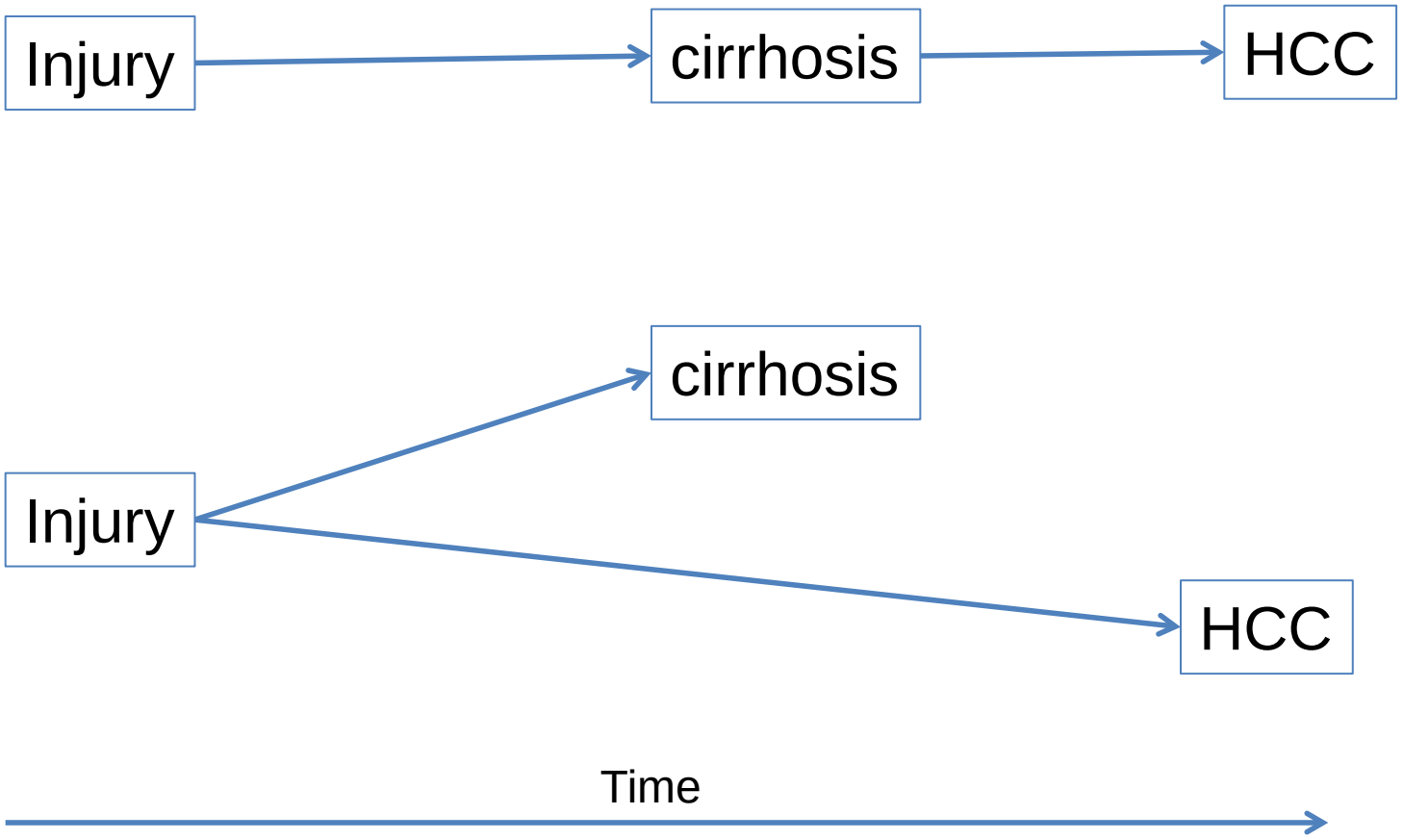
PREVENTION OF HCC BY HEPATITIS C TREATMENT

Morris Sherman

University of Toronto

Pathogenesis of HCC in chronic hepatitis C



The Ideal Study

- Prospective randomized controlled of outcome in treated vs non-treated subjects
  - Followed for long enough after treatment to allow for accumulation of events
  - Stratified by SVR vs no SVR
  - Stratified by cirrhosis (?F3 and F4) vs non-cirrhotics

Next best thing

- Retrospective case-control study comparing outcomes in treated vs untreated subjects matched for HCC risk using available risk scores (propensity matching)
  - Stratified by cirrhosis vs non-cirrhosis
  - Stratified by SVR vs non-SVR
    - ? Stratify by type of non-response

What's available

- Some retrospective case controls of SVR vs untreated
- Mostly retrospective cohort studies comparing outcomes in all treated patients (SVR vs no SVR)
  - Patients with SVR are different than those with no SVR, even after matching
    - Possibly have more severe liver disease
      - Responsible for poor response to Rx
      - Responsible for increased risk of bad outcome (including HCC)

COMPARISON VS NON-SVR

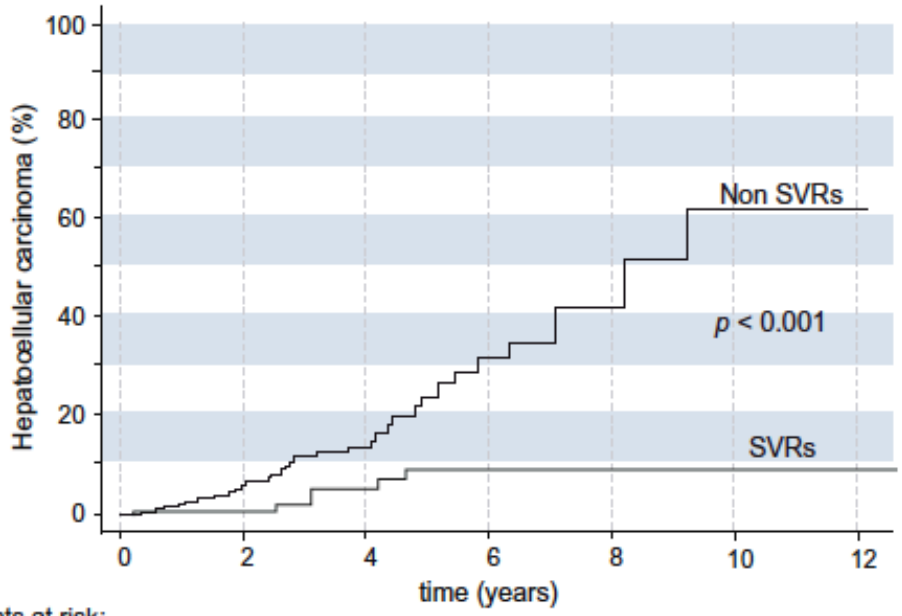
Effect of SVR on HCC incidence/risk

- N = 307

HCC incidence				
	Events	Person yrs	Rate/100 PY's (95% CI)	P value
All subjects	46	1164.7	3.94 (2,89-4.99)	
SVR	6	481.1	1.24 (0.28-2.20)	< 0.001
No SVR	40	683.5	5.85 (4.23-7.47)	

Cardoso et al J Hep 2010

Effect of SVR on HCC incidence/risk



Patients at risk:

SVRs	103	86	49	28	12	5	3
Non SVRs	204	151	73	28	8	5	3

Fig. 1. Cumulative incidence of hepatocellular carcinoma stratified according to response to treatment (p <0.001, by log-rank test). SVR, sustained virological response.

