ORIGINAL PAPER

Available from: URL: http://www.jgld.ro/2014/4/11
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.234.msy

The Metabolic Syndrome Is Not Correlated with the Short-term Risk of Decompensation in Patients with Cirrhosis

Bogdan Procopet[1,2,3], Oana Farcau[2], Marius Balagel[1], Dana Crisan[1,2], Horia Stefanescu[2], Andreea Pop[1,2], Petra Fischer[2], Alina Habic[1,2], Corina Radu[1,2], Marcel Tantau[1,2], Mircea Grigorescu[1,2]

1) Gastroenterology Department, Iuliu Hatieganu University of Medicine and Pharmacy;
2) Gastroenterology Department, Prof. Dr. Octavian Fodor Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania
3) Hepatic Hemodynamic Laboratory, Liver Unit, IDIBAPS, Hospital Clinic, Barcelona, Spain

Address for correspondence:
Bogdan Procopet
Prof. Dr. Octavian Fodor Regional Institute of Gastroenterology and Hepatology
Croitorilor 19-21, 400126 Cluj-Napoca, Romania
bogdanprocopet@gmail.com

Received: 11.07.2014
Accepted: 03.11.2014

ABSTRACT

Background & Aims: Obesity proved to favor clinical decompensation in patients with cirrhosis. Our aim was to investigate if metabolic syndrome (MS) in cirrhotic patients represents a risk factor for decompensation.
Methods: 704 cirrhotics, included in a MS prevalence study were considered for evaluation; 121 patients were excluded because they did not complete the follow-up and 303 because they were decompensated at the start of the study. The remaining 280 were followed-up for a median period of 28.1±18 months. Patients were censored at the end of follow-up or at occurrence of a liver related event (LRE). Liver related events were considered the following: decompensation (ascites, variceal bleeding, hepatorenal syndrome, jaundice, encephalopathy), hepatocellular carcinoma, portal vein thrombosis and infections.
Results: All MS criteria except the abdominal circumference were significantly different between decompensated and compensated patients. HDL-cholesterol levels were lower in decompensated patients. Among the 280 patients who completed the follow-up, 85 (30%) presented LREs. Ascites was the most frequent event. In the univariate analysis of the MS criteria we found a trend to significance of an inverse correlation between MS and LREs. There was no significant difference between patients with or without MS regarding survival free of LREs, 76.7% and 66.5%, respectively. None of the MS criteria reached the level of significance in discriminating patients with and without LREs.
Conclusions: In short term, presence of MS was not a risk factor for LREs. In short term, liver function and lower nutritional status influenced the prognosis. In decompensated patients, the MS defining criteria are not applicable.

Key words: liver related events – portal hypertension complications – metabolic syndrome – obesity – prognosis

Abbreviations: BMI: body mass index; EV: esophageal varices; HR: hazard ration; HVPG: hepatic venous pressure gradient; LRE: liver related event; MS: metabolic syndrome; PHT: portal hypertension; WC: waist circumference.

INTRODUCTION

In the natural history of cirrhosis the occurrence of decompensation results in a tremendous decrease of life expectancy, from approximately 97 % to 40% at one year [1]. It is now recognized that associated conditions such as co-infection with HIV, lack of treatment response in case of viral etiology, or active alcohol drinking, may accelerate the decompensation process [2, 3].

Metabolic syndrome (MS) is a very frequent condition in the western world. It is not a disease per se but a constellation of associated disorders that have as a central core visceral obesity and insulin resistance [4]. This entity, besides increasing the risk of cardiovascular and diabetes related death, promotes the development of non-alcoholic fatty liver disease which may progress to end-stage liver disease. Moreover, the progression of chronic liver diseases, in terms of fibrosis progression or lack of treatment response proved to be negatively influenced by the co-existence of the MS and its components [5-6].

Recently, it was demonstrated that overweight and obesity favors the occurrence of decompensation in patients who were previously compensated [7-9]. Additionally, it is known that insulin resistance is common among patients with cirrhosis, due to down regulation of insulin receptors and

reduced insulin clearance secondary to hepatic insufficiency and porto-systemic shunting [10]. It was also demonstrated that insulin resistance is positively correlated with portal hypertension (PHT) evaluated directly by hepatic venous pressure gradient (HVPG) measurement [11] or indirectly as the presence of esophageal varices (EV) [12]. Furthermore, obesity and diabetes represent independent risk factors for development of hepatocellular carcinoma in patients with NASH [13]. However, whether the presence of MS favors clinical decompensation in patients with cirrhosis is unclear.

