

**Table 5** Univariate analysis of factors associated with NR in 55 patients with genotype 1 continued PEGIFN/RBV >12 weeks

	NR (n = 17)	TR+SVR (n = 38)	P value
Gender (male/female)	8/9	31/7	0.022
Age (years)*	66 (53–83)	67 (48–80)	0.75
Body mass index (kg/m <sup>2</sup> )*	22.2 (19.3–30.0)	21.2 (15.6–28.5)	0.86
White blood Cell (×10 <sup>3</sup> /μL)*	5050 (4390–6130)	4280 (2470–6660)	0.6
Haemoglobin (g/dL)*	12.6 (9.3–17.4)	13.7 (8.7–15)	0.66
Platelet count (×10 <sup>4</sup> /mm <sup>3</sup> )*	10.1 (4.7–18.2)	12.1 (3.9–19.6)	0.43
T-bilirubin (mg/dL)*	0.7 (0.4–1.7)	0.8 (0.4–2.3)	0.45
Alanine aminotransferase (IU/L)*	45 (19–134)	45 (12–189)	0.75
Prothrombin time activity (%)*	86 (64–121)	88 (69–112)	0.79
Albumin (g/dL)*	3.8 (2.7–4.9)	4 (3.4–5.2)	0.106
Fibrosing stage(F1-3/F4/ND)	3/8/6	9/9/20	0.21
γ-glutamyl transpeptidase (IU/L)*	52 (12–219)	26 (15–294)	0.113
HbA1c (%)*	5.3 (4–10.8)	5.2 (4.2–8.8)	0.99
Indocyanine green retention rate (%)	18.7 (7.6–45.4)	15.4 (8–29.2)	0.21
HCV viral load (Log IU/mL)*	6.28 (2.1–6.7)	6.18 (1.2–6.7)	0.25
HCV Core70 (mutant/wild)	11/6	20/18	0.55
HCV Core91 (mutant/wild)	10/7	16/22	0.38
HCV ISDR (0–1/>2)	12/5	21/17	0.23
α-Fetoprotein (ng/mL)*	45.3 (5–63240)	10 (0.5–909.2)	0.054
IL28B genotype (TT/GG+TG)	8/9	33/5	0.005
Dose of PEGIFN at administration (μg/kg)*	80 (40–120)	80 (50–100)	0.34
Dose of RBV at administration (mg)*	600 (200–1000)	600 (200–800)	0.77
Therapy were completed (yes/no)	9/8	23/15	0.76

HCV, hepatitis C virus; ISDR, interferon sensitivity-determining region; NR, null response; PEGIFN/RBV, pegylated interferon-alpha plus ribavirin combination therapy; SVR, sustained viral response; TR, Transient viral response. \*Data are median and (range).

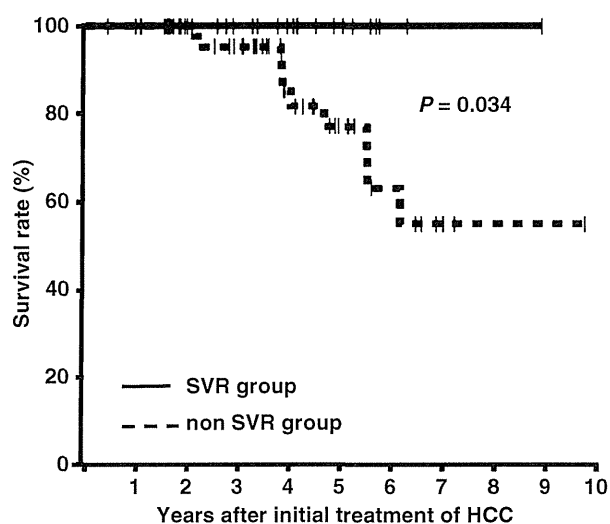
**Table 6** Multivariate analysis of factors associated with NR

Factor	Category	Odds rate (95%CI)	P value
IL28B genotype	TT	1	0.006
	GG+TG	7.8 (1.81–34.4)	
AFP	<30	1	0.015
	>30	5.6 (1.40–22.8)	

AFP, α-fetoprotein; NR, null response.

therapy in patients with HCV genotype 2 was reported in two independent studies [28,29]. Further studies of larger sample size are needed to confirm the relationship between IL-28B genotype and the viral response to PEGIFN/RBV after treatment of HCV-related HCC in patients infected with HCV genotype 2.