Cardoso et al J Hep 2010

Effect of SVR on HCC incidence/risk

- Predictors of HCC

Hepatocellular carcinoma			
Variable	Strata	Adjusted HR (95% CI)	P value
Age	< 60 vs > 60 yrs	3.18 (1.58-6.37)	0.001
Bilirubin	< 17 vs >16 umol/L	2.41 (1.13-5.13)	0.023
Albumin	<40 vs >39 g/L	3.02 (1.48-6.15)	0.002
Platelet count	<150 vs>149 $x10^9$/L	2.87 (1.07-7.73)	0.036
SVR	No vs Yes	3.06 (1.12-8.39)	0.029

Cardoso et al J Hep 2010

Effect of SVR on HCC incidence/risk

- N = 1013

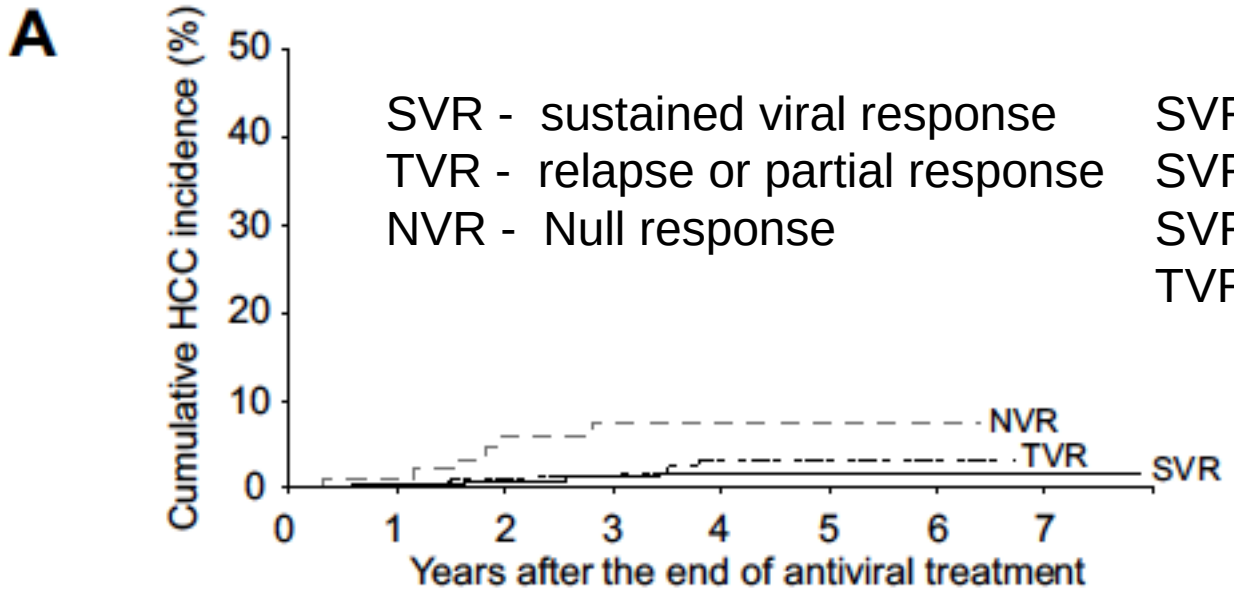
Table 2. Risk factors for the development of HCC by chronic hepatitis C patients treated with PegIFNα2b and RBV.

Characteristic	All patients n = 1013	HCC n = 47	non-HCC n = 966	*p* value*
Age (yr)	58 (50-65)	67 (58-71)	58 (49-65)	<0.001
Male, n (%)	498 (49.2)	32 (68.1)	466 (48.2)	0.007
Body mass index (kg/m²)	23.0 (21.1-25.2)	23.6 (21.6-25.7)	23.0 (21.1-25.2)	0.15
ALT (IU/L)	54 (35-89)	74 (46-100)	54 (34-89)	0.008
Albumin (g/L)	41 (39-44)	40 (37-42)	44 (41-46)	0.002
Platelet count (x10⁹/L)	159 (120-199)	110 (88-132)	161 (123-201)	<0.001
Hemoglobin (g/L)	136 (127-147)	136 (128-149)	136 (127-147)	0.89
Ferritin (ng/ml)	165 (84-376)	187 (80-462)	167 (80-306)	0.68
α-fetoprotein (ng/ml)	4.9 (3.0-9.3)	11.7 (6.8-32.7)	4.8 (3.0-8.7)	<0.001
Hemoglobin A1c (%)	5.5 (5.3-5.9)	5.8 (5.4-6.3)	5.5 (5.3-5.9)	0.96
HCV genotype (1/2), n (%)	710/303 (70.1/29.9)	38/9 (80.9/19.1)	672/294 (69.6/30.4)	0.09
Non-cirrhosis/cirrhosis, n	863/150 (85.2/14.8)	19/28 (40.4/59.6)	844/122 (87.4/12.6)	<0.001
Treatment duration (wk)	47 (24-48)	43 (23-48)	47 (24-48)	0.58
Virological response (SVR/TVR/NVR), n (%)	557/304/152 (55.0/30.0/15.0)	13/13/21 (27.7/27.7/44.7)	544/291/131 (56.3/30.1/13.6)	<0.001

Ogawa et al J Hep 2013

Effect of SVR on HCC incidence/risk

- Non-cirrhotics



SVR - sustained viral response
TVR - relapse or partial response
NVR - Null response

SVR vs TVR + NVR p=0.009
SVR vs TVR = ns
SVR vs NVR p= 0.003
TVR vs NVR p= 0.03

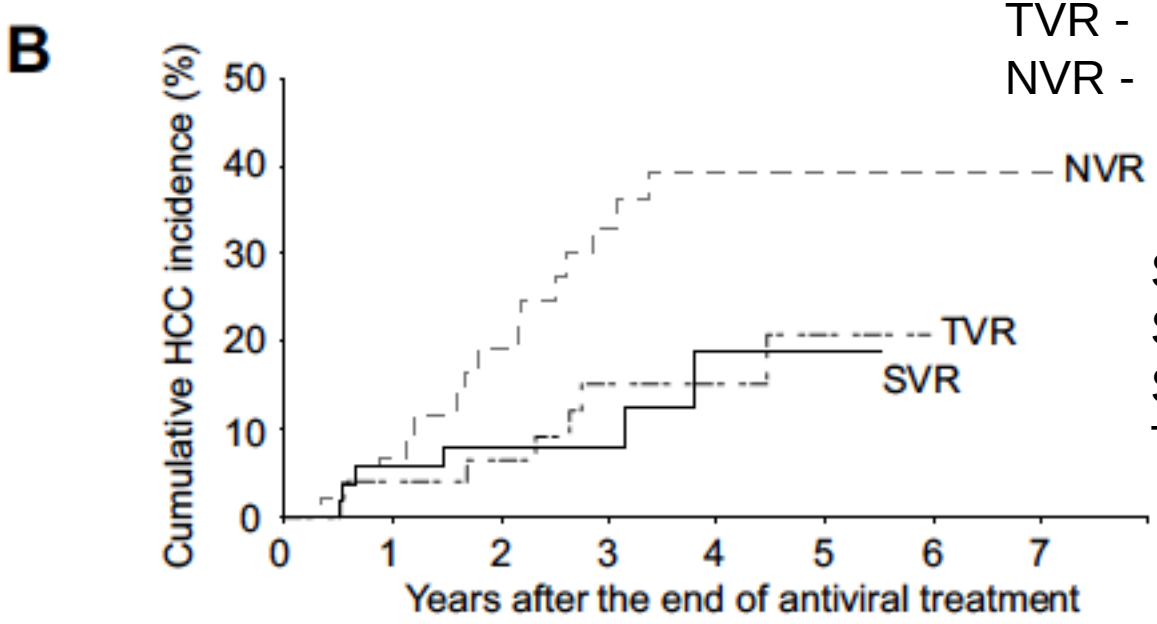
Patients at risk							
SVR	504	470	389	273	199	110	26
TVR	255	243	222	185	133	76	18
NVR	104	91	70	49	32	20	6

Ogawa et al J Hep 2013

Effect of SVR on HCC incidence/risk

- Cirrhotics

SVR - sustained viral response
TVR - relapse or partial response
NVR - Null response



Patients at risk							
SVR	53	46	34	22	10	3	0
TVR	49	44	38	27	18	9	0
NVR	48	40	30	22	14	9	1