The aim of this study was to evaluate: a) whether the prevalence and components of the MS are different between patients with compensated and decompensated cirrhosis from a contemporary population and b) if the MS and its components increase the risk of decompensation and other clinical events in patients with cirrhosis.

PATIENTS AND METHODS

Between November 2006 and November 2008, 10,089 inpatients and outpatients were screened at the 3rd Medical Clinic (Cluj-Napoca, Romania) for MS (Finalism study, CEEX 94/31.07.2006). In this study, MS was defined according to the 2004 AHA definition [14] and the prevalence of MS in the entire population was approximately 40%.

For the present study, only patients previously diagnosed with liver cirrhosis were included. The diagnosis of cirrhosis was based on specific findings on clinical examination, laboratory and imaging, and in a minority of patients on liver biopsy. Thus, 704 cirrhotic patients were considered for inclusion. Among these, 303 were decompensated at inclusion or had a previous episode of decompensation. From the remaining patients, 121 were not followed-up in our clinic. The remaining 280 fully compensated patients were followed-up. They were censored on the first occurrence of any liver-related event (LRE) (see the definition below) or on the last available visit on follow-up (Fig. 1).

For the first aim of this study (transversal design), decompensated patients were compared to compensated patients regarding the prevalence of MS and its components.

For the second aim of the study (longitudinal design), only fully compensated patients followed-up at our center were considered.

Clinical and laboratory data of the followed-up patients were gathered and analyzed retrospectively from the patients' records. Plasma albumin was not readily available at the time of the study in our Center and was not included in the routine assessment of cirrhotic patients; for this reason the Child-Pugh score could not be calculated.

In order to decrease the risk of selection bias in this retrospective analysis, data from a subgroup of 156 patients with rigorous follow-up (> 2 years of follow-up and > 4 visits) were studied separately.

Clinical history, physical examination including body weight, blood tests, abdominal ultrasonography, and the analyses for MS screening were done at the inclusion in all patients.

The MS criteria were reviewed in all 704 patients and MS was redefined according to the 2009 AHA definition [15] as the presence of at least 3 criteria among the following: increased waist circumference (WC) (≥ 94 cm in men; ≥ 80 cm in women), elevated serum triglyceride level (≥ 150 mg/dL), reduced HDL-cholesterol level (< 40 mg/dL in men; < 50 mg/dL in women), history of arterial hypertension, previously diagnosed diabetes, or elevated fasting glucose level (≥ 100 mg/dL). In decompensated patients with ascites, the WC was not

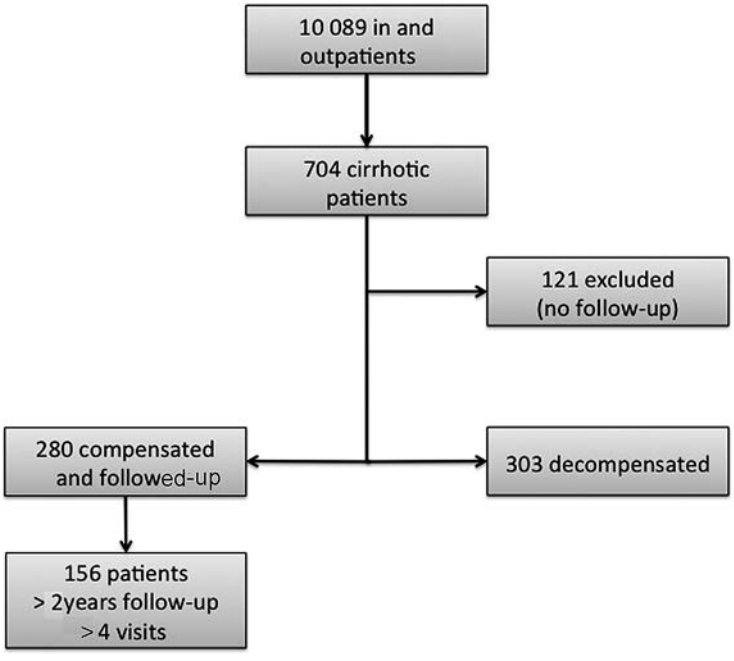

Fig. 1. Flowchart of the study.

considered as a positive criterion for MS diagnosis. The body mass index (BMI) was calculated according to World Health Organization as weight (in kilograms) divided by the square of the height (in meters).

