

Effect of spleen operation on antiviral treatment in hepatitis C virus-related cirrhotic patients

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Abstract

AIM: To investigate the impact of spleen operation (SO) on interferon- α (IFN- α)-based antiviral treatment in patients with hepatitis C virus (HCV)-related cirrhosis.

METHODS: Studies were systematically identified by searching electronic databases including MEDLINE, Cochrane Library, Elsevier, and Embase up to September 30, 2013, and relevant clinical studies were reviewed. Sustained virological response (SVR) rate and adherence to therapy were taken as the endpoints of interest.

RESULTS: A total of 603 patients from 16 studies were included in the systematic review. Of 372 patients who underwent SO followed by antiviral treatment, the total SVR rate was 39.5%. SVR was associated with HCV genotypes 2/3 (OR = 10.84; 95%CI: 5.47-21.47; $P < 0.00001$). IFN- α dose needed to be reduced in 29.4%, and IFN- α -based therapy was discontinued in 11.5% of patients. Analysis of controlled studies showed that SVRs were achieved in 34.1% of patients with SO and 31.1% of patients without SO. SO had no effect on the SVR rate in cirrhotic patients with genotype 1 HCV infection (OR = 1.28; 95%CI: 0.51-3.22; $P = 0.60$), but improved the SVR rate in patients with genotypes 2/3 infection, though the difference was not significant (OR = 0.36; 95%CI: 0.13-1.02; $P = 0.05$).

CONCLUSION: SO combined with IFN- α -based antiviral therapy may be suitable in cirrhotic patients with genotypes 2/3 HCV infection, but not in those with genotype 1 infection.

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Key words: Hepatitis C virus cirrhosis; Interferon, Ribavirin; Splenectomy; Partial splenic embolization

Core tip: Hematologic abnormalities caused by hypersplenism and interferon- α (IFN- α) severely affect IFN- α -based therapy in cirrhotic patients with hepatitis C virus (HCV) infection. Splenectomy and partial splenic embolization followed by IFN- α -based therapy have been increasingly performed to address cytopenias, including thrombocytopenia, in patients with HCV-related cirrhosis with hypersplenism. However, the therapeutic effect and long-term safety of such treatments remain controversial. We performed a systematic review and demonstrated that spleen operation can improve hematologic parameters before and during IFN- α -based antiviral therapy in cirrhotic patients infected with HCV. However, this treatment is more suitable for patients

with genotypes 2/3 HCV infection than for those with genotype 1.

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INTRODUCTION

The World Health Organization estimated that about 170 million persons worldwide might be infected with hepatitis C virus (HCV)^[1]. Over a 25-30-year period, 5%-25% of patients with chronic HCV infection will develop cirrhosis^[2,3]. Patients with HCV-related cirrhosis develop hepatic decompensation at a rate of 30% over 10 years, and hepatocellular carcinoma (HCC) at an estimated incidence of 3% per annum in North America, Europe, and Australia, and 8% in Asia and Africa^[4,5]. HCV eradication is the only therapeutic intervention able to delay or halt disease progression and improve the quality of life of infected patients. In patients with compensated cirrhosis, sustained virological response (SVR) is associated with a decreased incidence of end-stage liver diseases, including decompensated cirrhosis and HCC^[6].

In the past two decades, interferon- α (IFN- α)-based administration has been increasingly applied for chronic HCV infection. Moreover, a combination of pegylated IFN (PegIFN) α and ribavirin (RBV) has become the standard treatment, resulting in a SVR in 65%-82% of patients with genotypes 2 and 3 HCV, and 40%-54% of patients with genotype 1^[7]. However, cirrhosis has long been considered to be one of the strongest negative predictors of antiviral treatment outcomes^[8]. A landmark, prospective, randomized trial reported that the highest SVR rate (32%) was obtained in patients treated with PegIFN- α 180 μ g/wk, compared with those treated with conventional IFN- α -2a 3 MU three times weekly or PegIFN- α 90 μ g/wk, with no significant difference in the tolerance of the regimens among cirrhotic patients^[9]. Helbling *et al*^[10] reported an SVR rate of 32% for HCV genotypes 1/4 and 58% for genotypes 2/3 in patients with advanced fibrosis/cirrhosis receiving PegIFN- α -2a 180 μ g/wk and RBV 600-1200 mg/d.

Why do cirrhotic patients achieve such a low SVR? Cirrhotic patients are often men, of older age, and with high alcohol consumption, and commonly experience comorbidities such as obesity and diabetes mellitus, which negatively influence the safety and efficacy of IFN- α -based treatment^[11]. Importantly, hematologic abnormalities caused by hypersplenism and IFN- α severely affect adherence to antiviral therapy, and it can be difficult to maintain the IFN- α dose in cirrhotic patients complicated by hypersplenism. Thrombocytopenia and

neutropenia associated with hypersplenism can develop and/or be exacerbated following IFN- α therapy, possibly necessitating its discontinuation. In addition, the initiation of IFN- α therapy may be difficult in some of these patients^[12]. Feng *et al*^[13] found that 66.7% of cirrhotic patients who discontinued antiviral therapy did so because of significant neutropenia and thrombocytopenia.

As a novel anti-HCV strategy, direct-acting antiviral agents (DAAs) have received increasing attention in recent years^[14]. Some new, IFN-free administration protocols have also been used in clinical trials and achieved good outcomes^[15]. However, their relatively short period in clinical practice, less experience in cirrhotic patients, and higher costs mean that it will be difficult to administer antiviral treatment with DAAs in HCV-related cirrhotic patients worldwide, especially in developing countries, in the near future. It is therefore important to increase the rate of SVR to IFN- α -based therapy in patients with cirrhosis.

Splenectomy and partial splenic embolization (PSE) (collectively referred to as spleen operation, SO) followed by IFN- α -based therapy have been performed to address cytopenias, including thrombocytopenia, in patients with HCV-related cirrhosis with hypersplenism^[16]. However, the therapeutic effect and long-term safety of such treatments remain controversial. We therefore conducted a systematic review to clarify the impact of SO on antiviral treatment in patients with HCV-related cirrhosis.

