# Fibrosis and other histological features in chronic hepatitis C virus infection: a statistical model

V S Wong, D G D Wight, C R Palmer, G J M Alexander

**Abstract**

***Aims*—To study the inter-relation between hepatic fibrosis and other histological features of chronic hepatitis C virus (HCV) infection.**

***Methods*—Liver biopsy specimens from 200 consecutive patients with chronic HCV infection were graded and staged separately for necro-inflammatory activity and for fibrosis. The interaction between fibrosis and other histological features was evaluated by univariate and multivariate analysis, followed by hierarchical log linear modelling.**

***Results*—The most striking feature was the presence of portal tract inflammation in 177 (89%) of 200 samples. Lymphoid aggregates/follicles were observed either alone or as part of the general inflammatory infiltration of the portal tracts in 120 (60%) of 200 samples. Fatty change (macro- and microvesicular steatosis) was observed in 76 (38%) samples: mild to moderate in 60 (30%) and diffuse in 16 (8%). Bile duct damage was found in 30 (15%) of 200 specimens. Lobular activity was found in 154 (77%) of 200 samples and was significant in 44; piecemeal necrosis was present in 79 (40%). Thirty one (16%) patients had stage 0 liver fibrosis, 27 (14%) had stage 1, 69 (35%) had stage 2, 43 (22%) had stage 3, 16 (8%) had stage 4, and 12 (6%) had stage 5. On log linear analysis, piecemeal necrosis, lobular inflammation and steatosis were linked directly with fibrosis. Portal tract inflammation was linked directly and indirectly via piecemeal necrosis and lobular inflammation with fibrosis. The presence of lymphoid aggregates was associated with bile duct damage.**

***Conclusions*—Portal tract inflammation with lymphoid aggregates or follicles, together with fatty change, bile duct damage and/or lobular activity, are characteristic of chronic HCV infection, confirming previous reports. Piecemeal necrosis, lobular inflammation, portal inflammation, and steatosis are linked directly with fibrosis in this statistical model, suggesting a close inter-relation in the development of fibrosis/cirrhosis.**

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Following the recognition of post-transfusion non-A, non-B hepatitis in the 1970s, several studies have documented the histopathological changes in the livers of these patients.[1–4] However, because of the lack of specific serological tests to identify the underlying aetiological agent, these reports could not be entirely accurate or conclusive. The recent discovery of hepatitis C virus (HCV) combined with the development of sensitive and specific first and second generation assays to detect HCV infection[5–7] confirmed HCV as the major cause of post-transfusion hepatitis and a substantial proportion of sporadic non-A, non-B hepatitis.

The histological features of chronic hepatitis have traditionally been subdivided qualitatively into chronic persistent hepatitis, chronic lobular hepatitis and chronic active hepatitis in a classification which embraces all varieties of chronic hepatitis including autoimmune and viral disease.[8–10] This classification was later used to distinguish subgroups according to the degree of disease activity to provide prognostic information and criteria for the use of immunosuppressive therapy.[11] These studies also documented the role of lobular parenchymal lesions and piecemeal necrosis, particularly bridging hepatic necrosis, in the progression from chronic hepatitis into cirrhosis.[9 10] More recently, the concepts of grading and staging have been borrowed from tumour pathology and applied to chronic hepatitis. Activity, in the form of necro-inflammatory damage, is likened to the grade whilst fibrosis, or degree of damage, is likened to the stage.[12 13] The concept of an overall score has proved very useful in the context of clinical trials, allowing direct comparisons to be made between biopsy specimens both within the same patient and in different studies. However, the final aggregate score derived, a number, remains somewhat arbitrary as it is weighted by the arbitrary decision which has been taken between which individual features are scored and which are merely noted.