Liver related events were defined as one or more of the following: clinical decompensation (ascites, variceal bleeding, hepatorenal syndrome, jaundice defined as total bilirubin > 3mg/dL, and encephalopathy), hepatocellular carcinoma, non-tumoral portal vein thrombosis and bacterial infections.

A subanalysis restricted to PHT related events (ascites, hydrothorax, variceal bleeding) was also performed.

All patients signed a written informed consent approved by the Ethical Committee of the Cluj-Napoca Medical University at inclusion in the Finalism study and consented to the anonymous use of their data. The present study was designed respecting the ethical guidelines issued by the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki.

Statistical analysis

Data were expressed as mean ± standard deviation (SD) and qualitative variables as frequencies. The Anova or Mann-Whitney tests were used for quantitative variables for the comparison between groups; the chi-square and Fisher's exact tests were used for qualitative data where appropriate. For multivariate analysis, a Cox regression using backward LR model was used in order to determine the parameters associated with liver related or PHT-related events.

Actuarial rates of complications were calculated using the Kaplan–Meier plots and were compared by the Log rank test. A p value <0.05 was considered as the level of significance. Statistical analysis was performed using the SPSS software version 20 (SPSS Inc Chicago, IL, USA).

RESULTS

Patients' characteristics

The characteristics of all patients, including those decompensated at inclusion (303) and those who were followed-up (280) are listed in Table I. In the compensated group, 155 (55%) of 223 patients had EV, and of these 54 (24%) had large EV. In this group, 117 (41%) patients were following a prophylactic treatment with non-selective beta-blockers. When the groups of decompensated and compensated patients were compared, as expected, a significant difference was found concerning the variables related to the liver function and PHT: MELD score (p<0.001), total bilirubin (p=0.03), INR (p=0.001) and platelet count (p=0.008). Also, there was a significant difference between the two groups regarding the

Table I. Patients' characteristics.

Variable	All patients	Decompensated	Compensated	P*
No patients	583	303	280	-
Age (years) ± SD	57±10	57 ± 11	56±9	0.65
Male, n (%)	309 (53)	162 (53)	148 (53)	0.33
Etiology, n (%)				0.31
Alcohol	193 (33)	116 (38)	77 (27.5)	
HVB	75 (13)	35 (11.5)	40 (14)	
HVC	228 (39)	108 (35.5)	120 (43)	
Autoimmune	32 (5.5)	12 (4)	20 (7)	
NASH/cryptogenic	55(9.5)	32 (10)	23 (8.5)	
BMI (kg/m^2), n (%)				0.39
<18	8 (1.4)	6 (2)	2 (0.7)	
18-25	200 (35.6)	103 (34)	96 (34.3)	
25-30	201 (34)	108 (34.5)	94 (33.5)	
>30	174 (29)	86 (28)	88 (31.5)	
Metabolic syndrome, n (%)	191 (33)	85 (28)	106 (38)	0.001
History of arterial hypertension, n (%)	199 (34)	82 (27)	118 (42)	<0.001
History of diabetes, n (%)	154 (26)	61 (20)	94 (33)	<0.001
Waist circumference (cm), mean ± SD	95.3±17	95.5±18	95.1±16	0.86
Men	96.5±15	96.9±16	96±15	0.62
Women	93.4±20	93.1±21	93.6±20	0.83
Triglycerides (mg/dL), mean ± SD	136±131	125±96	146±159	0.005
HDL-C (mg/dL), mean ± SD	51±21	48±19	53±22	0.08
Men	49.8±20	46±16	53±23	0.01
Women	53±21	51±21	54±20	0.18
Glucose (mg/dL), mean ± SD	113±47	111±37	115±55	0.73
AST (U/L), mean ± SD	68±119	74±159	62±51	0.17
ALT (U/L), mean ± SD	62±66	58±67	64±66	0.43
Bilirubin (mg/dL), mean ± SD	1.68±2.5	1.8±2.5	1.4±2.4	0.03
INR	1.25±0.3	1.4±0.3	1.2±0.3	0.001
Platelets count 10^9/L, mean ± SD	145±116	103±66	150±120	0.008
MELD, mean ± SD	12.3± 6	15±5.9	10±5.8	<0.001

* Comparison between compensated and decompensated patients.

presence of MS: 38% in the compensated patients vs. 28% in decompensated patients (p=0.001). All the criteria of the MS except the WC were significantly different between the two groups (Table I). However, HDL-cholesterol level was lower in decompensated patients. The WC as well as BMI was not different.

