Factors associated with severity of hepatic fibrosis in people with chronic hepatitis C infection

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ABSTRACT

Objective: To determine factors associated with hepatic fibrosis development in people with chronic hepatitis C virus (HCV) infection.

Methods: As a requirement for access to interferon therapy through the S100 scheme in Australia, individual pretreatment demographic and clinical information was collected on 2986 patients from 61 hospital-based liver clinics from 1 October 1994 through 31 December 1996. Patients with both a hepatic fibrosis score and an estimated duration of HCV infection (910) were divided into 540 with no or minimal hepatic fibrosis (stage 0–1) and 370 with moderate to severe hepatic fibrosis (stage 2–3). Seven factors were examined: age at HCV infection, sex, ethnicity, source of infection, duration of infection, alcohol intake, and mean ALT level. A further analysis was performed for all 1135 patients with a hepatic fibrosis score disregarding age at and duration of HCV infection.

Results: In multivariate analysis, four factors were significantly associated with moderate to severe hepatic fibrosis: age at infection (OR, 2.33 for age 31–40 years, 5.27 for age >40 years, and 0.20 for age <15 years, compared with 15–20 years); duration of infection (OR, 1.44 for 11–20 years, 2.74 for 21–30 years, and 8.71 for >30 years, compared with <11 years); alcohol intake in previous six months (OR, 1.51 for any intake, compared with none); and mean ALT level (OR, 1.81 for 2–3 times, 2.27 for >3 times, compared with 1.5–2 times the upper limit of normal). In the analysis disregarding age at HCV infection and duration of HCV infection, older age was strongly associated with moderate to severe hepatic fibrosis (OR, 2.32 for age 36–40 years, 2.46 for age 41–50 years, 7.87 for age 51–60 years, and 7.15 for age >60 years, compared with 16–30 years). There was no association in either analysis with sex or source of HCV infection.

Conclusion: These factors may assist in targeting patients for both liver biopsy-based investigation and therapeutic intervention.

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A MAJOR FEATURE of hepatitis C virus (HCV) infection is the highly variable course of its natural history. Although most people develop chronic infection, with its consequent risk of cirrhosis, liver failure and hepatocellular carcinoma, only a minority will progress to these advanced liver disease endpoints.[1] A key question is whether patients at high risk of disease progression can be distinguished from those with a relatively benign disease course.

Factors previously shown to influence disease progression in chronic hepatitis C have included duration of infection, age at infection, sex, alcohol intake, and co-infection with HIV and hepatitis B virus (HBV).[2-6] Evidence about the role of other factors, such as source of HCV infection and ethnicity, is less clear. People with chronic HCV infection and persistently normal serum transaminase levels are less likely to progress to advanced liver disease than those with abnormal levels.[7] However, there is conflicting evidence as to the importance of serum transaminase levels in predicting progression among those with abnormal levels.[8-10]

Consensus guidelines for managing chronic HCV infection generally recommend antiviral therapy for people with moderate to severe hepatic fibrosis, while often recommending observation of people in whom fibrosis is either absent or minimal.[11] Thus, correlates of hepatic fibrosis severity could be used to develop assessment and monitoring strategies for chronic HCV infection, including selection of patients for liver biopsy and possible therapeutic intervention.

To assess factors that may influence the development of hepatic fibrosis, we analysed pretreatment demographic and clinical data for patients receiving interferon monotherapy during the mid-1990s in Australia.

METHODS

In Australia, interferon therapy became available under the Pharmaceutical Benefits Scheme for treating chronic HCV

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infection in 1994. Approved doctors practising in public hospital-based clinics could prescribe interferon therapy through the S100 scheme, which provides access to restricted therapies. Access to S100 interferon therapy required that individual pretreatment information was recorded and forwarded to a database established at the John Hunter Hospital, Newcastle. Access to S100 interferon during the study period also required confirmation of chronic hepatitis C by a positive HCV antibody test result on two occasions, and histological evidence of chronic hepatitis. Alanine aminotransferase (ALT) levels had to be elevated more than 1.5 times the upper limit of normal (ULN) on three occasions in the six months before beginning interferon therapy. Patients with HIV, other causes of chronic liver disease and established cirrhosis were excluded from receiving interferon through the S100 scheme.