MATERIALS AND METHODS

Literature retrieval

We searched the PubMed, Cochrane Library, Elsevier (ScienceDirect OnLine), and Embase databases using electronic and manual strategies for publications reporting the effects of splenectomy or PSE on anti-HCV treatment. Eligible trials were identified up to September 30, 2013, by electronic search. Manual search was used to follow references in identified trials. The terms "hepatitis C" or "HCV" and "interferon" and "splenectomy" or "splenic embolization" were used as search terms.

Inclusion and exclusion criteria

The inclusion and exclusion criteria were determined by all authors. Studies were considered for inclusion if they met the following criteria: (1) English or Chinese language; (2) participants with HCV-related cirrhosis; (3) splenectomy or PSE before IFN- α -based antiviral treatment; and (4) published in peer-reviewed journals as full papers. Studies were excluded if they involved: (1) unconfirmed HCV infection; (2) case reports or reviews; (3) *in vitro* or animal studies; (4) participants co-infected with other viruses; and (5) liver transplantation. In the event of duplicate reports of the same study subjects, we included the most recent one.

Data extraction

Data were extracted independently by two investigators

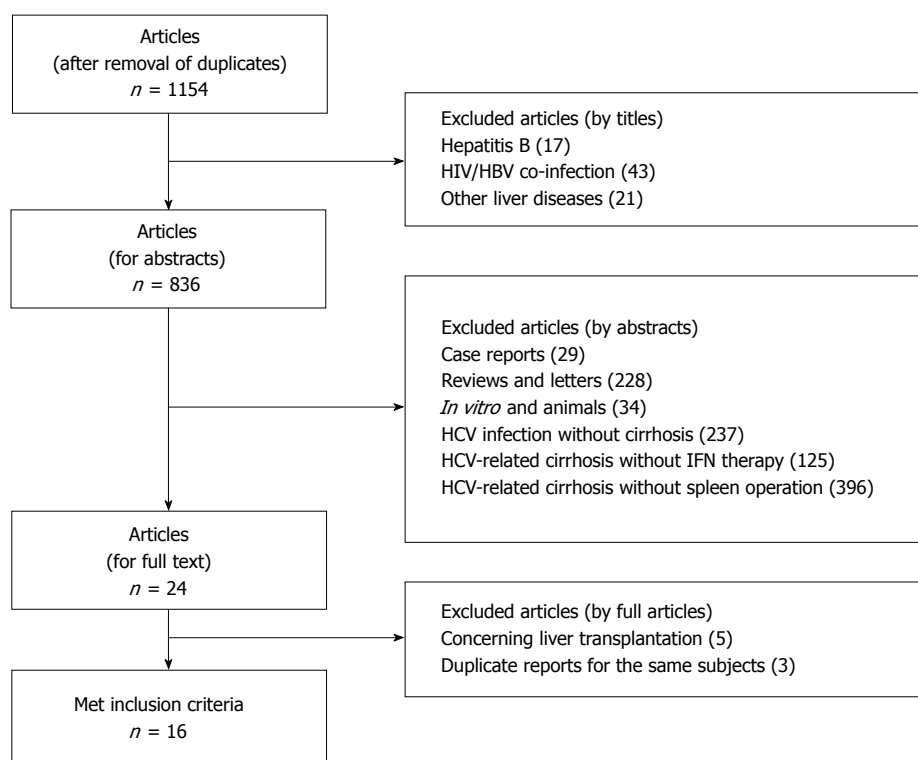


Figure 1 Flowchart of selection of studies for inclusion.

(FB and ZW). Inconsistent data were discussed with the other authors when necessary. Consensus was achieved for all data inclusion before analysis. The following data were extracted: first author, publication year, number of patients, study design, hematologic parameters pre-/post-operation, and protocols, outcomes and adverse effects of therapy. The primary outcome of interest was SVR rate. Additional data were obtained through direct communication with the investigators when necessary.

Data synthesis and statistical analysis

Meta-analysis was performed using Review Manager 5.2 (The Cochrane Collaboration, Oxford, United Kingdom). Dichotomous variable data are presented as odds ratio (OR) with 95%CI. χ^2 test was used to assess the heterogeneity. An I^2 value < 25% was regarded as no heterogeneity. A fixed-effects model was used when no significant heterogeneity existed among the studies analyzed; otherwise a random-effects model was used. The Mantel-Haenszel method was used to pool the effects. A P value < 0.05 was considered to be significant.

RESULTS

Literature review

Electronic and manual searches identified a total of 1154 citations. After review of the titles and abstracts, 1130 citations were excluded according to the eligibility and ineligibility criteria. The remaining 24 studies were selected for full article review. After careful examination of the full texts, eight studies were excluded because of liver

transplantation or duplicate reports for the same subjects. Sixteen studies were thus included in this systematic review (Figure 1)^[11,17-31]. There was full concordance between the two independent reviewers with respect to the final inclusion and exclusion of the studies reviewed.

Characteristics of included studies and antiviral treatment schedules

As shown in Table 1, among the 16 studies included in this review, 10 were from Japan, three from China, two from the United States and one from Spain. Seven were controlled, clinical studies, and nine were uncontrolled, retrospective, cohort studies. Among a total of 603 patients who received IFN- α and RBV treatment, 372 underwent prior SO. There were 11 and 4 studies where patients underwent splenectomy or PSE, respectively, and splenectomy and PSE were compared in one study.

PegIFN- α (2a or 2b) and conventional IFN- α were used in all participants. PegIFN- α combined with RBV was administered in 90.9% (338/372) of patients with SO plus IFN- α -based antiviral treatment. The majority of patients with HCV genotypes 1 and 2/3 were treated for 48 and 24 wk, respectively. Based on patient request and early virological response, a minority of patients increased the duration of antiviral therapy^[17,24]. The initial dosages of IFN- α and RBV are shown in Table 1. The dosages were adjusted if necessary, based on the adverse effects.