Complications during follow-up

Two hundred eighty patients were followed-up for a mean period of 28.1 ± 18 months. During follow up, 85 patients (30%) presented with at least one LRE. Complications are presented in Table II. The most frequent complication, as expected, was ascites followed by jaundice. None of these patients died or received a transplant during the follow-up until the end point.

The proportion of LREs was also similar in the subgroup of patients with rigorous follow-up (Table II). In this subgroup, the mean follow-up period was of 34.5 ± 18 months.

Table II. Total liver events and PHT related events in the follow-up cohort and in the subgroup with closer follow-up.

	280 patients with follow-up	156 patients with closer follow-up
Total liver events, no. of patients (%)	85 (30)	54 (35)
PHT events, no. of patients (%)	61 (21.7)	40 (25)
Ascites	54 (19.2)	37 (23.7)
Hydrothorax	5 (1.7)	4 (2.6)
Variceal bleeding	12 (4.2)	7 (4.5)
Jaundice	23 (8.2)	15 (9.6)
Hepatic encephalopathy	8 (2.8)	5 (3.2)
Hepatocellular carcinoma	11 (3.9)	8 (5.1)
Portal vein thrombosis	11 (3.9)	8 (5.1)
Infections (SBP)	17 (3)(6)	12 (3)(7.7)

PHT: portal hypertension; SBP: spontaneous bacterial peritonitis

Parameters associated with complications

All the clinical parameters were compared between patients with and without LRE. In the univariate analysis, the occurrence of complications was correlated with total bilirubin level, platelet count, INR, AST and MELD score. In the multivariate analysis, the only variable correlated with the end-point was MELD score (HR=1.024, p=0.03). In order to avoid colinearity with MELD score, INR and bilirubin were not included in the model. In the subgroup of 156 patients, the results were similar in the univariate and multivariate analysis.

Regarding PHT-related complications, in all the 280 patients bilirubin level, platelet count, INR, MELD scores, presence of EV and treatment with beta-blockers significantly correlated to this end-point. In the multivariate analysis, only MELD score (HR=1.032, p=0.04) and beta-blocker treatment (HR=0.4, p=0.03) correlated with PHT events. In the subgroup of 156 patients, the univariate analysis revealed that bilirubin, platelet count, INR, AST, MELD score, presence of MS, EV and beta-blocker treatment significantly correlated with the PHT events. In the multivariate analysis, beta-blocker treatment was the only variable correlated with PHT events (HR=0.35, p=0.06). Interestingly, in the last step, the variable eliminated from the model was the presence of MS, which doubled the risk of events.

Metabolic syndrome and the risk of LRE

Among all the variables included in MS definition none was correlated with the occurrence of LRE or PHT related complications (Table III).

Arterial hypertension and increasing BMI showed a trend to lower the risk of LREs. This trend was kept when PHT complications were analyzed and thus, the presence of MS, arterial hypertension, BMI and WC were inversely correlated with the complications' rate.

When the subgroup of 156 patients was analyzed the results obtained were similar.

The actuarial rate of remaining free of LREs according to the presence or absence of MS was 76.7% and 66.5%, respectively (Log Rank, p=0.2)(Fig. 2A).

Concerning the PHT events, the actuarial rate of remaining free of complications according to the presence or absence of MS was 83.5% and 74.6%, respectively (Log Rank, p=0.1) (Fig. 2B).

During the follow-up, 11 patients developed hepatocellular carcinoma in a mean interval of 23.4 ± 8.6 months. According to the presence of MS at the inclusion, there was no difference regarding the risk of hepatocellular carcinoma (5 out of the 11 patients had MS at the inclusion, Log rank, p=0.58).

