Hematologic indices improve with eradication of HCV in patients with cirrhosis and predict decompensation

Raffi Karagozian, Norman D. Grace, Amir A. Qamar

Brigham and Women's Hospital, Division of Gastroenterology, Hepatology and Endoscopy, Harvard Medical School, Boston, MA.

Abstract

Background : **Abnormal hematological indices (HI) are common in cirrhosis from hepatitis C virus (HCV). Eradication of HCV may ameliorate these abnormalities. The objectives of the current study were to assess whether HI improve with HCV eradication and whether they can predict prognosis in patients with cirrhosis during and after completion of antiviral therapy.**

Methods : **A retrospective cohort study of 153 patients with HCV cirrhosis treated with Peg-interferon and ribavirin was conducted. The primary endpoint was improvement in HI after successful antiviral therapy. The secondary outcome was clinical decompensation during and after completion of antiviral therapy and association with HI. A repeated measures 2-way ANOVA was performed to compare means. Multivariate analysis was used to identify predictors of clinical decompensation.**

Results : **One hundred fifty three patients met study criteria. The rate of sustained virological rate was 26%. Median follow-up was 55 months. Platelet and WBC counts improved with HCV eradication compared to those in whom treatment was unsuccessful ($p < 0.05$). On univariate analysis, the presence of thrombocytopenia was associated clinical decompensation prior to, on treatment and after completion of therapy. Thrombocytopenia (OR 14.8, p-value < 0.001) after completing treatment predicted clinical decompensation when controlled for albumin, MELD and age in multivariate analysis at 6 months after completion of therapy.**

Conclusions : **Platelet and leukocyte counts improve in patients with cirrhosis who respond to antiviral therapy against HCV. The presence of thrombocytopenia predicts decompensation on treatment and after completion of therapy.** (Acta gastroenterol. belg., **2014**, 77, **425-432**).

Key words : liver decompensation, hepatitis C, interferon, thrombocytopenia.

Introduction

Hematological indices are frequently abnormal in cirrhosis. Thrombocytopenia has been reported in 15-70% of patients with cirrhosis and portal hypertension, depending on the stage of disease (1). Leukopenia and anemia have also been reported in patients with cirrhosis at rates of 37-42% (2). The pathophysiology of hematological abnormalities in cirrhosis is complex and multifactorial. Hypersplenism secondary to portal hypertension is a major cause of abnormal hematological indices (HI). However, abnormalities may persist despite portal decompression, thus signifying the role of other factors (3). Studies in patients with chronic hepatitis C virus (HCV) suggest that it may cause direct bone marrow suppression and decreased thrombopoiesis (4). Increased destruction of platelets within the spleen and intrasplenic production of autoantibodies can also contribute to thrombocytopenia as well as other cytopenias (5).

There is limited data addressing the effect of successful eradication of HCV with antiviral therapy with peg-interferon (IFN) and ribavirin (RBV) on hematological indices. Few studies have addressed the effects of antiviral therapy on platelets with conflicting findings (6-8). These studies did not report the effects on hemoglobin and leukocytes and included patients who did not have cirrhosis. In a small study, Iga *et al*. followed platelet counts in 22 patients who completed six months of interferon based therapy (6). Twelve patients who responded to IFN therapy with clearance of HCV showed an increase in the platelet count, whereas the 10 patients who did not respond to IFN showed a reduction. In contrast, George *et al*. failed to demonstrate improvement in platelets on follow-up of 150 patients with cirrhosis who had reached sustained virologic response (SVR) (7). The HALT-C Trial reported improved platelet counts in 140 patients who achieved an SVR group compared to 386 patients (77 treatment relapse, 309 treatment non-responder) who failed treatment (8).

Thrombocytopenia has also been shown in previous studies to be associated with a reduced median survival in compensated cirrhosis (9). Thrombocytopenia and leukopenia in compensated cirrhosis have been demonstrated to be significantly associated with severe portal hypertension, hepatic decompensation, death and transplantation (2). As antiviral therapy is known to alter hematopoiesis, it is not known whether this may alter the capacity of abnormal HI to predict poor outcomes in cirrhosis associated with therapy. The objectives of this study were to assess if HI improve after HCV eradication and whether HI can predict hepatic decompensation in patients on treatment or who do not respond to therapy.

Methods

The study is a retrospective cohort study to evaluate the effects of antiviral therapy with Peg-interferon and ribavirin on hematological indices in hepatitis C patients

Correspondence to : Raffi Karagozian, M.D., Brigham and Women's Hospital, 75 Francis Street, Boston, MA, 02115. E-mail : Amir.A.Qamar@lahey.org

Submission date : 19/02/2014
Acceptance date : 16/09/2014

with cirrhosis and the ability of post treatment HI to predict prognosis. The Institutional Review Board at Partners Healthcare approved this study. A database was created by obtaining data from the Partners Research Patient Data Registry (RPDR). The RPDR is a centralized clinical data registry that gathers data from multiple hospitals within the Partners Healthcare Hospitals (which includes, but is not limited to, Brigham and Women's Hospital, Massachusetts General Hospital and Faulkner Hospital). The resulting data warehouse allows for user-defined queries to be performed to access both inpatient and outpatient data.