SVR vs TVR + NVR p=0.03
SVR vs TVR = ns
SVR vs NVR p= 0.03
TVR vs NVR p= 0.04

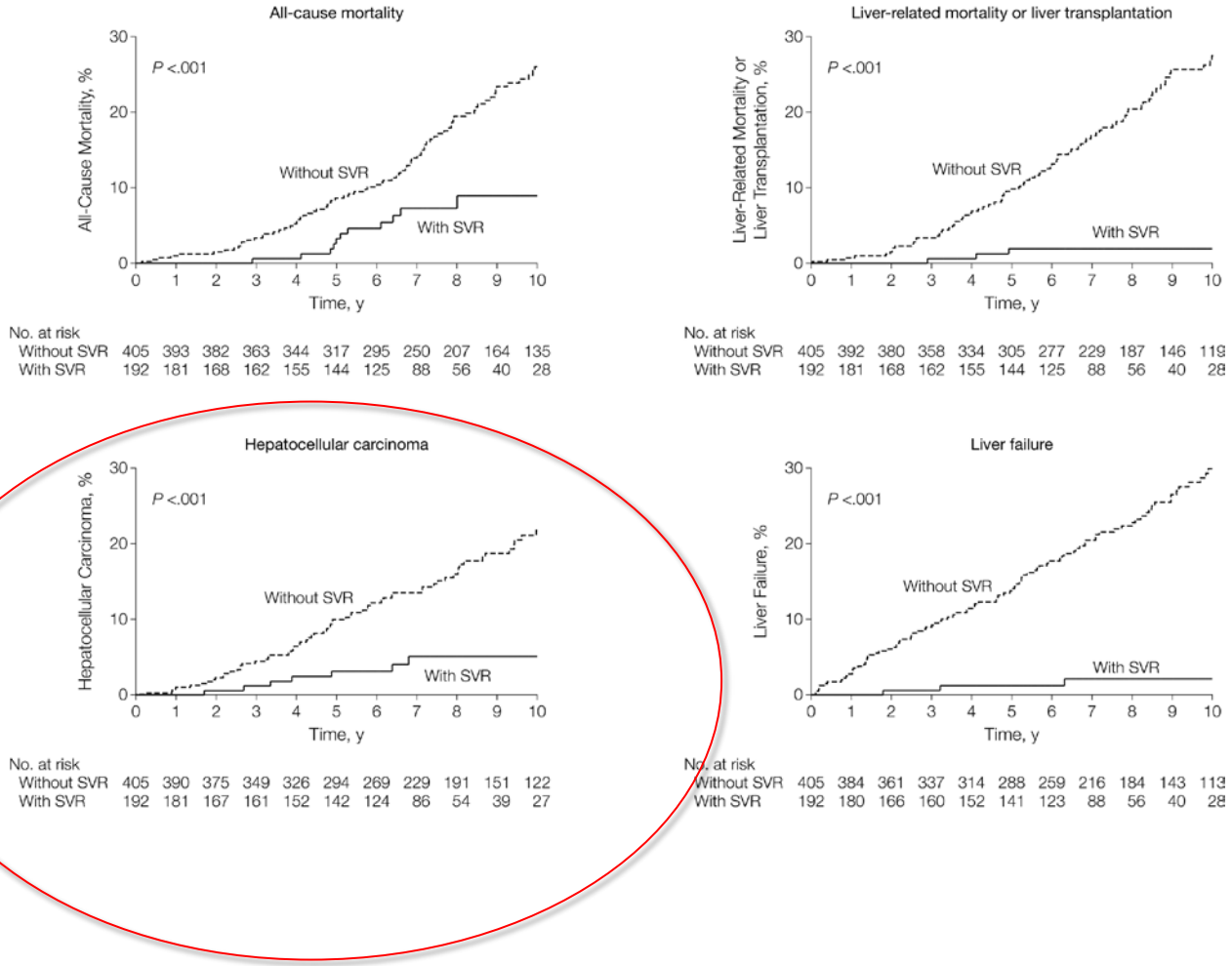
Ogawa et al J Hep 2013

Effect of SVR on HCC incidence/risk

Parameter		Hazard ratio (95% CI)	P Value
Age	< 60 years vs older	2.81 (1.39-5.69)	0.004
Gender	Male vs female	2.98 (1.46-6.05)	0.003
Platelet count	> $150x10^9$/L vs less	4.40 (1.57-10.44)	0.004
AFP	<10 ng/ml vs higher	2.50 (1.09-5.78)	0.03
Cirrhosis vs non-cirrhotic		3.22 (1.28-8.13)	0.01
Treatment outcome	TVR vs SVR	1.50 (0.65-3.44)	0.34
	NVR vs SVR	3.72 (1.69-8.18)	0.001

Ogawa et al J Hep 2013

Effect of SVR on HCC incidence/risk



Van der Meer et al JAMA 2012

Comparison treated vs untreated

- Older studies had small sample sizes and were not statistically well done

Effect of SVR on HCC incidence/risk

- Patients with HBV HCV co-infection treated for hepatitis C.
- Database analysis
  - No information on SVR
  - No treatment for hepatitis B
  - Propensity matching on likelihood of being treated
    - Sensitivity analysis
- 10,234 treated vs 120,863 untreated
- Also compared HCC risk in HBV/HCV infected vs HCV mono-infected

Lui et al Gut 2014

Effect of SVR on HCC incidence/risk

	All cause mortality		Liver-related mortality		Incidence of HCC	
Variable	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Anti-HCV therapy	0.42 (0.34-0.52)	<0.001	0.47 (0.37-0..60)	<0.001	0.76 (0.59-0.97)	0.030
Male sex	1.66 (1.55-1.78)	<0.001	1.68 (1.54-1.84)	<0.001	1.80 (1.65-1.97)	<0.001
Age	1.04 (1.04-1.05)	<0.001	1.05 (1.04-1.05)	<0.001	1.05 (1.05-1.06)	<0.001

Lui et al Gut 2014

Meta-analysis

- Observational studies
  - SVR vs no SVR
  - Treated vs untreated
- RCT’s

Effect of SVR on HCC incidence/risk

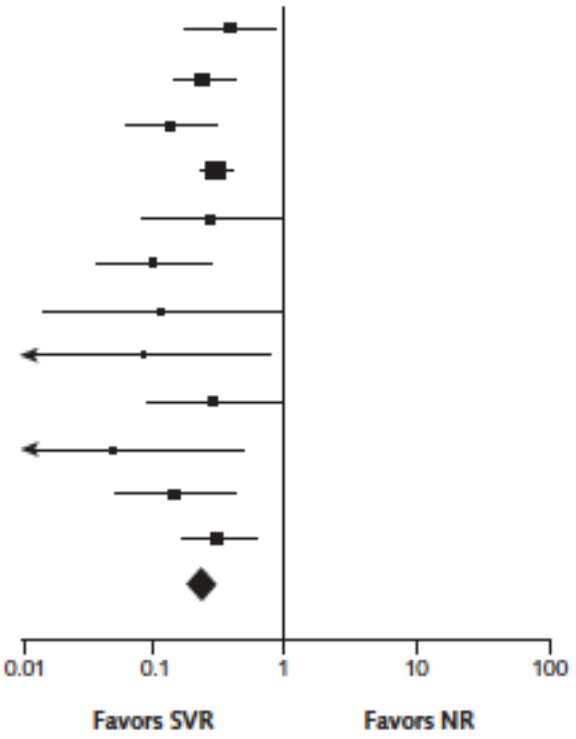
- Meta-analysis of observational studies

Figure 1. **Forest plot of adjusted hazard effects in persons at all stages of fibrosis.**

