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Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response

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Background. In Japan, generally, patients with chronic hepatitis C are aged. The aim of this study was to investigate the effect of interferon (IFN) therapy on the mortality of chronic hepatitis C patients over age 60. ***Methods.*** Seven-hundred and seven patients with histologically proven chronic hepatitis C were enrolled in this study; 649 received IFN therapy (IFN group) and 58 did not (control group). The standardized mortality ratio (SMR) and Cox proportional hazard regression analysis were used to evaluate the effect of IFN on the survival of the patients. ***Results.*** Mean follow-up periods in the IFN and control groups were 5.7 and 6.7 years, respectively. During follow-up, 13 patients in the control group died (7 of liver-related diseases) and 42 in the IFN group died (29 of liver-related diseases). The SMRs of the control and IFN groups were 1.40 (95% confidence interval [CI], 0.76–2.45) and 0.73 (95% CI, 0.52–0.98) for overall death, and 10.70 (95% CI, 4.29–22.05) and 5.05 (95% CI, 3.38–7.26) for liver-related death, respectively. Sustained and transient biochemical responders in the IFN group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively) showed lower liver-related mortality compared with the control group. In patients with sustained virological response, liver-related mortality was also very low (SMR, 0.65; 95% CI, 0.01–3.61). The risk for liver-related death of sustained and transient biochemical responders was also low compared with that of the control group (adjusted risk ratios 0.10 [95% CI, 0.01–0.95] and 0.50 [95% CI, 0.11–2.21], respectively). ***Conclusions.*** These results suggest that IFN treatment could reduce liver-related mortality in chronic hepatitis C patients over age 60, notably in patients showing a biochemical response and in those showing a sustained virological response.

Key words: interferon, chronic hepatitis C, aged, liver-related mortality, standardized mortality ratio

Introduction

A high prevalence of hepatitis C virus (HCV) infection is observed in patients with hepatocellular carcinoma (HCC) in Japan.[1–4] In the early 1990s, interferon (IFN) was introduced, and it is now widely used worldwide, as well as in Japan, for the treatment of patients with chronic hepatitis C. Hitherto, many studies, including our own reports, have shown that IFN therapy reduced the incidence of HCC in patients with chronic hepatitis C.[5–10]

Recently, several groups have studied the effect of IFN therapy on survival in patients with chronic hepatitis C. Most of these studies reported that IFN therapy improved the survival of HCV-related chronic hepatitis and cirrhosis, although some studies did not find any efficacy of IFN therapy on survival.[10–19] We also reported the beneficial effect of IFN therapy on survival in chronic hepatitis C patients. In that report, we also

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showed that the effect of IFN therapy on survival was notable in the patients exhibiting sustained and transient biochemical responses, as well as in those showing sustained virological response.[20]

Many clinical trials showed that IFN therapy resulted in normalization of serum aminotransferase levels and eradication of serum HCV RNA, although a sustained virological response was achieved in a limited number of patients.[21–25] Recently, a combination therapy of ribavirin and IFN, or pegylated IFN, has been shown to have efficacy superior to IFN monotherapy for chronic hepatitis C.[26–28]

Patients in Japan with chronic hepatitis C are, generally, aged.[29,30] Also, patients with HCV-related HCC have been shown to be old, with a peak around age 70.[31] Despite the beneficial effects of IFN therapy or combination therapy of IFN and ribavirin for chronic hepatitis C patients, these treatments have several adverse effects which are not tolerable, especially for aged patients who have illnesses other than liver disease.[32] If IFN therapy does not prolong life expectancy in aged patients with chronic hepatitis C, the indications for IFN therapy in these patients may be very limited. Therefore, it is very important to investigate whether IFN therapy could improve survival in aged patients with chronic hepatitis C.

The aim of this study was to evaluate the effect of IFN therapy on mortality in aged patients with chronic hepatitis C. We conducted a multicenter, large-scale, retrospective cohort study of chronic hepatitis C patients over 60 years of age.

Patients and methods

Patients

We found previously that IFN therapy improved the survival in patients with chronic hepatitis C.[20] Of the 2954 patients with chronic hepatitis C in that study, we enrolled 707 patients over age 60 in the present study, to investigate the effect of IFN therapy on mortality in aged patients. Accordingly, the inclusion criteria were the same as those of the previous study: (1) histological diagnosis of chronic hepatitis or cirrhosis; (2) no history of clinical signs, at entry into the study, of complications of cirrhosis, i.e., ascites, jaundice, encephalopathy, or variceal bleeding; (3) no evidence of HCC at entry into the study, as assessed by ultrasonography and/or computed tomography; (4) absence of serum hepatitis B surface antigen; (5) absence of coexisting liver diseases, such as autoimmune hepatitis or primary biliary cirrhosis; (6) absence of excessive alcohol consumption (>80 g/day); and (7) absence of human immunodeficiency virus antibodies.[20]

The IFN group comprised 649 patients who had started IFN therapy between 1992 and 1997 and had received a 4- to 12-month course of IFN, which was initiated within 1 month after liver biopsy. None of the patients had received IFN therapy before entry into this study. The control group consisted of 58 patients who had received liver biopsies between 1986 and 1997, but who did not undergo IFN therapy.

Biochemical responses to IFN therapy were categorized as follows. Patients whose alanine aminotransferase (ALT) levels decreased to the normal range during therapy and remained normal for up to 24 weeks after the end of the therapy were considered to have a sustained biochemical response. Patients whose ALT levels decreased to the normal range by the end of therapy, remained normal during therapy, but returned to abnormal levels during the 24 weeks following the end of the IFN therapy were considered to have a transient biochemical response. All other ALT patterns were classified as showing biochemical non-response. A sustained virological response was defined as persistent HCV RNA negativity during IFN therapy and follow-up. Patients showing positive HCV RNA after IFN therapy were classified as virological non-responders.

Follow-up

Abdominal ultrasonography or computed tomography and biochemical examinations, including α-fetoprotein, were carried out before a liver biopsy and every 3 to 6 months during follow-up, equally in the IFN and control groups. The starting date of follow-up for patients in the control and IFN groups was defined as the date of liver biopsy. Follow-up data that were not available were collected from the resident registry of the local municipal office. In the patients residing in Osaka whose follow-up data were not obtained, the Osaka Cancer Registry was used, and the data were available until the end of 1999.[6] Therefore, it was decided to use the date of death or the end of 1999 as the end of follow-up. Because the longest observation period of the patients in the IFN group was 96 months, only the follow-up data for the first 96 months were considered in the control group. Causes of death were divided into liver-related and liver-unrelated deaths. Causes of liver-related death included HCC, liver failure, and esophageal variceal bleeding.

Informed consent was obtained from each patient included in the study. The study protocol was in accordance with the Helsinki Declaration of 1975 (revised in 1983) and was approved by the Ethics Committee of the Osaka University Graduate School of Medicine.