Individual chart review was performed on 427 patients identified in the RPDR who received treatment for HCV from January 1, 2001 to December 31, 2010. All patients meeting the following criteria were included in the study : 1) age older than 18 years ; 2) completed therapy with peg-interferon and ribavirin for 48 weeks ; 3) compensated liver disease defined as an absence of a history of jaundice, variceal hemorrhage, ascites and hepatic encephalopathy ; 4) Metavir score of 4 on liver biopsy 5) absence of co-existing liver disease such as hemochromatosis, a-1-antitrypsin deficiency, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic liver disease and non-alcoholic steatohepatitis. To ensure similar exposure to peg-interferon and its possible effects on hematopoiesis, only patients completing treatment for 48 weeks were considered. Exclusion criteria included patients : 1) with early stage fibrosis ; 2) post-liver transplant recipients ; 3) early termination of HCV therapy ; 4) co-infection with HIV.

Clinical and laboratory data were collected at baseline and throughout the follow-up period. Abnormal HI was defined as the occurrence of anemia (hemoglobin $\leq$ 13.5 g/dl for men and 11.5 g/dL for women), leukopenia (white blood cell count (WBC) $\leq$ 4,000/mm^3) or thrombocytopenia (platelet count $\leq$ 150,000/mm^3). These values were based on previous published reports evaluating the incidence and prevalence of abnormal HI in cirrhosis (2). The following clinical, biochemical, virological, and histological variables were collected at the time of initiation of therapy : age, race, AST, ALT, alkaline phosphatase, albumin, total bilirubin, prothrombin time, platelets, white count, hematocrit, hemoglobin, Child-Pugh score, MELD score, HCV genotype and baseline viral load. Data were collected from the time of initiation of antiviral therapy. Subsequent hematologic indices data were collected at 6-month intervals until death, transplant or last hospital visit. Each patient chart was manually reviewed by the authors.

The primary endpoint was improvement in HI after successful antiviral therapy. Secondary outcome was decompensation defined by the occurrence of new ascites requiring treatment, encephalopathy requiring treatment, variceal hemorrhage, or new development of jaundice by clinical exam or total bilirubin elevation $\geq$ 2.5 mg/dL. Subjects were followed until the decompensation event, liver transplantation, death or last day of follow-up. Standard criteria for assessing sustained virologic response, treatment relapse and treatment non responder were used (10).

Student's *t* test was used to compare means and a Fisher exact test to compare proportions. A repeated measures 2-way ANOVA was performed to compare means of HI at baseline and subsequent time points. Univariate analysis was performed to determine whether thrombocytopenia, leukopenia, or anemia were independently associated with decompensation. Multivariate logistic regression was performed to identify predictors for clinical decompensation. The analysis controlled for potential confounding factors : serum albumin, Child-Pugh class, MELD score, and age. All statistical analysis was performed by Statistical Program for Social Sciences (SPSS 20.0.0 ; SPSS Inc, Chicago, IL).

Results

Baseline patient characteristics

One hundred and fifty three patients with compensated HCV cirrhosis fulfilled the inclusion criteria. The mean age was 57 years, with 101 (66%) males. The cohort consisted of 79.7% White, 6.5% Hispanic, 3.9% African-American and 9.8% belonged to other ethnic groups. The mean body mass index was 28.4. Prior to initiating antiviral therapy, the mean Child Pugh score was 5.2 (range 5-7). More than three-fourths (76.5%) of the patients were infected with HCV genotype 1, while genotype 2, 3 and 4 infections occurred in 9.8%, 11.8% and 2% respectively. Eighty-two percent of patients were treatment naïve (Table 1).

Post therapy patient characteristics

Twenty-two patients had missing hematologic indices data or occurrence of decompensation on therapy resulting in a total of 131 patients who were analyzed for post therapy hepatic decompensation (Fig. 1). The median clinical follow-up of 55 months was longer than for each hematological index (Platelet 51 months, WBC 47 months, Hemoglobin 49 months). Thirty-four patients (26%) achieved an SVR. Ninety-seven patients failed to achieve a sustained virological response. There were no differences in mean hematologic indices, MELD score, Child Pugh score and serum albumin at six-month post completion of therapy between SVR and non-SVR groups (Table 2). Additional six-month post-therapy characteristics are shown in Table 2a. Among the 131 patients, 76 (58%) patients were documented to be on full dose of peg-interferon and ribavirin at the end of treatment. Thirty-eight (29%) patients were on a reduced dose of peg-interferon or ribavirin at the end of treatment. Documentation was not sufficient to determine dose reductions at the end of treatment in 17 (13%) patients.