Study, Year (Reference)	log(Hazard Ratio)	SE	Total SVR	Total NR	Weight, %	Hazard Ratio IV, Random (95% CI)
Asahina et al, 2010 (36)	–0.944	0.388	686	1356	9.2	0.39 (0.18–0.83)
Hung et al, 2011 (46)	–1.423	0.273	1027	443	15.3	0.24 (0.14–0.41)
Kawamura et al, 2010 (50)	–1.985	0.407	1081	977	8.5	0.14 (0.06–0.31)
Kramer et al, 2011 (27)	–1.182	0.126	4292	10 276	31.2	0.31 (0.24–0.39)
Kurokawa et al, 2009 (51)	–1.277	0.631	139	264	4.0	0.28 (0.08–0.96)
Okanoue et al, 2002 (53)	–2.294	0.512	375	586	5.8	0.10 (0.04–0.28)
Osaki et al, 2012 (50)	–2.130	1.053	185	197	1.5	0.12 (0.02–0.94)
Pradat et al, 2007 (17)	–2.481	1.132	87	103	1.3	0.08 (0.01–0.77)
Sinn et al, 2008 (56)	–1.246	0.596	296	194	4.4	0.29 (0.09–0.93)
Takahashi et al, 2011 (57)	–3.022	1.163	89	114	1.3	0.05 (0.00–0.48)
Tateyama et al, 2011 (58)	–1.968	0.537	139	234	5.3	0.14 (0.05–0.40)
Yoshida et al, 1999 (61)	–1.164	0.324	789	1568	12.1	0.31 (0.17–0.59)
Total			9185	16 312	100.0	0.24 (0.18–0.31)

Heterogeneity: tau-square = 0.04; chi-square = 14.05; $P = 0.23$; $I^2 = 22\%$

Test for overall effect: $Z = 10.80$; $P < 0.001$



Morgan et al Ann Int Med 2013

Effect of SVR on HCC incidence/risk

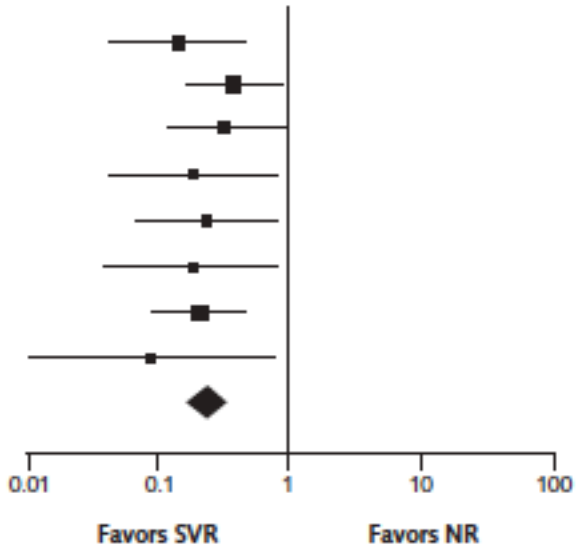
- Meta-analysis of observational studies

Figure 2. **Forest plot of adjusted hazard effects in persons with advanced liver disease.**

Study, Year (Reference)	log(Hazard Ratio)	SE	Total		Weight, %	Hazard Ratio IV, Random (95% CI)
			SVR	NR		
Braks et al, 2007 (37)	–1.966	0.601	37	76	11.2	0.14 (0.04–0.45)
Bruno et al, 2007 (38)	–0.954	0.425	124	759	22.4	0.39 (0.17–0.89)
Cardoso et al, 2010 (40)	–1.120	0.514	103	204	15.3	0.33 (0.12–0.89)
Hasegawa et al, 2007 (64)	–1.690	0.755	48	57	7.1	0.18 (0.04–0.81)
Hung et al, 2006 (65)	–1.468	0.622	73	59	10.4	0.23 (0.07–0.78)
Morgan et al, 2010 (52)	–1.721	0.764	140	309	6.9	0.18 (0.04–0.80)
van der Meer et al, 2012 (63)	–1.592	0.416	192	338	23.4	0.20 (0.09–0.46)
Velosa et al, 2011 (60)	–2.433	1.108	39	91	3.3	0.09 (0.01–0.77)
Total			756	1893	100.0	0.23 (0.16–0.35)

Heterogeneity: tau-square = 0.00; chi-square = 3.64; $P = 0.82$; $I^2 = 0\%$

Test for overall effect: $Z = 7.21$; $P < 0.001$



Morgan et al Ann Int Med 2013

Effect of SVR on HCC incidence/risk

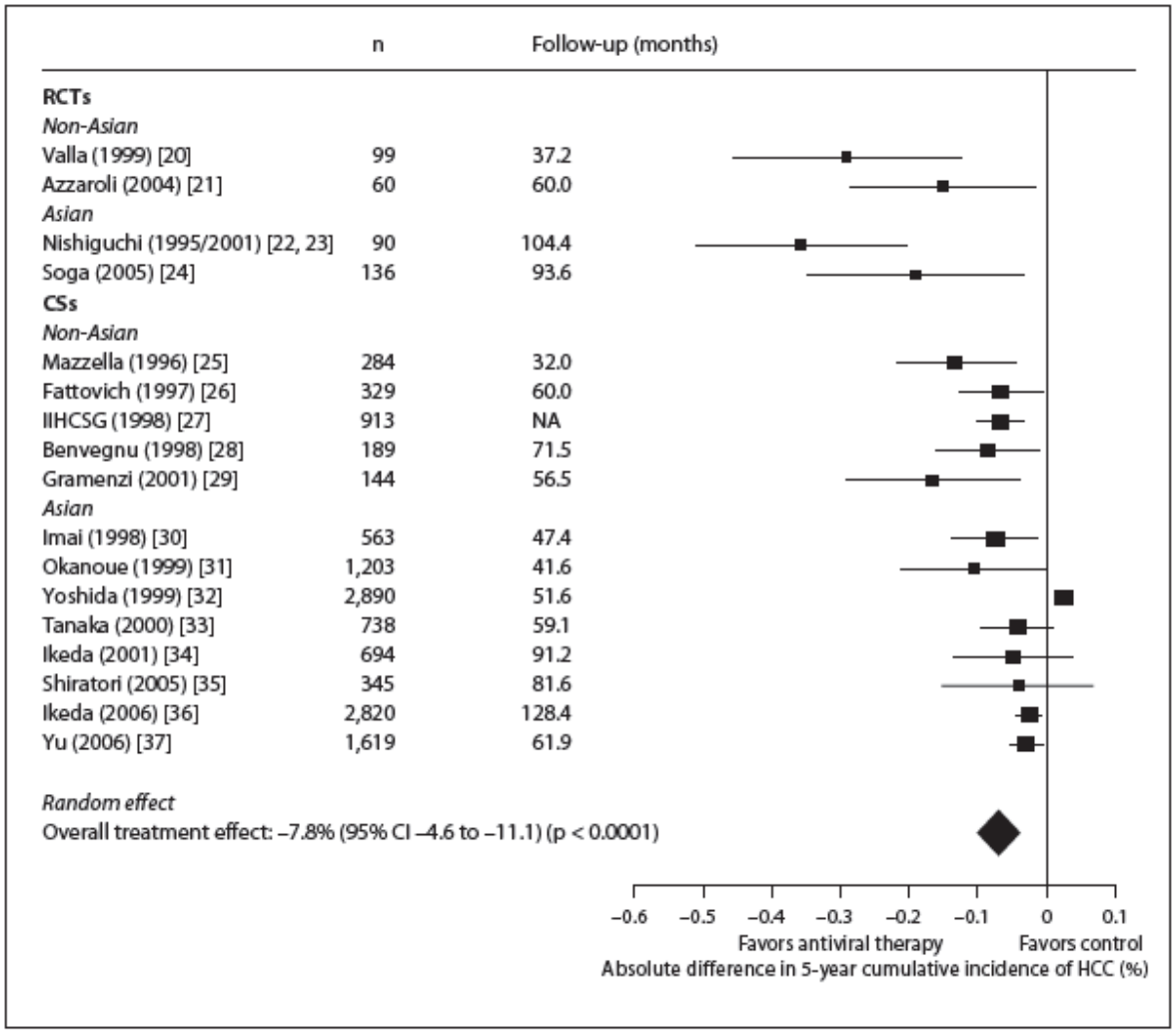
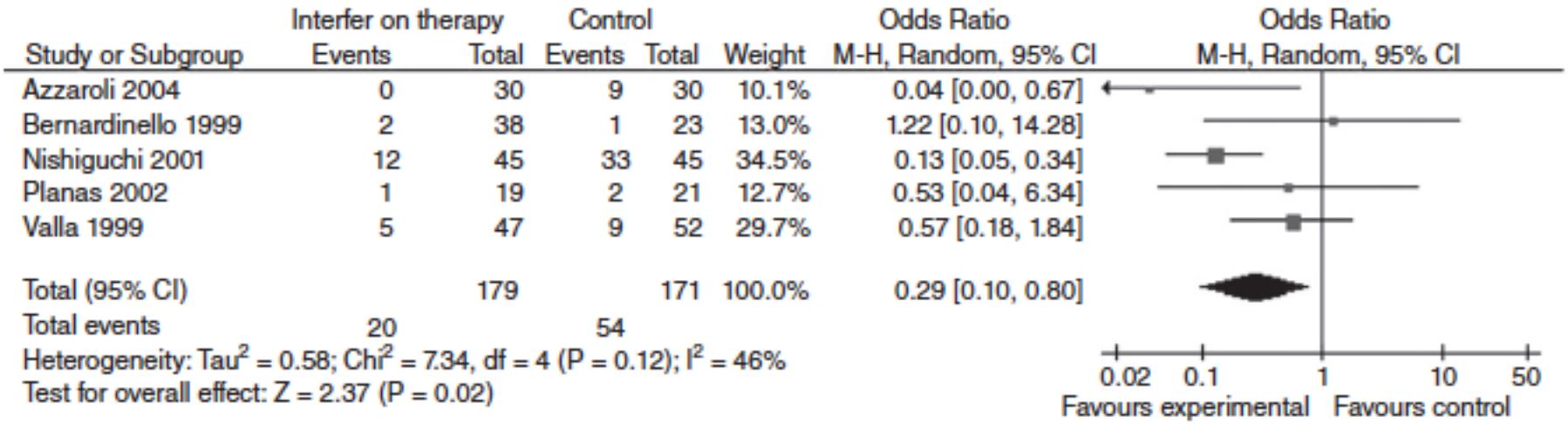