Characteristics of patients with SO and IFN combination treatment

The demographic characteristics of the subjects who

Table 1 Characteristics of included studies and schedules of antiviral treatment

Ref.	Number of patients, n (total/SO + IFN ¹)	Country	Study design	Spleen operation	Antiviral agents	Doses of IFN and RBV	Therapy duration
Aizawa <i>et al</i> ^[17] , 2013	90/30	Japan	Retrospective, controlled	Splenectomy (2 PSE)	PegIFN- α -2a or PegIFN- α -2b + RBV	PegIFN- α -2a: 180 ug/wk; PegIFN- α -2b: 1.0-1.5 μ g/kg per week; RBV: 600-1000 mg/d	GT 1: at least 48 wk; GT 2/3: at least 24 wk
Akahoshi <i>et al</i> ^[18] , 2012	100/97	Japan	Retrospective, cohort	Splenectomy	PegIFN- α -2b + RBV	PegIFN- α -2b: 1.5 μ g/kg per week; RBV: 600-1000 mg/d	GT 1: 48 wk; GT 2/3: 24 wk
Hayashi <i>et al</i> ^[11] , 2006	6/6	United States	Retrospective, cohort	Splenectomy	PegIFN- α -2b + RBV	PegIFN- α -2b: 1.5 μ g/kg per week; RBV: 600-1000 mg/d	GT 1: 48 wk; GT 2/3: 24 wk
Ikezawa <i>et al</i> ^[19] , 2010	10/10	Japan	Retrospective, cohort	Splenectomy	PegIFN- α -2a or PegIFN- α -2b + RBV	PegIFN- α -2a: 180 ug/wk; PegIFN- α -2b: 1.5 μ g/kg per week; RBV: 600-1000 mg/d	GT 1: 48 wk; GT 2/3: 24 wk
Ji <i>et al</i> ^[20] , 2013	13/13	China	Prospective, cohort	Splenectomy	PegIFN- α -2a (2) or PegIFN- α -2b (3) or IFN- α -2b (8) + RBV	PegIFN- α -2a: 180 ug/wk; PegIFN- α -2b: 1.5 μ g/kg per week; IFN- α -2b: 2.1-3.0 MU, tiw; RBV: 800-1000 mg/d	GT 1: 48 wk; GT 2/3: 24 wk
Kedia <i>et al</i> ^[21] , 2012	6/6	Japan	Retrospective, cohort	Splenectomy	PegIFN (2) or IFN (4) + RBV	NA	NA
Kercher <i>et al</i> ^[22] , 2004	11/11	United States	Prospective, cohort	Splenectomy	PegIFN + RBV	NA	NA
Liang <i>et al</i> ^[23] , 2008	9/9	China	Retrospective, cohort	Splenectomy	PegIFN- α -2a (6) or IFN- α -2b (3) + RBV	PegIFN- α -2a: 180 ug/wk; IFN- α -2b: 5MU tiw; RBV: 900-1200 mg/d	GT 1: 48 wk; GT 2/3: 24 wk
Moriwaka <i>et al</i> ^[24] , 2009	48/16	Japan	Retrospective, controlled	Splenectomy	PegIFN- α -2b (2) or IFN- α (14) + RBV	PegIFN- α -2b: 50 μ g/wk; IFN- α : 3.0-6.0 MU, tiw; RBV: 400 mg/d	1.4 yr (range: 0.2-12.4 yr)
Motomura <i>et al</i> ^[25] , 2012	127/37	Japan	Retrospective, controlled	Splenectomy	PegIFN + RBV	NA	NA
Shigekawa <i>et al</i> ^[26] , 2011	29/29 ²	Japan	Retrospective, cohort	Splenectomy	PegIFN- α -2a or PegIFN- α -2b + RBV	PegIFN- α -2a: 90 μ g/wk; or PegIFN- α -2b: 0.75 μ g/kg per week; RBV: 800 mg/d	GT 1: 48 wk; GT 2/3: 24 wk
Xie <i>et al</i> ^[27] , 2012	49/49	China	Retrospective, controlled	Splenectomy PSE	PegIFN- α -2a + RBV	PegIFN- α -2a: 135 or 180 μ g/wk; RBV: 800-1200 mg/d	NA
Foruny <i>et al</i> ^[28] , 2005	8/8	Spain	Retrospective, cohort	PSE	PegIFN- α -2a (2) or PegIFN- α -2b (6) + RBV	PegIFN- α -2a: 180 ug/wk; PegIFN- α -2b: NA; RBV: 8.8-18.18 mg/kg per day	24-48 wk
Miyake <i>et al</i> ^[29] , 2008	20/10	Japan	Case controlled	PSE	PegIFN- α -2b (5) or IFN- α -2b (5) + RBV	PegIFN- α -2b: 1.2 μ g/kg per week; IFN- α -2b: 6MU tiw; RBV: 400 - 800 mg/d	24-48 wk
Tahara <i>et al</i> ^[30] , 2011	53/30	Japan	Case controlled	PSE	PegIFN- α -2a (2) or PegIFN- α -2b (2) + RBV	NA	24-48 wk
Takahara <i>et al</i> ^[31] , 2011	24/11	Japan	Case controlled	PSE	PegIFN- α -2b + RBV	PegIFN- α -2b: 1.2 μ g/kg per week; RBV: 400-800 mg/d	GT 1: 48 wk; GT 2/3: 24 wk
Summary	603/372						

¹Total: All patients received IFN and RBV treatment; SO + IFN: Patients treated with spleen operation before IFN and RBV treatment; ²Among 35 patients enrolled in this study, six did not receive antiviral therapy because of HCC (2), cerebral infarction (2), colonic perforation (1) or other cancer (1). SO: Spleen operation; IFN: Interferon; RBV: Ribavirin; GT: Genotype; PSE: Partial splenic embolization; NA: Not available.

underwent SO plus IFN- α -based antiviral treatment are shown in Table 2. Their mean ages ranged from 45.4 \pm 11.1 to 63.3 \pm 6.6 years old. The total proportion of males was 50.0% (range: 20.0%-81.3%). Information on HCV genotype, which included genotypes 1, 2 and 3, was provided in 14 studies, and HCV genotype 1 accounted for 75.0% of subjects (237/316). Six studies described baseline viral load, and 16.1% (31/193) of patients in these studies had low viral load (< 10⁵ IU/mL). Child-Pugh scores were provided in 10 studies, and the total numbers of patients in these studies with classes A, B and C were 160, 72 and 2, respectively.

