Impact of Aging on the Development of Hepatocellular Carcinoma in Patients with Posttransfusion Chronic Hepatitis C

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BACKGROUND. Hepatitis C virus (HCV) infection is a heterogeneous disease, the natural history of which remains controversial. There is solid evidence that chronic HCV infection is responsible for the occurrence of hepatocellular carcinoma (HCC). The aim of the current cohort study was to determine the rate of the development of HCC from the time of primary HCV infection and to assess the risk factors for the development of HCC in chronic posttransfusion hepatitis C patients.

METHODS. Four hundred sixty-nine patients with clinically compensated HCV, who had undergone a single blood transfusion comprised the current study cohort. Patients with other risk factors for chronic liver disease were excluded. All patients were referred to the liver center at the National Nagasaki Medical Center between December 1980 and December 1998 and were followed prospectively until the end of the analysis (June 2000).

RESULTS. Follow-up data were obtained for 445 patients. The mean duration from HCV infection to the end of the observation was 28 years. Fifty-two patients (11.1%) progressed to HCC. The mean duration from the time of blood transfusion to the diagnosis of HCC was 31 years. Multivariate Cox regression analyses revealed age, fibrosis, duration from HCV infection to study entry, and alcohol consumption to be the independent factors affecting the development of HCC. The risk of developing HCC in patients age ≥ 56 years was increased 7.8-fold compared with that in patients age < 56 years. The mean age of patients at the time of HCC diagnosis was 65 years (range, 58–79 years).

CONCLUSIONS. At the time of diagnosis, 92% of the 52 HCC patients were age ≥ 60 years and 38 of the HCC patients (73%) were in their 60s. There was a significantly negative correlation between the duration from HCV infection to the development of HCC and the age of the patient at the time of infection (correlation coefficient = 0.702; \( P < 0.0001; Y = 61.1 - 0.82X \)), indicating that the age of patients, rather than the duration of HCV infection, is more significant for HCC development in patients with posttransfusion HCV. Moreover, these data may contribute to the design of an optimal follow-up schedule for patients with posttransfusion HCV.

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Chronic hepatitis C virus (HCV) infection affects approximately 3% of the world population. There is solid evidence from epidemiologic data that in a large proportion of patients, chronic HCV infection can lead to end-stage liver disease, such as cirrhosis and hepatocellular carcinoma (HCC). However, the exact percentage of infected
individuals who develop these serious complications remains controversial and to our knowledge has not yet been defined precisely.1,2

Some authors emphasize the apparently low rate of clinically significant liver disease due to posttransfusion hepatitis C, whereas others focus on the alarming number of patients with end-stage liver disease.2 This apparent paradox has been only partly resolved. In the patients with posttransfusion hepatitis C, sustained clearance of serum HCV-RNA was observed in 15–20% of patients.1,3 Among those patients who go on to develop chronicity, the majority remain asymptomatic for years. Some of the patients with chronic hepatitis C were found to have compensated cirrhosis.1,2 Other patients with chronic HCV infection appear to have persistently normal serum transaminase levels.4 It is important to prognosticate accurately any given patient’s likelihood of developing clinically serious or fatal complications, such as cirrhosis and HCC, for the screening and treatment of these potentially devastating diseases. Several studies have attempted to reveal prognostic factors for this diverse spectrum of diseases. However, it generally is difficult to study this aspect of the prognosis of chronic hepatitis C, because the interval between HCV infection and the development of significant liver disease is very long. Moreover, to our knowledge, the majority of previous studies of the natural history of chronic hepatitis C faced a major limitation, namely inadequate information regarding the duration of infection.5,6 To overcome this limitation, we studied 469 patients with chronic HCV who received a single blood transfusion by which the infection likely was acquired.

The objective of the current study was to identify predictive risk factors for HCC and to assess determinants of HCC development in patients with posttransfusion hepatitis C in whom the date of blood transfusion was documented, and to examine the effects of the duration of infection and patient age at the time of infection.

MATERIALS AND METHODS

Study Population

The study cohort was comprised of 469 consecutive patients with clinically compensated chronic hepatitis C referred to the liver center at the National Nagasaki Medical Center between December 1980 and December 1998 and followed until the end of the analysis (June 2000).