Fig. 2. Forest plot of the 17 studies of CHC included in the meta-analysis.

Shen et al Oncology 2012

Effect of SVR on HCC incidence/risk

- Meta-analysis of RCT's
- Cirrhotic patients



Study or Subgroup	Interfer on therapy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Azzaroli 2004	0	30	9	30	10.1%	0.04 [0.00, 0.67]
Bernardinello 1999	2	38	1	23	13.0%	1.22 [0.10, 14.28]
Nishiguchi 2001	12	45	33	45	34.5%	0.13 [0.05, 0.34]
Planas 2002	1	19	2	21	12.7%	0.53 [0.04, 6.34]
Valla 1999	5	47	9	52	29.7%	0.57 [0.18, 1.84]
Total (95% CI)		179		171	100.0%	0.29 [0.10, 0.80]
Total events	20		54			

Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 7.34$, df = 4 (P = 0.12); $I^2 = 46\%$

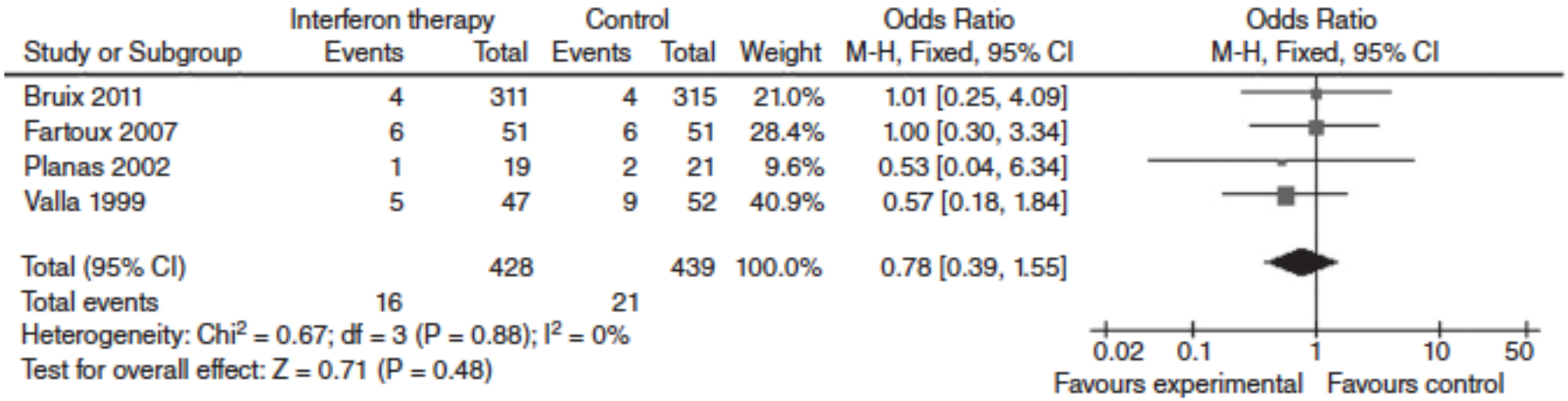
Test for overall effect: Z = 2.37 (P = 0.02)

Figure 2 Forrest plot for hepatocellular carcinoma development in hepatitis C virus-related cirrhotic patients: comparison of interferon-treated patients and untreated patients. The blocks and lines in figures indicate the estimate of odds ratio and 95% confidence interval (CI), and the sizes of blocks relate to the size of the individual study. The diamond indicates the overall estimate from the meta-analysis. M-H, Mantel–Haenszel method.

Qu et al Hepatology Research 2012

Effect of SVR on HCC incidence/risk

- Meta-analysis of RCT's
- Cirrhotic patients



Study or Subgroup	Interferon therapy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bruix 2011	4	311	4	315	21.0%	1.01 [0.25, 4.09]
Fartoux 2007	6	51	6	51	28.4%	1.00 [0.30, 3.34]
Planas 2002	1	19	2	21	9.6%	0.53 [0.04, 6.34]
Valla 1999	5	47	9	52	40.9%	0.57 [0.18, 1.84]
Total (95% CI)		428		439	100.0%	0.78 [0.39, 1.55]
Total events	16		21			

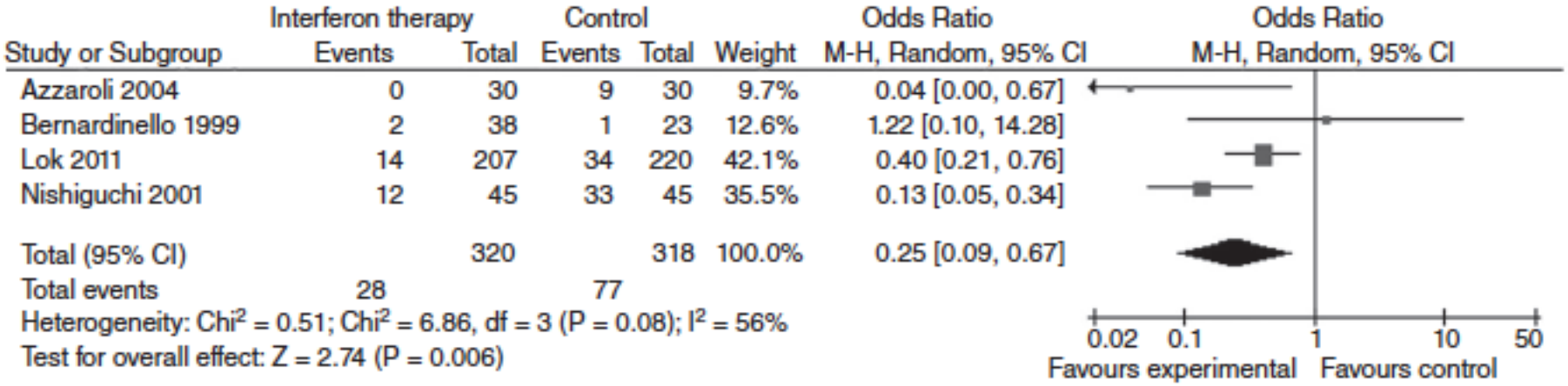
Heterogeneity: $Chi^2 = 0.67$; $df = 3$ ($P = 0.88$); $I^2 = 0\%$
Test for overall effect: $Z = 0.71$ ($P = 0.48$)

Figure 4 Forrest plot for hepatocellular carcinoma development in hepatitis C virus-related cirrhotic patients with short-term follow up (≤48 months): comparison of interferon treated patients and untreated patients. The blocks and lines in figures indicate the estimate of odds ratio and 95% confidence interval (CI), and the sizes of blocks relate to the size of the individual study. The diamond indicates the overall estimate from the meta-analysis. M-H, Mantel–Haenszel method.

Qu et al Hepatology Research 2012

Effect of SVR on HCC incidence/risk

- Meta-analysis of RCT's
- Non-cirrhotic patients



Study or Subgroup	Interferon therapy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Azzaroli 2004	0	30	9	30	9.7%	0.04 [0.00, 0.67]
Bernardinello 1999	2	38	1	23	12.6%	1.22 [0.10, 14.28]
Lok 2011	14	207	34	220	42.1%	0.40 [0.21, 0.76]
Nishiguchi 2001	12	45	33	45	35.5%	0.13 [0.05, 0.34]
Total (95% CI)		320		318	100.0%	0.25 [0.09, 0.67]
Total events	28		77			

Heterogeneity: $Chi^2 = 0.51$; $Chi^2 = 6.86$, df = 3 (P = 0.08); $I^2 = 56\%$

Test for overall effect: Z = 2.74 (P = 0.006)

Figure 5 Forrest plot for hepatocellular carcinoma development in hepatitis C virus-related cirrhotic patients with long-term follow up (>48 months): comparison of interferon-treated patients and untreated patients. The blocks and lines in figures indicate the estimate of odds ratio and 95% confidence interval (CI), and the sizes of blocks relate to the size of the individual study. The diamond indicates the overall estimate from the meta-analysis. M-H, Mantel–Haenszel method.

Qu et al Hepatology Research 2012

Effect of SVR on HCC incidence/risk

- Met-analysis
  - Comparing HCC incidence in SVR vs no SVR
  - Stratified by stage of fibrosis
    - 20 studies of all fibrosis stages
    - 6 studies of advanced fibrosis

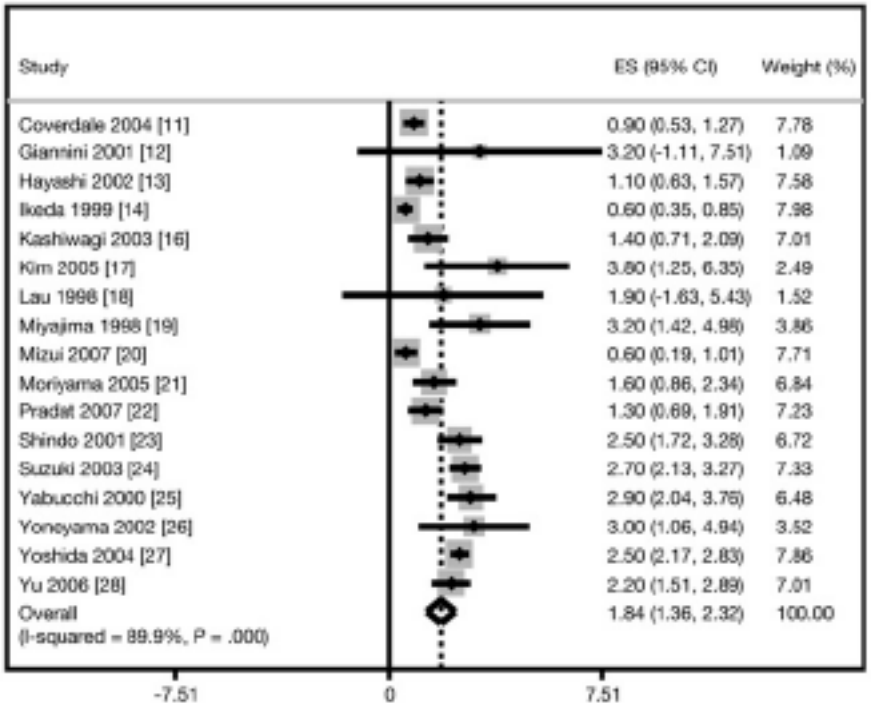
Singal et al Clin Gastro Hep 2010

Table 1. Descriptive Characteristics of Each Study

Study ID	First author[reference], location	Design	Nu
Studies that included all stages of fibrosis			
1	Arase,[11] Japan	Retrospective, single-center	
2	Coverdale,[12] Australia	Retrospective, single-center	
3	Giannini,[13] Italy	Retrospective, single-center	
4	Hayashi,[14] Japan	Retrospective, single-center	
5	Ikeda,[15] Japan	Retrospective, multi-center	
6	Kasahara,[16] Japan	Retrospective, multi-center	
7	Kashiwagi,[17] Japan	Retrospective, single-center	
8	Kim,[18] Japan	Retrospective, single-center	
9	Lau,[19] United States	Prospective, single-center	
10	Miyajima,[20] Japan	Retrospective, single-center	
11	Mizui,[21] Japan	Retrospective, single-center	
12	Moriyama,[22] Japan	Retrospective, single-center	
13	Pradat,[23] Europe	Prospective, multi-center	
14	Shindo,[24] Japan	Retrospective, single-center	
15	Suzuki,[25] Japan	Retrospective, single-center	
16	Yabuuchi,[26] Japan	Retrospective, single-center	
17	Yoneyama,[27] Japan	Retrospective, single-center	
18	Yoshida,[28] Japan	Retrospective, multi-center	836,
19	Yoshida,[5] Japan	Retrospective, multi-center	
20	Yu,[29] Taiwan	Retrospective, multi-center	
Studies that included only advanced fibrosis (F3-F4 or Ishak 4-6)			
21	Braks,[30] France	Retrospective, multi-center	
22	Bruno,[31] Italy	Retrospective, multi-center	
23	Mallet,[32] France	Prospective, single-center	
24	Nishiguchi,[33] Japan	Prospective, single-center	
25	Tanaka,[34] Japan	Retrospective, single-center	
26	Veldt,[35] Canada and Europe	Retrospective, multi-center	