Information was available on patients receiving S100 interferon therapy between 1 October 1994 and 31 December 1996 at 61 hospitals in all Australian States and Territories (Australian Capital Territory, 1; New South Wales, 22; Northern Territory, 2; Queensland, 9; South Australia, 6; Tasmania, 3; Victoria, 12; Western Australia, 6; full list available from the authors). Baseline (pretreatment) information was recorded by doctors on standardised forms and forwarded to the S100 database coordinator. Demographic (age, sex, country of birth, and ethnicity) and clinical (source of infection, estimated time of exposure, ALT levels, alcohol intake, and liver biopsy findings) variables were included. Data on hepatitis B virus serology, HCV genotype and HCV viral load were only available for a minority of patients.

Histopathological findings from liver biopsies performed in the six months before baseline assessment were recorded. Portal/periportal and lobular inflammatory activity and staging of fibrosis were generally graded on a five-point (0–4) scoring system according to Scheuer.[12] Histopathological classification systems in which the denominator for fibrosis was greater than four were used in some cases, but these patients were excluded from the analyses.

We performed analyses to examine factors which might distinguish patients with moderate to severe hepatic fibrosis (stage 2–3) from those with no or minimal hepatic fibrosis (stage 0–1). The fibrosis scores were grouped in this way, as consensus guidelines now generally recommend antiviral therapy for patients with moderate to severe hepatic fibrosis.[11] Patients with stage 4 fibrosis (cirrhosis) were not eligible for S100 interferon therapy, and were excluded.

Seven variables were initially examined among the subgroup of patients with a fibrosis score of 0–3 and a recorded estimated duration of HCV infection. These were age at infection, sex, ethnicity, source of infection, duration of infection, alcohol intake, and mean ALT level. Duration of infection was defined as the time interval between estimated time of exposure and date of liver biopsy.

1: Baseline demographic and clinical characteristics of patients with known and unknown hepatic fibrosis scores

	Known fibrosis score (*n*=1135)	Unknown fibrosis score (*n*=1640)	Total (*n*=2775)	*P**
Age at biopsy (years)				<0.0005
16–30	161 (14.2%)	299 (18.2%)	460 (16.6%)	
31–40	537 (47.3%)	802 (48.9%)	1339 (48.3%)	
41–50	292 (25.7%)	343 (20.9%)	635 (22.9%)	
51–60	98 (8.6%)	77 (4.7%)	175 (6.3%)	
60+	44 (3.9%)	38 (2.3%)	83 (3.0%)	
Unknown	3 (0.3%)	81 (4.9%)	84 (3.0%)	
Sex				0.41
Male	775 (68.3%)	1144 (69.8%)	1919 (69.2%)	
Female	360 (31.7%)	496 (30.2%)	856 (30.8%)	
Ethnicity				<0.0005
Asian	181 (15.9%)	135 (8.2%)	316 (11.4%)	
Caucasian	911 (80.3%)	1459 (89.0%)	2370 (85.4%)	
Other	41 (3.6%)	39 (2.4%)	80 (2.9%)	
Unknown	2 (0.2%)	7 (0.4%)	9 (0.3%)	
Source of infection				<0.0005
Blood product	153 (13.5%)	282 (17.2%)	435 (15.7%)	
IDU	600 (52.9%)	976 (59.5%)	1576 (56.8%)	
COBHP	168 (14.8%)	124 (7.6%)	292 (10.5%)	
Tattoo	57 (5.0%)	64 (3.9%)	121 (4.4%)	
Other	70 (6.2%)	96 (5.9%)	166 (6.0%)	
Unknown	87 (7.7%)	98 (5.9%)	185 (6.7%)	
Duration of infection (years)				0.015
<11	249 (21.9%)	390 (23.8%)	639 (23.0%)	
11–20	436 (38.4%)	658 (40.1%)	1094 (39.4%)	
21–30	158 (13.9%)	209 (12.7%)	367 (13.2%)	
>30	67 (5.9%)	58 (3.5%)	125 (4.5%)	
Unknown	225 (19.8%)	325 (19.8%)	550 (19.8%)	
Alcohol intake in the previous six months				0.003
No	514 (45.3%)	921 (56.2%)	1435 (51.7%)	
Yes	474 (41.8%)	667 (40.7%)	1141 (41.1%)	
Unknown	147 (12.9%)	52 (3.1%)	199 (7.2%)	
Mean ALT level (x upper limit of normal)				0.26
1.5–2	211 (18.6%)	299 (18.2%)	510 (18.4%)	
>2–3	343 (30.2%)	482 (29.4%)	825 (29.7%)	
>3	519 (45.7%)	640 (39.0%)	1159 (41.8%)	
Unknown	62 (5.5%)	219 (13.4%)	281 (10.1%)	

IDU = injecting drug use; COBHP = country of birth high prevalence; ALT = alanine aminotransferase.
*For comparison of known and unknown fibrosis groups.