In addition to chronic lobular hepatitis, the histological findings considered characteristic of chronic HCV infection include lymphoid aggregates within portal tracts, parenchymal fatty change and bile duct damage.[14–16] The relative importance of these additional types of hepatocellular damage in the pathogenesis of cirrhosis in HCV remains uncertain. The current study was therefore designed to evaluate independently the influence on the stage (or degree of fibrosis) of each of the three fea-

*Table 1A Stages of liver fibrosis and portal tract features in chronic HCV*

| | | Portal tract inflammation | | | Lymphoid aggregates | | | Bile duct damage | |
|---|---|---|---|---|---|---|---|---|---|
| Stage of fibrosis | n | 0 | 1 | 2 | 0 | 1 | 2 | 0 | 1 |
| 0 | 33 | 14 | 18 | 1 | 25 | 8 | 0 | 32 | 1 |
| 1 | 27 | 2 | 21 | 4 | 14 | 13 | 0 | 25 | 2 |
| 2 | 69 | 4 | 40 | 25 | 27 | 33 | 7 | 62 | 7 |
| 3 | 43 | 1 | 16 | 26 | 7 | 20 | 16 | 32 | 11 |
| 4 | 16 | 0 | 9 | 7 | 6 | 9 | 1 | 14 | 2 |
| 5 | 12 | 2 | 3 | 7 | 1 | 5 | 6 | 6 | 7 |
| Total | 200 | 23 | 107 | 70 | 80 | 90 | 30 | 170 | 30 |

*Table 1B Stages of liver fibrosis and acinar features in chronic HCV*

| | | Lobular inflammation | | | Piecemeal necrosis | | | Fatty change | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Stage of fibrosis | n | 0 | 1 | 2 | 0 | 1 | 2 | 0 | 1 | 2 | 3 |
| 0 | 33 | 20 | 12 | 1 | 31 | 2 | 0 | 26 | 5 | 1 | 0 |
| 1 | 27 | 5 | 19 | 3 | 25 | 2 | 0 | 22 | 4 | 1 | 0 |
| 2 | 69 | 12 | 44 | 13 | 44 | 20 | 5 | 47 | 17 | 1 | 4 |
| 3 | 43 | 2 | 25 | 16 | 13 | 18 | 12 | 19 | 17 | 1 | 6 |
| 4 | 16 | 4 | 9 | 3 | 5 | 7 | 4 | 3 | 6 | 1 | 5 |
| 5 | 12 | 3 | 1 | 8 | 3 | 4 | 5 | 7 | 2 | 2 | 1 |
| Total | 200 | 46 | 110 | 44 | 121 | 53 | 26 | 124 | 53 | 7 | 16 |

tures listed above, none of which is scored in the modified Knodell system,[13] as well as the four features that are scored individually.

## Methods

Two hundred consecutive patients seropositive for anti-HCV by second generation enzyme linked immunosorbent assay (Ortho Diagnostics, New Jersey, USA) undergoing routine liver biopsy (excluding six further cases seropositive for hepatitis B surface antigen) were studied. The indication for liver biopsy was the presence of anti-HCV antibody excluding only those with contraindications to liver biopsy such as thrombocytopenia or a prolonged prothrombin time. Other causes of chronic liver diseases were sought and excluded by clinical, serological, immunological, and biochemical criteria. These patients were all from Britain although they included a small number from local resident Italian communities. The epidemiological data were collected on a standard proforma.

### PREPARATION AND EVALUATION OF LIVER BIOPSY SPECIMENS

All biopsy specimens were fixed in 10% (v/v) neutral buffered formalin. Tissue sections, 3–4 mm thick, were cut and stained with haematoxylin and eosin and silver for reticulin fibres. The histological sections were graded and staged semiquantitatively by an experienced pathologist based on a modified scoring system which was similar to other semiquantitative systems,[11 12 17] and is very close to the recent modification of Knodell.[13] The scoring system takes into account three of the most common features seen in chronic HCV infection, namely lymphoid aggregates, bile duct damage and parenchymal fat.

### GRADED FEATURES

Periportal or periseptal interface hepatitis (piecemeal necrosis): 0 = none; 1 = mild (focal, few portal areas); 2 = mild/moderate (focal, most portal tracts). Lobular activity (spotty necrosis, apoptosis and focal inflammation): 0 = negligible inflammation; 1 = one focus in < 2/3 of lobules or nodules; 2 = foci in > 2/3 of lobules or nodules. Portal inflammation: 0 = none; 1 = mild, some or all portal areas; 2 = moderate, some or all portal areas. Lymphoid aggregates: 0 = none; 1 = occasional only; 2 = present in most inflamed portal tracts. Bile duct damage: 0 = absent; 1 = present. Fat: 0 = none or minimal; 1 = mild; 2 = moderate; 3 = diffuse. Confluent necrosis was encountered so infrequently that it was not scored individually.