As previously reported,5,7 the entry into the study was defined as the time of diagnosis of clinically compensated chronic hepatitis C. Initially, 499 patients who fulfilled the following inclusion criteria were enrolled: 1) positive serologic test for anti-HCV by a second-generation enzyme-linked immunoadsorbent assay that was performed on frozen samples for cases diagnosed before 1992; 2) positive results by polymerase chain reaction (PCR) for HCV-RNA, 3) existence of a documented date of blood transfusion; and 4) 2 years after a blood transfusion.

Thirty patients were excluded from the current study because of multiple blood transfusions (3 patients), an episode of the liver dysfunction before the blood transfusion (11 patients), history of hemophilia (1 patient), intravenous drug abuse (4 patients), history of acupuncture therapy (6 patients), possibility of other liver diseases such as hepatitis B-associated liver diseases (2 patients), autoimmune hepatitis (1 patient), hemochromatosis (1 patient), and the coexistence of HCC (1 patient).

Written informed consent was obtained from each patient.

Histologic Examination

Four hundred thirty-six patients (93%) underwent either peritoneoscopy and/or ultrasonography (US) guided liver biopsy at the time of study entry. All the liver tissue specimens were obtained by needle biopsy and evaluated by one pathologist (O.I.) who was unaware of the patients’ clinical condition. The degree of fibrosis and the intensity of inflammatory activity were graded according to the scoring system described by Desmet et al.8 with slight modification: F0, F1, F2, F3, and F4 were defined as none or minimal fibrosis, fibrous portal expansion, bridging fibrosis (portal-portal or portal-central linkage), bridging fibrosis with lobular distortion, and cirrhosis, respectively. F0, F1, and F2 were defined as “mild fibrosis” and F3 and F4 were termed “severe fibrosis” in the current report.

Alcohol Exposure

Past alcohol exposure was estimated based on the information in the case record concerning drinking patterns over a period of > 5 years. This was supplemented by a prospective survey. The cases were categorized into two groups (“excessive” and “nonexcessive” alcohol consumer) according to the amount of alcohol intake; excessive alcohol consumers had an alcohol consumption of > 50 g/day for 5 years during the time the patient was infected with HCV.

Laboratory Tests for Liver Disease and Virologic Markers

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin concentrations, platelets, and prothrombin time were determined at the time of the initial assessment using automated procedures in the clinical pathologic lab-
oratories of the Nagasaki Chuo National Hospital. HCV-RNA was detected by reverse transcriptase-PCR using a commercial kit (Amplicor HCV; Roche Diagnostic System, Basel, Switzerland). The sera that were positive for HCV-RNA were further subjected to a branched DNA signal amplification assay (Quantiplex HCV-RAN; Chiron Corporation, Emeryville, CA) for determination of the amount of HCV-RNA. The detection limit of the assay was \(0.5 \times 10^6\) genome mega-equivalents (Meq)/mL.

**Variables at Study Entry**

Various characteristics of the 469 patients were recorded at baseline assessment and included gender; age at entry; age at HCV infection; duration of HCV infection at the time of presentation; past alcohol intake; serum ALT, AST, alkaline phosphatase, and bilirubin concentrations; platelet count; prothrombin time; and the HCV-RNA titer. The prognostic value of interferon treatment also was analyzed. Data were collected in a standardized program and stored in a relational database.

**IFN Treatment**

IFN therapy was initiated 1–12 months after liver biopsy, and each patient was followed for at least 48 weeks after the completion of IFN therapy. A sustained responder (SR) was defined as a patient who demonstrated negative serum HCV-RNA findings on PCR and normal ATL levels for > 48 weeks after the completion of IFN therapy. A nonresponder (NR) was defined as a patient who demonstrated any other response.

**Methods of Follow-Up**

All patients were followed at least every 6 months by medical examinations at the outpatient clinic of the study institution or related private hepatology clinics. Imaging diagnosis was performed by US approximately every 6 months for each patient. When the disease was found to have developed into cirrhosis by peritoneoscopy or biopsy, frequent imaging by US and computed tomography (CT) was performed.

**Assessment of Outcome**

Outcome data were used to assess the development of and time to onset of HCC and death.

**HCC**

The diagnosis of HCC was based on elevated \(\alpha\)-fetoprotein level or abnormal abdominal imaging studies. One or more hepatic spaces occupying lesions observed by US or CT were demonstrated to have vascular patterns typical of HCC by angiography, dural-phase spiral CT, or magnetic resonance imaging. Alternatively, pathologic or histologic examination was performed using liver tissue obtained by fine-needle aspiration or at autopsy. Follow-up was terminated at the time of HCC development, death, or as of June 2000.