When all MS criteria were studied separately in the survival analysis, none reached the level of discrimination between patients with and without LRE or PHT related complications.

Table III. Comparison of metabolic syndrome and its components between patients with and without liver related and portal hypertension events.

Variable	LRE	No LRE	p	PHT events	No PHT events	p
Metabolic syndrome	31.7%	41.1%	0.1	29%	40%	0.08
Arterial hypertension	34.5%	46.3%	0.06	32.7%	45.5%	0.07
Diabetes	31.8%	33.6%	0.7	32.8%	33.1%	0.9
BMI, mean ± SD	27.1±5	28±5	0.09	27±5.6	28±5	0.05
Waist circumference (cm), mean ± SD	93±16	95±16	0.1	92±17	95±16	0.07
Triglycerides (mg/dL), mean ± SD	144±194	149±142	0.1	152±226	146±136	0.2
HDL-C (mg/dL), mean ± SD	52,8±23	53,1±21	0.9	52±21	53±22	0.9
Glucose (mg/dL), mean ± SD	112±31	117±63	0.7	111±30	117±61	0.8

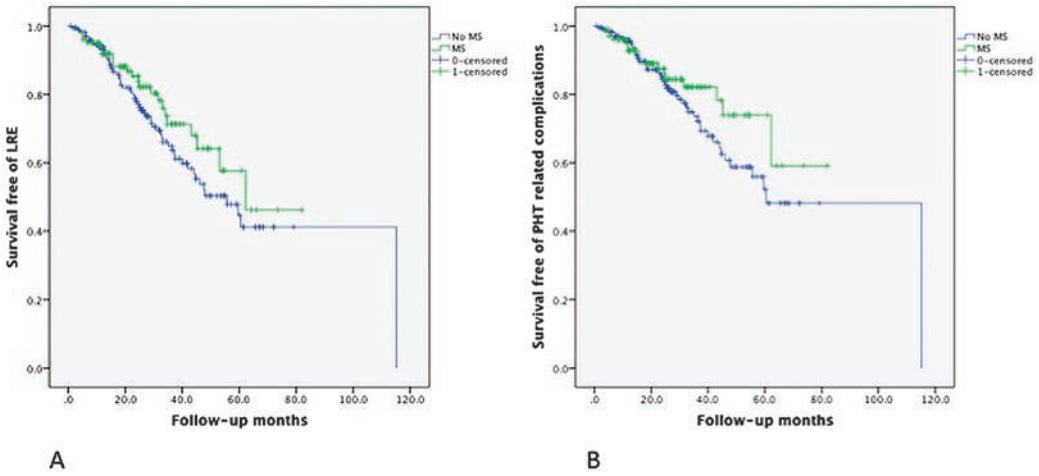

Fig. 2. A) Actuarial rates of remaining free of liver related events (LERs) according to the presence or the absence of metabolic syndrome (MS). B) Actuarial rates of remaining free of portal hypertension (PHT) related events according to the presence or the absence of MS.

In order to see if the results are influenced by the presence of the EV or beta-blocker treatment a subgroup analysis of patients without EV was performed. The survival without LRE and PHT related complications was still higher in patients with MS, without statistical significance.

DISCUSSION

The present study indicates that the presence of MS or of any of its defining criteria is not correlated with the risk of LRE or PHT complications in the short term (2-3 years).

Even if it is not surprising that patients with decompensation at inclusion had significantly less often MS, it should be emphasized that WC and BMI were not different between the two groups, probably in relation with ascites, which is the most frequent decompensation event. Moreover, HDL-cholesterol levels were inversely modified being higher in compensated patients. In this context we may conclude that in this subgroup of patients the MS defining criteria are not reliable enough, especially when other definitions of MS are used having WC as a mandatory criterion.

From the best of our knowledge, this is the first study that specifically addresses the problem of MS in patients with cirrhosis and the risk of decompensation. Until now there were a few studies that investigated some of the MS components and the results were controversial. In a recent study, the MS proved to be more prevalent in patients with advanced HBV hepatitis and cirrhosis [16]. In a prospective cohort of 56 patients of whom 38% were diagnosed with diabetes, there was a significant difference regarding 5 year survival between patients with diabetes (56.6%) and patients with normal oral glucose tolerance test (94.7%) [17]. However, those patients with impaired oral glucose tolerance test, who at least in part fulfilled the MS criteria regarding glucose metabolism, did not have a different survival rate compared to those with a normal test. In a very recent retrospective study the presence of diabetes proved to be an independent prognostic factor regarding death and transplantation [18], but in this cohort almost half of the patients had complications of cirrhosis, especially hepatocellular carcinoma and ascites. Diabetes only influenced transplantation-free survival in patients with a MELD score less than 10. New onset diabetes in patients with chronic hepatitis C proved to increase the risk of cirrhosis development and decompensation [19]. However, in this retrospective study, patients with new onset diabetes at inclusion were significantly older, with more advanced liver disease and with more co-morbidities resulting in a possible selection bias. In our study, patients with or without diabetes had similar actuarial rates of survival without LRE, 73% vs. 69%, respectively. Metabolic syndrome proved to increase the risk of cardiovascular events, but not the overall survival and treatment response to ursodeoxycholic acid, in 171 patients with primary biliary cirrhosis followed for 137 months [20]. However, only a few patients were in the cirrhotic stage at the moment of inclusion.

Insulin resistance and increased BMI were showed to favor fibrosis progression and decompensation in the HALT-C cohort, which included patients with severe fibrosis or cirrhosis due to chronic HCV infection [9]. In this study, despite the high incidence of MS criteria (> 25% of the patients had TG level > 150mg/dL; almost 50% had low HDL cholesterol levels and 45% of men and 66% of women had high WC), none of the MS defining variables were correlated with the end-point in a mean follow-up of almost 4 years.

During a longer follow-up (59 months) of a cohort of 161 perfectly compensated cirrhotic patients (HVPG >6 mmHg and no EV), overweight and obesity increased the risk of decompensation [8]. Moreover, obesity impaired the response to beta-blocker treatment, estimated as HVPG modification. However, in this study the analysis of the MS specific criteria was not done.

Interestingly and somewhat surprising, we found a "protective" effect (with significance trend) of the MS presence, arterial hypertension, increasing BMI and WC against LRE and PHT related complications. This effect was maintained even after the analysis of a subgroup of patients without EV and

without beta-blocker treatment. By this subgroup analysis we discarded a hidden protective effect of beta-blockers, known to favor development of MS and protect cirrhotic patients against PHT related complications. Nevertheless, we believe that this is a false "protective" effect and that it is most probably related to the associated nutritional degradation and systemic vasodilatation of the patients who decompensate more rapidly. It has been already proved that poor nutritional status impairs survival in patients with cirrhosis [21, 22].

There are two main drawbacks of this study. One is the retrospective design and, therefore, the increased risk of selection bias. In order to overcome this inconvenience we made a subgroup analysis of patients with a more rigorous follow-up, which we arbitrarily considered in those patients who were regularly seen for more than two years. With this subgroup analysis we also attenuated the second major limitation of this study: the relatively short follow-up period. In our study, we had a relatively higher than expected prevalence of EV (55%) in the compensated subgroup and therefore, these patients had probably a more advanced disease and a higher risk to decompensate. This population structure may partially explain the "protective" effect of MS. In order to avoid this potential bias, we performed a subgroup analysis in patients without EV and the effect of MS was maintained. Other limitations of the study are the lack of data about alcohol abstinence for alcoholic cirrhosis patients or antiviral therapy for patients with viral etiology, a treatment that certainly influences prognosis. More prospective and longer follow-up studies are required to better define the relation between MS and the risk of LREs in patients with compensated cirrhosis.

CONCLUSIONS

In the short term, the presence of metabolic syndrome or of any of its defining criteria did not increase the risk of decompensation in our cohort of patients with cirrhosis. Most probably, the severity of liver failure and a worsening nutritional status play a more relevant role in the short-term prognosis. In the decompensated stage of cirrhosis, the metabolic syndrome defining criteria did not contribute in any applicable way. Prospective studies with clear inclusion criteria and a longer follow-up period are required to reach a definitive conclusion regarding this issue.

Conflicts of interest: All authors disclose no conflicts of interest.

Funding: Patient's inclusion was supported in part by the grant of Romanian National Authority for Scientific Research -CEEX program FINALISM 94/31.07.2006

Authors' contributions: B.P.: study concept and design; data acquisition; analysis and interpretation of data; drafting of the manuscript; study supervision. O.F., M.B., A.P., P.F. , D.C. and A.H.: data acquisition ; H.S., C.R., D.C., M.T.: revised the manuscript for important intellectual content. M.G.: obtained funding, supervised the study and revised the manuscript for important intellectual content.

Acknowledgments: The authors thank Dr. Annalisa Berzigotti for the critical review of the paper that contributed to the improvement of the work. At the time of submission Dr. Bogdan Procopet and Dr. Horia Stefanescu are Marie Curie Fellows within the CLEVER project, which is funded by the European Commission under the Seventh Framework Programme (FP7-PEOPLE-2013-IAPP; Grant Agreement 612273).

REFERENCES

1. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217–231.
2. Bruno S, Crosignani A, Facciotto C, et al. Sustained virologic response prevents the development of esophageal varices in compensated, Child-Pugh class A hepatitis C virus-induced cirrhosis. A 12-year prospective follow-up study. Hepatology 2010;51:2069–2076.
3. Iacobellis A, Perri F, Valvano MR, Caruso N, Niro GA, Andriulli A. Long-term outcome after antiviral therapy of patients with hepatitis C virus infection and decompensated cirrhosis. Clin Gastroenterol Hepatol 2011;9:249–253.
4. Samson SL, Garber AJ. Metabolic Syndrome. Endocrinol Metab Clin North Am 2014;43:1–23.
5. Yoon H, Lee JG, Yoo JH, et al. Effects of metabolic syndrome on fibrosis in chronic viral hepatitis. Gut Liver 2013;7:469–474.
6. Hu KQ, Kyulo NL, Esrailian E, et al. Overweight and obesity, hepatic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States. J Hepatol 2004;40:147–154.
7. Younossi ZM, McCullough AJ. Metabolic syndrome, non-alcoholic fatty liver disease and hepatitis C virus: impact on disease progression and treatment response. Liver Int 2009;29 Suppl 2:3–12.
8. Berzigotti A, Garcia-Tsao G, Bosch J, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. Hepatology 2011;54:555-561.
9. Everhart JE, Lok AS, Kim HY, et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Gastroenterology 2009;137:549–557.
10. Berzigotti A, Abraldes JG. Impact of obesity and insulin-resistance on cirrhosis and portal hypertension. Gastroenterol Hepatol 2013;36:527-533.
11. Erice E, Llop E, Berzigotti A, et al. Insulin resistance in patients with cirrhosis and portal hypertension. Am J Physiol Gastrointest Liver Physiol 2012;302:G1458–G1465.
12. Cammà C, Petta S, Di Marco V, et al. Insulin resistance is a risk factor for esophageal varices in hepatitis C virus cirrhosis. Hepatology 2009;49:195–203.
13. Starley BQ, Calcagno CJ, Harrison SA. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. Hepatology 2010;51:1820–1832.
14. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–438.
15. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the international Diabetes Federation Task Force on Epidemiology and Prevention; National Heart,

Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640–1645.
16. Wong GL, Wong VW, Choi PC, et al. Metabolic syndrome increases the risk of liver cirrhosis in chronic hepatitis B. Gut 2009;58:111-117.
17. Nishida T, Tsuji S, Tsuji M, et al. Oral glucose tolerance test predicts prognosis of patients with liver cirrhosis. Am J Gastroenterol 2006;101:70–75.
18. Elkrief L, Chouinard P, Bendersky N, et al. Diabetes mellitus is an independent prognostic factor for major liver-related outcomes in patients with cirrhosis and chronic hepatitis C. Hepatology 2014;60:823-831.
19. Huang YW, Yang SS, Fu SC, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis C patients with new-onset diabetes: a nationwide cohort study. Hepatology 2014;60:807-814.
20. Floreani A, Cazzagon N, Franceschet I, Canesso F, Salmaso L, Baldo V. Metabolic syndrome associated with Primary Biliary Cirrhosis. J Clin Gastroenterol 2013.
21. Shiraki M, Nishiguchi S, Saito M, et al. Nutritional status and quality of life in current patients with liver cirrhosis as assessed in 2007-2011. Hepatol Res 2013;43:106–112.
22. Montano-Loza AJ, Meza-Junco J, Prado CM, et al. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol 2012;10:166–173.