



Prognosis and Causes of Death in Individuals with Hepatitis C

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Abstract

Many patients with Hepatitis C Virus (HCV) infection show progression to chronic hepatitis. About 30% of HCV infected individuals are known to show natural resolution in the acute phase of infection. However, the long-term prognosis after HCV eradication is unknown. We show the outcomes and causes of death of HCV-infected patients.

The subjects were 1115 individuals who tested positive for anti-HCV antibody between 1991 and 2016. 346 patients were HCV RNA-negative and 721 were positive. The average age at death for hepatitis C-infected individuals was 79.5 ± 8.1 years. The average age at death among individuals who showed spontaneous resolution of hepatitis C was 79.4 ± 9.2 years. In this group, the causes of death included liver-related disease (6%; 65.3 ± 9.6 years), cancers other than natural resolution (24.7%; 77.4 ± 7.5 years), pneumonia (20.3%; 84.2 ± 5.9 years), cerebrovascular disease (13.7%; 76.8 ± 11.2 years), heart disease (11.5%; 78.2 ± 9.1 years), renal disease (1.1%; 79.5 ± 6.4 years old), and others (22.5%; 82.7 ± 7.9 years). Patients with HCC died at a relatively young age (65.3 ± 9.6 years) compared with the others. The results of the present study suggest that even if the hepatitis C virus has been undetectable for a long period of time, the incidence of liver cancer is nevertheless higher than usual, and therefore the reasons for this require further investigation.

Keywords: Hepatitis C virus; Natural resolution; Direct acting antivirals; Hepato cellular carcinoma

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Received Date: 08 Aug 2018

Accepted Date: 30 Aug 2018

Published Date: 01 Sep 2018

Citation:

Okumoto K, Saito T, Nishina T, Mizuno K, Tomita K, Haga H, et al. Prognosis and Causes of Death in Individuals with Hepatitis C. *Ann Clin Hepatol*. 2018; 2(1): 1006.

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Introduction

Many patients with Hepatitis C Virus (HCV) infection show progression to chronic hepatitis [1]. It is estimated that around 80 million individuals are chronically infected with HCV worldwide, and that 350,000 die each year due to HCV-related liver disease [2]. One progression to liver cirrhosis or liver cancer occurs, the prognosis is poor. On the other hand, about 30% of HCV-infected individuals are known to show natural resolution in the acute phase of infection [3-5]. In recent years, treatment with Direct-Acting Antivirals (DAA) has been available, allowing most patients with chronic HCV infection to be cured [6]. However, the long-term prognosis after HCV eradication is unknown. In our department, HCV screening of local residents in an HCV endemic area has been carried out since 1991 [7,8]. As 25 years have now passed since the introduction of screening, the outcomes and causes of death of HCV-infected patients have become clear. The present report documents our findings for this patient population.

Methods

The subjects were 1115 individuals who tested positive for anti-HCV antibody between 1991 and 2016. Forty eight cases were excluded because the course was unknown, leaving a total of 1067. Causes of death were investigated by reference to death certificates and a postal questionnaire. At the first visit, 346 patients were HCV RNA-negative and 721 were positive. We show characteristics of subjects in Table 1.

Result

Among the 346 patients negative for HCV RNA, 183 (males 75, females 108) were confirmed to have died. Nine patients with IFN or DAA therapy were excluded.

Among the 721 patients positive for HCV RNA, death was confirmed in 397, of whom 361 people could not be confirmed as HCV RNA-negative by the time of death. The average age at death for hepatitis C-infected individuals was 79.5 ± 8.1 years (males 77.9 years, females 81.1 years). Liver

Table 1: Characteristics of subjects.

	HCV RNA+ N=721	HCV RNA- N=346	
Male/Female	299/422	125/221	NS
BMI	23.2 ± 2.9	23.3 ± 3.0	NS
AST	44.3 ± 42.1	36.1 ± 36.8	P<0.01
ALT	40.4 ± 48.8	30.4 ± 42.9	P<0.01
γGTP	29.1 ± 36.5	26.9 ± 49.8	NS
HBsAg (+/-)	12/709	5/341	NS
Average age at death	79.5 ± 8.1	79.4 ± 9.2	NS

related death was most common among the HCV RNA(+) patients who died (27%; mean age at death 75.8 ± 7.9 years), followed by other cancers (20%; 78.5 ± 7.3 years) and respiratory disease (13%; 83.2 ± 6.5 years) (Table 2). We could not identify the details of liver related death such as ascites, variceal rupture because this study investigated by reference to death certificates and a postal questionnaire. Among cases of cancer death, hepatocellular carcinoma accounted for the majority (45%; 74.3 ± 7.9 years) (Table 3). Meanwhile, the average age at death among individuals who showed spontaneous resolution of hepatitis C (HCV RNA-negative) was 79.4 ± 9.2 years (males 75.9 years, females 81.6 years). In this group, the causes of death included liver related disease (6%; 65.3 ± 9.6 years), cancers other than liver cancer (24.7%; 77.4 ± 7.5 years), pneumonia (20.3%; 84.2 ± 5.9 years), cerebrovascular disease (13.7%; 76.8 ± 11.2 years), heart disease (11.5%; 78.2 ± 9.1 years), renal disease (1.1%; 79.5 ± 6.4 years old), and others (22.5%; 82.7 ± 7.9 years) (Table 2). Among the various types of cancer death, liver cancer predominated at 19% (Table 3). Patient's with HCC died at a relatively young age (65.2 ± 9.6 years) compared with the others significantly (p<0.01). There was no

significant difference in survival age between HCV-RNA positive and negative (Figure 1). The survival age in two groups was comparable (Figure 1).