Table 1. — **Selected patient and baseline characteristics of the cohort**

	Total Cohort (%) (n = 153)
Age (mean years)	56.8
Gender	
Male	101 (66)
Race	
White	122 (79.7)
African-American	6 (3.9)
Hispanic	10 (6.5)
Other	15 (9.8)
Biochemistry (mean)	
ALT (U/L)	92
AST (U/L)	85
Total Bilirubin (mg/dL)	0.8
Alkaline Phosphatase (U/L)	95
Albumin (g/dL)	3.96
MELD score	7.98
Child Pugh Score	5.2
INR	1.1
Hematologic Indices	
White Blood Cells ($\times 10^3$/mm^3)	6.2
Hemoglobin (gm/dL)	14.2
Platelets ($\times 10^3$/mm^3)	181
Baseline platelet count < 150,000//mm^3	45 (29.4)
Baseline platelet count < 100,000/mm^3	17 (11.1)
HCV genotype	
1*	117 (76.4)
2	15 (9.8)
3	18 (11.8)
4	3 (2)
Viral Load < 600,000	45 (29)
Treatment Naive	125 (82)

*54 patients were infected with genotype 1a, 46 with genotype 1b and 2 with both genotype 1a and 1b. Further genotype information was not available for 15 patients.

Long term improvement in thrombocytopenia and leukopenia with SVR

Thirty four percent (39/116) of patients from the non-SVR group compared to 19% (7/37) of patients in the SVR group (p = 0.10) had thrombocytopenia at baseline. Twenty percent (23/116) of patients from the non-SVR group compared to 3% (1/37) of patients in the SVR group had leukopenia at baseline (p = 0.01). Twenty eight percent (32/116) of patients from the non-SVR group compared to 24% (9/37) of patients in the SVR group (p = 0.83) had anemia at baseline. During follow-up, platelet (p = 0.02) and white blood cell counts (p = 0.04) significantly improved in patients with HCV eradication compared to those in whom treatment was unsuccessful (Fig. 2a, 2b). There was no difference in hemoglobin between SVR and non-SVR groups on follow-up (p = 0.96) (Fig. 2c). Further analysis of anemia was not done in the study based on the lack of significant difference in hemoglobin with HCV eradication. Missing data among the three hematologic indices varied on follow-up thus accounting for the different number of patients followed.

Normalization of hematological indices after achievement of SVR

Thrombocytopenia resolved from baseline in patients with SVR compared to those without a response to treatment at 18 months and 36 months after initiating treatment. At 18 months, 42.8% (3/7) of the SVR patients had normalization of platelet counts compared to 15% (5/34) of the non-SVR patients. (p = 0.09). At 36 months, 60% (3/5) of the SVR patients had normalization of platelet counts compared to 12.1% (4/33) of the non-SVR patients (p = 0.02). No improvement in leukopenia was observed on follow-up. However, only one patient with leukopenia prior to initiating antiviral therapy achieved an SVR.

Baseline thrombocytopenia and on treatment hepatic decompensation

Fattovich et al's platelet count cutoff of 100,000/mm^3 was used to analyze on treatment decompensation. On treatment hepatic decompensation occurred in a significantly higher proportion of patients with baseline platelet counts less than 100,000/mm^3 (n = 8/17, 47.1%) compared to patients with higher counts (n = 3/136, 2.2%), p-value 0.00001. Multivariate analysis controlled for baseline Child Pugh class and MELD score showed only a platelet count of less than 100,000/mm^3 to be a predictor of on treatment hepatic decompensation (Table 3).

Baseline thrombocytopenia and long term hepatic decompensation

The occurrence of long term hepatic decompensation was higher in patients with thrombocytopenia defined as a platelet count < 150,000/mm^3 55.6% (n = 25/45) compared with patients with normal baseline platelet counts 9.3% (n = 10/108), p-value 0.0001. On Kaplan Meier analysis, none of the patients who achieved SVR suffered hepatic decompensation (6 patients in the thrombocytopenia group and 31 patients in the baseline normal platelets group). Among patients who did not achieve an SVR, hepatic decompensation was more likely to occur in patients with thrombocytopenia at baseline 64.1% (n = 25/39) compared to patients with normal platelet counts 13% (n = 10/77) (Fig. 3) (p = 0.0001).

The risk of long-term hepatic decompensation was also found to be significantly higher when an even lower baseline platelet cutoff of 100,000/mm^3 was analyzed. For patients with baseline platelet counts < 100,000/mm^3, 82.3% (n = 14/17) suffered hepatic decompensation. In patients with baseline platelet counts > 100,000/mm^3, 15.4% (n = 21/136) developed hepatic decompensation (p = 0.0001). There was only one patient with a