Impact of SO on hematologic parameters

As shown in Table 2, all patients had thrombocytopenia and/or leukopenia at baseline. Platelet and leukocyte

counts were significantly elevated after SO compared with those at baseline. The platelet count increased 2.05-7.96-fold and the leukocyte count 1.44-2.71-fold compared with pre-operation levels. There was no significant difference in hemoglobin levels between before and after SO.

Outcomes of SO plus IFN treatment

Among the 372 subjects who underwent SO followed by anti-HCV therapy, 11 were receiving treatment when the paper was written and 147 achieved SVR (39.5%). Excluding the patients still receiving treatment, the total SVR rate was 40.7%, and the SVR rates in patients infected with genotype 1 and genotype 2/3 were 29.7% (73/246) and 74.3% (55/74), respectively (Table 3). There was no evidence of substantial between-study het-

Table 2 Baseline characteristics of spleen operation plus interferon-treated subjects and hematologic parameters pre-/post-spleen operation

Ref.	Age	Male/ female	HCV genotype, <i>n</i> (1/2 and 3)	HCV RNA (low/high)	Child-Pugh, <i>n</i> (A/B/C)	Pre-spleen operation			Post-spleen operation		
						Leukocyte ($\times 10^9/L$)	Hemoglobin (g/L)	Platelet count ($\times 10^9/L$)	Leukocyte ($\times 10^9/L$)	Hemoglobin (g/L)	Platelet count ($\times 10^9/L$)
Aizawa <i>et al</i> ^[17] , 2013	61.0 \pm 7.1	16/14	25/5	0/30	NA	3.41 \pm 1.27	125 \pm 22	60 \pm 14	5.13 \pm 1.34	122 \pm 19	167 \pm 51
Akahoshi <i>et al</i> ^[18] , 2012	58.1 \pm 7.0	54/46	80/20	12/88	61/39/0	3.19 \pm 1.14	128 \pm 15	56 \pm 21	5.17 \pm 1.34	125 \pm 14	222 \pm 98
Hayashi <i>et al</i> ^[11] , 2006	45.4 \pm 11.1	4/3	4/2 ¹	NA	5/2/0	2.20 \pm 1.70	NA	32.4 \pm 12.3	NA	NA	224.4 \pm 74.9
Ikezawa <i>et al</i> ^[19] , 2010	62.5 (51-69)	4/6	9/1	8/2	9/1/0	3.84 \pm 0.36	NA	64.2 \pm 6.9	5.53 \pm 0.64	NA	209 \pm 40.6
Ji <i>et al</i> ^[20] , 2013	51.8 \pm 8.0	4/9	9/4	11/2	9/4/0	2.10 \pm 0.49	NA	48.2 \pm 15.9	5.70 \pm 1.42	NA	186.0 \pm 70.6
Kedia <i>et al</i> ^[21] , 2012	NA	NA	1/5	NA	NA	NA	NA	NA	NA	NA	NA
Kercher <i>et al</i> ^[22] , 2004	45.4 (27-55)	7/4	NA	NA	11/0/0	NA	NA	55.4 \pm 20.8	NA	NA	441.1 \pm 164.8
Liang <i>et al</i> ^[23] , 2008	47.6 \pm 13.9	6/3	4/5	NA	6/3/0	2.10 \pm 0.70	121 \pm 16	36 \pm 12	5.10 \pm 1.20	131 \pm 14	190 \pm 65
Moriwaka <i>et al</i> ^[24] , 2009	52 (36-60)	13/3	11/5	NA	7/1/2008	3.20 (1.80-5.60)	NA	44 (27-78)	5.20 (3.70-9.00)	NA	110 (79-275)
Motomura <i>et al</i> ^[25] , 2012	58 \pm 1	19/18	32/5	NA	NA	NA	125 \pm 3	59 \pm 2	NA	NA	168.7 \pm NA
Shigekawa <i>et al</i> ^[26] , 2011	63.3 \pm 6.6	12/23	26/9	NA	10/1/2024	3.05 \pm 1.05	NA	48 \pm 15	4.52 \pm 0.98	NA	155 \pm 55
Xie <i>et al</i> ^[27] , 2012	45.6 (32-65)	22/27	NA	NA	NA	NA	NA	NA	NA	NA	NA
Foruny <i>et al</i> ^[28] , 2005	NA	5/3	7/1	NA	2/6/0	2.11 (1.30-0.59)	129 (101-149)	46.2 (21-70.3)	5.57 (3.51-7.05)	141 (124-152)	180.5 (113-214)
Miyake <i>et al</i> ^[29] , 2008	61 (42-70)	2/8	6/4	0/10	NA	3.59 (2.62-6.33)	130 (112-151)	75 (44-115)	5.70 (2.48-8.34)	122 (111-138)	161 (113-293)
Tahara <i>et al</i> ^[30] , 2011 ²	57.5 (36-71)	12/13	13/12	0/30	25/0/0	3.55 (1.50-7.20)	134 (99-160)	70 (32-101)	5.40 (2.60-8.10)	126 (101-160)	174 (90-338)
Takahara <i>et al</i> ^[31] , 2011	62 (44-72)	5/6	10/1	NA	NA	4.71 (2.95-6.33)	127 (112-151)	93 (61-117)	7.20 (2.84-11.8)	122 (111-138)	191 (113-302)
Summary		185/186	237/79	31/162	160/72/2						

¹Genotype was unavailable in one patient; ²Authors compared PSE-treated patients (25) with PSE-untreated patients (23) with thrombocytopenia receiving PEG-IFN- α -2b plus RBV over the same period. Another five patients were treated with IFN- α -2b (3) or PEG-IFN- α -2a (2) plus RBV. SO: Spleen operation; IFN: Interferon; NA: Not available; PSE: Partial splenic embolization.

erogeneity ($I^2 = 0\%$; $P > 0.1$) and a fixed-effects model was therefore used to pool the results. Meta-analysis demonstrated that SVR was associated with genotypes 2/3 in cirrhotic patients (OR = 10.84; 95%CI: 5.47-21.47; $P < 0.00001$) (Figure 2).

Only two studies showed virological response in relation to different baseline viral loads, and there were no data on the relationship between Child-Pugh score and antiviral outcomes.