**Cause of death**

The time and cause of death were recorded from the death certificate and medical records or from information obtained from related private hepatology clinics.

**Lost to follow-up**

When a patient had not been monitored at the study institution or related private hepatology clinics for \(>1\) year, the patient was considered to be lost to follow-up.

**Statistical Analysis**

The data were analyzed statistically using the chi-square test and the Student \(t\) test. The rate of the appearance of HCC was analyzed using the Kaplan–Meier method, and differences in curves were tested using the log-rank test. Univariate and multivariate Cox regression models were used to calculate the hazard ratios and their 95% confidence intervals (95% CIs) for factors potentially associated with HCC. The 15 factors examined included gender, age at infection > 30 years, serum ALT > 50 (IU/L), serum AST > 40 (IU/L), alkaline phosphatase > 87 (IU/L), prothrombin time < 80%, albumin < 3.4 (g/dL), HCV-RNA titer > 1.0 (Meq/L), serum bilirubin > 1.0 (mg/dL), platelet count < 100 (10^3/L), excessive alcohol consumption, lack of IFN treatment, duration from infection to study entry of \(\geq 26\) years, severe fibrosis, and age at study entry \(\geq 56\) years. The correlation between the patient age at the time of HCV infection and the duration between HCV infection to HCC development was evaluated by the Pearson correlation coefficient.

**RESULTS**

**Clinical Features of the Patients**

Clinical features of the patients at the time of presentation (i.e., at entry to the current study) are shown in Table 1. There were 227 male and 242 female patients, with a mean age of 54.7 years and a mean infection period of 28.1 years (range, 2.5–57.4 years). The median age at the time of infection through blood transfusion was 30.0 years. Biopsy samples were obtained from 436 patients within 6 months. Histologic staging of F0 or F1, F2, F3, and F4 were noted in 144 patients (33%), 87 patients (20.0%), 69 patients (15.8%), and 136 patients (31.2%), respectively, and the mean score
TABLE 1
Clinical Characteristics of 469 Patients with Chronic Hepatitis C

| Variable                        | All patients (n = 469) |
|---------------------------------|------------------------|
| Age at entry (yrs)              | 54.7 (12.2) a          |
| Gender (M/F)                    | 227/242                |
| Age at infection (yrs)          | 30 (birth-76)          |
| Serum ALT (IU/L)                | 50 (9-366)             |
| Serum AST (IU/L)                | 61 (10-491)            |
| Alkaline phosphatase (IU/L)     | 183 (62-1152)          |
| Prothrombin time (%)            | 81 (12) a              |
| Serum bilirubin (per mg/dL)     | 0.7 (0.2-3.2)          |
| Platelets (10^6/L)              | 132 (63) a             |
| HCV-RNA titer (Meq/mL)          | 1.4 (0-24)             |
| Fibrosis score                  | 2.4 (1.2) a            |

HCV: hepatitis C virus; M: male; F: female; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Data are expressed as the median (range) or * as the mean (standard deviation).

TABLE 2
Outcomes of 469 Patients with Chronic Hepatitis C

| Outcome                  | No. of cases (%) | Follow-up (yrs) |
|--------------------------|------------------|-----------------|
| Alive                    | 414 (88.3)       | 5.6 (3.1) a     |
| Lost to follow-up        | 24 (5.1)         | 0.7 (0.2-0.9)   |
| Died liver-related       | 27 (5.8)         | 8.6 (1.1-12)    |
| Died nonliver-related    | 4 (0.9)          | 6.8 (3-12)      |
| HCC development          | 52 (11.0)        | 7.7 (4.7) a     |

HCC: hepatocellular carcinoma.

Follow-up data are expressed as the median (range) or * the mean (standard deviation).

of fibrosis was 2.4. There were 41 excessive alcohol consumers and 145 patients who received IFN therapy during the follow-up period.

Long-Term Outcomes
Follow-up data were obtained for 445 patients (94.9%) (Table 2). Twenty-four patients (5.1%) were lost to follow-up and 27 (5.8) died of liver-related complications. During an average of 5.6 years (range, 1–20 years) under the current study observation, 52 patients (11.0%) had their disease progress to HCC. Of these 52 HCC patients, 22 died (42.3%).