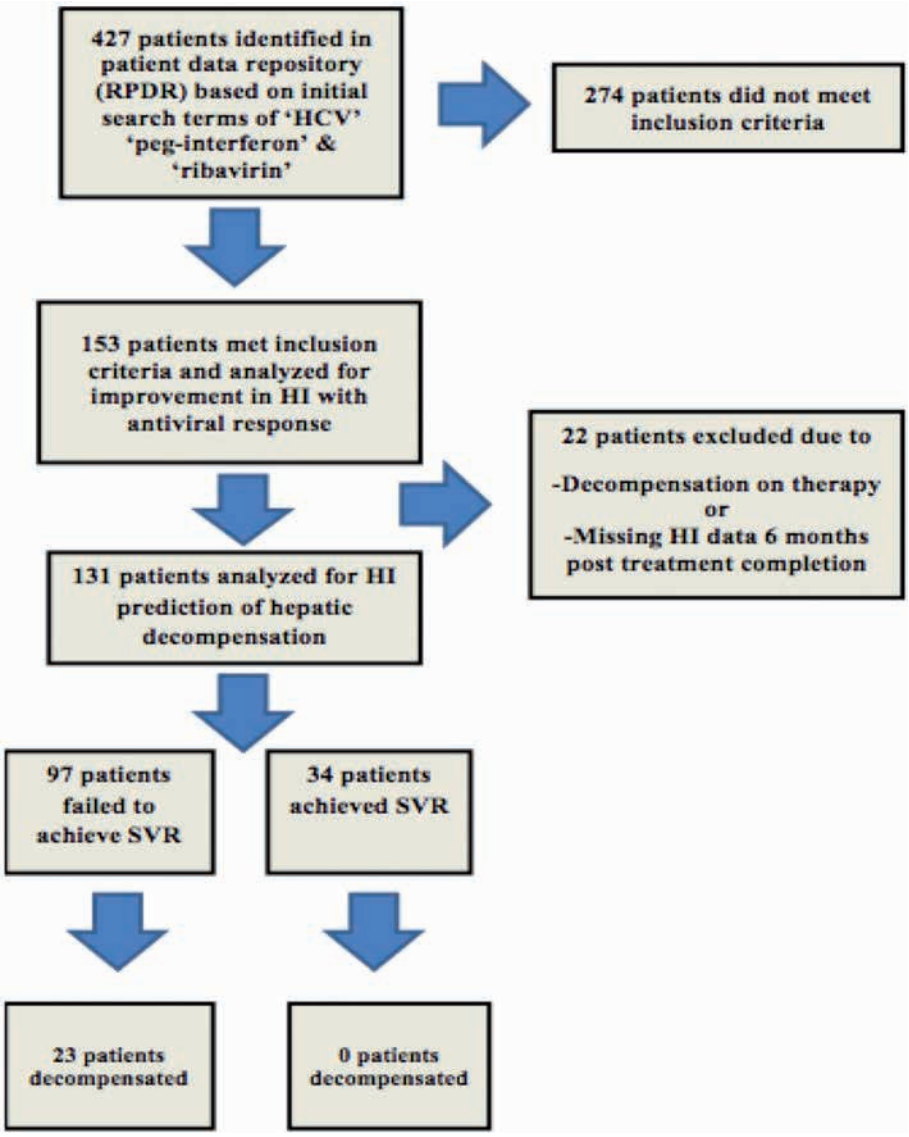
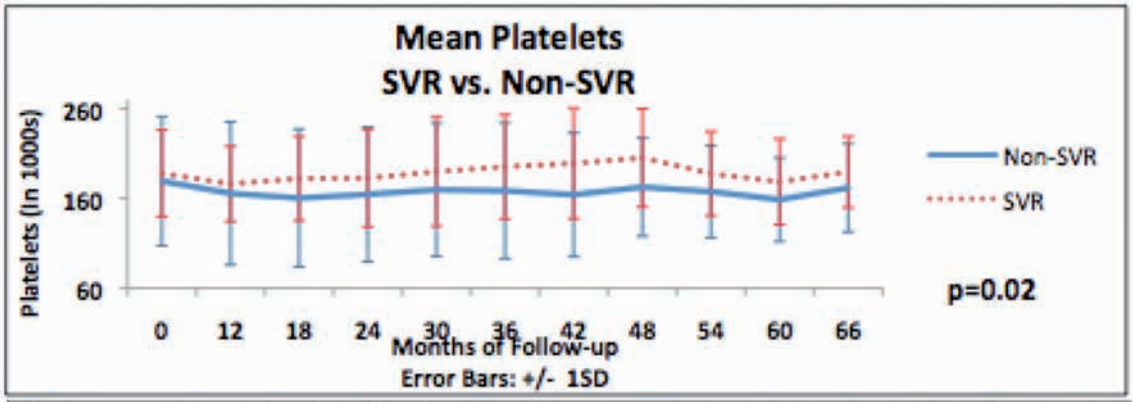


Fig. 1. — Patients included in study (HI : hematologic indices)

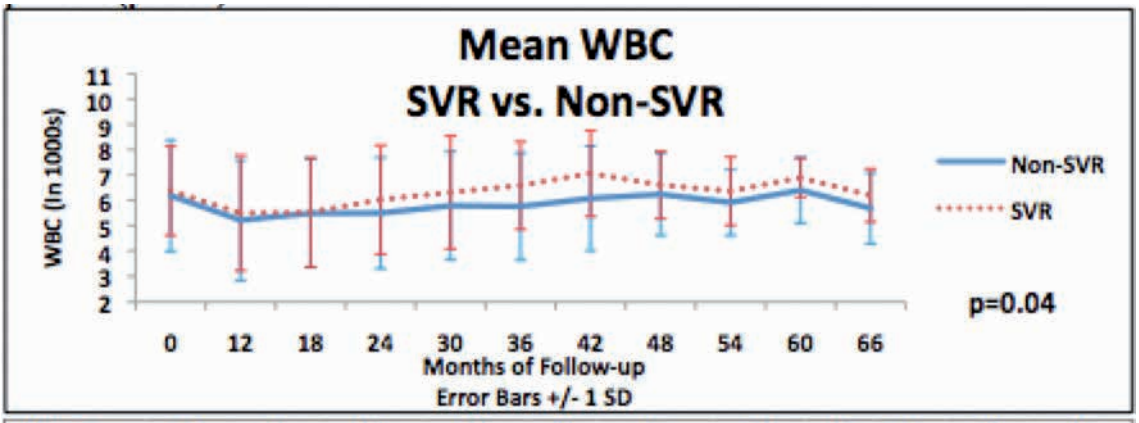
Table 2. — **Patient Characteristics Six-Months Post Completion of Therapy. Patients who decompensated on therapy or with missing data were excluded from the analysis**

