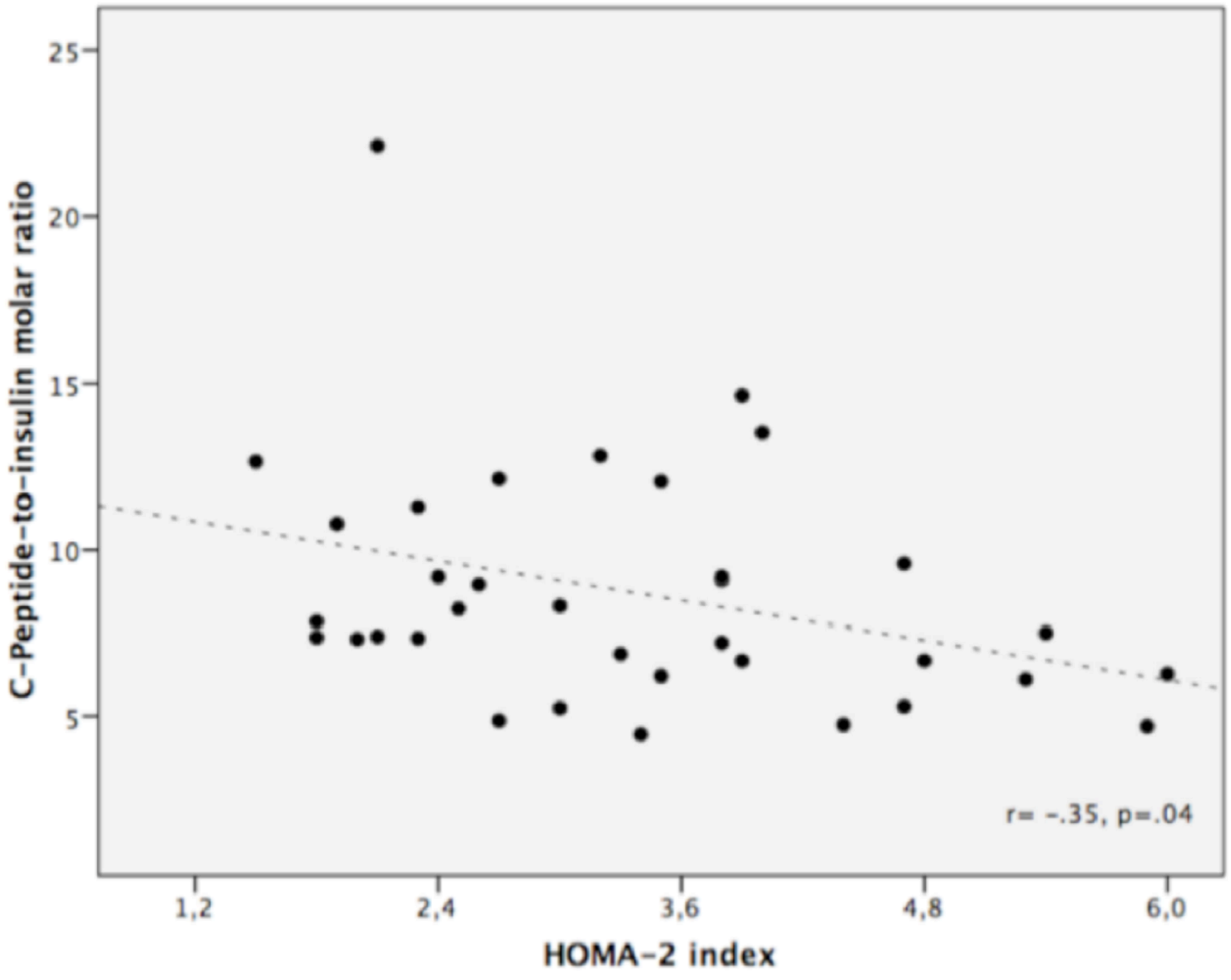


Figure b2


C-Peptide-to-insulin molar ratio
25
20
15
10
5
1,2
2,4
3,6
4,8
6,0
HOMA-2 index
r= -.35, p=.04