Cumulative Probability and Predictive Risk Factors for the Development of HCC.
Figure 1 shows the cumulative probability of HCC development, which was 5.2%, 18%, 37%, and 46%, respectively, at 5 years, 10 years, 15 years, and 20 years. The study population was classified into 2 groups according to the median patient age at the time of infection, with those who were age ≥30 years defined as “older” and those age < 30 years old defined as “younger.” In the younger group (n = 243), 21 patients (8.6%) developed HCC, whereas in the older group (n = 226), 31 patients (13.7%) developed HCC. The cumulative progression rates as determined by the Kaplan–Meier method and the probability of HCC did not differ significantly between the 2 groups using the log-rank test (P = 0.12).

With regard to patient age at study entry, we divided the study population into 2 groups according to the median age, with those who were age ≥56 years defined as “older” and those age < 56 years defined as “younger.” In the younger group (n = 224), 9 patients (4.0%) developed HCC, whereas 43 patients in the older group (n = 245) developed HCC (17.6%). The cumulative incidence of HCC was based on the patient age at study entry. The cumulative incidence of HCC in the older group was significantly higher than that in the younger group (P < 0.0001).

With regard to fibrosis, the relations between the cumulative incidence of HCC and the histologic staging was examined. The cumulative incidence of HCC in 231 patients with severe fibrosis was found to be significantly higher than that in 205 patients with mild fibrosis (P < 0.0001).

Effect of IFN Therapy on the Development of HCC
One hundred forty-five patients received IFN therapy during the follow-up period. Forty-two of these patients (29%) were SRs. One hundred three patients (71%) were NRs. Two SRs and two NRs developed HCC.

Independent Predictors of the Development of HCC
The independent predictors of the development of HCC are summarized in Table 3. Cox proportional hazards regression analysis was performed to determine the factors that affected the development of HCC. According to univariate analysis, 7 of 15 factors (serum bilirubin > 1.0 mg/dL, platelets < 100 [10/L], excessive alcohol consumption, lack of IFN treatment, duration from infection to entry ≥26 years, severe fibrosis, and age at presentation ≥56 years) significantly affected the incidence of HCC. However, other factors (gender, age at HCV infection, serum ALT, serum AST, alkaline phosphatase, prothrombin time, albumin, and HCV-RNA titer at study entry) did not appear to affect the development of HCC.

Multivariate Cox regression analyses were performed on the seven significant variables in the model because of the possibility that the variables were correlated mutually. Of these seven variables, four factors (alcohol consumption, duration from HCV infection to entry, fibrosis, and age at study entry) were found to be associated independently with HCC development. The risk of developing HCC in excessive consumers of...
alcohol was 2.21-fold higher than that in nonexcessive alcohol consumers. With regard to the duration of infection, the risk of HCC in patients with a 26-year duration of HCV infection at study entry was increased 4.56-fold compared with that in patients with a duration of HCV infection ≤ 26 years. The risk of developing HCC in patients with severe fibrosis was 4.38-fold higher than that in patients with mild fibrosis. The risk of developing HCC in patients age ≥ 56 years at the time of study entry was increased 7.84-fold compared with the patients age < 56 years.

**Characteristics of HCC Patients**

Of the 52 HCC patients, 92% were age ≥ 60 years at the time of diagnosis. The mean age of the patients at the time of HCC diagnosis was 65 years (standard deviation of 4.8 years; range, 58–79 years). Thirty-eight of the 52 HCC patients (73%) were in their 60s and only 4 patients were age < 60 years at the time of diagnosis (Fig. 2).

Figure 3 shows the relations between the period from blood transfusion to the diagnosis of HCC and the age of the patient at the time of blood transfusion.
There was a significantly negative correlation between the period from blood transfusion to the diagnosis of HCC and the age of the patient at the time of blood transfusion (correlation coefficient = 0.702; \( P < 0.0001; Y = 61.1 - 0.82X \)).

**DISCUSSION**

In the current study, we examined the development of HCC in patients with chronic hepatitis C who had received a blood transfusion in Japan. This study allowed the accurate calculation of timing to various outcomes of hepatitis C, including HCC. The interval between HCV infection and the development of significant liver disease is reported to be very long. Kiyosawa et al. reported that the mean duration between blood transfusion and the diagnosis of HCC was approximately 29 years (standard deviation of 13 years) \( (n = 21) \), and Tong et al. reported it to be 28 years (standard deviation of 11 years) \( (n = 14) \). This duration has been confirmed further by several investigators in other countries. Our data, which indicated a duration of 31 years (standard deviation of 8 years) \( (n = 52) \) between a blood transfusion and the appearance of clinical HCC, are consistent with those found in previous studies.