Impact of SO on adherence to antiviral treatment

Eleven of the included studies provided data about IFN- α dose reduction during antiviral treatment. Of those who underwent SO plus antiviral treatment, 29.4% (47/160) needed a reduction of IFN- α dose, partly because of thrombocytopenia recurrence, while 11.5% (35/305) discontinued IFN- α -based therapy for other reasons, including HCC occurrence, neutropenia, severe fatigue, severe thrombocytopenia, and depression (Table 3).

HCC

Excluding the study by Aizawa *et al*^[17], in which HCC patients were not classified on the basis of whether or not they underwent SO, 11.9% (19/160) of patients who underwent SO plus IFN developed HCC during follow-up. In a comparative study, HCC occurred in 17.4% (8/46) of patients with SO and 50.0% (16/32) of patients without SO (Table 4).

Outcomes of and adherence to antiviral therapy in controlled studies

The outcomes of and adherence to antiviral therapy in patients with and without SO from six controlled studies are compared in Table 4. SVR was achieved in 34.1% (44/129) of patients with SO and 31.1% (71/228) of patients without SO. The fixed-effects model demonstrated no significant difference between the two groups (OR = 0.84; 95%CI: 0.52-1.36; $P = 0.48$) (Figure 3). Stratified analysis according to HCV genotype showed that SO

Table 3 Outcomes of antiviral therapy in cirrhotic patients with spleen operation plus interferon treatment

Ref.	SVR rate	SVR rate (GT)	IFN dosage reduction	Discontinuation of therapy	Reasons of discontinuation therapy	HCC
Aizawa <i>et al</i> ^[17] , 2013	6/30	GT 1: 3/25 GT 2/3: 3/5	12/30	41/120 ²	HCC occurrence 10; No VR 10; Fatigue 5; Thrombocytopenia 3; Fundal hemorrhage 2; Interstitial pneumonia 2; Anemia, auditory disturbance, pruritus, depression, presyncope, liver function flare, infection and death of accident 1, respectively	112
Akahoshi <i>et al</i> ^[18] , 2012	36/97 ¹	GT 1: 19/80 GT 2/3: 17/20	NA	8/97	Depression 3; Neutropenia 2; Appearance of HCC 2; Pneumococcal meningitis 1	2
Hayashi <i>et al</i> ^[11] , 2006	2/6	GT 1: 1/3 GT 2/3: 1/2	0/6	0/6	NO	NA
Ikezawa <i>et al</i> ^[19] , 2010	5/10	GT 1: 4/9 GT 2/3: 1/1	2/10	1/10	Angina 1	NA
Ji <i>et al</i> ^[20] , 2013	8/13	GT 1: 4/9 GT 2/3: 4/4	1/13	0/13	NO	NA
Kedia <i>et al</i> ^[21] , 2012	4/6	GT 1: 1/1 GT 2/3: 3/4	0/6	0/6	NO	NA
Kercher <i>et al</i> ^[22] , 2004	3/11	NA	8/11	0/11	NO	NA
Liang <i>et al</i> ^[23] , 2008	3/9	GT 1: 1/4 GT 2/3: 2/5	0/9	2/9	Neutropenia 1; Anemia 1	NA
Morihara <i>et al</i> ^[24] , 2009	4/16	GT 1: 0/7 GT 2/3: 4/4	0/16	3/16	Severe thrombocytopenia 1; NSAID-induced liver injury 1; peripheral neuropathy 1	4
Motomura <i>et al</i> ^[25] , 2012	16/37	NA	NA	NA	NA	NA
Shigekawa <i>et al</i> ^[26] , 2011	9/29	GT 1: 3/21 GT 2/3: 6/8	NA	11/29	HCC 9; Neutropenia 1; Peritonitis 1	9
Xie <i>et al</i> ^[27] , 2012	30/49	GT 1: 30/49	NA	1/49	Hypothyroidism 1	NA
Foruny <i>et al</i> ^[28] , 2005	3/8	GT 1: 2/7 GT 2/3: 1/1	0/8	2/8	Intolerance (with no evidence of hematological toxicity) 1; Neutropenia 1	NA
Miyake <i>et al</i> ^[29] , 2008	6/10	GT 1: 2/6 GT 2/3: 4/4	3/10	2/10	Hepatic coma 1; Plural effusion 1	NA
Tahara <i>et al</i> ^[30] , 2011	9/30	GT 1: 1/15 GT 2/3: 8/15	16/30	4/30	Neutropenia2; Severe fatigue 2	4
Takahara <i>et al</i> ^[31] , 2011	3/11	GT 1: 2/10 GT 2/3: 1/1	5/11	1/11	Hepatic coma 1	NA
Summary	147/372 ³	GT 1: 73/246 GT 2/3: 55/74	47/160	35/305 ⁴		19/160 ⁴

¹Among a total of 100 patients, three did not start IFN therapy because of no recovery of platelet counts (2) and the appearance of HCC before IFN therapy (1); ²Not classified on the basis of spleen operation or no spleen operation; ³Among the 372 subjects who underwent spleen operation followed by anti-HCV therapy, 11 were still receiving treatment when the paper was drafted; ⁴Excluding Aizawa *et al* (2013) because no classification on the basis of spleen operation or no spleen operation. SVR: Sustained virological response; GT: Genotype; IFN: Interferon; HCC: Hepatocellular carcinoma; NA: Not available.

Table 4 Comparison of antiviral therapy between patients with and without spleen operation based on controlled studies

Ref.	SVR		SVR for GT-1		SVR for GT-2/3		IFN dosage reduction		Discontinuation		HCC	
	SO	Non-SO	SO	Non-SO	SO	Non-SO	SO	Non-SO	SO	Non-SO	SO	Non-SO
Aizawa <i>et al</i> ^[17] , 2013	6/30	12/60	3/25	8/50	3/5	4/10	NA	NA	NA	NA	NA	NA
Morihara <i>et al</i> ^[24] , 2009	4/11 ¹	7/32	0/7	1/18	4/4	6/14	0/16	8/32	3/16	8/32	4/16	16/32
Motomura <i>et al</i> ^[25] , 2012	16/37	38/90	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Miyake <i>et al</i> ^[29] , 2008	6/10	3/10	2/6	0/6	4/4	3/4	3/10	5/10	2/10	1/10	NA	NA
Tahara <i>et al</i> ^[30] , 2011	9/30	5/23	1/15	1/14	8/15	4/9	16/30	10/23	4/30	2/23	4/30	NA
Takahara <i>et al</i> ^[31] , 2011	3/11	6/13	2/10	4/8	1/1	2/5	5/11	11/13	1/11	1/13	NA	NA
Summary	44/129	71/228	8/63	14/96	20/29	19/42	24/67	34/78	10/67	12/78	8/46	16/32