Table 1. Baseline characteristics of the interferon and control groups

	Interferon group						
	Virological response		Biochemical response				
	Sustained response (n = 161)	Non-response (n = 484)	Sustained response (n = 206)	Transient response (n = 144)	Non-response (n = 299)	Total (n = 649)	Control group (n = 58)	P value
Age (years; mean ± SD)	63.6 ± 3.0	63.3 ± 2.9	63.8 ± 3.1	63.0 ± 2.8	63.1 ± 2.8	63.3 ± 2.9	64.1 ± 3.1	0.06
Age distribution (years; %)								
60–64	67.7	71.1	63.6	75.0	72.9	70.4	56.9	0.03
≥65	32.3	28.9	36.4	25.0	27.1	29.6	43.1	
Male/Female	110/51	272/212	134/72	80/64	171/128	385/264	31/27	0.38
Histologic staging score (%)								
0	0.6	0.2	0.5	0.0	0.3	0.3	5.2	0.06
1	24.8	18.2	27.7	25.0	12.4	20.0	31.0	
2	29.2	27.7	26.7	28.5	28.8	28.0	20.7	
3	39.8	46.9	40.3	39.6	50.5	44.8	31.0	
4	5.6	7.0	4.9	6.9	8.0	6.8	12.1	
ALT (IU/l; mean ' SD)	113 ' 82	107 ' 68	110 ' 86	87 ' 45	117 ' 69	108 ' 71	105 ' 80	0.75

Histological evaluation

In all patients, liver biopsy was undertaken before IFN therapy. Sections were stained with hematoxylin-eosin and Azan-Mallory and analyzed by two pathologists in a blinded manner. For the assessment of liver histology, the classification of Desmet et al.[33] was used.

Statistical analysis

To compare the distribution of age at liver biopsy and histological staging between the IFN and control groups, the Wilcoxon rank-sum test was used. Differences in age at liver biopsy and ALT between the two groups was assessed for significance by Student's t-test. The χ^2 test was used to compare sex differences. The Kaplan-Meier method was used to compare the cumulative survival rates in the IFN and control groups.

We compared the observed number of deaths with the expected number of deaths, which was calculated by applying sex-, 5-year age, 5-year calendar time, and cause-specific mortality rates for the general population in Japan, as prepared by the Statistics and Information Department, Japan Ministry of Health and Welfare.[34] The standardized mortality ratio (SMR) was expressed by dividing the observed number of deaths by the expected number of deaths. Survival was also analyzed by Cox proportional hazards regression. For analysis, age, sex, stage of liver fibrosis (stages 0,1/2/3/4), time of liver biopsy (until 1992/after 1993), and IFN therapy were used as variables. SMRs and hazard risk ratios were expressed with 95% confidence intervals (CIs).

Data analysis was performed with the SAS/PC statistical package (SAS Institute, Cary, NC, USA). All reported P values were two-sided, and a P value of less than 0.05 was considered to be significant.

Results

Baseline characteristics

In the IFN group, 206 patients (31.7%) had a sustained biochemical response, 144 (22.2%) had a transient biochemical response, and 299 patients (46.1%) were biochemical non-responders. Four sustained biochemical responders whose serum HCV RNA was not examined during follow-up were excluded from the analysis. Accordingly, 161 patients (25.0%) of the 645 IFN-treated patients were classified as sustained virological responders. Table 1 shows the baseline characteristics of the IFN and control groups. Age at entry, sex, histologic staging score, and serum ALT level did not differ between the two groups. The proportion of patients more than 65 years of age in the control group was higher than that in the IFN group (P = 0.03).

Table 2. Cumulative survival rate calculated from overall deaths

	Interferon group					
	Virological response		Biochemical response			
	Sustained response	Non-response	Sustained response	Transient response	Non-response	Total	Control group
Mean follow-up period (years: mean ± SD)	5.7 ± 1.6	5.7 ± 1.7	5.6 ± 1.7	5.7 ± 1.8	5.8 ± 1.6	5.7 ± 1.7	6.7 ± 1.7
4-Year survival rate	99.3%	96.2%	98.4%	99.2%	95.0%	97.0%	93.0%
8-Year survival rate	94.6%	86.8%	94.3%	93.0%	83.4%	88.7%	73.9%
P Value[a]	<0.001	0.0197	<0.001	0.0036	0.1212	0.0031	

[a] The log rank test was used to determine the difference against the control group

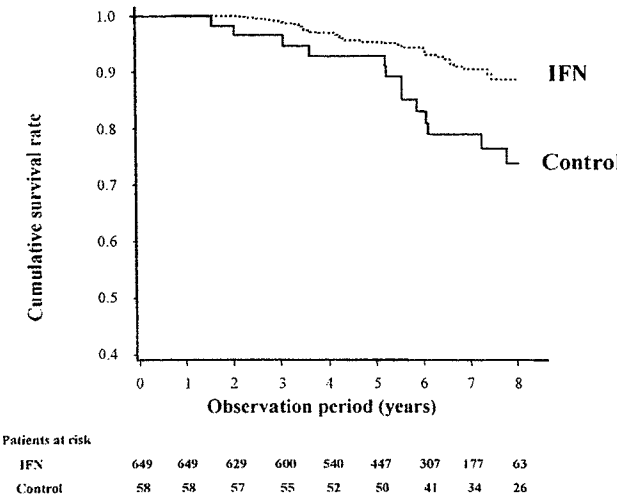

Fig. 1. Cumulative survival rates in the interferon (*IFN*; *dotted line*) and control (*solid line*) groups. Log-rank test of the two curves showed a significant difference between the two groups (P 0.003)

Cumulative survival and cause of death

The mean follow-up periods of the IFN and control groups were 5.7 and 6.7 years, respectively. The mean follow-up periods of the patients with each response in the IFN group are shown in Table 2. Figure 1 shows the cumulative survival rates of the IFN and control groups, estimated by the Kaplan-Meier method. The 8-year survival rates of the IFN and control groups were 88.7% and 73.9%, respectively (log-rank test; P = 0.003; Table 2). The cumulative survival rates of sustained virological responders were significantly higher than those for virological non-responders (log-rank test; P = 0.02). The 8-year survival rates of sustained virological responders and virological non-responders were 94.6% and 86.8%, respectively (Table 2). The cumulative survival rates of both the sustained and transient biochemical responders were significantly higher than that of the biochemical non-responders (log-rank test; P = 0.007 and P = 0.049; Fig. 2). The 8-year survival rates of sustained and transient biochemical respon-ders and biochemical non-responders were calculated to be 94.3%, 93.0% and 83.4%, respectively (Table 2).

During follow-up, 42 of the 649 IFN-treated patients and 13 of the 58 control patients died. The numbers of liver-related and liver-unrelated deaths in the IFN and control groups are shown in Table 3. Liver-related deaths corresponded to 69% of all deaths (29/42) in the IFN group and 54% of all deaths (7/13) in the control group. HCC was the major cause of liver-related deaths in both groups. Only one liver-related death (17%) was found in the deaths of sustained biochemical respond-

Table 3. Causes of death in the interferon and control groups

	Interferon group					Control group (n = 58)
	Virological response		Biochemical response			
	Sustained response (n = 161)	Non-response (n = 484)	Sustained response (n = 206)	Transient response (n = 144)	Non-response (n = 299)	Total (n = 649)
All deaths (n)	4	38	6	6	30	42	13
Liver-related deaths (n)	1	28	1	4	24	29	7
Hepatocellular carcinoma	1	25	1	3	22	26	5
Other causes	0	3	0	1	2	3	2
Liver-unrelated deaths (n)	3	10	5	2	6	13	6

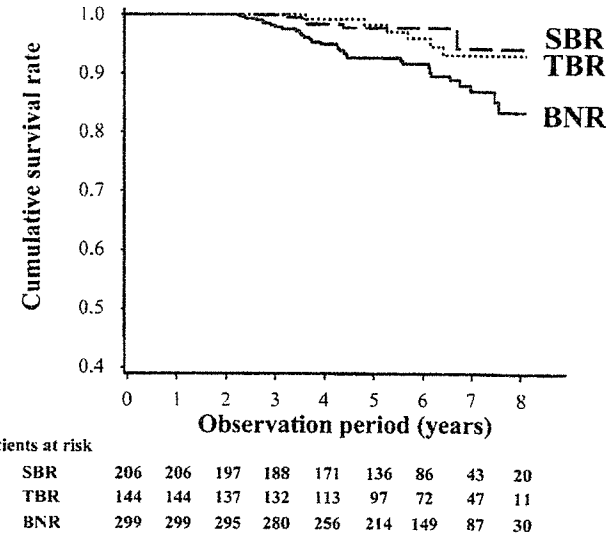

Fig. 2. Cumulative survival rates in the IFN-treated patients, categorized by sustained biochemical response (*SBR*; *dashed line*), transient biochemical response (*TBR*; *dotted line*), and biochemical non-response (*BNR*; *solid line*). Log-rank test showed significant differences between SBR and BNR (P = 0.007) and between TBR and BNR (P = 0.049)

ers. In the control group, 6 patients died of causes other than liver disease; 2 patients died of stomach cancer; 1 patient each died of lung cancer, colon cancer, and cerebral infarction; and in 1 patient, the cause of death was a traffic accident. In the IFN group, we identified 13 liver-unrelated deaths; 4 patients died of stomach cancer; 3 died of lung cancer; and 1 each died of breast cancer, colon cancer, esophageal cancer, pneumonia, chronic renal failure, and multiple myeloma.