2: Factors associated with moderate to severe hepatic fibrosis (fibrosis score, 2–3) in patients with an estimated age at HCV infection

	Fibrosis score 0–1 (*n* = 540)	Fibrosis score 2–3 (*n* = 370)	OR	95% CI
Age at infection (years)				
< 15	67 (12.4%)	31 (8.4%)	0.20*	0.09–0.46
15–20	205 (38.0%)	147 (39.7%)	1.00	
21–30	216 (40.0%)	124 (33.5%)	0.91	0.66–1.27
31–40	41 (7.6%)	45 (12.2%)	2.33*	1.38–3.92
> 40	11 (2.0%)	23 (6.2%)	5.27*	2.32–11.94
Sex				
Male	358 (66.3%)	269 (72.7%)	1.00	
Female	182 (33.7%)	101 (27.3%)	0.79	0.58–1.09
Ethnicity				
Asian	47 (8.7%)	34 (9.2%)	1.00	
White	483 (89.4%)	320 (86.5%)	1.07	0.53–2.16
Other	9 (1.7%)	15 (4.0%)	2.64	0.90–7.73
Unknown	1 (0.2%)	1 (0.3%)	1.48	0.08–27.45
Source of infection				
Blood product	76 (14.1%)	72 (19.5%)	1.00	
IDU	355 (65.7%)	225 (60.8%)	0.95	0.60–1.49
COBHP	37 (6.9%)	25 (6.8%)	0.76	0.27–2.18
Tattoo	29 (5.4%)	23 (6.2%)	1.02	0.50–2.10
Other	33 (6.1%)	19 (5.1%)	0.79	0.39–1.59
Unknown	10 (1.8%)	6 (1.6%)	0.80	0.24–2.62
Duration of infection (years)				
< 11	155 (28.7%)	94 (25.4%)	1.00	
11–20	267 (49.4%)	169 (45.7%)	1.44	1.00–2.06
21–30	81 (15.0%)	77 (20.8%)	2.74*	1.70–4.41
> 30	37 (6.9%)	30 (8.1%)	8.71*	3.32–22.80
Alcohol intake in the previous six months				
No	247 (45.7%)	151 (40.8%)	1.00	
Yes	222 (41.1%)	175 (47.3%)	1.51*	1.11–2.05
Unknown	71 (13.2%)	44 (11.9%)	1.21	0.75–1.96
Mean ALT level (x upper limit of normal)				
1.5–2	121 (22.4%)	52 (14.1%)	1.00	
> 2–3	154 (28.5%)	115 (31.1%)	1.81*	1.18–2.76
> 3	224 (41.5%)	194 (52.4%)	2.27*	1.52–3.39
Unknown	41 (7.6%)	9 (2.4%)	0.46	0.20–1.07

OR = adjusted odds ratio; IDU = injecting drug use; COBHP = country of birth high prevalence; ALT = alanine aminotransferase. *Significant at $P < 0.05$.

Alcohol intake was estimated from the recorded mean consumption in the previous six months. Mean ALT was calculated from three ALT measurements carried out within six months of the liver biopsy, and expressed as a multiple of ULN for the particular laboratory.

As duration of HCV infection is often difficult to assess, a second analysis was performed to examine factors associated with hepatic fibrosis in the absence of duration of infection. We analysed six variables for all patients with a hepatic fibrosis score of 0–3, whether or not there was an estimated duration of infection. These variables were age at liver biopsy, sex, ethnicity, source of infection, alcohol intake, and mean ALT level.

For both analyses univariate and multivariate models were used to examine associations between selected variables and hepatic fibrosis score. In univariate analyses χ^2 tests were used to examine categorical variables. All selected variables were entered into a multivariate logistic regression model to examine independent associations.

Finally, we assessed the relationship between hepatic fibrosis score and both mean ALT level and inflammatory score (portal/periportal, lobular, and combined) using a Wilcoxon-type test for trend.[13] Values were considered statistically significant if the P value was < 0.05 or if the 95% confidence intervals did not cross unity.

