

Hepatitis C Infection and Hepatocellular Carcinoma in Thailand: A Long Term Study of 63 HCV Patients

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Abstract

Out of 102 seropositive for hepatitis C antibody, chronic active hepatitis, cirrhosis and cirrhosis with hepatocellular carcinoma were cross sectionally found in 25.4, 12.7 and 9.8 percent. Sixty-three cases, 29 males and 34 females were followed for more than 5 years (more than 10 years in 20.6%) 15.9 percent developed hepatocellular carcinoma. The cumulative risk for death from hepatocellular carcinoma at year 10 after the diagnosis of HCV infection is 60 percent. (*J Infect Dis Antimicrob Agents 1999;16:1-5.*)

In Thailand hepatitis B virus (HBV) was found in the serum of Thai in 9.4 percent¹ while hepatitis C virus (HCV) was recorded among the volunteer blood donors as 0.6-2 percent²⁴ therefore the health impacts of HCV on the Thai seem to be much less than those of HBV. However in a recent study in the blood donors in the Northeastern Thailand. HCVAB was found to be 5.2 percent.⁵ Hepatocellular carcinoma (HCC) is generally considered as a number one killer among the Thai males and it had been cited as related mostly to HBV. In a recent serological study by Phornphutkul and associates⁴ from Chiang Mai, Northern Thailand in 247 HCC cases, HBV, HBV plus HCV and HCV were found in 69, 13.6 and 18.3 percent, respectively. In many countries HCV has been found to be a major risk factor for HCC.⁶⁻⁹ However, Nomura et al¹⁰ found a strong association between HCC and HBV, not with HCV. Kaklamani et al¹¹ suggested the additive roles of HBV and HCV rather than either virus to have risk of developing HCC. Prior to the availability of HCV

antibody detection we knew that 64 percent of post transfusion hepatitis among the Thai were non A non B virus which were later proved to be HCV.¹² We have an opportunity to perform a cross section study of 102 HCV positive patients and a long term study of 5 to 15 years or more on 63 HCV hepatitis which will be reported.

SUBJECTS AND METHODS

Patients who attended at our clinic with the clinical diagnosis of possible viral hepatitis were subjected to serological screening for HBV, HAV IgM and HCV AB (using the third generation antigen by microparticle enzyme immunoassay). Lately PCR for HCV RNA was done in some cases. Patients were asked to make regular visits every 1-3 months depending upon their clinical setting and regular blood tests including ALT, AST, antinuclear factor, alfa fetoprotein (AFP) and some other biochemical tests were performed. Sonogram of the abdomen was done every 6 months. All are private patients with medium to higher income

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and liver biopsy was permitted to be performed in only 4 cases.

Two clinical aspects of HCV are studied; one is the cross section of the clinico-biochemical presentation of all HCV cases who visit the clinic and another aspect is a long term study of the clinical outcome of 63 HCV cases who were followed for 5-15 years or more.

RESULTS

Patients who came to the hospital with clinical features suggestive of hepatitis or other liver diseases were tested for HCV antibody during 1990-1996. The result was shown in Table 1, out of 3,008 cases 224 or 7.4 percent were positive for HCV AB. A total of 102 documented HCV hepatitis cases regularly attended at our clinic. They came from every part of the country, mainly from Bangkok as shown in Table 2. Twenty-four came from neighboring countries namely 22 from Cambodia, one each from Malaysia and India. Out of these 102 cases co-infection with HBV was found in 6 cases and with HIV in 2 cases. Age and sex distribution were presented in Table 3 and male to female ratio was 1.3:1. Pearson chi-square value was

Table 1. Frequencies of HCV seropositive among clinically suspected hepatitis or chronic liver diseases during 1990-1996 at Vichaiyut Hospital.

Year	No. test	No. positive	Percent
1990	420	18	4.3
1991	228	19	8.3
1992*	52	6	11.5
1993	601	37	6.2
1994	247	31	12.6
1995	404	44	10.9
1996	1,056	69	6.5
Total	3,008	224	7.4

* Incomplete data

Table 2. Geographical locations of 102 HCV cases.

Bangkok	61
Northeast	9
South	2
Central	6
Outside Thailand	24
Total	102

4.227 which indicates that age and sex are independent (P value 0.238). The clinical diagnosis of these 102 patients at the time of analysis is presented in Table 4.

Out of these 102 patients 63 Thai patients who were followed for more than 5 years are subjected to the long term study of the clinical progression. Age and sex distribution were presented in Table 5. Number of years of the follow-up of these 63 patients was shown in Table 6. Seventy-six percent of cases were followed for 6 years or more and more than 10 years in one third.

Table 3. Age and sex distribution of 102 HCV cases.