Effect of SVR on HCC incidence/risk

- HCC rate/year in non-responders
  - All stages of fibrosis

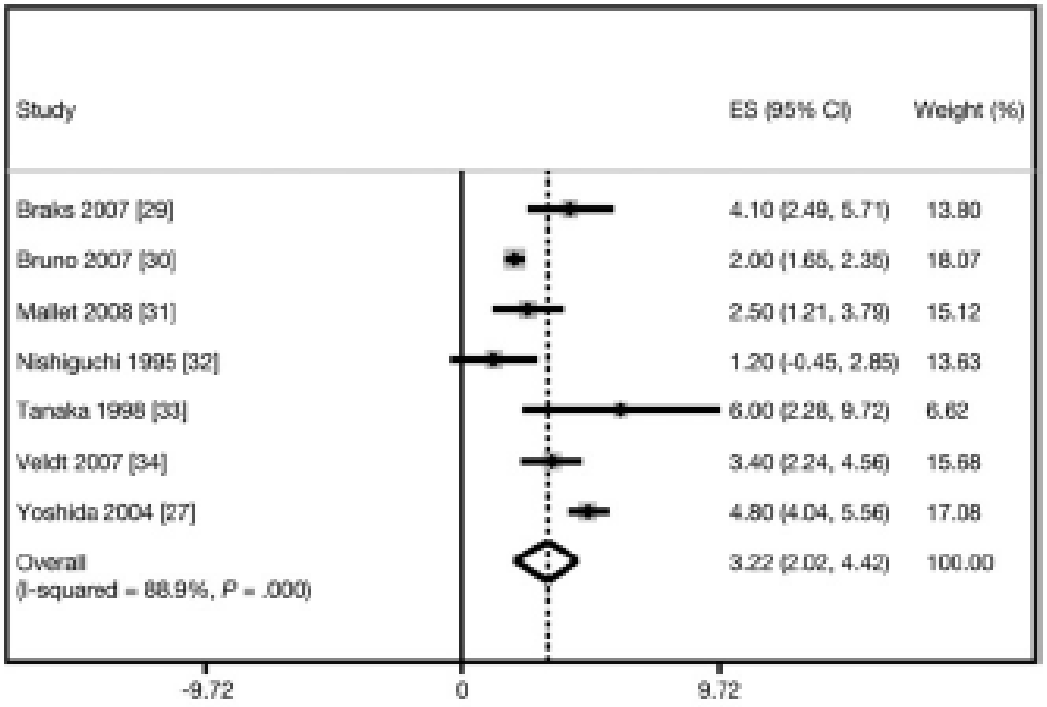


Singal et al Clin Gastro Hep 2010

Pooled rate 1.84/yr

Effect of SVR on HCC incidence/risk

- HCC rate/yr in non-responders
  - Advanced fibrosis

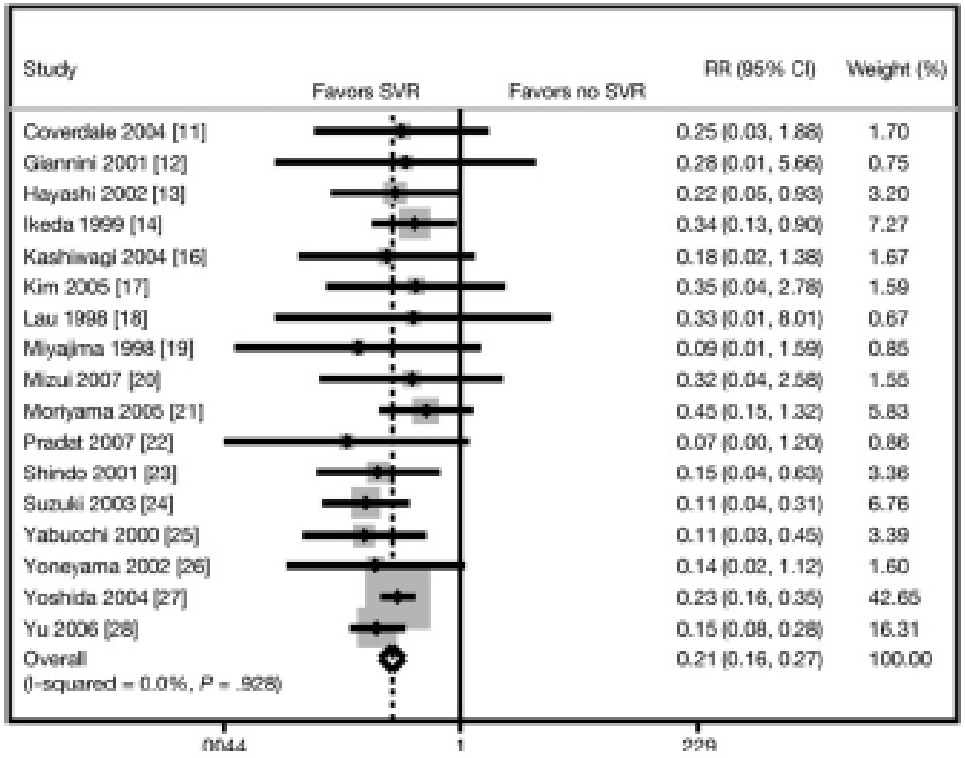


Singal et al Clin Gastro Hep 2010

Pooled rate 3.22/yr

Effect of SVR on HCC incidence/risk

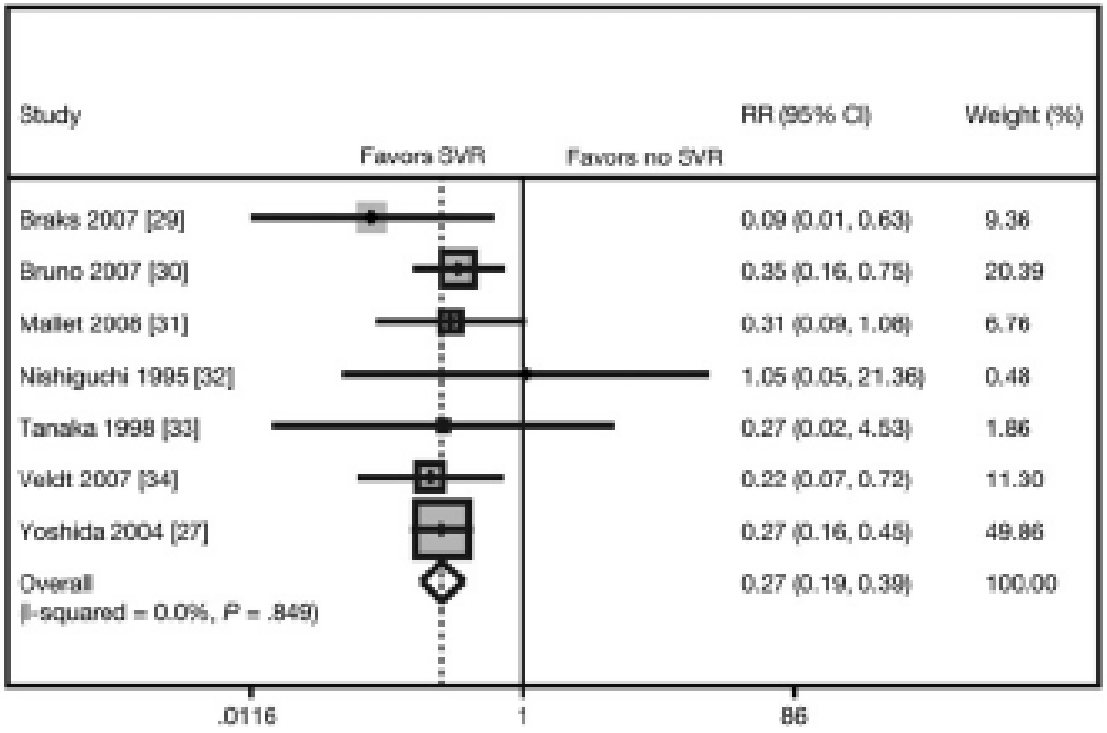
- Relative risk of HCC in non-responders vs SVR
  - All stages of fibrosis



Singal et al Clin Gastro Hep 2010 Pooled rate RR, 0.21; 95% CI, 0.16 – 0.27)

Effect of SVR on HCC incidence/risk

- Relative risk of HCC in non-responders vs SVR
  - Advanced fibrosis



Singal et al Clin Gastro Hep 2010

Pooled rate RR, 0.32; 95% CI, 0.23– 0.44)

Effect of SVR on HCC incidence/risk

- Meta-analysis
  - Treated vs untreated
  - Evaluated SVR vs non-SVR
  - Evaluated long term therapy

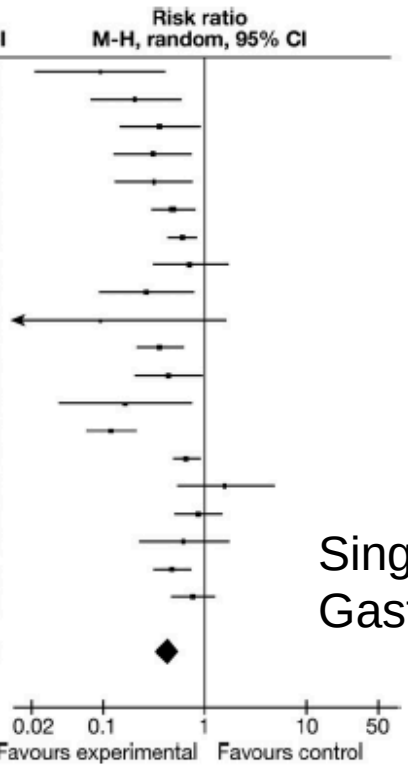
Singal et al Clin Gastro Hep 2010

Effect of SVR on HCC incidence/risk

- Cirrhosis
  - Treated vs untreated (no accounting for SVR)