RESULTS

Over the 26 months, we recruited 2986 patients from 61 hospitals. Most came from New South Wales (1314) and Victoria (638). However, the numbers from the other States and Territories were in approximate proportion to their populations. Patients who had previously received interferon therapy (172) and those in whom a clearly different histological scoring system was used (39) were excluded from the original study population.

Among the remaining 2775 patients, 69% were male and the median age at liver biopsy was 37 years. The most common sources of HCV exposure were a history of injecting drug use (IDU) (56.8%) and transfusion of blood products (15.7%). An additional 10.5% were born in a country of relatively high background HCV prevalence, and 6.7% had an unknown source. After Australia (71.2%), the most common countries or regions of birth were Vietnam (8.2%), Europe (6.1%) and other South-East Asian countries (3.6%). Ethnicity was recorded as "white" for 85.4%, "Asian" for 11.4%, and "other" in 2.9% of cases.

Individual fibrosis scores were recorded in 1135 patients (40.9%). Among these, the distribution of hepatic fibrosis score was 0 (22.1%), 1 (37.3%), 2 (27.8%), and 3 (12.9%). Patients with and without a fibrosis score are compared in Box 1. There was a higher proportion of Asian patients and those with a high HCV prevalence in their country of birth as their source of infection in the group with known fibrosis scores.

Both an individual hepatic fibrosis score of 0–3 and estimated duration of infection were available for 910 patients (32.8%), who were therefore included in the first analysis of factors associated with hepatic

3: Baseline demographic and clinical characteristics among patients with and without estimated duration of infection

	Known duration of infection (*n*=2225)	Unknown duration of infection (*n*=550)	*P*
Age at biopsy (years)			<0.0005
16–30	414 (18.6%)	46 (8.4%)	
31–40	1157 (52.0%)	182 (33.1%)	
41–50	512 (23.0%)	123 (22.4%)	
51–60	97 (4.4%)	78 (14.2%)	
60+	45 (2.0%)	37 (6.7%)	
Unknown	0 (0.0%)	84 (15.2%)	
Sex			0.86
Male	1537 (69.1%)	382 (69.5%)	
Female	688 (30.9%)	168 (60.5%)	
Ethnicity			<0.0005
Asian	141 (6.3%)	175 (31.8%)	
Caucasian	2027 (91.1%)	343 (62.4%)	
Other	50 (2.3%)	30 (5.4%)	
Unknown	7 (0.3%)	2 (0.4%)	
Source of infection			<0.0005
Blood product	358 (16.1%)	77 (14.0%)	
IDU	1508 (67.8%)	68 (12.4%)	
COBHP	90 (4.0%)	202 (36.7%)	
Tattoo	110 (5.0%)	11 (2.0%)	
Other	125 (5.6%)	41 (7.5%)	
Unknown	34 (1.5%)	151 (27.4%)	
Alcohol intake in the previous six months			0.003
No	1126 (50.6%)	309 (56.1%)	
Yes	949 (42.7%)	192 (35.0%)	
Unknown	150 (6.7%)	49 (8.9%)	
Mean ALT level (x upper limit of normal)			0.58
1.5–2	427 (19.1%)	83 (15.1%)	
>2–3	674 (30.3%)	151 (27.5%)	
>3	963 (43.3%)	196 (35.6%)	
Unknown	161 (7.3%)	120 (21.8%)	
Fibrosis score			0.58
0–1	540 (24.3%)	129 (23.4%)	
2–3	370 (16.6%)	96 (17.5%)	
Unknown	1315 (59.1%)	325 (59.1%)	

IDU = injecting drug use; COBHP = country of birth high prevalence; ALT = alanine aminotransferase.

fibrosis. In univariate analysis, age at infection, mean ALT level and sex were associated with hepatic fibrosis score. In multivariate analysis, moderate to severe hepatic fibrosis was associated with older age at infection, longer duration of infection, higher mean ALT level, and alcohol intake in the previous six months (Box 2).

A comparison of patients with and without estimated duration of infection is shown in Box 3. Patients without estimated duration of infection were older, more likely to be Asian, and to have a high HCV prevalence in their country of birth as their source of infection. However, there was no significant difference in sex, mean ALT level and fibrosis score between these two groups.