Our results suggest that IL-28B genotype could be potentially used as a marker for the viral response to PEGIFN/RBV therapy. Furthermore, PEGIFN/RBV therapy should be recommended after curative treatment for HCV-related HCC for patients who are likely to achieve pSVR [those with IL-28B genotype (TT)]. In addition, the SVR rate



**Fig. 3** Comparison of cumulative survival rates in the sustained viral response (SVR) and non-SVR groups. The cumulative survival rate was significantly higher in the SVR group than in the non-SVR group ( $P = 0.034$ ).

might improve by IFN therapy and combination therapy HCC and HCV. On the other hand, it might be better to

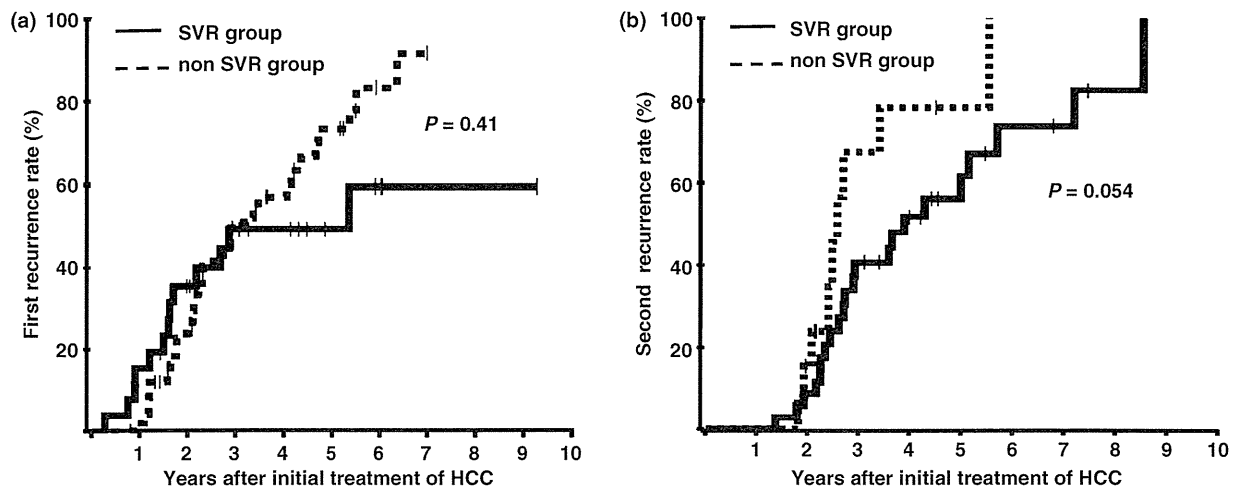


Fig. 4 Cumulative recurrence rates after curative treatment of hepatocellular carcinoma. (a) Rates of first recurrence for the sustained viral response (SVR) and non-SVR groups ( $P = 0.41$ ). (b) Rates of second recurrence for the SVR and non-SVR groups. The second recurrence rate for the SVR group tended to be lower than that for the non-SVR group ( $P = 0.054$ ).

administer low-dose intermittent IFN therapy for patients considered to show NR [those with IL-28B genotype (GG+TG)]. This therapy might result in the improvement of liver function and prevention of HCC recurrence, even if not to obtain SVR.

In conclusion, with regard to the prognosis of patients who undergo curative treatment for HCC, it is desirable to achieve SVR with interferon therapy even after treatment of

HCC. IL-28B genotype could potentially be a suitable marker for the response to PEGIFN/RBV combination therapy after treatment of HCV-related HCC.

#### DISCLOSURES

The authors declare no conflict of interest.