Study or subgroup	Antiviral therapy Events	Total	Control Events	Total	Weight	Risk ratio M-H, random, 95% CI
Azzaroli 2004	2	71	9	30	2.3%	0.09 [0.02, 0.41]
Benvegnu 1998	4	75	20	77	3.8%	0.21 [0.07, 0.57]
Bruno 1997	6	83	16	80	4.4%	0.36 [0.15, 0.88]
Fattovich 1997	7	193	16	136	4.6%	0.31 [0.13, 0.73]
Gramenzi 2001	6	72	19	72	4.6%	0.32 [0.13, 0.74]
HCC Study Group 1998	21	232	48	259	6.9%	0.49 [0.30, 0.79]
Ikeda 1998	32	113	271	581	8.0%	0.61 [0.45, 0.82]
Imai 1998	8	32	7	20	4.6%	0.71 [0.31, 1.67]
Mazella 1996	5	193	9	92	3.6%	0.26 [0.09, 0.77]
Mura 1999	0	28	5	29	0.8%	0.09 [0.01, 1.63]
Nischiguchi 2001	12	45	33	45	6.6%	0.36 [0.22, 0.61]
Okanue 1999	7	40	22	55	5.2%	0.44 [0.21, 0.92]
Serfaty 1998	2	59	9	44	2.3%	0.17 [0.04, 0.73]
Shioda 1999	22	588	18	58	6.3%	0.12 [0.07, 0.21]
Shiratori 2005	84	271	35	74	8.0%	0.66 [0.49, 0.88]
Sofia 1999	11	103	4	59	3.5%	1.58 [0.53, 4.73]
Testino 2002	15	51	24	71	6.5%	0.87 [0.51, 1.49]
Valla 1999	5	47	9	52	3.8%	0.61 [0.22, 1.70]
Yoshida 1999	33	230	32	107	7.2%	0.48 [0.31, 0.74]
Yu 2006	36	165	19	68	6.9%	0.78 [0.48, 1.26]
Total (95% CI)		**2691**		**2009**		**0.43 [0.33, 0.56]**

Heterogeneity: $Chi^2 = 59.10$, df = 19 ($P < .00001$)
Test for overall effect: Z = 6.27 ($P < .00001$)



Singal et al Clin Gastro Hep 2010

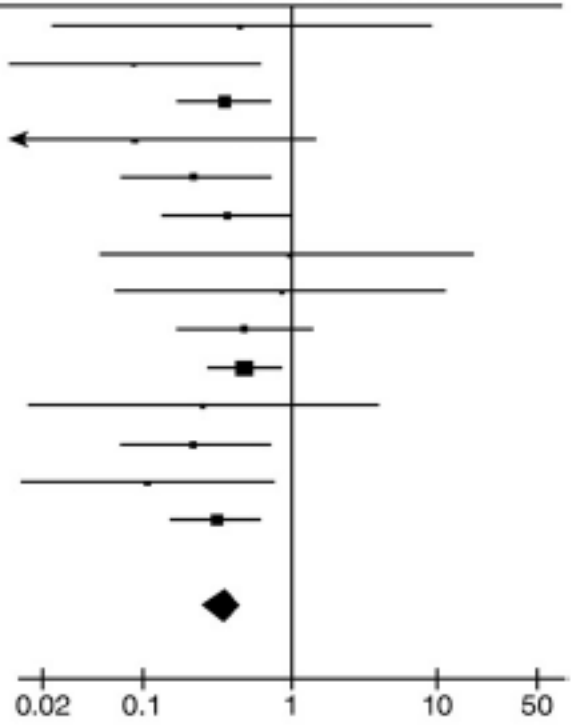
Figure 2. Forrest plot for HCC development in patients with HCV cirrhosis: comparison of treated patients with antiviral therapy (IFN or IFN and RBV) and untreated patients.

Effect of SVR on HCC incidence/risk

- Cirrhosis
  - SVR vs non-SVR

Study or subgroup	SVR Events	SVR Total	NSVR Events	NSVR Total	Weight	Risk ratio M-H, random, 95% CI
Azzaroli 2004	0	21	2	50	1.0%	0.46 [0.02, 9.27]
Braks 2007	1	37	24	76	2.3%	0.09 [0.01, 0.61]
Bruno 2007 (1)	7	124	122	759	16.0%	0.35 [0.17, 0.73]
Floreani 2008 (2)	0	40	5	38	1.1%	0.09 [0.00, 1.51]
Hasegawa 2007 (3)	3	48	16	57	6.3%	0.22 [0.07, 0.72]
Hung 2006	5	73	11	59	8.7%	0.37 [0.14, 1.00]
Nishiguchi 1995	0	7	2	38	1.0%	0.97 [0.05, 18.43]
Okanoue 1999	0	2	7	38	1.3%	0.87 [0.06, 11.79]
Shioda 1999	4	204	18	448	7.6%	0.49 [0.17, 1.42]
Shiratori 2005	11	64	73	207	26.9%	0.49 [0.28, 0.86]
Tanaka 1998	0	8	10	47	1.2%	0.25 [0.02, 3.96]
Veldt 2008	3	142	32	337	6.4%	0.22 [0.07, 0.71]
Yoshida 1999 (4)	1	53	30	168	2.2%	0.11 [0.01, 0.76]
Yu 2006	9	85	27	80	18.3%	0.31 [0.16, 0.63]
Total (95% CI)		**908**		**2402**		**0.35 [0.26, 0.46]**

Heterogeneity: $Chi^2 = 8.67$, df = 13 ($P = .80$)
Test for overall effect: Z = 7.06 ($P < .00001$)



Singal et al Clin Gastro Hep 2010

Effect of SVR on HCC incidence/risk

- Maintenance therapy in initial treatment failures

Study or subgroup	Maintenance IFN Events	Total	Control Events	Total	Weight	Risk ratio M-H, fixed, 95% CI
Afdhal 2004 [COPILOT]	7	270	8	264	26.7%	0.86 [0.31, 2.33]
DiBisceglie 2008 [HALT-C]	4	208	10	220	32.1%	0.42 [0.13, 1.33]
Erhardt 2007	0	44	6	44	21.4%	0.08 [0.00, 1.33]
Fartoux 2007	6	51	6	51	19.8%	1.00 [0.35, 2.89]
Total (95% CI)		**573**		**579**		**0.58 [0.33, 1.03]**

Heterogeneity: $Chi^2 = 3.82$, df = 3 ($P = .28$)
Test for overall effect: Z = 1.87 ($P = .06$)

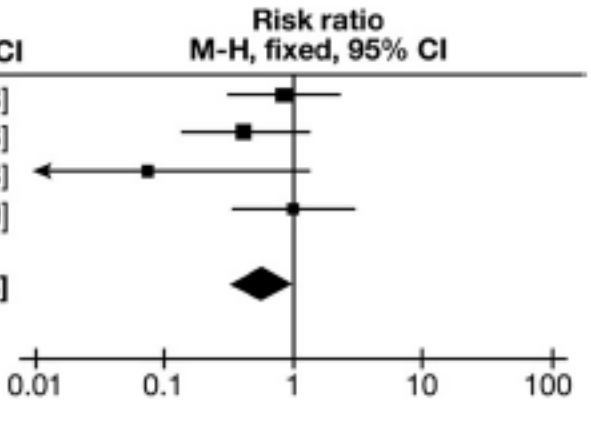


Figure 4. Forrest plot for HCC development in patients with HCV cirrhosis who did not respond to initial antiviral therapy (IFN or IFN and RBV): comparison of maintenance IFN and controls or no treatment.

Singal et al Clin Gastro Hep 2010

Summary

- Studies of HCC incidence following SVR compared to no treatment
  - Beneficial effect of SVR
- Studies of HCC incidence comparing SVR to no SVR shows that HCC incidence is reduced
- Maintenance therapy in treatment failures does not reduce HCC incidence
- Confirmed by meta-analysis

Remaining questions

- Does reduced HCC incidence mean that HCC screening is not necessary in the initial post treatment phase?
  - No data
- Is HCC incidence further reduced with time?
- Will a point be reached where HCC screening is not required?