Cox proportional hazard regression analysis

Cox proportional hazard regression analysis revealed that the risk of overall death in the IFN group was lower than that in the control group, with a marginally significant difference (risk ratio, 0.37; 95% CI, 0.13–1.05; Table 4). The patients with a sustained virological response had a low risk of overall death (risk ratio, 0.15; 95% CI, 0.04–0.59) compared with the control group. Sustained and transient biochemical responders also showed low risks of overall death (risk ratio, 0.18; 95% CI, 0.05–0.65; and risk ratio, 0.24; 95% CI, 0.07–0.87). The risk of liver-related death in the IFN group was similar to that in the control group (Table 4). However, the patients with sustained virological and biochemical response had a low risk of liver-related death compared to the control group (risk ratio, 0.12; 95% CI 0.01–1.16 and risk ratio, 0.10; 95% CI, 0.01–0.95, respectively). In transient biochemical responders, the risk ratio for liver-related deaths was 0.50 (95% CI, 0.11–2.21).

Table 4. Risk ratios for death in interferon and control groups

	All deaths			Liver-related deaths		
	Risk ratio	95% CI	*P* value	Risk ratio	95% CI	*P* value
Control group	1.00			1.00		
IFN group	0.37	0.13–1.05	0.06	0.80	0.25–2.53	0.71
Sustained virological response	0.15	0.04–0.59	0.01	0.12	0.01–1.16	0.07
Virological non-response	0.44	0.16–1.23	0.12	0.97	0.31–3.05	0.96
Sustained biochemical response	0.18	0.05–0.65	0.01	0.10	0.01–0.95	0.05
Transient biochemical response	0.24	0.07–0.87	0.03	0.50	0.11–2.21	0.36
Biochemical non-response	0.54	0.19–1.53	0.24	1.26	0.40–4.03	0.69

Age, sex, time of liver biopsy (until 1992/after 1993) and histologic staging score were adjusted in the Cox proportional hazard analysis

SMR

The SMRs in the IFN and control groups are shown in Table 5 and Fig. 3. In the control group, overall mortality was slightly higher than that in the sex- and age-matched general population (SMR, 1.40; 95% CI, 0.76–2.45). On the other hand, overall mortality in the IFN group was significantly lower compared with that of the general population (SMR, 0.73; 95% CI, 0.52–0.98). Liver-related mortality was high in the control group (SMR, 10.70; 95% CI, 4.29–22.05), and it was also high in the IFN group (SMR, 5.05; 95% CI, 3.38–7.26), although it was half of that in the control group. In the patients with sustained virological response, liver-related mortality (SMR, 0.65; 95% CI, 0.01–3.61) was very low compared with that in the control group, and it was similar to that for the general population. On the contrary, liver-related mortality was high in virological non-responders (SMR, 6.71; 95% CI, 4.46–9.70).

In terms of biochemical response, the SMRs for liver-related death of sustained and transient biochemical responders in the IFN groups were low compared with that in the control group (SMR, 0.53; 95% CI, 0.01–2.97 and SMR, 3.25; 95% CI, 0.87–8.32, respectively). In the patients with biochemical non-response, liver-related mortality was high, and was equal to that in the control group (SMR, 9.12; 95% CI, 5.84–13.57).

The IFN group showed lower liver-unrelated mortality than the general population (SMR, 0.25; 95% CI, 0.13–0.43), whereas the control group had liver-unrelated mortality similar to the general population (SMR, 0.71; 95% CI, 0.26–1.55).

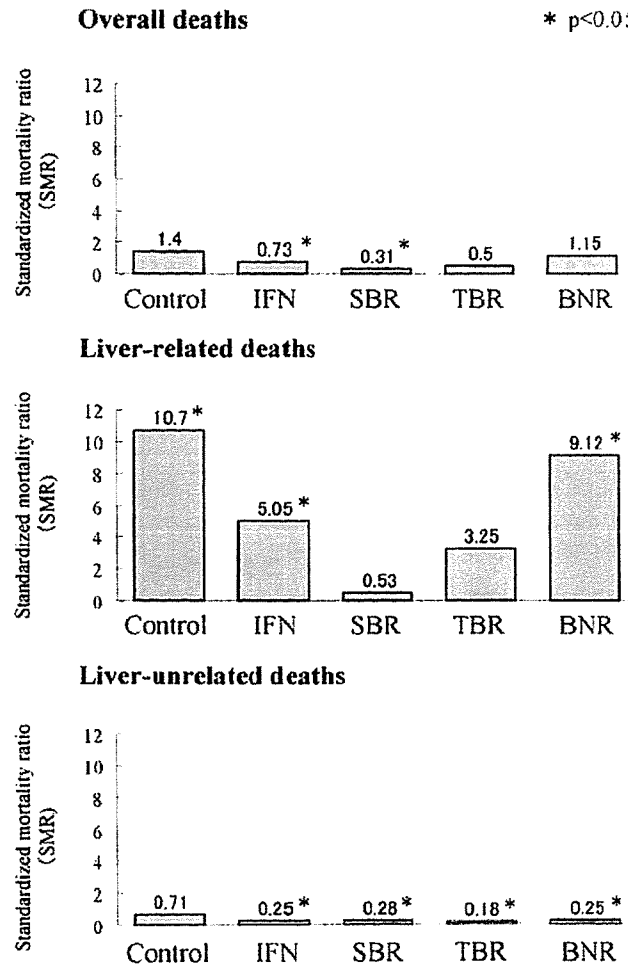

Fig. 3. Standardized mortality ratios (*SMRs*) for overall, liver-related, and liver-unrelated deaths. *SBR*, sustained biochemical response; *TBR*, transient biochemical response; *BNR*, biochemical non-response. When the SMR did not include unity, we considered the difference from the expected number of deaths to be significant

Discussion

There have been a few reports regarding the effect of IFN therapy on survival in chronic hepatitis C patients.[10,16–19] Yoshida et al.[17] reported that IFN therapy had a preventive effect on liver-related death, bringing

Table 5. Standardized mortality ratios (SMRs) in interferon and control groups

	All deaths			Liver-related deaths			Liver-unrelated deaths		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
Control group	13	9.1	1.40 (0.76–2.45)	7	0.7	10.70 (4.29–22.05)	6	8.4	0.71 (0.26–1.55)
Interferon group	42	57.8	0.73 (0.52–0.98)	29	5.7	5.05 (3.38–7.26)	13	52.0	0.25 (0.13–0.43)
Sustained virological response	4	15.8	0.25 (0.07–0.65)	1	1.5	0.65 (0.01–3.61)	3	14.3	0.21 (0.04–0.61)
Virological non-response	38	41.7	0.91 (0.64–1.25)	28	4.2	6.71 (4.46–9.70)	10	37.6	0.27 (0.13–0.49)
Sustained biochemical response	6	19.5	0.31 (0.11–0.67)	1	1.9	0.53 (0.01–2.97)	5	17.6	0.28 (0.09–0.66)
Transient biochemical response	6	12.1	0.50 (0.18–1.08)	4	1.2	3.25 (0.87–8.32)	2	10.9	0.18 (0.02–0.66)
Biochemical non-response	30	26.2	1.15 (0.77–1.64)	24	2.6	9.12 (5.84–13.57)	6	23.5	0.25 (0.09–0.55)