### STAGING FEATURES

The fibrosis score has been extended to take account of the intermediate degrees of fibrosis seen so frequently in these biopsy specimens.[17] Fibrosis: 0 = none; 1 = confined to portal tracts; 2 = portal tracts plus spurs radiating into parenchyma; 3 = linkage of some portal tracts but intact architecture; 4 = linkage of most portal tracts with architectural distortion; 5 = cirrhosis.

### STATISTICAL ANALYSIS

Values are expressed as mean (SD). The relation of each of the necro-inflammatory components to the stage of liver fibrosis was tested by univariate analysis. These parameters were analysed by the $\chi^2$ test for trend utilising the maximum number of fibrosis categories to be valid (usually four). Subsequently, fibrosis was modelled as a continuous variable by forward linear regression.[18] The interactions among portal tract inflammation, lymphoid aggregates, lobular inflammation, piecemeal necrosis, bile duct damage, fatty change, and liver fibrosis were further explored multivariately by hierarchical log linear modelling. This is a statistical technique that can be used to produce simple "maps" showing inter-relations between categorical variables, in particular whether any two are associated (not necessarily causally) and if so the strength of the association (with smaller p values indicating stronger links).[19] All analyses were done using SPSS software (version 6).

## Results

The median age of the 200 patients was 36 years (range 15–77); 56 were women. The

probable sources of infection were intravenous drug use (n = 129, 65%), previous blood transfusion (n = 33, 17%), contaminated blood products (haemophiliacs; n = 12, 6%), and unknown (n = 24, 12%). The median estimated duration of infection (time from exposure to the first risk factor) was 14 years (range two to 36 years). Sixty patients (30%) had consumed alcohol to excess previously and 38 (19%) still drank to excess at the time of the liver biopsy (excess as defined by >21 units/week for men and >14 units/week for women).

HISTOLOGY

Overall, the histological pattern included all the described histological categories of chronic hepatitis: chronic persistent hepatitis, chronic active hepatitis, chronic lobular hepatitis, and cirrhosis. No hepatocellular carcinomas were detected in any of the biopsy specimens. The frequency of individually assessed histological features (periportal, portal and lobular inflammatory changes) is shown in table 1. Six (3%) patients had histological features consistent with dual aetiologies (mainly alcohol).

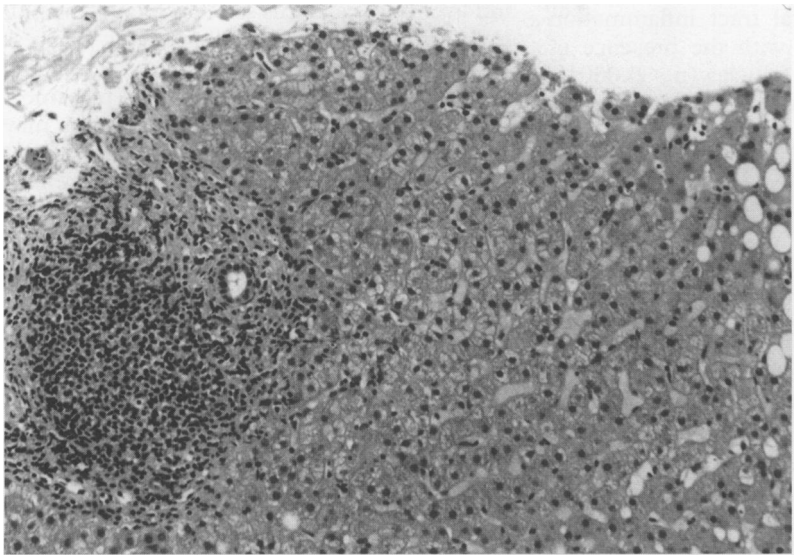

*Figure 1 Photomicrograph of a liver biopsy specimen showing the distinctive features of chronic HCV infection. The portal tract (on left) contains a fairly well-defined lymphoid aggregate, without germinal centre, but no interface hepatitis. The parenchyma includes a few small aggregates of inflammatory cells together with a little macrovesicular fat (right).*