Sex \ Years	<20	21-30	31-40	41-50	51-60	>60	Total
Male	1	4	10	20	16	7	58
Female	0	3	16	12	7	6	44
Both	1	7	26	32	23	13	102

Table 4. Clinical diagnosis of 102 HCV seropositive cases.

Acute hepatitis	2
Normal clinico-biochemical study	4
Mild hepatitis ⁽¹⁾	47
Chronic Active Hepatitis ⁽²⁾	26
Cirrhosis	13
Cirrhosis C hepatocellular carcinoma	10
Total	102

⁽¹⁾ ALT/AST < 3 times normal

⁽²⁾ ALT/AST > 3 times normal

Table 5. Age and sex distribution of 63 HCV cases.

Sex \ Years	21-30	31-40	41-50	51-60	>61	Total
Male	3	8	11	5	2	29
Female	4	9	11	6	4	34
Total	7	17	22	11	6	63

Table 6. Years of follow-up on 63 HCV cases.

Year	Number of Patients
5-6	15
>6-7	7
>7-8	7
>8-9	7
>9-10	6
>10-15	17
>15	4
Total	63

The probable modes of infection were summarized in Table 7, it was not known in majority of cases (44.4%), however 27 cases (42.9%) were post transfusion HCV hepatitis cases who were previously diagnosed as non A non B hepatitis. They received 1-28 units of blood with average of 5 units; one unit in a case, 2 units in 11 cases, 4 units in 2 cases and 10 units or over in 5 cases. Intrafamilial contact with known infected spouse(s) was noted in 4 cases. Definite history of very frequent intravenous or hypodermic injections for treatment of medical conditions using non disposable needles during the past years were found in 3 cases and a case of HIV positive homosexual was documented. Only one patient has history of regular alcoholic drinking prior to the study and he stopped completely afterwards.

The initial clinical presentation and the final clinical diagnosis are summarized in Table 8. Twenty patients who first presented with features of acute hepatitis associated with high ALT/AST more than 3 times

Table 7. The probable modes of infection in 63 HCV cases.

Unknown	28 (44.4%)
Post transfusion	27 (42.9%)
Intrafamilial contacts	4 (6.3%)
Frequent medicine injections	3 (4.8%)
Homosexual (+HIV)	1 (1.6%)

normal turned to be milder hepatitis with lower ALT/AST than 100 units in 9 cases, prolonged aggressive hepatitis with ALT/AST persistently higher than 200 in 5 cases, two cases developed cirrhosis and other 4 cases died of HCC associated with cirrhosis.

Other 30 patients who were initially diagnosed as mild hepatitis, three cases turned to be persistently aggressive hepatitis and 2 died of HCC. Seven chronic active hepatitis became HCC in 2 cases or 28.6 percent. Out of 6 cirrhotic patients on the first visit 2 cases became HCC or 33.3 percent. All together out of 63 HCV cases 16 (25.4%) developed cirrhosis and 10 of them (15.9%) turned to be HCC. All HCC were confirmed by liver biopsy or necropsy. Therefore the attack rate for HCC on the long term HCV infection was 15.9 percent and it is higher in certain clinical settings.

Table 9 revealed a duration from the first visit to the time of diagnosis of HCC among the 4 groups; obviously, it is most rapid (5 years) in already cirrhotic patients, and longer term (14 years) for those who presented with mild hepatitis. HCC developed within 5-16 years (average 9.5 years). Cumulative risk for death from HCC in HCV patients with cirrhosis is shown in Fig. 1. The cumulative risk for HCC at year 9 is 50 percent. The cumulative survival of 63 HCV patients was shown in Fig. 2.

Alfa lymphoblastiod interferon (IFN α n1) was given 3 MU thrice weekly for 6 months to 17 patients

Table 8. The first and final clinical diagnosis of 63 HCV cases.

First Clinical Diagnosis	No. Case	Last clinical diagnosis			
		Mild Hepatitis	Chronic Aggressive Hepatitis	Cirrhosis	Cirrhosis \bar{c} HCC
Acute Hepatitis	20	9	5	2	4 (20%)
Mild Hepatitis	30	25	3	-	2 (6.7%)
Chronic Active Hepatitis	7	2	3	-	2 (28.6%)
Cirrhosis	6	-	-	4	2 (33.3%)
Total	63	36	11	6	10 (15.9%)

Table 9. Duration from the first visit to the diagnosis of hepatocellular carcinoma among 63 HCV cases.