A difference from the expected number of deaths was considered significant when the 95% confidence interval (CI) of SMR did not include unity

about improved survival of chronic hepatitis C patients, as assessed by multivariate analysis and SMR. Recently, we also reported that IFN therapy improved survival by preventing liver-related deaths in patients with chronic hepatitis C, in a multicenter, large-scale, retrospective cohort study.[20] In that study, we showed that liver-related mortality, as well as overall mortality, was much higher in untreated patients than in IFN-treated patients, as assessed by SMR. Furthermore, we found that patients showing sustained and transient biochemical responses to IFN therapy had a very low risk of death compared with untreated patients.

In this study, we evaluated the effect of IFN therapy on survival in patients over 60 years of age with histologically proven chronic hepatitis C, by SMR and by risk ratio calculated by Cox proportional hazard regression analysis. Compared with the general population, liver-related mortality was high in the IFN-treated patients (SMR, 5.05), but it was much lower than that in the control group (SMR, 10.70). Yoshida et al.[17] also examined the effect of IFN therapy on liver-related mortality in chronic hepatitis C patients over 60 years of age in their large-scale retrospective cohort study, and reported that the SMR for liver-related death in IFN-treated patients was much lower than that in the untreated patients, which was consistent with our result. In our IFN group, sustained virological responders and sustained biochemical responders had very low liver-related mortality (SMR, 0.65 and 0.53, respectively), which was equal to that in the sex- and age-matched general population. Multivariate regression analysis also showed that IFN therapy reduced the risk of liver-related death in sustained virological responders by 88% and in sustained biochemical responders by 90%. The overall mortality in the control group was not high (SMR, 1.40), whereas that in the IFN group was significantly lower in comparison with the sex- and age-matched general population (SMR, 0.73). These results may reflect a selection bias due to the nature of the liver biopsy procedure, which was undergone by all of the patients in our study. This kind of selection bias may occur, as aged patients sometimes have illnesses other than liver disease, which make a liver biopsy difficult. Furthermore, IFN-treated patients had a significantly lower risk of liver-unrelated mortality compared with the untreated patients. It seems likely that this may be attributed not to the beneficial effect of IFN therapy on liver-unrelated mortality but to a selection bias in using IFN; only the patients who had no serious diseases, such as cardiovascular disease, received IFN therapy. However, our study indicated that IFN therapy could reduce liver-related mortality, particularly in patients with sustained virological or biochemical response.

In the patients with a transient biochemical response, liver-related mortality was low when compared with the

control group, as assessed by SMR. The SMR of the transient biochemical responders (3.25; 95% CI, 0.87–8.32), which included unity, was lower than that in the control patients (10.70; 95% CI, 4.29–22.05). Similarly, the risk ratio for liver-related death in transient biochemical responders was 0.50, although this was not significant. On the other hand, SMR, as well as the risk of liver-related death estimated by multivariate analysis in the biochemical non-responders (SMR, 9.12; adjusted risk ratio, 1.26), was similar to that in the control patients. These data suggest that a reduction in liver-related mortality by IFN therapy can be expected in patients showing a transient biochemical response. Retreatment or long-term treatment with IFN might lead to an improved survival rate in transient biochemical responders, although such treatment may not be easy with some aged patients.

There was no difference between the baseline characteristics of the IFN and control groups, except for the age distribution. However, because our study was a retrospective cohort study, it had some limitations. Because the time at liver biopsy in the control group was earlier than that in the IFN group, lead-time bias may have existed. The survival of the IFN group could be higher than that of the control group. To minimize this bias, 5-year time-specific mortality rates for the general population were prepared in the SMR analysis. Furthermore, the time at liver biopsy was included as a variable for the multivariate analysis. Another limitation of our study is the small number of patients in the control group compared with the IFN group. This limitation may also be overcome by calculating the SMRs of the IFN and control groups, representing the ratio of the observed number of deaths to the expected number of deaths, calculated after taking sex-, calendar time-, and cause-specific mortality rates for the general population into consideration. The beneficial effect of IFN therapy on survival in the aged patients with chronic hepatitis C resulting from the SMR analysis was consistent with that of the Cox proportional hazard regression analysis.

In conclusion, we showed in this study that IFN therapy reduced liver-related mortality in aged patients with chronic hepatitis C, especially in those exhibiting a biochemical response and in those showing a sustained virological response. IFN therapy is recommended for aged patients with chronic hepatitis C in whom a biochemical response or a sustained virological response can be expected, after screening for diseases other than chronic hepatitis C.

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研究速報 PP2-15

肝細胞癌における合併症と治療を考慮した医療費推定の試み

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合併症を起こしやすい肝硬変症を基礎疾患とする肝細胞癌患者を対象として医療費変動の主要な説明要因および医療費推定の検討を行った．

肝細胞癌で入院した患者を対象に，レセプト請求データから入院期間，実施された診療行為および診療報酬請求額を抽出した．肝硬変症の非代償性合併症および肝細胞癌への治療の種別とその実施の有無を関連する診療行為から判定し，診療報酬請求額を目的変数とした単変量解析および多変量解析を行った．

単変量解析から合併症や治療の有無により入院日数および診療報酬請求額に有意な差が見られ，さらに，それぞれの要因で分けた診療報酬請求額と入院日数の間に有意な相関が見られた．そのため，得られた医療費の重回帰モデルでは入院期間が最も有意な変数で，以下，肝細胞癌治療，非代償性合併症の順で有意であった．検証用データにおいてもモデルによる予測額と実際額との相関係数(Spearman)は0.89と良好であった．

今回のような診療報酬請求データをもとにした統計モデルによって合併症などの病態や治療による医療費の主たる変動要因を明らかにし，それらの組み合わせの医療費を推定することが可能と考えられた．

■キー・ワード：医療費，肝細胞癌，合併症

Estimation of Inpatient Cost for Hepatocellular Carcinoma with its Complications and the Specific Treatments：Ishida H[*1], Inoue Y[*1], Kurokawa F[*2], Hino K[*3], Okita K[*2]

Appropriate estimation of inpatient cost is difficult especially among the complicated cases with several complications or combination of specific treatments. We made a regression model to estimate inpatient cost per admission for hepatocellular carcinoma(HCC) with or without decompensated complications. 260 patients hospitalized due to HCC in our hospital were tracked retrospectively. For each case, the period of hospitalization and records of underwent specific medical interventions during it were extracted from the insurance claim data.

Relationship between the total costs(insurance reimbursement) included basic hospital charge and each 0-1 variable corresponding to execution of the specific medical interventions for each complication or HCC therapy(resection, percutaneous ethanol injection, Chemo-lipiodol therapy or parental anticancer agent injection, etc.) was investigated using univariate and multivariate analysis.

As a result of multivariate analysis, a model consisted of several variables of medical interven-

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tion : resection, Chemo-lipiodol therapy and parental anticancer agent injection, and complication : ascites and edema, and variceal bleeding in addition to the period of hospitalization was obtained. It predicted total inpatient cost with the high correlation coefficient(0.89) among HCC cases of separated data set for validation.