¹Five patients were receiving treatment. SO: Spleen operation; Non-SO: No spleen operation; SVR: Sustained virological response; GT: Genotype; IFN: Interferon; HCC: Hepatocellular carcinoma; NA: Not available.

did not increase the SVR rate in cirrhotic patients with genotype 1 HCV infection (8/63 *vs* 14/96; OR = 1.28; 95%CI: 0.51-3.22; *P* = 0.60) but did improve the virological response in individuals infected with genotypes 2/3 (OR = 0.36; 95%CI: 0.13-1.02; *P* = 0.05) (Figure 4). The

random-effects model showed no difference between patients with and without SO in terms of the incidence of IFN dosage reduction (24/67 *vs* 34/78; OR = 2.41; 95%CI: 0.63-9.18; *P* = 0.20). There was no significant difference in withdrawal of IFN- α -based therapy between

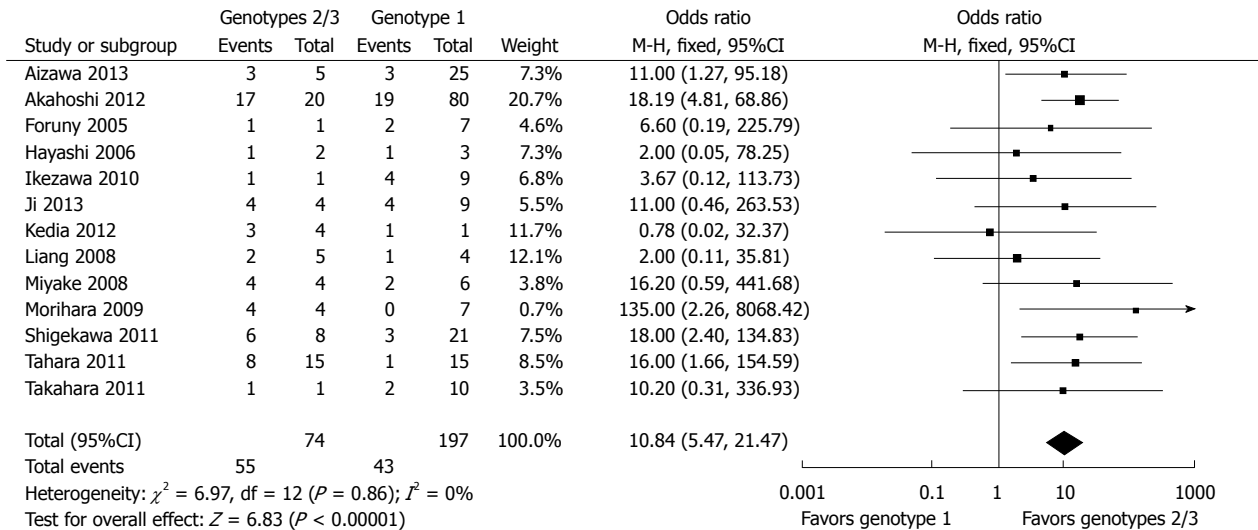


Figure 2 Impact of hepatitis C virus genotype on antiviral treatment outcomes in cirrhotic patients with spleen operation.

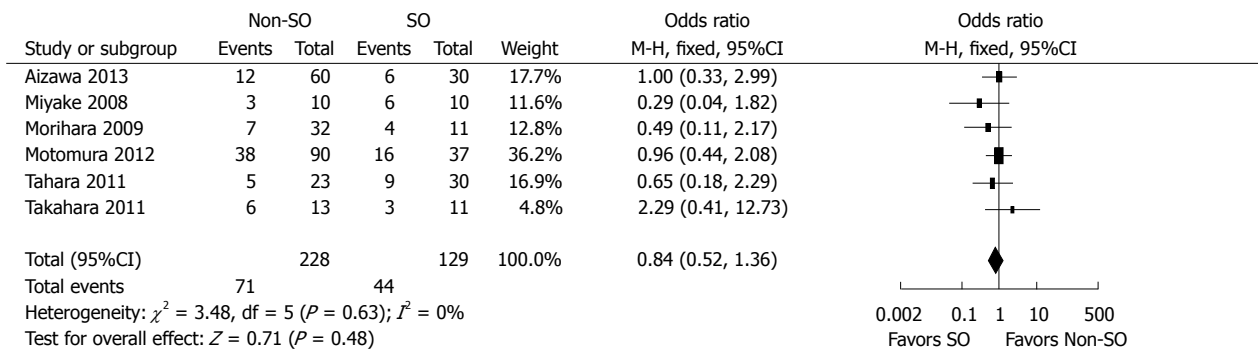


Figure 3 Impact of spleen operation on sustained virological response in six controlled studies. SO: Spleen operation; Non-SO: No spleen operation.

patients with SO plus IFN and those with IFN- α -based treatment alone (10/67 *vs* 12/78; OR = 0.88; 95%CI: 0.34-2.29; $P = 0.80$) (Figure 5).

DISCUSSION

Thrombocytopenia and neutropenia are common manifestations of liver cirrhosis and have been reported to occur in up to 76% of cirrhotic patients^[32]. Although the exact mechanisms are not fully understood, portal hypertension associated with cirrhosis generally diverts the flow of blood from the portal system towards the spleen, resulting in spleen congestion and hypersplenism, with increased destruction of platelets and neutrophils. As the current standard of care, IFN-based treatment exacerbates thrombocytopenia and neutropenia as a result of IFN-induced bone marrow suppression, as well as the direct inhibitory effect of IFN on megakaryocytes, necessitating dose reductions or discontinuation of antiviral treatment in up to 25% of patients^[22].