#### REFERENCES

- 1 Takano S, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995; 21: 650–655.
- 2 Tsukuma H, Hiyama T, Tanaka S et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993; 328: 1797–1801.
- 3 Shiratori Y, Shiina S, Imamura M et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. *Hepatology* 1995; 22: 1027–1033.
- 4 Ikeda K, Saitoh S, Tsubota A et al. Risk factors for tumor recurrence and prognosis after curative resection of hepatocellular carcinoma. *Cancer* 1993; 71: 19–25.
- 5 Kubo S, Nishiguchi S, Shuto T et al. Effects of continuous hepatitis with persistent hepatitis C viremia on outcome after resection of hepatocellular carcinoma. *Jpn J Cancer Res* 1999; 90: 162–170.
- 6 Kumada T, Nakano S, Takeda I et al. Patterns of recurrence after initial treatment in patients with small hepatocellular carcinoma. *Hepatology* 1997; 25: 87–92.
- 7 Nagasue N, Uchida M, Makino Y et al. Incidence and factors associated with intrahepatic recurrence following resection of hepatocellular carcinoma. *Gastroenterology* 1993; 105: 488–494.
- 8 Davis GL, Balart LA, Schiff ER et al. Treatment of chronic hepatitis C with recombinant interferon alfa. A multicenter randomized, controlled trial. Hepatitis Interventional Therapy Group. *N Engl J Med* 1989; 321: 1501–1506.
- 9 Di Bisceglie AM, Martin P, Kassianides C et al. Recombinant interferon alfa therapy for chronic hepatitis C. A randomized, double-blind, placebo-controlled trial. *N Engl J Med* 1989; 321: 1506–1510.
- 10 Jeong S, Aikata H, Katamura Y et al. Low-dose intermittent interferon-alpha therapy for HCV-related liver cirrhosis after curative treatment of hepatocellular carcinoma. *World J Gastroenterol* 2007; 13: 5188–5195.
- 11 Mazzaferro V, Romito R, Schiavo M et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. *Hepatology* 2006; 44: 1543–1554.
- 12 Sakaguchi Y, Kudo M, Fukunaga T, Minami Y, Chung H, Kawasaki T. Low-dose, long-term, intermittent interferon-alpha-2b therapy after radical treatment by radiofrequency ablation delays clinical recurrence in patients with hepatitis C virus-related hepatocellular carcinoma. *Intervirology* 2005; 48: 64–70.
- 13 Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H.

- Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. *Br J Surg* 2002; 89: 418–422.
- 14 Ikeda K, Arase Y, Saitoh S *et al*. Interferon beta prevents recurrence of hepatocellular carcinoma after complete resection or ablation of the primary tumor—A prospective randomized study of hepatitis C virus-related liver cancer. *Hepatology* 2000; 32: 228–232.
  - 15 Kubo S, Nishiguchi S, Hirohashi K *et al*. Effects of long-term postoperative interferon-alpha therapy on intrahepatic recurrence after resection of hepatitis C virus-related hepatocellular carcinoma. A randomized, controlled trial. *Ann Intern Med* 2001; 134: 963–967.
  - 16 Nishiguchi S, Tamori A, Kubo S. Effect of long-term postoperative interferon therapy on intrahepatic recurrence and survival rate after resection of hepatitis C virus-related hepatocellular carcinoma. *Intervirology* 2005; 48: 71–75.
  - 17 Suou T, Mitsuda A, Koda M *et al*. Interferon alpha inhibits intrahepatic recurrence in hepatocellular carcinoma with chronic hepatitis C: a pilot study. *Hepatol Res* 2001; 20: 301–311.
  - 18 Shiratori Y, Shiina S, Teratani T *et al*. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. *Ann Intern Med* 2003; 138: 299–306.
  - 19 Lin SM, Lin CJ, Hsu CW *et al*. Prospective randomized controlled study of interferon-alpha in preventing hepatocellular carcinoma recurrence after medical ablation therapy for primary tumors. *Cancer* 2004; 100: 376–382.
  - 20 Hung CH, Lee CM, Wang JH, Tung HD, Chen CH, Lu SN. Antiviral therapy after non-surgical tumor ablation in patients with hepatocellular carcinoma associated with hepatitis C virus. *J Gastroenterol Hepatol* 2005; 20: 1553–1559.
  - 21 Jeong SC, Aikata H, Katamura Y *et al*. Effects of a 24-week course of interferon-alpha therapy after curative treatment of hepatitis C virus-associated hepatocellular carcinoma. *World J Gastroenterol* 2007; 13: 5343–5350.
  - 22 Manns MP, McHutchison JG, Gordon SC *et al*. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358: 958–965.
  - 23 Fried MW, Shiffman ML, Reddy KR *et al*. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; 347: 975–982.
  - 24 Suppiah V, Moldovan M, Ahlenstiel G *et al*. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; 41: 1100–1104.
  - 25 Ge D, Fellay J, Thompson AJ *et al*. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; 461: 399–401.
  - 26 Tanaka Y, Nishida N, Sugiyama M *et al*. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; 41: 1105–1109.
  - 27 Thomas DL, Thio CL, Martin MP *et al*. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009; 461: 798–801.
  - 28 Kawaoka T, Hayes CN, Ohishi W *et al*. Predictive value of the IL28B polymorphism on the effect of interferon therapy in chronic hepatitis C patients with genotypes 2a and 2b. *J Hepatol* 2011; 54: 408–414.
  - 29 Mangia A, Thompson AJ, Santoro R *et al*. An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. *Gastroenterology* 2010; 139: 821–827.
  - 30 Huang JF, Yu ML, Huang CF *et al*. The efficacy and safety of pegylated interferon plus ribavirin combination therapy in chronic hepatitis c patients with hepatocellular carcinoma post curative therapies – a multi-center prospective trial. *J Hepatol* 2011; 54: 219–226.
  - 31 Hagihara H, Nouse K, Kobayashi Y *et al*. Effect of pegylated interferon therapy on intrahepatic recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. *Int J Clin Oncol* 2010; doi: 10.1007/s10147-010-0150-x.
  - 32 Liver Cancer Study Group of Japan. The general rules for the clinical and pathological study of primary liver cancer. *Jpn J Surg* 1989; 19: 98–129.
  - 33 Ohnishi Y, Tanaka T, Ozaki K, Yamada R, Suzuki H, Nakamura Y. A high-throughput SNP typing system for genome-wide association studies. *J Hum Genet* 2001; 46: 471–477.
  - 34 Suzuki A, Yamada R, Chang X *et al*. Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. *Nat Genet* 2003; 34: 395–402.
  - 35 Kitamura S, Tsuge M, Hatakeyama T *et al*. Amino acid substitutions in core and NS5A regions of the HCV genome can predict virological decrease with pegylated interferon plus ribavirin therapy. *Antivir Ther* 2010; 15: 1087–1097.
  - 36 Mori N, Imamura M, Kawakami Y *et al*. Randomized trial of high-dose interferon-alpha-2b combined with ribavirin in patients with chronic hepatitis C: Correlation between amino acid substitutions in the core/NS5A region and virological response to interferon therapy. *J Med Virol* 2009; 81: 640–649.
  - 37 Kawaoka T, Hiraga N, Takahashi S *et al*. Prolongation of interferon therapy for recurrent hepatitis C after living donor liver transplantation: analysis of predictive factors of sustained virological response, including amino acid sequence of the core and NS5A regions of hepatitis C virus. *Scand J Gastroenterol* 2010; 45: 1488–1496.
  - 38 Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; 19: 1513–1520.
  - 39 Tomimaru Y, Nagano H, Eguchi H *et al*. Effects of preceding interferon therapy on outcome after surgery for hepatitis C virus-related hepatocellular carcinoma. *J Surg Oncol* 2010; 102: 308–314.

- 40 Elefsiniotis IS, Vezali E, Mihas C, Saroglou G. Predictive value of complete and partial early virological response on sustained virological response rates of genotype-4 chronic hepatitis C patients treated with PEG-interferon plus ribavirin. *Intervirology* 2009; 52: 247–251.
- 41 Lagging M, Wejstal R, Uhnöo I *et al.* Treatment of hepatitis C virus infection: updated Swedish Consensus recommendations. *Scand J Infect Dis* 2009; 41: 389–402.
- 42 Reau N, Satoskar R, Te H *et al.* Evaluation of early null response to pegylated interferon and ribavirin as a predictor of therapeutic nonresponse in patients undergoing treatment for chronic hepatitis C. *Am J Gastroenterol* 2011; 106: 452–458.
- 43 Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. *Hepatology* 2007; 46: 1688–1694.