Clinical Diagnosis on First Visit	Hepatocellular Carcinoma		Duration	
	No. Case	Years	(Average)	
Acute Hepatitis	4	9, 9, 10, 11	(9.7)	
Mild Hepatitis	2	12, 16	(14)	
Chronic Hepatitis	2	7, 11	(9)	
Cirrhosis	2	5, 5	(5)	
All	10	5-16	(9.5)	

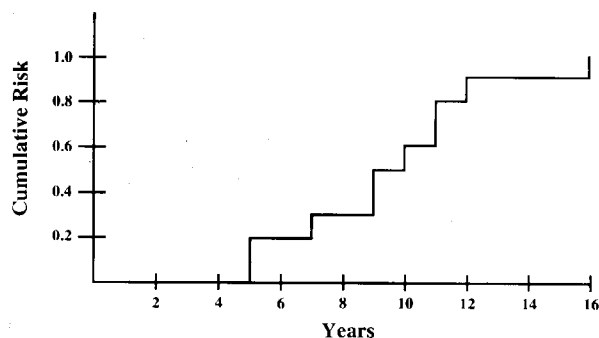


Fig. 1 Cumulative risk for mortality from hepatocellular carcinoma in HCV patients with cirrhosis.

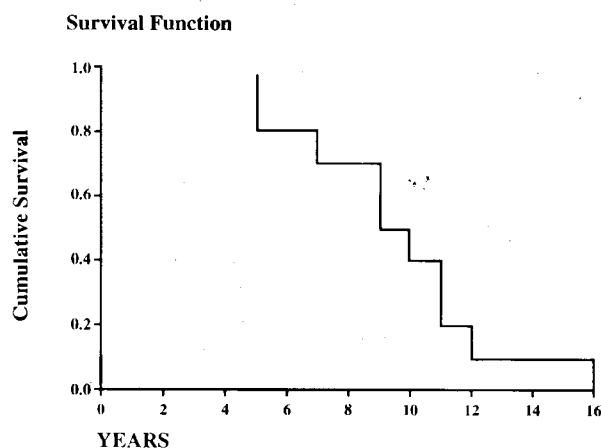


Fig. 2 Cumulative probability of survival of 63 HCV patients on 5-16 years follow-up.

* (Kaplan GL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Ass* 1958;53:457-81.

(10 M 7 F); sustained response was noted in 3 (17.6%) and no response in 4 (23.5%), other 7 responded with recurrence. Another 3 responded but they are still too early to be concluded. None of the treated patients developed HCC.

DISCUSSION

HCV infection is not unusual in cases of liver ailment among the Thais and it is recently found to be more so in the neighboring countries such as Laos and Cambodia.¹³ It attacks all ages and may present as acute hepatitis, mild hepatitis, chronic active hepatitis as well as cirrhosis. Among the known modes of infection; post transfusion hepatitis is most common (42.9%). In our study of 38 post transfusion HCV hepatitis when the definite time of infection can be pinned down, overt clinical cirrhosis was recognized as early as year five.¹⁴ There may be some different in time of disease progression between post trans-

fusion infection and other modes of infection because in the post transfusion HCV infection the occurrence of cirrhosis is found in 44.7 percent¹⁴ compared to 25.4 percent in this study. Yet chronic liver disease including cirrhosis is extremely common among HCV than that of HBV namely 16 out of 63 HCV cases (25.4%) compared to 9 out of 148 cases (6.1%) of HBV in our studies. This is probably the only long term study of HCV infection in Thailand and the Southeast Asian Nations.

The most significant finding of this study is the recognition of a very high incidence of HCC (15.9%) among chronic HCV infection which is in agreeable with 13.1 percent of HCC in post transfusion HCV infection.¹⁴ All of HCC cases are associated with the preceding cirrhosis. HCC was first occurred in the fifth year after the clinical diagnosis of cirrhosis or about 9.5 years after the first recognition of HCV infection. The cumulative risk for death from HCC at year 9 is 50 percent. Compare to our similar long term study in HBV, HCV induces much higher incidence of HCC namely 10 HCC out of 63 HCV cases compared to 1 out of 148 HBV cases. The prevalence of HCC varies according to the different clinical setting; low (6.7%) in the mild hepatitis group, higher (20%) in acute hepatitis and highest among the chronic active hepatitis and cirrhosis (28.6% and 33.3%, respectively). Gentilini P, et al¹⁵ from Italy followed 321 HCV and 84 HBV related cirrhosis for 8 ± 3 years and the incidence of HCC was similar in patients with either HBV or HCV related diseases. HCC occurred in 5 percent of patients after 5 years, 23.9 percent after 10 years and 50.1 percent after 15 years. In another study¹⁶ of 384 European HCV cirrhotic patients the 5 years risk of HCC was 7 percent. The progression of HCV infection in Thailand is more rapid and the magnitude of risk for HCC is higher than HCV infection in Europe. Therefore HCV should be considered as a serious infection and we should make the best effort to terminate the infection whenever possible. It has been demonstrated that in Thailand the genotypes 1 and 3 are the two most common genotypes in about 70 percent and 30 percent, respectively.¹⁷ Both genotypes are generally considered as potential for inducing severe liver diseases. In this country alpha interferon demonstrates limited efficacy (response rate 55.6%) and the sustained remission of biochemical hepatitis after interferon therapy may occur in low percentage (14%).¹⁸ This might be related to

either certain genotypes or the different in modes of infections or different in the host response. It is interesting to note that out of 22 cases from Cambodia of whom we do not know the specific genotypes, 13 were treated with the same regimen of interferon and the response was found to be higher (84.6%).¹⁸ In this study interferon therapy normalized the abnormal level of alfa fetoprotein in all cases but it is too early to know whether it may prevent the occurrence of HCC. At the end of the study all 10 HCC with cirrhosis and 2 out of 6 cirrhotic patients died of liver diseases.