Splenectomy and PSE are therefore used to elevate platelet and neutrophil levels and improve the adherence to IFN-based therapy in HCV-related cirrhotic patients with hypersplenism^[17,18]. They were recommended in Ja-

pan for cirrhotic patients with thrombocytopenia before initiation of IFN- α treatment in 2008^[33]. In the current review, the platelet count increased by a mean of 2.80-fold and leukocyte count by a mean of 1.83-fold compared with pre-operation levels. It was also reported that platelet counts could remain high during IFN and RBV therapy, which could enable PEG-IFN- α /RBV therapy to be performed safely, with a higher SVR^[18].

In this systematic review, 39.5% (147/372) of cirrhotic patients who underwent SO achieved SVR, giving a total SVR rate of 40.7% (147/361), excluding those patients who were still receiving treatment. Additionally, patients infected with genotype 1 HCV achieved an SVR rate of 29.7% (73/246), which was similar to the reported approximately 30% of cirrhotic patients infected with HCV genotypes 1/4 who obtained SVR even without SO^[9,10]. Based on the data from six controlled studies, SVRs were achieved in 34.1% (44/129) of patients with SO and 31.1% (71/228) of patients without SO. Splenectomy and PSE did not significantly increase the SVR in cirrhotic patients with genotype 1 HCV infection, but did increase the SVR in individuals with genotypes 2/3 infection, as supported by stratified analysis of controlled studies^[10].

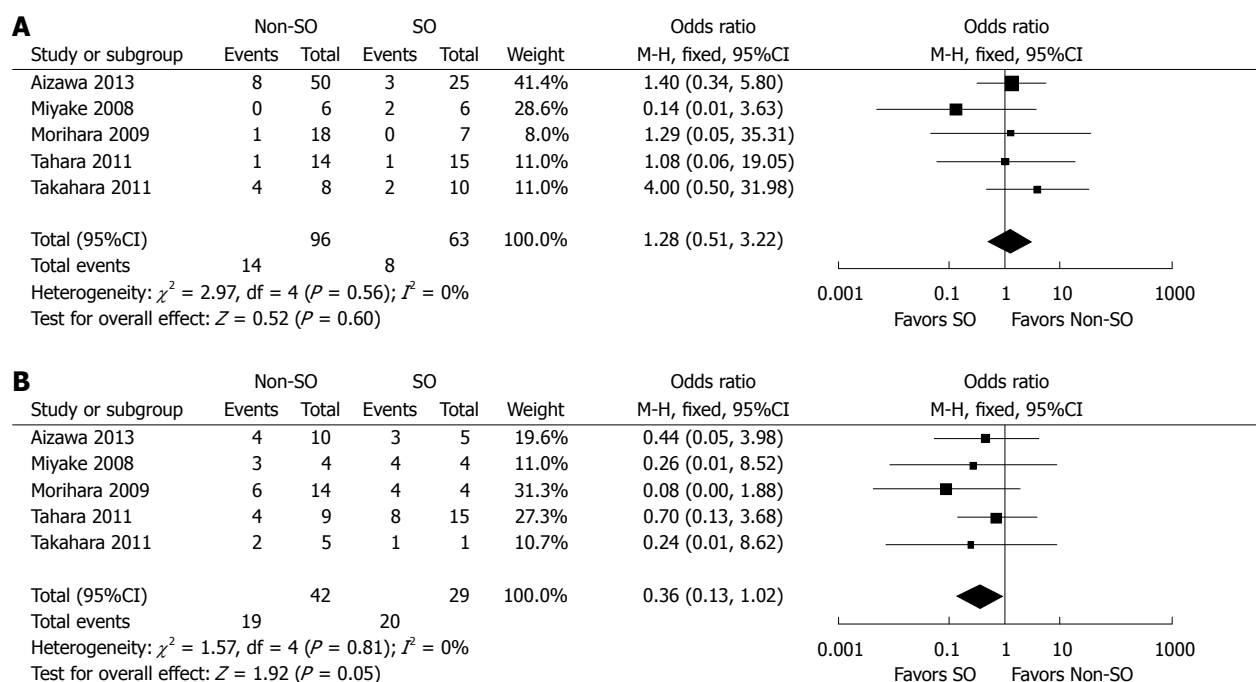


Figure 4 Impact of spleen operation on sustained virological response of different hepatitis C virus genotypes in controlled studies. Spleen operation did not increase sustained virological response rate in cirrhotic patients with genotype 1 hepatitis C virus infection (A), but did improve virological response in genotypes 2/3-infected individuals (B). SO: Spleen operation; Non-SO: No spleen operation.

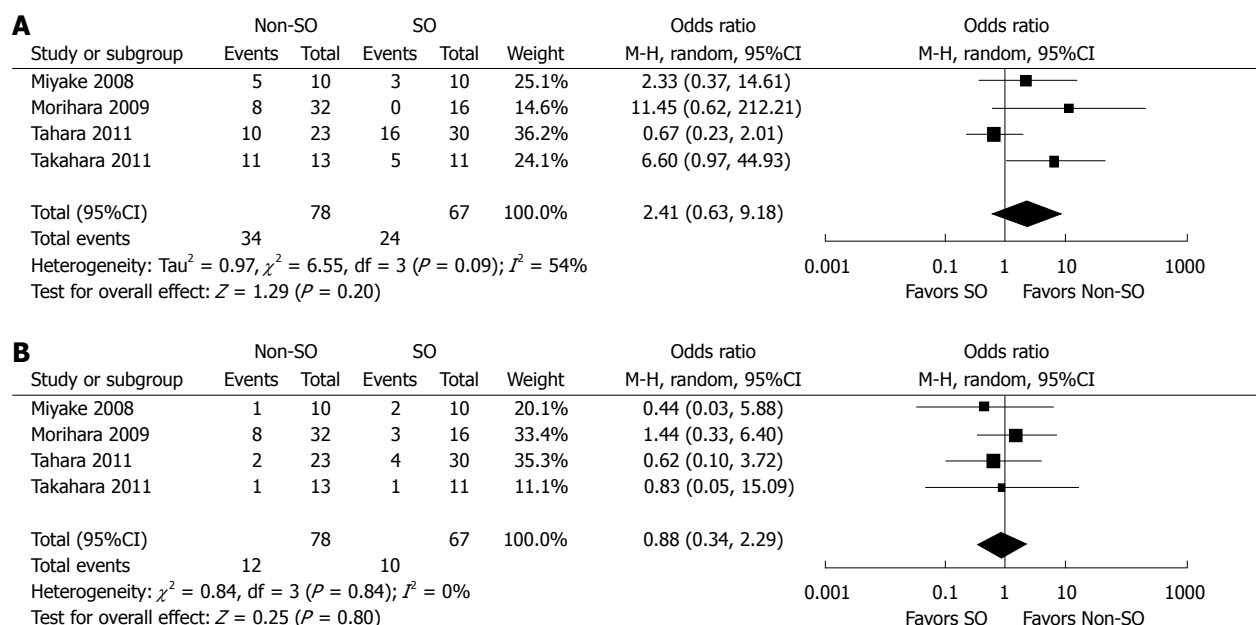


Figure 5 Comparison of adherence to antiviral therapy in controlled studies. The random-effects model showed that spleen operation decreased the incidence of interferon (IFN) dosage reduction (A). There was no significant difference in withdrawal of IFN α -based therapy between patients with SO plus IFN and those with IFN α treatment alone (B). SO: Spleen operation; Non-SO: No spleen operation.

Adherence is another important factor affecting SVR in cirrhotic patients. Higher SVR rates were reported in patients with genotype 1 infection who received more than 80% of their PegIFN- α and RBV dosage for more than 80% of the expected duration^[34]. Hematologic parameters remained at relatively high levels during IFN-based treatment in most patients who underwent SO. Antiviral therapy was only withdrawn in 2.6% (11/425)

of cases because of thrombocytopenia and neutropenia, which was far lower than that reported in some studies^[13]. Overall, dose reduction of IFN occurred in 29.4% (47/160) of cirrhotic patients with SO, while 11.5% (35/305) of individuals discontinued therapy. A recent national survey conducted by Ikeda *et al*^[16] showed that, among all patients who received pretreatment (splenectomy or PSE), discontinuation of IFN occurred in 22%

of cases of splenectomy, 28% of cases of PSE and 33% of those without pretreatment. Stratified analysis of controlled studies showed that SO before antiviral therapy could decrease the incidence of IFN dose reduction (though the difference was not significant), but had little effect on discontinuation of therapy.

SVR is known to decrease the incidence of HCC in chronic hepatitis C (CHC) patients with compensated cirrhosis^[6]. However, the spleen is thought to confer antitumor immunity, and SO, especially splenectomy, leads to reduction and dysfunction of T cells and decreased specific humoral immunity, which may increase the risk of carcinogenesis^[27]. We also analyzed the effect of combination therapy on hepatocarcinogenesis in cirrhotic patients with splenomegaly. In the current study, 11.9% of patients with SO plus IFN- α developed HCC during follow-up. A comparative study showed that splenectomy and SPE could suppress the occurrence of HCC in a small population sample, which may have been partly the result of the antiviral and antitumor activities of IFN- α .

The orally active thrombopoietin receptor agonist eltrombopag was recently used to treat thrombocytopenia resulting from IFN- α in CHC patients with cirrhosis^[35]. However, its long-term efficacy in patients with hypersplenism remains unclear, because the enlarged spleen can immediately destroy the increased platelets. PegIFN λ plus RBV may be used to treat these patients with hematologic abnormalities because of slightly decreased blood cells^[36]. However, DAAs, with fewer adverse effects (especially IFN-free) and short duration, have greatly altered the therapeutic principles for CHC, and may be the most promising strategy for treating these cirrhotic patients^[37].

There were some limitations to our study. Most included studies were retrospective, uncontrolled and observational studies and there was a lack of randomized controlled trials. Furthermore, the small number of study subjects made it difficult to perform subgroup analysis on the basis of factors such as baseline Child-Pugh score, viral load, and comorbidities. Small case-controlled studies could only provide information on the possible impact of SO on the outcomes of and adherence to antiviral treatment, but it is difficult to draw firm conclusions from them. We therefore compared the results for SVR and adherence to therapy with those reported in the literature. Information from small case-controlled studies and short follow-up periods was insufficient to clarify the impact of SO on HCC occurrence. However, despite these limitations, several conclusions can be drawn from careful consideration of the available data.

In conclusion, splenectomy and PSE can elevate platelet and leukocyte levels and improve the tolerance to IFN- α -based antiviral therapy in cirrhotic patients with HCV infection. Stratified analysis showed that SO does not improve the outcomes of antiviral therapy in cirrhotic patients with genotype 1 HCV infection, but may be indicated in patients with genotypes 2/3 infection receiving IFN- α therapy, who are more likely to achieve an SVR by dose maintenance. We suggest that the strategy

of SO combined with IFN- α in cirrhotic patients with HCV infection may be replaced by new, IFN-free therapies, especially DAAs, in the future.

COMMENTS

Background

As we well knew, the sustained virological response (SVR) rate is very low in cirrhotic patients with hepatitis C virus (HCV) infection. One of important reasons is that hematologic abnormalities caused by hypersplenism and interferon- α (IFN- α) severely affect IFN- α -based therapy. Splenectomy and partial splenic embolization followed by IFN- α -based therapy have been increasingly performed to address cytopenias, including thrombocytopenia, in patients with HCV-related cirrhosis with hypersplenism. However, the therapeutic effect and long-term safety of such treatments remain controversial.

Research frontiers

To investigate the efficacy and safety of spleen operation (SO) on IFN- α -based antiviral treatment in patients with HCV-related cirrhosis.

Innovations and breakthroughs

The number of studies on this topic was small, and therefore, the authors aimed to summarize all of these findings which they could research and proposed the position of spleen operation in HCV-related cirrhosis by a systematic review.

Applications

The results demonstrated that SO combined with IFN- α -based antiviral therapy may be suitable in cirrhotic patients with genotypes 2/3 HCV infection, but not in those with genotype 1 infection. And so, spleen operation should be reassessed and performed with careful considerations for those cirrhotic patients with genotype 1 infection in clinical practice.

Peer review

The manuscript is an interesting systematic review on the impact of spleen operation on antiviral therapy in HCV-related cirrhotic patients. It deals with a difficult subject that is not well documented. The results demonstrated that spleen operation combined with IFN- α -based antiviral therapy may be suitable to HCV cirrhotic patients with genotypes 2/3 other than those with genotype 1.

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