n = 131	SVR (%) 34/131 (26)	Non-SVR (%) 97/131 (74)	p value
Age (mean)	56.9	57.4	0.69
Hematologic Indices 6 months post therapy (mean)			
Platelets (× 1000/mm^3)	183	169	0.21
WBC (× 1000/mm^3)	5.5	5.6	0.85
HGB (gm/dL)	13.0	13.7	0.07
MELD Score	8.8	7.4	0.25
Child Pugh Score	5.1	5.2	0.70
Albumin (g/dl)	3.8	4.0	0.21



Month	0	12	18	24	30	36	42	48	54	60	66
Patients											
SVR	37	34	34	33	30	27	21	15	9	8	5
Non-SVR	116	113	111	106	98	88	75	58	47	33	17

Fig. 2a. — Time course of mean (+/- SD) platelet counts in patients studied. Repeated measures 2-way ANOVA showed a significant difference in mean platelet counts between SVR and non-SVR patients (p = 0.02).



Month	0	12	18	24	30	36	42	48	54	60	66
Patients											
SVR	37	36	34	33	30	26	20	13	11	5	1
Non-SVR	116	115	111	108	96	88	73	51	36	20	10

Fig. 2b. — Time course of mean (+/- SD) WBCs in patients studied. Repeated measures 2-way ANOVA showed a significant difference in mean WBC between SVR and non-SVR patients (p = 0.04).

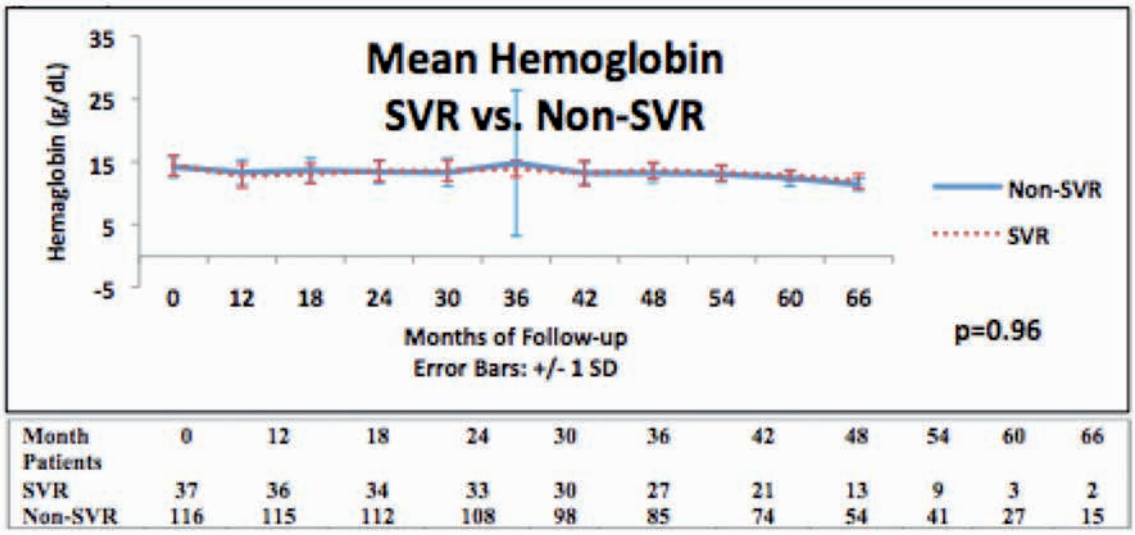
Table 3. — **Adjusted Odds Ratio for On-Treatment Decompensation based on baseline treatment variables (n = 153)**

	Adjusted OR (95%CI)	P-Value
Platelet < 100,000	5.86 (1.49-22.98)	0.01
Child-Pugh class (A vs B)	0.25 (0.06-1.04)	0.06
MELD Score	1.1 (0.99-1.25)	0.07

baseline platelet count < 100,000/mm^3 who achieved an SVR. The patient did not suffer long term hepatic decompensation. Similarly, none of the patients with baseline platelet counts > 100,000/mm^3 who achieved an SVR suffered long term hepatic decompensation.

Post treatment HI and long term occurrence of hepatic decompensation

Decompensation occurred in 23 of 131(17.5%) patients on follow-up (Table 4). In patients who did not achieve an SVR on follow-up, decompensation occurred



Month	0	12	18	24	30	36	42	48	54	60	66
Patients											
SVR	37	36	34	33	30	27	21	13	9	3	2
Non-SVR	116	115	112	108	98	85	74	54	41	27	15

Fig. 2c. — Time course of mean (+/- SD) hemoglobin in patients studied. Repeated measures 2-way ANOVA showed no significant difference in mean Hgb between SVR and non-SVR (p = 0.96).