The analysis of predictors of hepatic fibrosis among all 1135 patients with a fibrosis score, omitting the duration of HCV infection (and age at infection) variable, but including age at liver biopsy, is shown in Box 4. In univariate analysis, age at liver biopsy, ethnicity, and mean ALT level were associated with hepatic fibrosis score. In multivariate analysis, moderate to severe hepatic fibrosis was associated with age at biopsy greater than 35 years, "other" ethnicity, alcohol intake in the previous six months, and higher mean ALT level. As ALT data were from many different laboratories, we repeated the analyses reported in Boxes 2 and 4 using absolute ALT groupings rather than times the upper limit of normal, but the significant associations were unchanged (data not shown).

There was a significant positive rank correlation between the hepatic fibrosis score and both the portal/periportal and lobular measures of inflammatory activity. However, the correlation was greatest for portal/periportal activity (Box 5). Although statistically significant, the correlation between mean serum ALT level and hepatic fibrosis score was weaker than that for either of the two histological inflammatory scores.

DISCUSSION

Current antiviral therapy guidelines strongly recommend therapeutic intervention for patients who have developed moderate to severe hepatic fibrosis,[11] as the risk of progression to advanced liver disease is relatively high in this group.[14] Our study suggests that, in chronic HCV infection, more severe hepatic fibrosis is associated with older age at infection, longer duration of infection, alcohol intake, and higher ALT levels. In contrast, sex, ethnicity and source of infection did not influence the extent of hepatic fibrosis.

There were several limitations in our methods. First was the use of cross-sectional data to examine a longitudinal process. Cross-sectional analyses rely on estimation of time of HCV exposure, which is often problematic. To help counter this, we analysed separately patients in whom hepatic fibrosis score and time of HCV exposure were recorded, and all patients with hepatic fibrosis score with no regard to time of HCV exposure. Secondly, a large proportion of patients did not have a hepatic fibrosis score recorded, and there were differences in demographic and clinical characteristics between patients with and without a fibrosis score. Thirdly, being based on liver clinic populations, the participants were probably not totally

4: Factors associated with moderate to severe hepatic fibrosis (score, 2–3)

	Fibrosis score 0–1 (*n*=669)	Fibrosis score 2–3 (*n*=466)	OR	95% CI
Age at biopsy (years)				
16–30	120 (17.9%)	41 (8.8%)	1.00	
31–35	147 (22.0%)	77 (16.5%)	1.49	0.94–2.37
36–40	178 (26.6%)	135 (29.0%)	2.32*	1.50–3.60
41–50	168 (25.1%)	124 (26.6%)	2.46*	1.57–3.87
51–60	36 (5.4%)	62 (13.3%)	7.87*	4.22–14.70
>60	17 (2.5%)	27 (5.8%)	7.15*	3.25–15.74
Unknown	3 (0.5%)	0		
Sex				
Male	442 (66.1%)	333 (71.5%)	1.00	
Female	227 (33.9%)	133 (28.5%)	0.86	0.65–1.14
Ethnicity				
Asian	106 (15.8%)	75 (16.1%)	1.00	
Caucasian	549 (82.1%)	362 (77.7%)	1.48	0.87–2.50
Other	13 (1.9%)	28 (6.0%)	4.74*	2.13–10.53
Unknown	1 (0.2%)	1 (0.2%)	2.18	0.13–37.81
Source of infection				
Blood product	80 (12.0%)	73 (15.7%)	1.00	
IDU	368 (55.0%)	232 (49.8%)	0.96	0.63–1.44
COBHP	91 (13.6%)	77 (16.5%)	0.91	0.50–1.65
Tattoo	32 (4.8%)	25 (5.4%)	1.07	0.55–2.09
Other	42 (6.3%)	28 (6.0%)	1.03	0.56–1.91
Unknown	56 (8.3%)	31 (6.6%)	0.56	0.31–1.01
Alcohol intake in the previous six months				
No	312 (46.6%)	202 (43.4%)	1.00	
Yes	266 (39.8%)	208 (44.6%)	1.35*	1.02–1.79
Unknown	91 (13.6%)	56 (12.0%)	1.11	0.74–1.67
Mean ALT level (x upper limit of normal)				
1.5–2	144 (21.5%)	67 (14.4%)	1.00	
>2–3	205 (30.6%)	138 (29.6%)	1.60*	1.09–2.34
>3	270 (40.4%)	249 (53.4%)	2.41*	1.67–3.46
Unknown	50 (7.5%)	12 (2.6%)	0.54	0.26–1.15

OR = adjusted odds ratio; IDU = injecting drug use; COBHP = country of birth high prevalence; ALT = alanine aminotransferase. *Significant at $P < 0.05$.

representative of the Australian population with hepatitis C. Finally, different histopathological classification systems for liver biopsy grading and staging were used, but final analyses were limited to patients whose fibrosis was staged under a five-point scoring system.

A link between age at HCV infection and the presence of hepatic fibrosis is supported by the strong and consistent trend of increasing risk with age at infection, and the independence of effect. This relationship has been seen in several previous cross-sectional studies.[2,15,16] Some recent longitudinal studies have found very low rates of progression to advanced liver disease among young adults infected through injecting drug use and contaminated anti-D immunoglobulin injections,[17-19] and among children infected through blood transfusion.[20] This association may also partly explain the relatively more rapid disease progression in adult post-transfusion cohorts,[21-24] as the median age at infection in these studies was generally 40–50 years.

We also found that duration of chronic HCV infection was independently associated with presence of hepatic fibrosis. Again, such a finding is consistent with other studies.[1,2] The cross-sectional nature of our study precludes examination of the possible non-linearity of disease progression, recently hypothesised by others.[25]

Our study shows that age alone is an important predictor of hepatic fibrosis score. The risk of moderate to severe hepatic fibrosis increased significantly after 35 years of age in our study population. This finding suggests that older patients with chronic HCV infection and abnormal ALT levels who are unable to identify their time of HCV exposure (and therefore their duration of infection) should strongly consider liver-biopsy staging of disease.

Alcohol intake is often difficult to estimate accurately, and consumption may be modified after HCV infection is diagnosed. Current alcohol intake of less than 70 g per week was also a requirement for access to interferon therapy. In our study, alcohol intake in the previous six months was not reported for many patients, and only a small percentage (3%) gave a history of heavy intake (> 40 g/day). Despite this, alcohol intake was associated with the presence of hepatic fibrosis, as several other studies have noted,[2,26,27] although the increase in the odds ratio was relatively small.

The relationship between serum transaminase levels and risk of liver disease progression remains controversial. Although risk of disease progression is considerably higher among people with abnormal serum transaminase levels compared with those with consistently normal levels,[7] there is conflicting evidence on the association between degree of ALT abnormality and extent of histological fibrosis. Several studies have shown either no correlation[8,28,29] or a very weak correlation[30,31] between ALT level and hepatic fibrosis. However, these studies have had relatively small study populations, with fewer than 100 patients undergoing liver biopsy. Our findings suggest a "dose–response" pattern for this relationship.

The pathogenesis of hepatic fibrosis in chronic HCV infection is not well understood; however, an association between inflammatory activity and fibrogenesis is likely. Progression to cirrhosis appears to occur more commonly in patients with chronic HCV infection and high-grade necroinflammatory activity on liver biopsy.[32] Our findings suggest that portal/periportal inflammatory activity may play

5: Relationship between hepatic fibrosis score, necroinflammatory activity and alanine aminotransferase levels

Fibrosis score*	No. of patients	Mean inflammatory score			Mean ALT level (x ULN)
		Portal/periportal	Lobular	Combined	
0	222	1.4	1.3	2.7	3.2
1	368	1.7	1.5	3.2	3.6
2	257	2.1	1.7	3.8	3.9
3	126	2.5	1.8	4.3	4.1
P for trend		<0.0005	<0.0005	<0.0005	<0.0005
Correlation coefficient		0.50	0.30	0.48	0.17

ALT = alanine aminotransferase; ULN = upper limit of normal. *Hepatic fibrosis on a five-point scoring system (patients with a score of 4 were excluded).

a more important role in fibrogenesis than lobular activity. This finding is consistent with the fact that the initial focus of hepatic fibrosis is in the portal region.

This study adds to previous Australian reports[14,33,34] and contributes to a clearer picture of the natural history of chronic hepatitis C, particularly in the Australian context. As patients with moderate to severe hepatic fibrosis have a greatly increased risk of progression to advanced liver disease compared with those with earlier stages of disease,[14] the factors that we have identified should improve our ability to predict patients with progressive disease. Patients with higher ALT levels, longer duration of infection, older age, and those who drink alcohol warrant special attention, with more intensive follow-up. These factors may also assist in targeting antiviral therapeutic intervention.

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COMPETING INTERESTS

None identified.

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