This study suggested that the model consisted of several specific medical interventions corresponding to each complication or treatment obtained from insurance claim data can reveal significant factors causing considerable variance of costs and predict more precisely cost of the complicated disease status.

Key words : Cost of illness, Hepatocellular carcinoma, Complication

1. 緒　論

医療経済において医療費の適切な推定は中心となる課題であり，費用効果分析などの関連する研究においてもその精度の高さは重要である．しかし，医療費推定の方法論についての研究は多くはない[1,2]．

疾患別に医療費の推定を行う場合には，該当する患者の総医療費をもとに平均値あるいは中央値により求める方法が一般的であるが，相当数の症例がないとばらつきの少ない信頼性の高い費用を求めることは容易ではない．さらに合併症などにより複合化した病態を有する場合には，その合併症の治療により医療費の変動が大きくなるため，多数の症例を集積し，それぞれの病態に合併症の組み合わせを加えて層別化した後に医療費を推定することが必要となる．例えば，2003年から導入された包括支払い制度のDPC(Diagnosis procedure combination)ごとの診療点数は，個別の疾患群やその特異的な治療が行われた実際の症例をもとにした医療費，厳密には診療報酬点数の積み上げによる保険償還額であり，調査医療機関から提出された多数の類似症例の層別化による平均入院日数およびその費用から求められ，行政が保有する大規模データベースとして期待が寄せられている．しかし，このような大規模データベースといえども層別化後にも十分と言える多症例のデータを得る保証はないため，複合病態において比較的少ない症例数であってもばらつきの少ない医療費を推定する方法を開発することは重要な課題と考えられる．

一方，医療費の推定ならびにその変動要因を明らかにするために多変量解析が用いられることが増えている[3,4]．この推定モデルによって，合併症および種々の治療に伴う診療行為に要する医療費を，総医療費における独立したコンポーネントとして切り分けることが可能であれば，その組み合わせにより医療費の推定が可能になると考えられる(**図1**)．

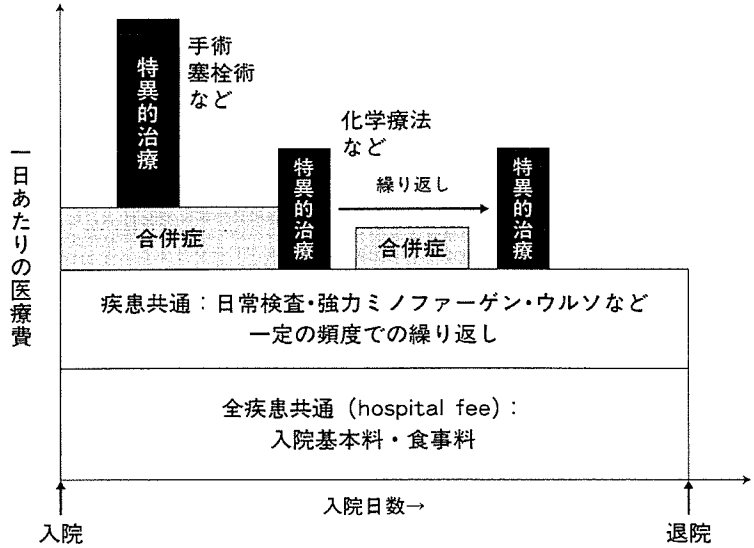
今回，複合した病態を有する患者の入院医療費の推定を課題として，様々な合併症およびその状態に応じた治療選択がなされる肝細胞癌患者の入院医療費の推定を診療報酬請求データをもとに多変量解析を用いて行った．

2. 目　的

診療報酬請求データから抽出された種々の合併症に対する治療および肝細胞癌に対する治療の実施の有無を変数とし，総医療費に対する変数毎の有意性の検証を行うとともに，重回帰モデルを作成し，それぞれの変数の総医療費に関わる寄与度について検討する．そして得られた医療費推定モデルにおいて有意となった変数を独立したコンポーネントとして捉える医療費の構成モデル(**図1**)の妥当性を考察する．

3. 対象と方法

対象症例はモデル作成群と検証群の2群とした．モデル作成群は，当大学附属病院に肝細胞癌の診断・治療目的で入院し2003年7月1日から2004年3月31日までに退院となったのべ260症例(実患者187人，うち男性141人，年齢は50～85歳で平均およびその標準偏差は68.3±7.7歳)であり，この中で入院期間が5日未満のもの，情報に欠損



入院医療費は，全疾患共通の入院基本料や食事料などの hospital fee や日々投与される一般的な処方・注射などを基盤として，肝細胞癌に対する特異的な治療としての手術や腫瘍塞栓術のような回数は少ないが1回あたりの点数の高い治療や繰り返しの注射・処置や合併症の治療などの項目から構成される．

図1　入院医療費の構成概念図

のあるもの，さらに敗血症性ショックを合併し入院となった患者などを除いたのべ236例を最終的な解析対象とした．モデル検証群は，2002年7月1日から10月31日までの期間に同様に肝細胞癌の診断で入院したのべ92症例(実患者85名，うち男性63名，年齢は20～86歳で平均およびその標準偏差は68.7±9.0歳)であり，モデル作成群と同じ条件で対象外となった症例を除く80例を最終対象とした．

この検討における医療費は，保険支払いの立場での入院基本料や管理加算などのいわゆる hospital fee を含む診療報酬請求額および入院期間中に実施された一つ一つの診療行為に対応する医事点数のみを合計し hospital fee を含まない診療行為請求額とした．

データの集計および解析は次のような手順で行った．

1．個々の症例について入院中の診療行為の明細，最終的な診療報酬請求額をレセプト請求データから抽出した．さらに診療行為の明細と医事点数を掛け合わせ入院基本料などの hospital fee を除いた診療行為のみの診療行為請求額を算定した．

2．慢性肝炎および肝硬変症における抗炎症基礎治療，肝硬変症の非代償性合併症，すなわち，腹水・浮腫，肝性昏睡，食道静脈瘤に対する治療，さらには肝細胞癌の特異的治療，すなわち，手術，経皮的エタノール注入(PEIT 療法)，抗がん剤とリピオドール(およびスポンゼル)による冠動脈化学栓術(Chemo-lipiodol 療法)，化学療法(塞栓剤を用いない経動脈的あるいは経静脈的化学療法)に用いられる代表的な薬剤や診療行為に着目し(**表1**)，個々の症例の診療行為の明細から合併症に対する治療の有無，肝細胞癌治療実施の有無の判定を行った．なお，肝細胞癌の遠隔転移に対し放射線療法(体外照射)が実施された患者数は4人と少なく最終的な検討対象には入れなかった．

3．2で得られた合併症や肝細胞癌治療の有無により一入院期間における診療報酬請求額および診療行為請求額に差があるかどうかを検定するために単変量解析を行った．さらに，それらの請求額に対する入院日数および合併症の有無や肝細胞癌治療法の種別との関連を多変量解析にて検討した．

統計解析には StatFlex ver.5(アーテック社)を用いた．単変量解析では合併症ならびに肝細胞癌の治療行為別(要因)に入院あたりの診療報酬請求額との関連を Mann-Whitney 検定を用いて $P<0.05$ を有意水準として検討した．また，入院日数とそれぞれの請求額との相関については Spearman

表1　肝細胞癌および合併症に対する医療行為の特異的マーカー

合併症・治療		診療行為・薬剤
抗炎症基礎治療		強力ミノファーゲンC・ウルソ・プロヘパール等
合併症	腹水・浮腫	ラシックス・アルダクトンなど利尿剤(＋アルブミン)
	肝性脳症	アミノレバン・モニラック・ラクツロース＋アンモニア測定
	食道静脈瘤	食道静脈瘤結紮術・食道静脈瘤硬化療法・オルダミン
肝細胞癌治療	手術	手術術式(肝切除術)
	PEIT 療法	エタノール局所注入
	Chemo-lipiodol 療法	抗がん剤＋リピオドール (＋スポンゼル)
	化学療法	抗がん剤－リピオドール (－スポンゼル)
	放射線療法	放射線治療管理料・体外照射