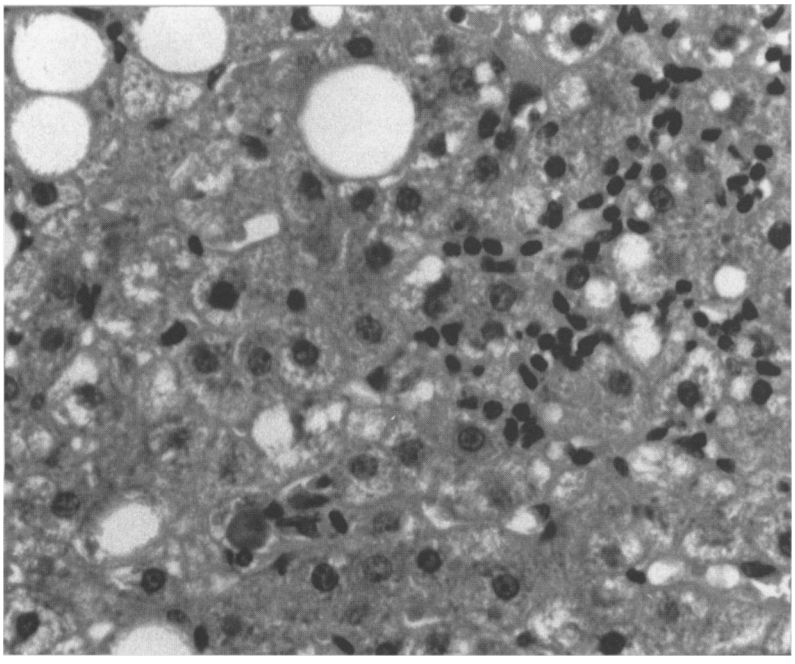

*Figure 2 Chronic HCV infection. High magnification of a similar biopsy specimen showing parenchymal necro-inflammatory activity in more detail. As well as fat, the field also includes an apoptotic body (left of centre) and focal lymphocytic infiltration (upper right).*

*Table 2 The mean (1 SD) value of each component of necro-inflammatory activity including bile duct damage in relation to stages of liver fibrosis*

| *Histological features (grade, n)* | *Mean (SD) fibrosis score†* |
|---|---|
| Portal tract inflammation | |
| 0 = 23 | 1.00 (1.57) |
| 1 = 107 | 1.87 (1.27) |
| 2 = 70 | 2.79 (1.09) |
| Lymphoid aggregates and follicles | |
| 0 = 80 | 1.48 (1.29) |
| 1 = 90 | 2.27 (1.25) |
| 2 = 30 | 3.20 (1.03) |
| Bile duct damage | |
| 0 = 170 | 1.92 (1.30) |
| 1 = 30 | 3.09 (1.36) |
| Lobular inflammation | |
| 0 = 46 | 1.40 (1.60) |
| 1 = 110 | 2.05 (1.11) |
| 2 = 44 | 2.93 (1.26) |
| Fatty change* | |
| 0 = 124 | 1.77 (1.32) |
| 1 = 60 | 2.45 (1.35) |
| 2 = 16 | 3.19 (1.26) |
| Piecemeal necrosis | |
| 0 = 121 | 1.55 (1.24) |
| 1 = 53 | 2.72 (1.12) |
| 2 = 26 | 3.35 (1.02) |

*Fatty change was analysed as three levels (0=0, 1/2=1 and 3=2).
†Fibrosis was analysed as four levels (0=0, 1/2=1, 3=2, 4/5=3).

The most consistent feature was the presence of portal tract inflammation in 177 (89%) of 200 samples. Lymphoid aggregates or follicles in portal tracts were observed either alone or as part of the general inflammatory infiltration of the tracts in 120 (60%) samples (fig 1). The structures varied from simple aggregations of lymphoid cells to well-formed follicles with germinal centres. Lobular activity (in the form of diffuse or focal infiltration by lymphocytes with or without spotty lytic necrosis and apoptotic bodies) was found in 154 (77%) samples (fig 2) but was of higher grade in only 44. Fatty change (macro- and microvesicular steatosis) was found in 76 (38%) samples and was mild to moderate in 60 (30%) and diffuse in 16 (8%). Significant bile duct damage was found in only 30 (15%) specimens. