



UNIVERSITA' DEGLI STUDI DI MESSINA
DIPARTIMENTO DI MEDICINA CLINICA E
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Dottorato di Ricerca in
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Hypergammaglobulinemia is a strong predictor of disease progression,
hepatocellular carcinoma development and death in patients with
compensated cirrhosis

PhD STUDENT:

Dott. FILOMIA ROBERTO

SUPERVISOR:

Prof. GIOVANNI RAIMONDO

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Introduction

Cirrhosis represents the end stage of chronic liver disease (CLD) due to different causes, including viral hepatitis, autoimmune and genetic illnesses, alcohol abuse and metabolic disorders. In addition, cirrhosis itself is largely the most important risk factor for the development of hepatocellular carcinoma (HCC). In fact, cirrhosis is a major health problem worldwide and accounts for significant morbidity and mortality¹. Moreover, its incidence is apparently rising as a consequence of the hepatitis B virus (HBV) and hepatitis C virus (HCV) outbreak that occurred in the second half of the past millennium, as well as of the spread of CLD related to metabolic disorders that has been observed in the last decades.²⁻⁴

Actually, the term cirrhosis includes clinical conditions with different grades of severity that have been categorized by applying various scoring systems.

The natural history of cirrhosis is characterized by an asymptomatic phase, termed 'compensated' cirrhosis followed by a rapidly progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction, termed 'decompensated cirrhosis'.

In the compensated phase, portal pressure may be normal or below the threshold level identified for the development of varices or ascites ('clinically significant portal hypertension'). As the disease progresses, portal pressure increases and liver function decreases, resulting in the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy and

jaundice. The development of any of these complications marks the transition from a compensated to a decompensated phase⁵.

Although many prognostic models have been proposed in the last two decades to predict mortality in cirrhosis, the Child–Pugh score is by far the most largely used both in clinical practice and in clinical research⁵.

Child-Pugh (C-P) score, based on three biochemical (albumin, bilirubin and prothrombin time) and two clinical (ascites and encephalopathy) parameters, identifies three classes (A, B, and C) corresponding to different stages of cirrhosis^{6,7}.

In a systematic review D'amico et al showed that the Child–Pugh score and/or its components was the most consistent and 'robust' predictor of death in cirrhosis in particular when considered studies that included only patients with compensated cirrhosis⁵.

In addition to these markers of liver insufficiency, in the compensated stage, significant predictors that come to light are those related to portal hypertension, such as the presence of varices, splenomegaly and platelet count as well as gamma-globulin levels.

In particular, presence of esophageal varices at time of first observation was associated to a significantly higher cumulative incidence of hepatic decompensation, HCC development and death^{8,9}.

Indeed, patients in C-P class A (compensated phase) usually have a mild and often totally asymptomatic disease that may either be clinically stable over time or may quite rapidly progress towards C-P class B and C and/or to HCC development, finally leading to death^{5,10,11}.

The lack of reliable and routinely available predictors makes it difficult to foresee the clinical outcome in many patients with compensated C-P class A cirrhosis.

Aim

The aim of this study was to evaluate the clinical/biochemical/ultrasonographic/endoscopic parameters at the time of diagnosis and during the subsequent long-lasting follow-up in patients with C-P class A cirrhosis due to unknown or not curable causes, with the final objective of finding any possible predictor of clinical outcome in these patients in which the natural history of the disease cannot be influenced by currently available treatments or by lifestyle changes.

Materials and methods

Six-hundred-thirty-one consecutive patients attending the Liver Unit of the University Hospital of Messina from January 1st, 2004 to December 31st, 2010 were diagnosed as having C-P class A cirrhosis. Diagnosis and staging of cirrhosis were performed according to histology in 85 cases who underwent liver biopsy and to the established clinical, ultrasonographic, endoscopic and biochemical criteria in 187 cases. The design of this observational cohort study foresaw the exclusion of patients with a well-defined and potentially treatable cause of the disease. Consequently, 299 out of 631 individuals were excluded because their cirrhosis was HBV-related (114 cases), auto-immune or primary biliary (36 cases), alcohol-related (106 cases), or HCV related treatable with IFN-based therapies (43 cases) that were the only therapeutic approaches available at the time of the patients' enrolment. Therefore, a total number of 332 patients were included in the study, 107 of whom had cryptogenic cirrhosis and 225 had HCV-related cirrhosis untreatable by IFN, as defined by one or more of the following conditions: lack of response to previous treatment, presence of leuko-thrombocytopenia, age >70 years or presence of major co-morbidities that contraindicated IFN therapy. In accordance with previous studies evaluating the clinical outcome in compensated cirrhosis^{6,10,11}, all patients were followed-up after diagnosis for a minimum of 60 months [to death or to orthotropic liver transplantation (OLT)] through clinical and biochemical examinations performed every 3-6 months, US performed every six months, and esophagogastroduodenoscopy (EGD) scheduled at intervals according to international guidelines.¹²⁻¹⁴ In particular, data of haematological tests included: hemoglobin (Hb) values, counts of red blood cells (RBC), white blood cells (WBC), and platelets (PLT); values of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltranspeptidase (GGT), bilirubin, cholesterol, triglycerides, total

proteins, albumin and gamma-globulin, creatinine, urea, and international normalized ratio (INR). All data collected at basal time and at the subsequent controls were recorded in a digitalized dataset. The study was performed in accordance with the principles of the Declaration of Helsinki and it was approved by the Ethics Committee of the Messina University Hospital. Written informed consent was obtained from each patient.

Statistical analysis

Continuous numerical variables are expressed as median and range (minimum-maximum) and categorical variables as number and percentage. Examined continuous variables did not present normal distribution as verified by Kolmogorov Smirnov test and the non-parametric approach was consequently used. Mann Whitney U test was used to compare patients with HCV and cryptogenic liver disease for continuous variables. Kruskal Wallis test was applied in order to compare distribution of follow-up time among different categories of patients (stable disease over time, onset of HCC and C-P class progression). For categorical variables [such as gender, etiology, comorbidities, hypertension, diabetes and presence of esophageal varices (EV)], χ^2 test or exact Fisher test (when appropriated) was applied. Univariate Logistic Regression Models were estimated to assess the possible dependence of the outcomes of interest (stable clinical picture over time, C-P score progression, development of HCC, death/OLT) by all the examined variables [sex, age, body mass index (BMI), liver disease aetiology, diabetes, presence of esophageal/gastric varices, PLT, Hb, RBC, WBC, AST, ALT, GGT, bilirubin, albumin, gamma-globulin, cholesterol, triglycerides, INR, creatinine, and urea]. Multivariate logistic regression models were estimated including variables resulting significant at univariate analyses. Survival curves were plotted using the Kaplan–Meier method, and comparisons between subgroups were performed by log-rank test. Survival curves of patients with compensated cirrhosis at presentation included patients who developed HCC during the study period. The Cox regression model was used to identify prognostic factors of survival. Statistical analysis was performed using SPSS 17.0 for Window package; two sided $p < 0.05$ was considered to be statistically significant.

Results

Three-hundred-thirty-two consecutive C-P class A cirrhotic patients with either untreatable HCV-related (225 cases) or cryptogenic (107 cases) liver disease were enrolled. None of them had history of liver disease decompensation and none had any evidence of bacterial infection. According to the design of the study, 60 (42 with cryptogenic, 18 with HCV-related cirrhosis) out of 332 patients were excluded from the final analysis because they were either lost to follow-up (52 cases), developed HCC within twelve months after enrolment (5 cases) or developed a non-hepatic malignancy within sixty months after starting follow-up (3 cases: 1 lung cancer, 1 breast cancer, 1 leukemia). Consequently, a total of 272 cases were finally analysed (figure 1). These patients were followed-up for a median time of 96 months (range 21-144) by clinical/biochemical/instrumental tests. Baseline characteristics of the included patients are reported in table 1. Comparing the two subsets of patients (HCV-related and cryptogenic cirrhosis), no statistically significant difference concerning age, sex distribution, BMI, arterial hypertension, portal vein diameter, presence/absence and sizes of esophageal varices, counts of RBD, WBC and PLT, Hb values, serum albumin, bilirubin, INR, GGT, creatinine and urea was observed at basal time. On the contrary, presence of diabetes, higher cholesterol values, and spleen longitudinal diameter were significantly associated with cryptogenic cirrhosis ($p<0.001$, $p=0.02$ and $p=0.01$ respectively), whereas AST and ALT values were significantly higher in the HCV group ($p=0.001$) as was the gamma-globulin amount ($p=0.02$).

Ninety-seven/272 (36%) individuals showed a stable clinical picture and no C-P class progression over the whole follow-up period, although 21 of them developed or showed increasing size of EV without bleeding events or other signs of liver disease deterioration. One-hundred-four/272 (38%) patients developed HCC [80/207 (38.6%) with HCV-related

and 24/65 (36.9%) with cryptogenic cirrhosis, $p=0.80$]. Seventy-one/272 additional patients (26%) progressed towards C-P class B or C without developing HCC. Of note, the median follow-up was comparable between patients with stable grade of liver disease over time and patients who showed progression of C-P score grade or who developed HCC ($p=0.5$, by Kruskal Wallis test) (table 2). A total number of 123 patients died during the follow-up, and 8 underwent OLT. Of these cumulative 131 individuals (48%), 88 had HCC, 31 developed liver failure without HCC, and 4 died because of non-hepatic malignant tumors. Finally, no statistically significant difference in terms of clinical evolution was observed between subjects with HCV-related and cryptogenic cirrhosis (figure 2).

When we examined the possible association between all parameters collected at the time of cirrhosis diagnosis and the study outcomes (namely, stable C-P class A over time, worsening of C-P score, HCC development and death), the univariate logistic regression analysis showed that a clinical picture stable over time was associated with older age, absence of diabetes as well as of EV, levels of serum albumin >3.5 gr/dl (conventionally, the lower value in the normal range) and of gamma-globulin <1.8 gr/dl (the median value in our cohort of patients and the optimal cut-off by ROC curve), PLT $>150,000$ mmc³ and cholesterol values >151 mg/ml (table 3a). Older age, absence of both diabetes and EV, serum albumin >3.5 mg/dl and serum gamma-globulin <1.8 mg/dl maintained the significant association with disease stability of the disease at the multivariate regression analysis ($p<0.001$, $p=0.04$, $p<0.001$, $p=0.01$, $p<0.001$, respectively) (table 3a).

C-P score progression was associated with younger age, HCV positivity, diabetes, presence and size of EV, PLT $<150,000$ mmc, serum albumin <3.5 gr/dl, serum gamma-globulin ≥ 1.8 gr/dl, and lower cholesterol values. The statistical significance was maintained at the multivariate regression analysis for the presence of EV, lower serum albumin and cholesterol

values and hypergammaglobulinemia ($p<0.001$, $p=0.03$, $p=0.01$, $p=0.02$ respectively) (table 3b).

The univariate logistic regression analysis showed that HCC development was associated with younger age and gammaglobulinemia ≥ 1.8 gr/dl, and these associations were confirmed by multivariate regression analysis ($p<0.01$, $p<0.001$) (table 3c).

At univariate logistic regression analysis, death was associated with younger age at the time of diagnosis as well as with the presence of EV, albumin values <3.5 g/dl, gamma-globulin values ≥ 1.8 g/dl, and bilirubin levels >1 mg. Only younger age and increased gamma-globulin values were confirmed to be associated with the death at multivariate analysis ($p<0.001$, $p=0.01$) (table 3d). However, multivariate Cox regression analysis showed that only gamma-globulin values ≥ 1.8 g/dl at the time of cirrhosis diagnosis was a significant predictor of death ($p<0.02$; Hazard Ratio 1.9 95% CI). Of note, Log Rank test showed such an effect was maintained when patients with HCC and those with progression of cirrhosis without HCC were evaluated separately ($p=0.01$ and $p=0.05$, respectively). Kaplan-Maier's survival analysis confirmed that patients with gamma-globulin levels ≥ 1.8 mg/dl had a significantly higher risk of death compared to those with gamma-globulin levels <1.8 mg/dl ($p<0.01$) (Figure 3). This higher risk was maintained when Kaplan-Maier's analysis was performed on the subgroup of patients who developed HCC and on the subgroup of those who experienced liver deterioration over time ($p=0.48$, $p<0.01$, respectively. Figure 4A and 4B). Of note, patients with hypergammaglobulinemia at baseline maintained or even increased the gammaglobulin values over time. Indeed, the values were significantly higher at the end of the follow-up than at basal time ($p=0.003$ by Will-Coxon test).

Finally, the time of occurrence of both liver decompensation events and HCC development was significantly shorter in patients with gamma-globulin values ≥ 1.8 g/dl ($p=0.01$ and $p>0.001$, respectively) (Figure. 4 A-B)

Discussion

As expected, this study showed a spectrum of different possible outcomes in patients with compensated cirrhosis. In fact, more than one third of the examined patients maintained the clinical stability over the whole follow-up, whereas a similar number of cases developed HCC. About one fourth of the patients showed evidence of liver disease deterioration and progression of the cirrhosis score over time without developing HCC. Finally, about 50% of the patients died or underwent OLT. Of great interest, the clinical evolution appeared to be wholly comparable between subjects with HCV-related and cryptogenic cirrhosis in our cohort, suggesting that the cause of the liver disease had a marginal or no influence at all on the outcome and survival of C-P class A patients, at least in the absence of curative etiologic therapies. Some important information have arisen from the analysis of a quite large number of routinely available parameters collected at the time of cirrhosis diagnosis. Our results, in fact, showed that patients in whom cirrhosis occurs at a more advanced age, who do not have diabetes and gastro-esophageal varices, and who show albumin and gamma-globulin values >3.5 gr/dl and <1.8 gr/dl, respectively, have a longer survival and higher chances to maintain a stable disease over time. On the contrary, the presence at basal time of EV, lower serum albumin and cholesterol values and hypergammaglobulinemia were predictors of C-P score progression over time. In addition, younger cirrhotics (i.e., under 63 years of age in our cohort) with hypergammaglobulinemia have a higher risk of developing HCC and of dying as shown by multivariate logistic regressions analyses. In particular, values of serum gamma-globulin ≥ 1.8 gr/dl increased between 2.7 and 3 times the risk of liver disease progression, HCC development and death over time. Moreover, hypergammaglobulinemia remained the only and strong predictor of death at Kaplan Mayer analysis in our C-P class A cirrhotics. In this context, one should consider that patients included in this study attended the liver unit of

a tertiary care academic center, where cirrhotics are carefully followed-up, promptly diagnosed and treated when clinical complications and worsening of the disease occur. Consequently, events such as – for instance – development of EV of advanced grade that are known to negatively impact on the natural history of the cirrhosis, had no significant effect on survival in our cohort, likely because of timely administration of therapy with beta-blockers and/or band ligation. Long-lasting elevation of serum gamma-globulin levels is known to be a frequent occurrence in patients with chronic liver disease, and it may be considered an indirect marker of the persistent high grade of intrahepatic inflammation maintained by the agent (or factor) responsible for the liver disease.¹⁵⁻¹⁷ In fact, the normalization of serum gamma-globulin values is an event that may occur in cirrhotic patients when they undergo effective curative treatment, as observable in chronic hepatitis B patients treated with nucleot(s)ide analogues and in many cured chronic hepatitis C subjects. Indeed, several studies performed in the past decade had identified increased gamma-globulin levels among the biochemical predictors of severe fibrosis and cirrhosis development in patients with HCV as well as HBV chronic hepatitis.¹⁸⁻²¹ However, serum gamma-globulin is usually not evaluated as a possible prognostic indicator in patients with already well-defined cirrhosis, and indeed the most recent studies aimed at investigating the clinical outcome in cirrhotic patients have not included evaluation of gamma-globulin values among the parameters potentially capable of prognosticating the disease evolution.^{4 7-9 22-24} Our results provide clear evidence that hyper-gamma-globulinemia may help in identifying the C-P class A cirrhotics with poorer prognosis and make gamma-globulin measurement – that is an easy to perform and cheap test – a very useful prognostic tool that should be routinely used in this set of patients.

Figures and tables

Figure 1 - Flowchart of enrolment. C-P class A cirrhotic patients with HCV related or cryptogenic cirrhosis

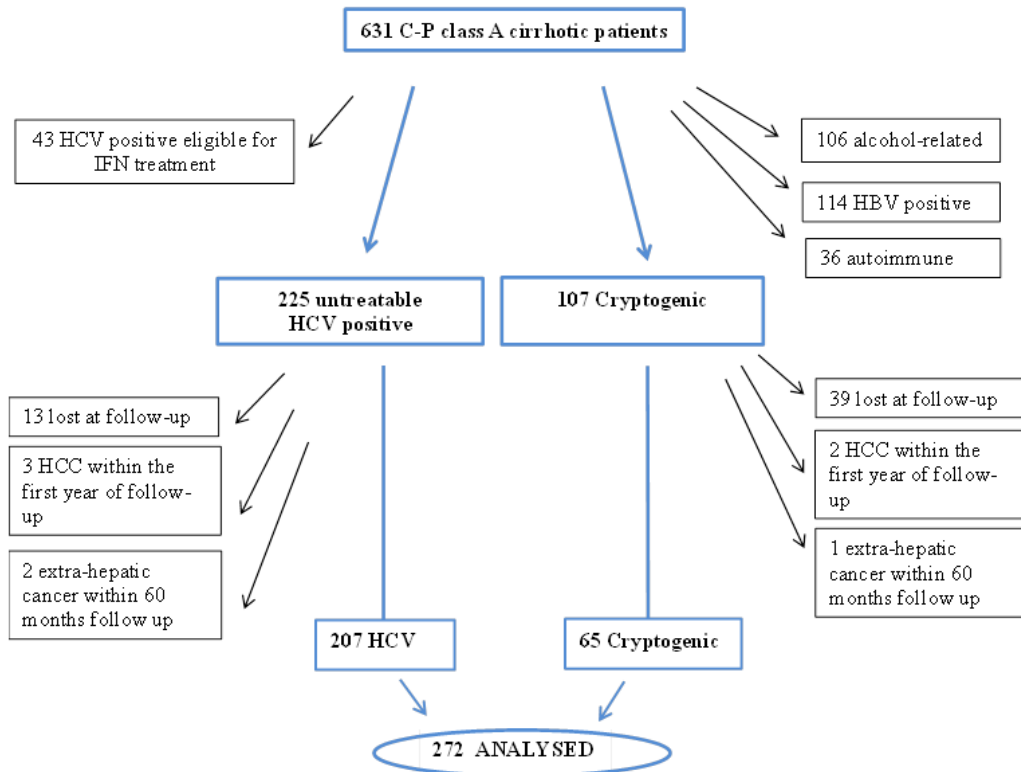


Figure 2 - Clinical outcome in 272 subjects with HCV-related (207) and cryptogenic (65) cirrhosis.

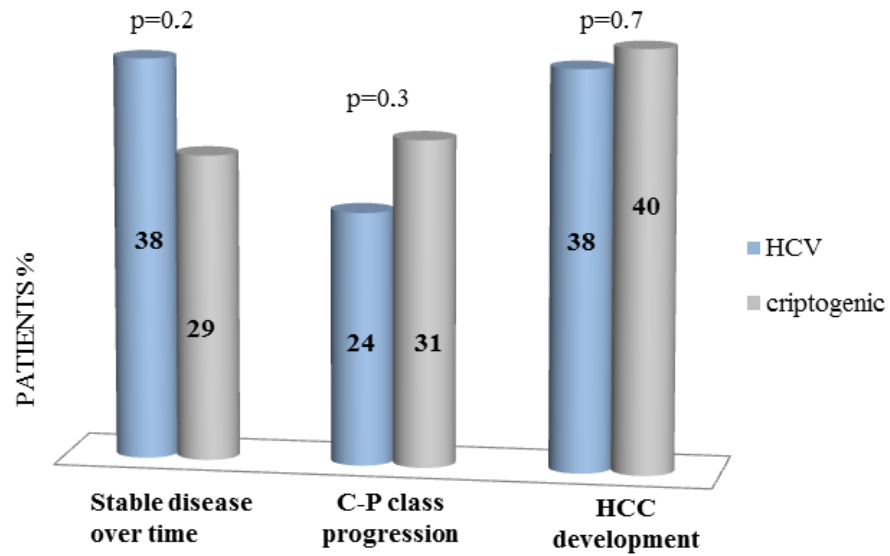


Figure 3 - Survival curves of 272 C-P class A cirrhotic patients with gamma-globulin <1.8 gr/dl (blue line) and ≥ 1.8 gr/dl (grey line).

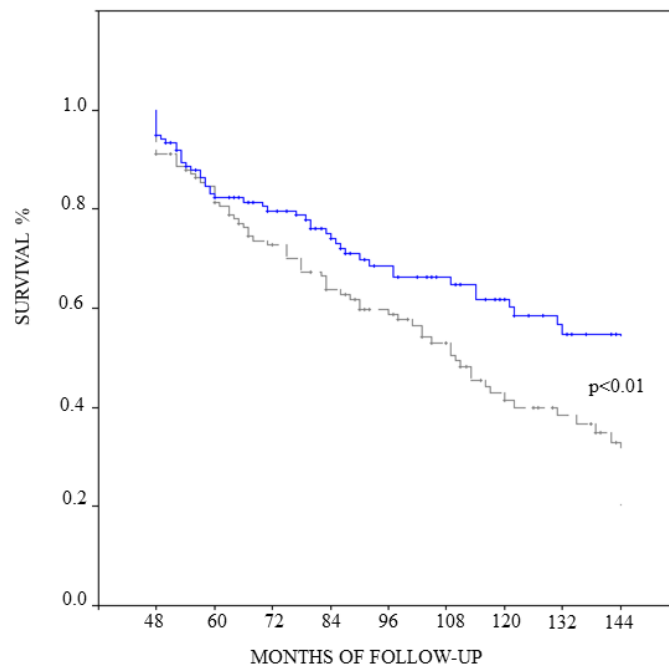


Figure 4 – Survival curves in patients with gamma-globulin <1.8 gr/dl (blue line) and ≥ 1.8 gr/dl (grey line) according with liver decompensation events (A) and HCC development (B).

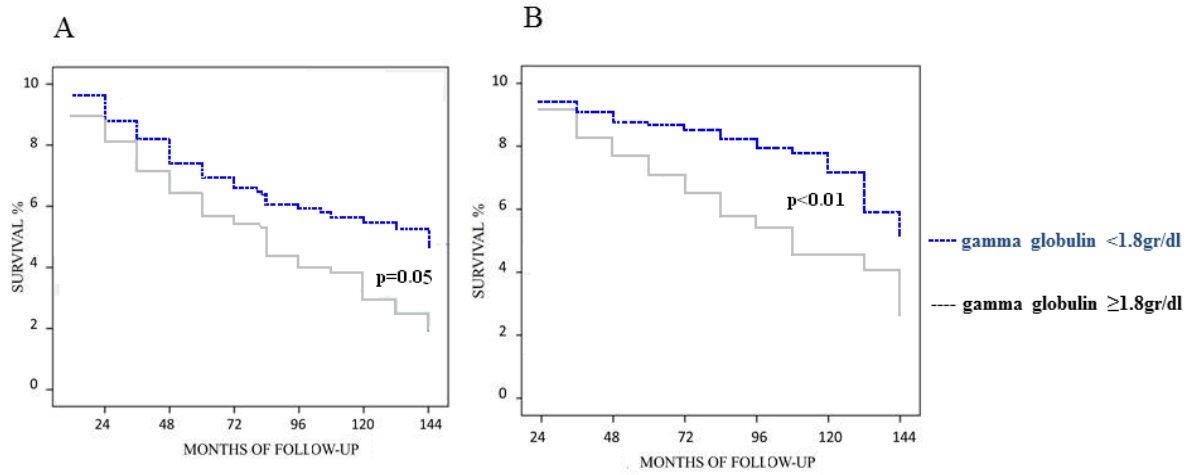


Figure 5 – Incidence of liver decompensation events (A) and HCC development (B) in patients with gamma-globulin <1.8 gr/dl (blue line) and ≥ 1.8 gr/dl (grey line).

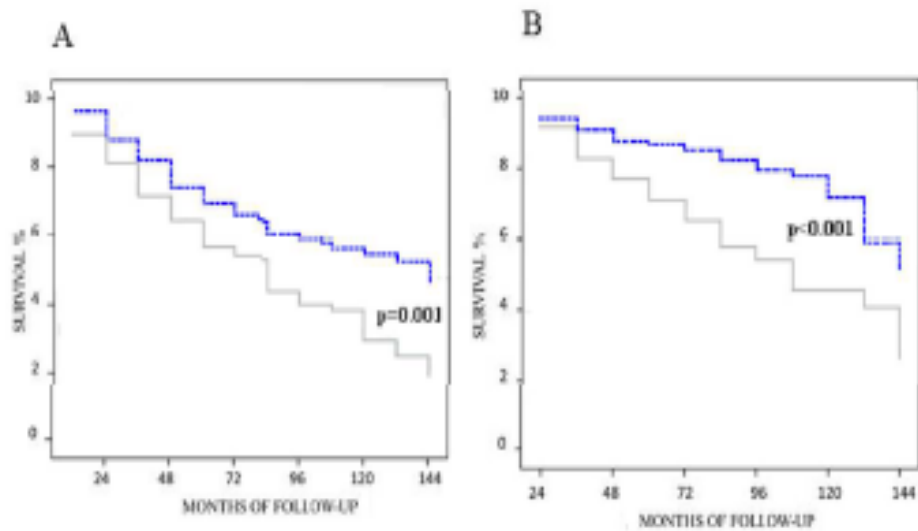


Table 1. Demographic, clinical, biochemical, and instrumental data of 272 C-P class A cirrhotic patients with untreatable HCV-related (207 cases) or cryptogenic (65 cases) cirrhosis.

	Overall Patients	HCV group	Cryptogenic group	p value
Age, years (range)	63 (34-81)	63 (34-81)	64 (34-81)	0.8
Male, N (%)	155 (57)	119 (57)	36 (55)	0.8
BMI kg/m ² , Mean (±SD)	26.0 (3.8)	25.9 (3.1)	27.2(5.6)	0.07
Diabetes, N (%)	109 (40)	69 (33)	40 (62)	<0.001
Esophageal varices,				
Absent N (%)	110 (40.4)	90 (43.5)*	20 (30.8)*	
Small size N (%)	115 (42.3)	88 (42.5)*	27 (41.5)*	
Medium size N (%)	29 (10.7)	17 (8.2)*	12(18.5)*	
Large size N (%)	18 (6.6)	12(5.8)*	6 (9.2)*	*0.06
Portal vein diameter [25]	12.2 (9-18)	12.7	12.0	0.06
Longitudinal size of the Spleen [25]	142.3 (82-180)	139.6	150.1	0.01
Arterial Hypertension, N (%)	141 (52)	109 (53)	32 (49)	0.6
PLT, mmc x 10 ³	112 (58-562)	113 (69-562)	101(58-273)	0.2
RBC, mmc x10 ⁶	4.5 (2.8- 6.6)	4.5 (2.9-6.6)	4.4 (2.8-6.3)	0.2
Hb gr/dl, Median (range)	13.2 (10.3-17.2)	13.3 (10.3-17.2)	12.8(11.1-16.3)	0.3
WBC, mmc x 10 ³	4.8 (2.2-12.6)	5.1 (2.2-12.6)	4.5 (2.7-11.9)	0.4
Total protein, gr/dl	7.5 (5.6-9.9)	7.6 (5.9-9.9)	7.2 (5.6-9.1)	0.2
Albumin, gr/dl	3.9 (2.5-4.9)	3.9 (2.5-4.9)	4 (3-4.9)	0.8
Gamma globulin, gr/dl	1.7 (0.8-3.8)	1.8 (0.8-3.8)	1.6 (0.8-2.6)	0.02
AST, U/L	57 (14-330)	71 (14-330)	39 (19-163)	<0.001
ALT, U/L	66 (10-306)	81 (14-306)	35(10-246)	<0.001
GGT U/L	67 (9-289)	66 (9-279)	78(11-289)	0.06
Bilirubin total, mg/dl	1 (0.4-2.8)	0.9 (0.4-2.8)	0.9 (0.4-2.8)	0.5
INR	1 (0.9-2.1)	1.1 (0.9-2.1)	1.1 (0.9-2.1)	0.3
Cholesterol, mg/dl	151 (65-282)	149 (65-282)	161 (92-289)	0.02
Triglycerides, mg/dl	93 (45-340)	87 (45-340)	99 (95-340)	0.2
Creatinine, mg/dl	0.85 (0.4-2.3)	0.8(0.4-2.3)	0.8 (0.4-2.1)	0.5
Urea, mg/dl	36 (11-97)	36 (11-97)	36 (13-64)	1

All numerical parameters are expressed as median and range excepted for those otherwise indicated

Bold characters identify statistically significant variables

Abbreviations: BMI (body mass index) RBC (red blood cells), Hb (Hemoglobine), WBC (white blood cells), PTL (platelets), ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gamma glutamyltranspeptidase) INR (international normalized ratio)

Table 2. Duration of follow-up and clinical outcomes in 272 C-P class A cirrhotic patients

	N. of cases (%)	Months of follow-up Median (range)	p-value
Stable C-P class A	97 (36)	95 (60-144)	p=0.5
C-P class progression without HCC	71 (26)	95 (10-144)	
HCC development	104 (38)	98 (20-144)	

Table 3a. Logistic regression analyses of different variables with respect to clinical stability over time

Variables	Univariate model			Multivariate model		
	OR	95% C.I.	p-value	O.R	95% C.I.	p-value
Sex	1.2	0.69-2.07	0.50			
Age	0.9	0.89-0.94	<0.001	0.93	0.96-0.99	<0.001
BMI	1	0.92-1.06	0.9			
Etiology	1.3	0.67-2.49	0.47			
Diabetes	0.5	0.26-0.37	0.01	0.45	0.21-0.96	0.04
Varices*	0.23	0.14-0.38	<0.001	0.26	0.14-0.49	<0.001
Portal vein diameter	0.8	0.7-0.9	0.07			
Longitudinal size of the Spleen	0.98	0.97-0.99	0.06			
PLT	1.0	1.00-1.01	0.03	0.99	0.98-1.01	0.25
RBC	1.1	1.06-1.19	<0.001	1.09	0.99-1.16	0.19
Hb	1.0	0.9-1.1	0.52			
WBC	1.3	1.07-1.14	<0.001	1.08	1.01-1.16	0.42
AST	1.0	0.99-1.04	0.78			
ALT	1.0	1.01-1.02	0.64			
GGT	1.0	0.99-1.01	0.13			
Bilirubin	0.8	0.35-1.48	0.38			
Albumin	6.7	3.27-14.2	<0.001	0.35	0.16-0.76	0.01
Gamma globulin	0.3	0.14-0.46	<0.001	0.26	0.13-0.53	<0.001
Cholesterol	1.0	1.00-1.01	0.047	0.34	1.09-0.87	1.00
Triglycerides	1.0	0.99-1.00	0.10			
INR	1.0	0.99-1.03	0.13			
Creatinine	0.4	0.10-1.19	0.09			

Bold characters identify statistically significant variables at multivariate analysis

Abbreviations: BMI (body mass index) RBC (red blood cells), WBC (white blood cells), PTL (platelets), ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gamma glutamyltranspeptidase) INR (international normalized ratio).

*Varices: absent, small, medium and large size

Table 3b. Logistic regression analyses of different variables with respect to progression of C-P score

Variables	Univariate model			Multivariate model		
	OR	95% C.I.	p-value	O.R	95% C.I.	p-value
Sex	1.0	0.59-1.55	0.87			
Age	1.0	1.01-1.06	<0.01	1.03	0.99-1.06	0.07
BMI	1.1	0.94-1.07	0.82			
Etiology	2.4	1.35-4.31	<0.01	0.46	0.25-1.02	0.06
Diabetes	2.5	1.50-4.05	<0.001	1.69	0.91-3.21	0.09
Varices *	3.6	2.4-5.3	<0.001	3.4	2.1-5.4	<0.001
Portal vein diameter	1.3	0.8-1.6	0.08			
Longitudinal size of the Spleen	1.1	1.0-1.2	0.09			
PLT	1.0	0.97-0.99	<0.01	0.99	0.99-1.00	0.35
RBC	0.9	0.86-0.95	0.66			
Hb	0.9	0.8-1.1	0.26			
WBC	0.9	0.76-1.02	0.15			
AST	1.0	0.99-1.01	0.53			
ALT	1.0	0.99-1.00	0.03	0.99	0.99-1.03	0.40
GGT	1.0	0.98-1.05	0.06			
Bilirubin	1.6	0.86-3-15	0.12			
Albumin	3.56	0.18-6.74	<0.001	2.41	1.11-5.23	0.03
Gamma globulin	2.38	1.46-3.86	<0.001	1.75	0.94-3.22	0.02
Cholesterol	0.98	0.97-0.99	<0.01	0.98	0.97-0.99	0.01
Triglycerides	0.99	0.94-1.03	0.47			
INR	0.05	0.03-0.57	0.27			
Creatinine	0.86	0.34-2.16	0.76			

Bold characters identify statistically significant variables at multivariate analysis

Abbreviations: BMI (body mass index) RBC (red blood cells), Hb (Hemoglobin), WBC (white blood cells), PTL (platelets), ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gamma glutamyltranspeptidase) INR (international normalized ratio).

*Varices: absent, small, medium and large size

Table 3c. Logistic regression analyses of different variables with respect to HCC development

Variables	Univariate models			Multivariate model		
	OR	95% C.I.	p-value	OR	95% C.I.	p-value
Gender	1.6	0.95-2.72	0.074			
Age	1.0	1.01-1.07	0.002	1.04	1.01-1.07	<0.01
BMI	0.9	0.87-1.01	0.09			
Etiology	1.5	0.79-2.75	0.22			
Diabetes	0.9	0.54-1.53	0.73			
Varices *	1.0	0.8-1.4	0.93			
Portal vein diameter	0.9	0.8-1.1	0.77			
Longitudinal size of the Spleen	1.0	0.9-1.1	0.51			
PTL	1.0	0.97-1.04	0.13			
RBC	1.0	0.92-1.02	0.18			
Hb	0.9	0.8-1.0	0.21			
WBC	0.9	0.81-1.11	0.48			
Albumin	1.2	0.63-2.16	0.62			
Gamma globulin	3.2	1.86-5.44	<0.001	3.05	1.76-5.29	<0.001
AST	1.0	0.99-1.06	0.49			
ALT	1.0	0.99-1.04	0.87			
GGT	1.0	0.99-1.01	0.24			
Bilirubin	0.7	0.36-1.38	0.30			
Cholesterol	1.0	0.98-1.01	0.26			
Triglycerides	1.0	0.98-1.00	0.42			
INR	1.2	0.22-6.21	0.87			
Creatinine	0.8	0.32-2.29	0.75			

Bold characters identify statistically significant variables at multivariate analysis

Abbreviations: BMI (body mass index) RBC (red blood cells), WBC (white blood cells), PTL (platelets), ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gamma glutamyltranspeptidase) INR (international normalized ratio).

*Varices: absent, small, medium and large size

Table 3d. Logistic regression analyses of different variables with respect to death

Variables	Univariate model			Multivariate model		
	OR	95% C.I.	p-value	OR	95% C.I.	p-value
Gender	1.1	0.69-1.86	0.62			
Age, years	1.1	1.06-1.13	<0.001	1.09	1.06-1.13	<0.001
Etiology	1.2	0.63-2.07	0.58			
Diabetes	1.4	0.84-2.28	0.22			
Varices	1.4	1.1-1.9	0.02	1.27	0.9-1.79	0.16
Portal vein diameter	1.1	0.9-1.3	0.12			
Longitudinal size of the Spleen	1.1	1.0-1.2	0.07			
PLT	1.0	0.98-1.01	0.10			
RBC	1.0	0.93-1.03	0.31			
Hb	0.9	0.8-1.2	0.89			
WBC	0.9	0.74-1.01	0.71			
Albumin	3.3	1.73-6.47	<0.001	1.74	0.82-3.69	0.15
Gamma globulin	2.3	1.40-3.83	<0.001	2.078	1.03-3.72	0.01
AST	1.0	0.98-1.01	0.07			
ALT	1.0	0.97-1.02	0.18			
GGT	1.0	0.99-1.05	0.24			
Cholesterol	1.0	0.98-1.01	0.44			
Bilirubin	2.4	1.13-5.02	0.02	2.08	0.91-4.75	0.08
Triglycerides	1.0	0.99-1.03	0.51			
INR	1.6	0.05-3.66	0.36			
Creatinine mg/dl	1.8	1.05-8.56	0.47			

Bold characters identify statistically significant variables at multivariate analysis

Abbreviations: BMI (body mass index) RBC (red blood cells), Hb (Hemoglobine), WBC (white blood cells), PTL (platelets), ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gamma glutamyltranspeptidase) INR (international normalized ratio)

*Varices: absent, small, medium and large size

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