診療行為明細の中で肝細胞癌に対する治療と非代償性肝硬変症に対する治療の実施の有無を判断するために指標とした薬剤，検査，処置行為，術式．

順位相関により検討を行った．多変量解析では診療報酬請求額および診療行為請求額を従属変数とし，入院日数に加えて非代償性肝硬変症の腹水・浮腫，肝性昏睡および食道静脈瘤の3種類の合併症，手術，PEIT 療法，Chemo-lipidol 療法および化学療法の肝細胞癌に対する4種類の治療法，そして抗炎症基礎療法の有(1)，無(0)を説明変数とした重回帰分析を行った．この際，あらかじめ変数の分布型解析を行い，入院中の診療報酬請求額と診療行為請求額に対しては0.36乗，入院日数に対しては0.2乗の Box-Cox 変換を行った．最適な重回帰モデルは変数増減法により，$P<0.05$ であればモデルに組み込み，$P<0.15$ であればモデル内に残す条件でより小さな赤池情報量基準が得られるように変数を取捨選択した．

4. 結　果

モデル作成群236例において入院日数のメジアンならびに2.5，97.5パーセンタイル値は19日，6日，67日であり，診療報酬請求額のそれらはそれぞれ689,000円，192,000円，2,217,000円であった．合併症および肝細胞癌に対して実施された治療頻度の内訳は**表2**の通りであった．単変量解析では，抗炎症基礎治療の実施群と非実施群の間で入院日数および診療報酬請求額に有意差を認めなかった．一方，合併症のある群および肝細胞癌の治療が実施された群は合併症や肝細胞癌の治療がされなかった群と比較して入院日数は長く，診療報酬請求額は高かった．特に，食道静脈瘤に対する治療および手術，化学療法が実施された群はメジアンが100万円を超える請求額となっていた．但し，Chemo-lipiodol 療法においては治療が実施された群で入院日数は逆に短く，また，PEIT 療法および Chemo-lipiodol 療法では実施，非実施群間で診療報酬請求額には有意差を認めなかった．

入院日数と診療報酬請求額の間では，Spearman の順位相関にて0.78と高い相関を示した．また，合併症および肝細胞癌の診療行為別に入院日数と診療報酬請求額あるいは診療行為請求額との間で，前者では0.71～0.92と高い相関を認め，後者でも0.43～0.69と中等度の相関を認めた(**表3**)．

診療報酬請求額に対する多変量解析(**表4**)では，入院日数はt値が20.81と高く診療報酬請求額に影響する最も有意な要因であった．これは単変量解析で相関が高かったことと一致する結果であった．入院日数以外には，手術，Chemo-lipiodol 療法，化学療法などの肝細胞癌治療，肝硬変症の合併症である腹水・浮腫や食道静脈瘤では有意であったが，PEIT 療法，肝性脳症は有意な要因ではなかった．また，診療報酬請求額の推定に対する寄与度を有意度および回帰係数から見ると，入院日数を除いて肝細胞癌に対する治療の寄与度が高く，合併症に対する治療の寄与度は低いという結果であった．一方，入院日数に依存する入院基本料などの hospital fee を除いた診療行為請求額に対する多変量解析(**表5**)でも，診療報酬請求額と同様の要因が有意であったが，その寄与度は回帰係数から手術が最も高く，以下，Chemo-lipiodol 療法と

表2　診療行為の有無による入院日数，診療請求額(千円)

診療行為		あり	なし	p値
抗炎症基礎治療	N*	194	42	
	入院日数	19(12, 30)**	17(10, 28)	NS
	診療請求額	707(503, 1,107)	524(354, 1,076)	NS
合併症				
腹水・浮腫	N	116	120	
	入院日数	23(14, 31)	15(10, 29)	0.002
	診療請求額	800(568, 1,397)	600(431, 854)	<0.001
肝性脳症	N	58	178	
	入院日数	24(15, 39)	17(11, 28)	<0.001
	診療請求額	998(635, 1,487)	642(451, 999)	<0.001
食道静脈瘤	N	11	225	
	入院日数	35(28, 47)	17(12, 30)	<0.001
	診療請求額	1,361(1,070, 1,737)	654(476, 1,057)	<0.001
肝細胞癌治療				
手術	N	19	217	
	入院日数	29(26, 33)	17(11, 30)	0.001
	診療請求額	1,476(1,374, 1,904)	647(465, 1,005)	<0.001
PEIT 療法	N	28	208	
	入院日数	31(17, 39)	17(12, 29)	0.005
	診療請求額	889(534, 1,136)	655(482, 1,082)	NS
Chemo-lipiodol 療法	N	124	112	
	入院日数	15(10, 27)	23(15, 33)	<0.001
	診療請求額	687(551, 920)	693(366, 1,397)	NS
化学療法	N	23	215	
	入院日数	36(16, 59)	17(12, 28)	0.001
	診療請求額	1,454(572, 1,963)	654(484, 1,041)	0.005

* 症例数
**メジアン(25％値，75％値)を示す．

表3　診療行為別の入院日数と診療報酬請求額，診療行為請求額との相関

診療行為	診療報酬請求額	診療行為請求額
抗炎症基礎治療	0.783	0.502
合併症		
腹水・浮腫	0.820	0.626
肝性脳症	0.841	0.622
食道静脈瘤	0.747	0.433
肝細胞癌治療		
手術	0.718	0.612
PEIT 療法	0.858	0.602
Chemo-lipiodol 療法	0.897	0.475
化学療法	0.924	0.690

表4　診療報酬請求額*に対する多変量解析結果

治療・合併症	回帰係数(SE)	t値	p値
入院日数**	51.10 (2.46)	20.81	<0.001
手術	109.19 (10.53)	10.37	<0.001
Chemo-lipiodol	50.20 (5.80)	8.66	<0.001
化学療法	49.07 (9.69)	5.06	<0.001
腹水・浮腫	14.67 (5.32)	2.76	0.006
食道静脈瘤	28.77 (12.48)	2.31	0.022

R=0.89
*0.36 乗で Box-Cox(べき)変換後
**0.2 乗で Box-Cox 変換後

化学療法が同程度の寄与度になった．肝硬変症の合併症は診療報酬請求額の場合と同様に診療行為請求額においても寄与度は低い結果であった．

モデルの適合性については，**表4**に示したモデル作成群での診療報酬請求額の予測値と実際額との重相関係数は0.89であり，手術，Chemo-lipiodol 療法，化学療法における予測額と実際額の平均値の比較(**表6**)でも近似した値が得られた．

一方，モデル作成群とは異なる80例のモデル検証患者群のデータセットに得られた重回帰モデルを適用し，予測値と実際の診療報酬請求額の相関を見ると0.89(Spearman 順位相関係数)と高い結果が得られた(**図2**)．

表5　診療行為請求額*に対する多変量解析結果

治療・合併症	回帰係数(SE)	t値	p値
入院日数**	51.42 (7.99)	6.44	<0.001
手術	186.56 (18.80)	9.92	<0.001
Chemo-lipiodol	112.38 (10.36)	10.85	<0.001
化学療法	106.96 (17.16)	6.23	<0.001
腹水・浮腫	24.83 (9.49)	2.62	0.010
食道静脈瘤	59.68 (22.25)	2.68	0.008

R=0.74
*0.36乗でべき変換後　　**0.2乗でべき変換後

表6　モデルによる予測額と実際額の比較(モデル作成群)