SUMMARY

Hepatitis C virus is not too uncommon among the Southeast Asians yet its impacts on the liver ailment is so great. It is highly responsible for the development of chronic liver diseases including cirrhosis and hepatocellular carcinoma. In this long term study of more than 5 years 15.9 percent of HCV patients developed hepatocellular carcinoma associated with cirrhosis, which is much higher percentage than that of HBV. The cumulative risk for death from hepatocellular carcinoma at year 10 after the diagnosis of HCV infection is 60 percent. Hepatitis virus C will remain to be a major problem since the effective treatment as well as protective vaccine is not yet available.

References

1. Punyagupta S, Olson LC, Harinasuta U, Akarawong K, Varawidhya W. The epidemiology of hepatitis B antigen in a high prevalence area. *Am J Epidemiol* 1973;97:349-54.
2. Nujprayoon C. Safety of the Blood Supply in Thailand. *JAMA SEA* 1996 April:5-6.
3. Suwanagool S, Tiengrim S, Ratanasuwana W, et al. Seroprevalence of anti HCV among HIV infected persons and general population. *J Med Assoc Thai* 1995;78:611-7.
4. Phornphutkul K, Peerakome S, Yousukon A, Toriyama K, Shimotohno K. Hepatitis C infection in Northern Thailand. Faculty of Medicine, Chiang Mai University, Thailand. Presented at the Annual Scientific Meeting of the Gastroenterological Association of Thailand on Jan 31-Feb 2, 1996, Chiang Rai, Thailand.
5. Songsivilai S, Jirathongthai S, Wongsena W, Trangpitayakorn C, Dharakul T. High prevalence of hepatitis C infection among blood donors in Northeastern Thailand. *Am J Trop Med Hyg* 1997;57:66-9.
6. Khan M, Ganger D, Jensen DM. Hepatitis C: the major risk factor associated with hepatocellular carcinoma. *Gastroenterol* 1995;108 (Suppl. A):1096.
7. Colombo M, Kuo G, Chov QL, et al. Prevalence of antibodies to hepatitis C virus in Italian patient with hepatocellular carcinoma. *Lancet* 1989;2:1006-8.
8. Kiyosawa K, Furuta S. Clinical aspects and epidemiology of hepatitis B and C virus in hepatocellular carcinoma in Japan. *Cancer Chemotherapy Pharmacol* 1992;31:S150-6.
9. Yu MC, Tong MJ, Coursaget P, et al. Prevalence of hepatitis B and C virus markers in Black and White patients with hepatocellular carcinoma in the United States. *J Natl Cancer Inst* 1990;82:1038-47.
10. Nomura A, Stemmerman GN, Chyou PH, Tabor E. Hepatitis B and C virus serologies among Japanese Americans with hepatocellular carcinoma. *J Inf Dis* 1996;173:1474-6.
11. Kaklamani E, Trichopoulos D, Tzonou A, et al. Hepatitis B and C viruses and their interaction in the origin of hepatocellular carcinoma. *JAMA* 1991;265:1974-6.
12. Punyagupta S. Post transfusion hepatitis: role of non A non B hepatitis virus. *J Infect Dis Antimicrob Agents* 1987;4: 86-91.
13. Songsivilai S. Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. (Personal Communication)
14. Punyagupta S, Siwadune T. The long term outcome of thirty-eight post transfusion hepatitis C. Submitting for publication (Personal communication)
15. Gentilini P, Laffi G, La Villa G, et al. Long course and prognostic factors of virus-induced cirrhosis of the liver. *Am J Gastroenterology* 1997;92:66-72.
16. Fattovich G, Ginstina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C; a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-72.
17. Songsivilai S, Kanistanon P, Panyavinin W, Neelamek M, Dharakul T. Improved amplification system for detection of hepatitis C virus genome that simultaneously differentiates viral genotypes. *Southeast Asian J Trop Med Public Health* 1996;27:237-43.
18. Jidpugdeebodin S, Punyagupta S. Lymphoblastoid Interferon in 36 Chronic Hepatitis C Infections. (1998) Submitted for publication in the Journal of Infectious Diseases and Antimicrobial Agents.