To our knowledge, there have been a number of reports regarding the cumulative probability of HCC development in HCV-infected patients. In Japan, Ikeda et al. reported that the cumulative probability for HCC development in patients with cirrhosis was 21.5% \( (n = 349) \) at 5 years. They reported in another study that the cumulative probability of HCC development in patients with chronic hepatitis C (excluding cirrhosis) was 4.8% at 5 years \( (n = 1500) \), whereas Takano et al. reported a probability of approximately 4% \( (n = 124) \) in patients with chronic hepatitis C at 5 years, and Aizawa et al. reported a probability of approximately 9% \( (n = 153) \) at 5 years in patients with chronic HCV or cirrhosis. In the U.S., Hu et al. reported that the cumulative probability of HCC development in patients with compensated cirrhosis was 10% at 5 years \( (n = 112) \). In France, Serfaty et al. reported that the cumulative probability of HCC development in patients with compensated cirrhosis was 11.5% at 4 years \( (n = 103) \). The current study data \( (n = 469) \) demonstrated a probability of 5.2% at 5 years in all patients. We found the cumulative probability of HCC development to be 3.2% \( (n = 300) \) in patients with chronic hepatitis C (F0, F1, F2, and F3) and 10% \( (n = 136) \) in patients with cirrhosis (F4) at 5 years after liver biopsy. Our values did not differ significantly from those of other studies but were slightly lower than those found in other Japanese data. One possible reason is that our subjects all had chronic hepatitis C acquired after blood transfusion. Some authors noted that sporadic cases had more liver-related complications or reduced survival compared with cases of HCV acquired from blood transfusion.
not. Multivariate regression analysis revealed that IFN therapy was not an independent factor. Some multivariate regression studies demonstrated the same outcome as the current study. However, IFN was reported to prevent the development of HCC even in patients in whom the therapy was not effective. Further follow-up studies of IFN-treated patients are essential given that the incidence of HCC in patients with chronic HCV infection increases with its progress over the time of follow-up.

Although alcohol consumption can be classified using different criteria, we used criteria similar to those used in previous studies (i.e., that daily alcohol consumption was 50 g/day for ≥5 years’ duration after the patient was infected with HCV). The risk of developing HCC in such excessive consumers was 2.21-fold greater than that in nonexcessive consumers. There is solid evidence that excessive alcohol intake is a risk factor for the progression of liver disease caused by HCV. The current study data appear to support that view.

Some authors have reported that the longer the duration of exposure, the more severe the liver disease. For example, Niederau et al. noted that the incidence of severe liver disease with a duration of exposure >14 years was 17.2-fold higher than that with a duration of exposure <5 years. However, their study population (n = 838) had various etiologic factors for HCV infection in their medical history (e.g., the rate of treatment with blood products or transfusion was 32.3% and the rate of unknown etiology was 40.6%). Thus, the exact duration from the time of HCV infection to HCC development was not clear. The current study data demonstrated that the duration of exposure had a significant effect on the development of HCC.

The current study data also indicated that severe fibrosis is one of the prognostic factors for HCC development. Using multivariate Cox regression analyses, some previous studies demonstrated that fibrosis could be a dependent factor for the development of HCC. The previous study confirmed that conclusion.

Increasing patient age at the time of diagnosis of chronic liver disease was shown to be associated with increased histologic severity and cirrhosis in many previous studies. Multivariate analysis in those studies confirmed increasing patient age at the time of diagnosis to be an independent factor for progression from chronic hepatitis to cirrhosis and the incidence of HCC. However, aging was associated with histologic severity and induced carcinogenesis, and the authors did not provide clear data regarding a relation between aging and HCC development by multivariate Cox regression analyses. The results of the current study demonstrated that age at diagnosis was an independent factor for HCC development by multivariate Cox regression analyses in a cohort study. In the current study, the risk of developing HCC in the group of patients age ≥56 years at the time of study entry was increased 7.84-fold compared with the group of patients age <56 years. Age was found to be the most important risk factor for the development of HCC.