治療	入院日数*	実際額**	予測額**
手術	30	1,656	1,622
Chemo-lipiodol療法	18	787	797
化学療法	42	1,372	1,274

*平均　　**平均(千円)

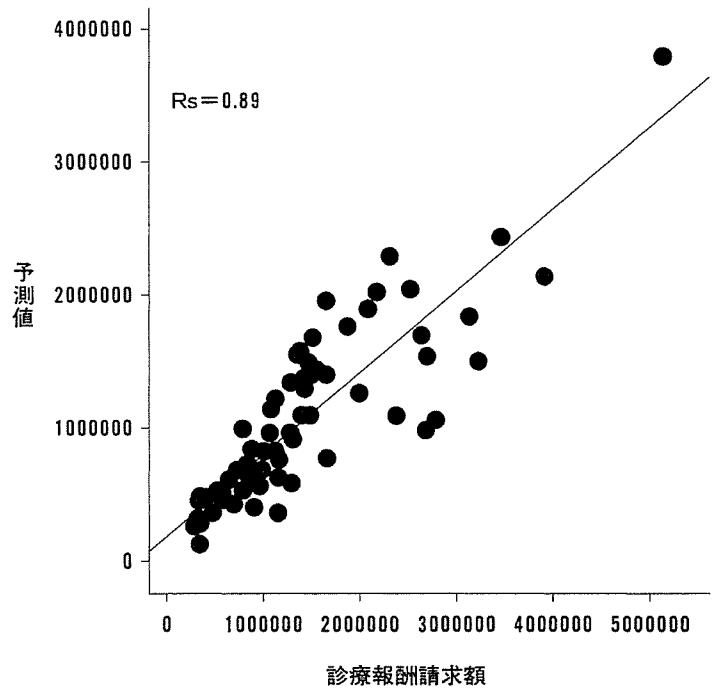


図2　検証用データにおけるモデルによる予測額と実際の診療報酬請求額との相関

5. 考　察

医療費の正確度の高い推定は，疾患が社会に与える影響の大きさを測る上でも，あるいは，費用効果分析などにより様々な治療における医療資源の配分を考える上でも不可欠である．しかし，我が国での疾患別の医療費についての正確な情報は少なく，医療経済の研究における重要な課題となっている．

一方，複数の病態が併存している患者では，それぞれの病態に特異的な検査や治療のみでなく複数の病態に共通の検査や治療がなされることからその病態毎に機械的に分けて医療費の算出を行うことは容易ではない．実際の症例を用いた検討でも，様々な合併症をもつ症例が多く含まれることから，その病態の純粋な医療費を推定するには，その中で層別化し，合併症が全くない，あるいは，特定の合併症だけを有する症例のみを集めて検討することが多い[5]．

そこで，本研究では，それぞれの合併症や特異的治療にかかる経費は医療費の中で部分的な独立したコンポーネントを構成するという仮定に立ち，

肝硬変症を基礎疾患として非代償性の合併症を伴うことが多い肝細胞癌を対象として，複合病態における医療費推定モデルを作成し，一入院あたりの医療費における肝細胞癌治療や合併症の寄与度およびモデルの適合性を検討した．

結果として診療報酬請求額に対して適合性の高いモデルが得られ，診療報酬請求額および診療行為請求額に対する変動要因としての合併症および治療の寄与度をみると，いずれも入院日数は有意であり，また，肝細胞癌治療の方が合併症より寄与度が大きい傾向を認めた．また，それぞれの治療はいずれも入院日数との相関が強かったが，有意な要因として上がらなかった抗炎症基礎治療，PEIT 療法や肝性脳症に対する治療は，入院日数の増加に伴って増加する診療報酬請求額にそれらの医療費分が包含されてしまうのに対して，有意となった手術，Chemo-lipiodol 療法等では，治療の有無により係数分の請求額が加わると理解できることから，**図1**のような医療費を構成するコンポーネントとしての考え方は妥当であると考えられた．

今回は従来から行われてきた診療録から肝硬変症の合併症，肝細胞癌に対する治療の情報を得るのではなく，診療請求上の行為明細から判定を行った．これは，レトロスペクティブな診療録の確認では実施された医療行為について十分な情報が得られない場合が多く，また，診療報酬請求の観点からは，実際に請求の対象となった診療行為に注目する方がより正確な推定が可能になると考えたからである．実際，診療行為明細には入っている処置などが診療録の記載からは確認できないケースが多くあり，有用な方法と考えられた．一方，診療行為明細には，患者毎に異なる様々な行為が含まれていることから，医療費推定の対象とする病態に直接関連すると考えられる診療行為を的確に把握することが重要であり，当然，その如何により推定の正確度が影響されることになる．

医療費の推定方法は医療費を考える立場(perspective)，すなわち，医療提供者，患者，保険支払者，社会などの立場で異なるが，一般的には個々の患者に実際に行われた医療行為に用いられた薬剤や医療材料，医師，看護師など医療提供者の費用，さらには施設や機器利用に伴う費用などをひとつひとつ積み上げる micro-costing の手法がとられることが多い[2]．しかし，今回の医療費の推定は保険支払者の立場で行い，診療報酬請求に伴う保険償還額を医療費とした．我が国では，国民医療費の増大から近年，従来の出来高支払い制に加えて包括評価支払い制度が導入され，DPC に基づく診療報酬額の割り当てが行われているが，この基盤となっているのは，それぞれの DPC 別の出来高による診療報酬額の調査であり，今回の検討もそれと同様のアプローチである．そのため，DPC をもとにした包括支払い制度の妥当性を評価する上でも今回の検討は意義あるものと考える．すなわち，DPC そのものが基本的に疾患と手術，処置，副傷病名の有無の組み合わせであり，今回の検討における手術，処置，そして，肝硬変症の合併症の寄与度の相対的な大きさの結果は，それに相似するものと考えられた．

さらに，肝硬変症の合併症である腹水・浮腫，肝性脳症，食道静脈瘤は，それぞれ治療により医療資源を消費するものであるが，肝細胞癌と複合した病態においては，入院日数と肝細胞癌に対する治療によって医療費のほとんどの部分が決定されるという結果は，例えば，費用効果分析などでは，肝細胞癌がある場合に肝硬変症の合併症別に分ける必要性があるかどうかを考える上で重要な情報と考えられた．

今回の検討の限界として，次の2点が挙げられる．1つは，食道静脈瘤や PEIT 療法などで患者数が少ないことが解析に影響した可能性があり，今後，それらの患者数を増やしての検討が必要となる．2つには，推定モデル作成に線形回帰である重回帰分析を用いたが，有意とされた要因それぞれが入院日数と相関が強く，また，変数の正規化のために Box-Cox 変換を行ったことにより，モデルで有意とされた要因毎に単純なブロック組み立てのように加算できる形にはならなかった．一般的には医療費は分布が正規分布とはならないため，その歪度を考慮に入れる必要があるが，そのため，正規分布を前提としない一般化線形モデルなど，より適切な手法について検討する必要がある[6]．

6. 結　語

複合病態における医療費(診療報酬請求額・診療行為請求額)の推定の例として肝細胞癌患者を対象として入院日数とともに実施された診療行為に着目した多変量回帰モデルを作成した．モデルは入院日数が最も有意な因子であったが，肝細胞癌治療や非代償性肝硬変症の合併症がそれぞれ独立した有意な因子として挙げられ，その回帰係数から寄与度が推定できることが示唆された．この結果により，病態(合併症)，治療それぞれの因子をコンポーネントとして捉えて医療費を推定することが可能と考えられた．今後，適用するモデルの妥当性の検証が必要であるが，今回のアプローチは，従来の病態別，治療別に層別化された患者集団に基づく医療費推定に代わって，主要な変動要因の抽出およびその組み合わせでの平均的医療費の推定に有用と考えられた．

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Risk factors for development of hepatocellular carcinoma in patients with chronic hepatitis C after sustained response to interferon

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Background. Interferon (IFN) is expected to prevent the progression of hepatitis C virus infection to cirrhosis and the development of hepatocellular carcinoma (HCC), but there have been several reports of the development of HCC after a sustained response to IFN. Our aim was to elucidate the incidence and clinical features of, and risk factors for, HCC in sustained responders to IFN, taken for the treatment of chronic hepatitis C. ***Methods.*** We designed a retrospective cohort study conducted at 16 major Hospitals. The subjects were a total of 1056 patients showing sustained responses, 29 of whom developed HCC. ***Results.*** The incidence of HCC per 100 person-years was 0.56 (95% confidence interval, 0.35–0.76) in sustained responders. By the Cox proportional hazard model, we found that older age, higher serum aspartate aminotransferase level, and lower platelet count before IFN therapy were independent risk factors associated with the development of HCC. A risk index of HCC development, based on the coefficients of these risk factors, was used to classify patients into three groups, with low, intermediate, and high risk. The incidence rates of HCC for these three groups were 0.11, 0.44, and 1.98 per 100 person-years, respectively. The median period to the development of HCC was 4.6 years (range, 1.4–9.0 years), and there were no other specific clinical features of the HCC that developed in these patients. ***Conclusions.*** This study suggests that the risk of development of HCC is not completely eliminated in sustained responders to IFN. These findings may be useful in determining a follow-up strategy after a sustained response to IFN.

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Key words: hepatitis C virus, hepatocellular carcinoma, interferon, sustained response

Introduction

Hepatitis C virus (HCV) infection is one of the most common causes of chronic hepatitis, and it is also a major risk factor for hepatocellular carcinoma (HCC).[1,2] Chronic hepatitis C is often asymptomatic and mild, but may slowly progress to liver cirrhosis and eventually to HCC.[3–5] Therefore, it has been assumed that eradication of HCV would provide the most effective means of preventing HCC.

Currently, interferon (IFN) represents the mainstay of treatment for chronic hepatitis C.[5–9] IFN therapy can lead to a decrease in serum transaminase activity, and to the disappearance of serum HCV RNA in patients with chronic hepatitis C. These patients appear to benefit by the prevention of progression to cirrhosis and HCC.[5,7,10–14] However, HCC can still occur in patients who are treated successfully with IFN, i.e., those showing a sustained response to the therapy.[5,10–25] The incidence and clinical features of HCC, and the risk factors for carcinogenesis, have not yet been investigated, although they have been documented in individuals and in small numbers of patients.[5,10–25] We investigated a large cohort of patients showing a sustained response to IFN therapy given for chronic hepatitis C. Our aims were to assess the incidence of HCC in these patients and to discover the clinical variables that may be associated with the development of HCC. Our study also focused on the clinical features of HCC. We designed a multicenter retrospective cohort study, because a single-institution study would have provided inadequate numbers of sustained responders who developed HCC.

Patients and methods

Patients

This study was conducted at 16 major hospitals belonging to the Japanese Society of Gastroenterology, Kyushu Division. A large cohort of sustained responders to IFN therapy given for chronic hepatitis C, in whom HCC had, or had not, been detected, was assembled consecutively by means of data collection instruments. All sustained responders included in the study were positive for HCV RNA before IFN therapy, and were followed up for more than 1 year after termination of IFN therapy, during the period July 1988 to August 2001. Sustained response was defined as the presence of HCV RNA negativity (determined by using qualitative HCV RNA assay) more than 6 months after the termination of IFN therapy. Diagnosis of HCC was based either on histological examination or on typical computed tomographic and/or angiographic findings at each institution. Patients were excluded if HCC was detected within 1 year after the termination of IFN therapy, because in such cases it was highly likely that the cancer had been present at the end of the IFN therapy. In Japan, at the time of the study, the standard schedule was 6–10 MU IFN-α every day for the first 2–4 weeks and then the same dose given three time a week for the following 20–22 weeks, or 6 MU IFN-β every day for 6–8 weeks.

During the study period at the 16 hospitals, a total of 3504 patients with chronic hepatitis C had received IFN therapy and had been followed up for more than 1 year thereafter, and a sustained response was obtained in 1091 (31.1%) of them. Among the sustained responders, 30 patients (2.7%) developed HCC. By means of the data collection instrument, we requested individual clinical data before IFN therapy for all sustained responders, as well as clinical data at the time of diagnosis of HCC for patients who had developed HCC. The clinical data for all 1091 sustained responders identified were obtained from the 16 hospitals (8 university hospitals and 8 regional hospitals) listed in the appendix. Of these patients, 35 were excluded from the analysis because of the development of HCC within 1 year after IFN therapy (1 patient) or insufficient clinical records before commencement of IFN therapy (34 patients). The final study population comprised a total of 1056 patients showing sustained response to IFN therapy given for chronic hepatitis C, 29 of whom had developed HCC.

Methods

To identify risk factors for the development of HCC in sustained responders to IFN therapy, we used univariate analysis and multivariate analysis to investigate 23 variables before IFN therapy for their relationship to the development of HCC. These variables were chosen by considering possible factors involved in the development of HCC, as indicated by previous investigations,[1-5,10-25] or suggested from our own clinical experience. Each variable, which was classified as host-related or treatment-related, was divided into one of two subgroups on the basis of clinically meaningful values. HCV RNA load was determined quantitatively by competitive reverse-transcription polymerase chain reaction (RT-PCR), branched-DNA probe assay, or Amplicor-HCV monitor assay.[26-28] When the serum HCV RNA level was more than 10^6 equivalents/ml by branched DNA assay, more than 10^6 copies/ml by competitive RT-PCR, or more than 10^5 copies/ml by Amplicor-HCV monitor assay, it was designated as a high viral load; an HCV RNA level of 10^5 copies/ml by the Amplicor-HCV monitor assay has already been demonstrated to correspond to approximately 10^6 equivalents/ml by the branched DNA probe assay or 10^6 copies/ml by competitive RT-PCR.[26-28] HCV subtype was classified by either the method of Okamoto et al.,[29] or Tanaka et al.'s method.[30] Genotypes 1a and 1b corresponded to serological group 1, and genotypes 2a and 2b corresponded to serological group 2, according to the Simmonds et al.[31] classification.[31] The data from liver biopsies that were done within 6 months before IFN therapy were included in this study. Assessments of the staging of liver fibrosis and the grade of inflammatory activity were based on the classification of Desmet and colleagues,[32] in which staging is defined as follows: F0 (no fibrosis), F1 (fibrous portal expansion), F2 (bridging fibrosis), F3 (bridging fibrosis with architectural distortion), and F4 (cirrhosis), and grading is defined as follows: A0 (no activity), A1 (mild activity), A2 (moderate activity), and A3 (severe activity).

To elucidate the clinical features of HCC that developed in sustained responders, 17 variables at the time of diagnosis of HCC were investigated. Number of tumors, maximum tumor size, portal vein invasion, hepatic vein invasion, and bile duct invasion were examined by ultrasonography, computed tomography, and/or angiography. The period to the development of HCC was measured from the day of termination of IFN therapy to the day when HCC was first diagnosed by imaging modalities, such as ultrasonography or computed tomography. The follow-up period for the detection of HCC after termination of IFN therapy was defined as the interval during which checks for HCC were done using tumor markers and/or imaging modalities.

Statistical analysis

Follow up ended with the last recorded visit before August 31, 2001. Incidences were calculated in person-