Discussion

Causes of death among patients showing spontaneous resolution of hepatitis C have been unclear. In the present study we investigated the outcomes, causes of death and ages at death among individuals with a history of hepatitis C who had been registered as HCV antibody-positive at our institution since 1991. It is one problem that there are some patients with false positive HCV antibody in HCV RNA negative group. We have already reported on individuals who showed resolution of HCV by 2003 [9]. In that study, individuals showing natural resolution had a low ZTT level, and no change in the liver was demonstrated by US. The cause of death was liver-related in a greater proportion of HCV RNA-positive individuals, including liver cancer, variceal rupture, liver failure and liver cirrhosis. However, the mean age at death in individuals who were HCV RNA-positive was not significantly different from that in individuals who were negative (79.5 years vs. 79.4 years).

This may have been attributable to the fact that HCV-positive individuals continue to receive treatment regularly. In addition, a higher proportion of HCV RNA-positive individuals develop lymphoma and bile duct cancer, suggesting an association with HCV. The proportion of deaths due to kidney disease was also higher than that among individuals who were HCV RNA-negative. Hepatitis C is known to cause cryoglobulinemia, which may lead to kidney failure. Among patients with hepatitis C infection, 11% died due to hepatocellular carcinoma, and this was the most common form of cancer in this group, followed by pancreatic cancer, which was

Table 2: Cause of death and age.

	HCV RNA+(N=361)		HCV RNA-(N=163)		General mortality rate in region (%)
	N (%)	Age	N (%)	Age	
Liver related disease	98(27)	75.8 ± 7.9	11(6)	65.3 ± 9.6	0.4
Liver cancer in liver related disease	62(17)	74.3 ± 7.9	11(6)	65.3 ± 9.6	5.3
Cancer except for liver cancer	73(20)	78.5 ± 7.3	45(25)	77.4 ± 7.5	28
Pulmonary disease	47(13)	83.2 ± 6.5	37(20)	84.2 ± 5.9	3.9
Heart disease	41(11)	82.2 ± 8.4	21(11)	78.2 ± 9.1	18.7
Cerebral disease	37(10)	79.9 ± 7.7	25(14)	76.8 ± 11.2	11.3
Kidney disease	9(3)	76.7 ± 6.9	2(1)	79.5 ± 6.4	2.3
Others	57(16)	82.4 ± 8.4	42(23)	82.7 ± 7.9	35.4

Table 3: Cause of cancer death.

	HCV RNA+(N=135)		HCV RNA-(N=56)		General mortality rate in region (%)
	N (%)	Age	N (%)	Age	
Liver	62(45)	74.3 ± 7.9	11(19)	65.3 ± 9.6	5.3
Lung	14(10)	78.5 ± 7.0	8(14)	71.9 ± 9.1	19.5
Stomach	12(8)	79.8 ± 6.3	8(14)	74.1 ± 9.6	16
Pancreas	8(5)	77.9 ± 6.7	9(16)	80 ± 5.7	8.6
Bile duct	6(4)	77.8 ± 5.0	1(1)	71 ± 0.0	0
Prostate	6(4)	74.8 ± 14.6	1(1)	90 ± 0.0	0
Lymph node	6(4)	74.8 ± 14.6	2(3)	78 ± 0.0	1.7
Colon	4(3)	76.0 ± 4.2	6(10)	79.2 ± 4.0	16.3
Others	16(12)	81.6 ± 5.9	10(18)	80.1 ± 4.4	32.6

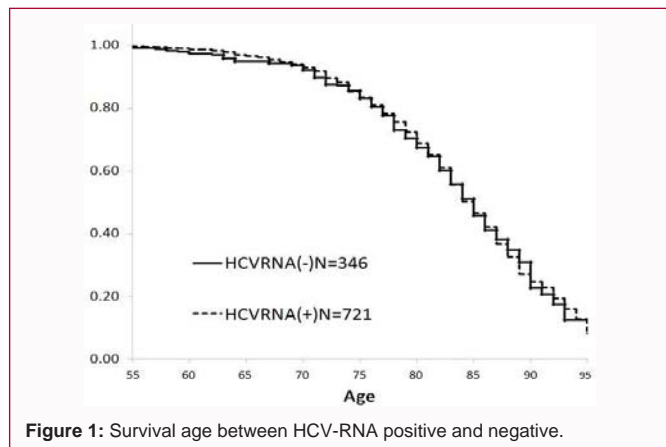


Figure 1: Survival age between HCV-RNA positive and negative.

different from the cause of death in this region. As this study was based on diagnosis obtained from death certificates and a questionnaire, other causes of death such as heart failure would have been recorded as such, even if individuals also had liver cancer. Furthermore, in the absence of autopsy, it would not have been possible to determine whether liver cancer had contributed to the cause of death. However, no report prior to this one has investigated the causes of overall death among patients with hepatitis C, including those negative for HCV RNA, and therefore we consider that the present data are useful when considering the causes of death in such patients. In the future, due to the spread of DAA treatment, it is anticipated that a greater number of individuals infected with hepatitis C will survive longer. At the same time, the incidence of hepatocellular carcinoma is expected to decrease, even though it can still occur after SVR.

Conclusion

The results of the present study suggest that even if the hepatitis C virus has been undetectable for a long period of time, the incidence of liver cancer is nevertheless higher than usual, and therefore the reasons for this require further investigation.

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