The most striking finding of the current study was that the majority of patients with posttransfusion chronic HCV developed HCC after the age of 60 years regardless of when they acquired the HCV infection. Of 52 HCC patients, 92% were age ≥60 years at the time of diagnosis. The mean age of patients at the time of HCC diagnosis was 65 years (standard deviation of 4.8 years; range, 58–79 years). Thirty-eight of the 52 HCC patients (73%) were in their 60s and only 4 patients were age <60 years at the time of diagnosis (Fig. 2). Some previous studies indicated that patient age at the time of diagnosis of HCC among chronically HCV-infected patients ranged from 63–68 years. Shiratori et al. reported that 70% of HCC patients who were HCV carriers (n = 48) were age ≥60 years at the time of HCC diagnosis. Shimajiri et al. reported that among 648 HCC patients who were HCV antibody-positive, 24% were age <60 years, and that heavy drinking and the presence of HBV coinfection were found to be related independently to the development of HCV antibody-positive HCC at a younger age. However, these reports were not prospective studies and included patients who were infected with HCV through various routes. Because the history of posttransfusion hepatitis is long, to our knowledge there are only limited numbers of reports regarding when the patients develop HCC. Kiyosawa et al. found in their prospective study that the mean interval between the blood transfusion (the presumed source of HCV infection) and the diagnosis of HCC was approximately 29 years in the 21 patients in their study. In the current study, the mean age of patients at the time of HCC diagnosis was 64.4 years (standard deviation of 5.8 years; range, 53–74 years) and only 4 patients were age <60 years. The current study data and those of Kiyosawas et al. indicate that it is rare to find HCC in a patient with posttransfusion hepatitis C who is age <60 years.

Figure 3 shows the relation between the period from blood transfusion to the diagnosis of HCC and the age of the patient at the time of blood transfusion. There was a significantly negative correlation between the period from blood transfusion to the diagnosis of HCC and the age of the patient at blood transfusion (correlation coefficient = 0.702; P < 0.0001; Y = 61.1–
0.82X). This figure indicates that regardless of when the patients acquired the HCV infection, they developed HCC at approximately the same time of life. Noda et al. examined the relation between the period from blood transfusion to the diagnosis of HCC and the age of the patient at the time of blood transfusion in 85 HCC patients. In a retrospective and preliminary study, patients were collected from 11 hospitals for the purpose of investigating whether habitual alcohol intake and the age at HCV infection were factors for the progression of chronic hepatitis C to cirrhosis and HCC in patients with history of blood transfusion. Our Y intercept was 6 years higher than that reported by Noda et al. The reason for this discrepancy may be that the current study was a cohort study and we were able to determine precisely the time from blood transfusion to the diagnosis of HCC and the age of the patient at the time of blood transfusion. The current study data thus demonstrated the natural history of blood transfusion-related chronic hepatitis C.

It is not clear why the majority of patients developed HCC in their 60s, regardless of the duration of the infection. We previously reported that the rate of progression of fibrosis to cirrhosis in patients with chronic hepatitis C was accelerated by aging. In addition, Poynard et al. concluded that the progression of liver fibrosis is closely related to patient age at the time of HCV infection. They found that the rate of progression of fibrosis was proportional to patient age at the time of HCV infection, which is the main factor associated with progression to fibrosis. Similarly, the rate of progression of fibrosis in the current study was proportional to patient age at the time of HCV infection (data not shown). The histologic deterioration that promotes HCC development may take place rapidly in the seventh decade of life.

Based the results of the current study, it would be natural to speculate that host-dependent factors associated with age may play a pivotal role in hepatocarcinogenesis in patients with posttransfusion hepatitis C. Aging may be associated with progressive loss of various stress tolerances due to a decline in the functional reserve of multiple organ systems. It has been shown that aging is associated with aberrant cytokine function and decreased capacity for DNA repair, which may facilitate the development of HCC. However, we are unable to explain the precise relation between patient age and HCC development. Further assessment of the role of aging in the progression of HCV is needed.

Posttransfusion chronic hepatitis C is a disease with considerable mortality and morbidity. Age, fibrosis, duration of HCV infection, and alcohol consumption appear to be associated independently with HCC development. However, the majority of HCC patients in the current study developed HCC when they were age > 60 years regardless of the duration of HCV infection. The current study may be useful in establishing an adequate follow-up policy for patients with posttransfusion chronic hepatitis C.

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