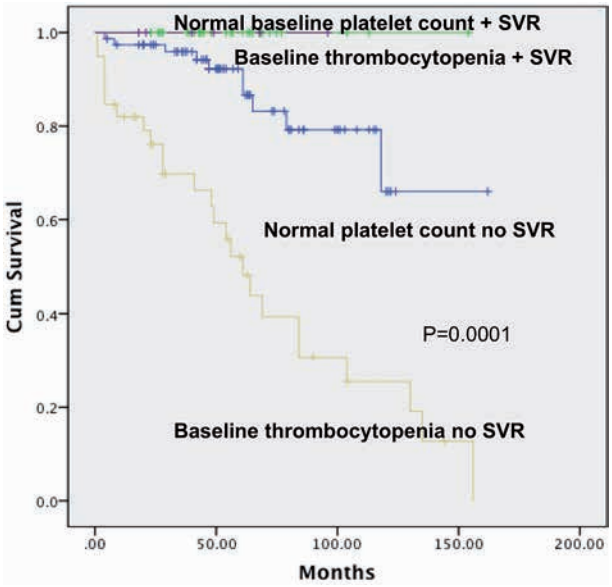


Fig. 3. — Kaplan-Meier analysis of hepatic decompensation related to SVR and thrombocytopenia.

in 23 of 97(23.7%). Among patients who decompensated, seventeen developed jaundice (73.9%), thirteen patients developed ascites (56.5%), eleven patients developed encephalopathy (47.8%), and six patients had variceal hemorrhage (26.1%) on follow-up. No patient who achieved an SVR had hepatic decompensation on follow-up. Six patients (6.2%), all from the non-SVR group, developed HCC on follow up (p > 0.05) (Table 4). On univariate analysis, when excluding SVR patients, the presence of thrombocytopenia (OR 15.6, 95% CI 4.2-58.5, p-value < 0.001) 6 months after completing therapy was significantly associated with clinical decompensation while leukopenia (OR 2.6, 95% CI 0.96-6.9 p-value 0.06) and anemia (OR 2.3, 95% CI 0.88-5.9, p-value

Table 4. — **Clinical Decompensation and HCC : non-SVRPatients**[a]

	Non-SVR n = 97
Patients with ≥ 1 clinical decompensation event	23
Decompensation Events	
Jaundice*	17
Ascites**	13
Hepatic Encephalopathy***	11
Variceal Hemorrhage****	6
HCC	6

[a] 9 patients had a single decompensating event, 14 patients had ≥ two decompensating events on follow-up.
* defined as jaundice by clinical exam or total bilirubin ≥ 2.5 mg/dl.
** defined as ascites requiring treatment.
*** defined as encephalopathy requiring medications.
***** as documented in patient charts.

0.09) were not (Table 5a). Multivariate analysis of variables at 6 months after completion of therapy, excluding SVR patients, continued to show thrombocytopenia (OR 14.8, 95% CI 3.94-55.3, p-value < 0.001) to predict clinical decompensation when controlled for albumin (OR 0.50, p-value 0.27), MELD (OR 1.1, p-value 0.63) and age (OR 0.98, p-value 0.54) (Table 5b).

Discussion

The natural history of hematologic indices after treatment for HCV has not been well characterized and the available literature reports conflicting results (6-8). In contrast to previous studies, we chose to obtain data points at six month intervals and analyzed for differences on long-term follow-up. Using a repeated measures ANOVA, over long-term follow-up there was a significant increase in platelets and leukocytes in patients who have achieved SVR compared to those that did not. There

Table 5a. — **Unadjusted Odds Ratio for Overall Decompensation based on post treatment hematologic indices (6 months after completion of therapy) in non-SVR patients**

	Unadjusted OR (95%CI)	P-Value
Thrombocytopenia	15.6 (4.2, 58.5)	< 0.001
Leukopenia	2.6 (0.96, 6.9)	0.06
Anemia	2.3 (0.88, 5.9)	0.09

Table 5b. — **Adjusted Odds Ratio for Decompensation based on post treatment variables (at 6 months post completion of therapy) in non-SVR patients (n=97). Patients who achieved an SVR were excluded**

	Adjusted OR (95%CI)	P-Value
Presence of Thrombocytopenia	14.8 (3.94-55.3)	< 0.001
Serum Albumin (g/dL)	0.50 (0.15-1.7)	0.27
MELD Score	1.1 (0.75-1.6)	0.63
Age	0.98 (0.91-1.05)	0.54

may be several explanations for this observation. Firstly, with eradication of the virus, the direct bone marrow suppressive effect is lost (11). Secondly, eradication of HCV may also improve portal hypertension as has been shown by previous authors. Rincon *et al*. demonstrated a reduction in portal hypertension in patients who achieved a response to antiviral therapy (12). Reduction of portal hypertension long term may reduce splenic sequestration and gradually improve hematologic abnormalities. A progressive decline in liver function in patients with HCV-related chronic liver disease is also associated with a decrease in thrombopoietin production, which may be halted with HCV eradication (13-14). Notably, anemia was not found to improve with viral eradication. This would suggest that HCV does not have a major role in the occurrence of anemia in patients with cirrhosis. Furthermore, the bone marrow suppressive effects of interferon and ribavirin are not likely to have influenced the findings in this study due to the long duration of follow-up after discontinuation of therapy. Missing data between the three hematological indices varied due to different reasons for patients to have a single index to be assessed.

Predicting clinical outcomes in patients with compensated cirrhosis from HCV can be challenging. Most previous studies have used baseline parameters to predict long term outcomes (15-21). The use of Child Pugh or MELD scores is limited as most patients who complete antiviral therapy are well compensated. The presence of esophageal varices on an upper endoscopy indicates clinically significant portal hypertension, but the detection of varices requires an invasive study (22). As previously reported, baseline thrombocytopenia and leukopenia are significant predictors for clinical decompensation (2).

In the present study, the ability of the HI to predict *on treatment and l*ong-term outcome was assessed. The presence of thrombocytopenia (platelet count less than 150,000/mm^3) at baseline and six months after completion of therapy was significantly associated clinical decompensation. Leukopenia and anemia after completion of therapy were not significant predictors for hepatic decompensation. Interestingly, none of the patients who achieved an SVR, developed HCC. This observation is consistent with other studies that have shown a lower risk of hepatocellular carcinoma in patients who respond to antiviral therapy (23,24,25). When assessing post-therapy predictors (six months after completion of therapy) of hepatic decompensation in patients who did not achieve an SVR, the presence of thrombocytopenia remained the only significant predictor for decompensation when controlled for age, serum albumin and MELD score. These findings suggest that persistent thrombocytopenia in patients who do not respond to antiviral therapy is superior to MELD score and hypoalbuminemia in predicting hepatic decompensation on follow-up. Similar findings were reported by the HALT-C investigators. Dienstag *et al*. evaluated 1,024 patients with either advanced fibrosis or cirrhosis who received peginterferon and placebo (26). During a median follow-up of 6 years, patients with a platelet count less than 100,000/mm^3 were eleven times more likely to experience a decompensation event then patients with a platelet count greater than 200,00/mm^3. Ghany *et al*. from the same group evaluated 470 patients with advanced fibrosis or cirrhosis from the same study who did not receive maintenance peginterferon therapy and showed the cumulative incidence of clinical decompensation was significantly greater when patients' platelet counts were less than 150,000 mm^3 at baseline compared to patients with counts greater than this threshold (27). The current study only assessed patients with cirrhosis and no advanced fibrosis patients were not included likely giving a more accurate assessment of thrombocytopenia as a predictor of clinical decompensation in this population. Furthermore, the novelty of this study is demonstrating the risk of hepatic decompensation as a function of the HI in responders versus non-responders, independent of the efficacy of the treatment regimen used for HCV.

Baseline thrombocytopenia (< 150,000/mm^3) was also found to be a predictor of decompensation on treatment with peginterferon and ribavirin. It remained significant when controlled for Child-Pugh class and MELD score at baseline. Previous studies have assessed for predictors of

decompensation on treatment with peginterferon and ribavirin. Baseline MELD score, albumin < 35 g/dl, platelet count < 100,000/mm^3 have been associated with poor outcome (28,29).

Limitations of this study include the retrospective collection of data, which may result in misclassification bias and unavailability of certain data. The follow-up in the current study ended in 2010. This was prior to the FDA approval of protease inhibitors in 2011 and general availability of IL28B genotype testing or assessment of interferon lambda 4 genetic variation. This limits additional analysis of the effect of SVR on improvement of hematological indices.

The effect of obesity on the current findings, particularly the risk of hepatic decompensation cannot be assessed due to lack of data. Only six patients in the cohort were African-American, none of whom achieved an SVR. This limits the ability to generalize the current findings.

In summary the eradication of HCV in patients with compensated cirrhosis is associated with improvements in platelet and leukocyte counts. Thrombocytopenia before, on and after antiviral therapy is a strong predictor of hepatic decompensation in patients with compensated cirrhosis. Patients with cirrhosis with persistent thrombocytopenia after unsuccessful antiviral therapy may benefit from enhanced follow-up care for decompensation and early consideration for direct acting antiviral agents.

Author contributions

Raffi Karagozian : Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis.

Norman D. Grace : Study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

Amir A. Qamar : Study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, administrative, technical, and material support, study supervision.

References

1. QAMAR A.A., GRACE N.D. Abnormal hematologic indices in cirrhosis. *Can. J. Gastroenterol.*, 2009, **23** : 441-445.
2. QAMAR A.A., GRACE N.D., GROSZMANN R.J. *et al*. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. *Clin. Gastroenterol. Hepatol.*, 2009, **7** : 689-695.
3. AFDHAL N.H., ESTABAN R. Introduction : thrombocytopenia in chronic liver disease - treatment implications and novel approaches. *Aliment. Pharmacol. Ther.*, 2007, 26 Suppl 1 : 1-4.
4. WANG C.S., YAO W.J., WANG S.T. *et al*. Strong association of hepatitis C virus (HCV) infection and thrombocytopenia : implications from a survey of a community with hyperendemic HCV infection. *Clin. Infect. Dis.*, 2004, **39** : 790-796.
5. AFDHAL N.H., MCHUTCHISON J., BROWN R. *et al*. Thrombocytopenia associated with chronic liver disease. *Journal of Hepatol.*, 2008, **48** : 1000-1007.
6. IGA D., TOMIMATSU M., ENDO H. *et al*. Improvement of thrombocytopenia with disappearance of HCV RNA in patients treated by interferon-α therapy : possible etiology of HCV-associated immune thrombocytopenia. *Eur. J. Haematol.*, 2005, **75** : 417-423.
7. GEORGE S.L., BACON B.R., BRUNT E.M. *et al*. Clinical virologic, histologic, and biochemical outcomes after successful HCV Therapy : a 5-year follow-up of 150 patients. *Hepatology*, 2009, **49** : 729-738.
8. MORGAN T.R., GHANY M.G., KIM H.Y. *et al*. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. *Hepatology*, 2010, **52** : 833-844.
9. D'AMICO G., MORABITO A., PAGLIARO L. *et al*. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig. Dis. Sci.*, 1986, **31** : 468-475.
10. GHANY M.G., NELSON D.R., STRADER D.B. *et al*. An update on treatment of genotype 1 chronic hepatitis C virus infection :, 2011 practice guideline by American Association of the Study of Liver Diseases. *Hepatology*, 2011, **54** : 1433-1444.
11. WEKSLER B.B. Review article : the pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. *Aliment. Pharmacol. Ther.*, 2007, **26** Suppl 1 : 13-19.
12. RINCON D., RIPOLL C., LOIACONO O. *et al*. Antiviral therapy decreases hepatic venous pressure gradient in patients with chronic hepatitis C and advanced fibrosis. *Am. J. Gastroenterol.*, 2006, **101** : 2269-2274.
13. GOULIS J., CHAU T.N., JORDAN S. *et al*. Thrombopoietin concentrations are low in patients with cirrhosis and thrombocytopenia are restored after orthotopic liver transplantation. *Gut*, 1999, **44** : 754-758.
14. GIANNINI E., BOTTA F., BORRA P. *et al*. Relationship between thrombopoietin serum levels and liver function in patients with chronic liver disease related to hepatitis C virus infection. *Am. J. Gastroenterol.*, 2003, **98** : 2516-2520.
15. GHANY M.G., LOK A.S., EVERHART JE. *et al*. Predicting clinical and histologic outcomes based on standard laboratory tests in advanced chronic hepatitis C. *Gastroenterology*, 2010, **138** : 136-146.
16. LOK A.S., GHANY M.G., GOODMAN Z.D. *et al*. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests : results of the HALT-C cohort. *Hepatology*, 2005, **42** : 282-292.
17. LEROY V., HILLERET M.N., STURM N. *et al*. Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C. *J. Hepatol.*, 2007, **46** : 775-782.
18. WAI C.T., GREENSON J.K., FONTANA R.J. *et al*. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology*, 2003, **38** : 518-526.
19. FORNS X., AMPURDANES S., LLOVET J.M. *et al*. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology*, 2002, **36** : 986-992.
20. IMBERT-BISMUT F., RATZIU V., PIERONI L. *et al*. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection : a prospective study. *Lancet*, 2001, **357** : 1069-1075.
21. GHANY M.G., KLEINER D.E., ALTER H. *et al*. Progression of fibrosis in chronic hepatitis C. *Gastroenterology*, 2003, **124** : 97-104.
22. GARCIA-TSAO G., GROSZMANN R.J., FISHER R.L. *et al*. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology*, 1985, **5** : 419-424.
23. MORGAN R.L., BAACK B., SMITH B.D. *et al*. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma : a meta-analysis of observational studies. *Ann. Intern. Med.*, 2013, **158** (5 Pt 1) : 329-337.
24. OGAWA E., FURUSYO N., KAJIWARA E. *et al*. Efficacy of pegylated interferon alpha 2-b and ribavirin treatment in patients with chronic hepatitis C : a prospective, multicenter study. *J. Hepatol.*, 2013, **58** (3) : 495-501.
25. NG V., SAAB S. Effects of sustained virologic response on outcomes of patients with chronic hepatitis C. *Clin. Gastroenterol. Hepatol.*, 2011, **9** (11) : 9323-930.
26. DIENSTAG J.L., GHANY M.G., MORGAN T.R. *et al*. A prospective study of the rate of progression in compensated histologically advanced chronic hepatitis C. *Hepatology*, 2011, **54** : 396-405.
27. GHANY M.G., KIM H.Y., STODDARD A. *et al*. Predicting clinical outcomes using baseline and follow-up laboratory data from the hepatitis C long-term treatment against cirrhosis trial. *Hepatology*, 2011, **54** : 1527-1537.
28. DULTZ G., SEELHOF M., HERMANN E. *et al*. Baseline MELD score predicts hepatic decompensation during antiviral therapy in patients with chronic hepatitis C and advanced cirrhosis. *PLoS One*, 2013, **8** (8) : e71262.
29. HEZODE C., FONTAINE H., DORIVAL C. *et al*. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. *J. Hepatol.*, 2013, **59** (3) : 434-41.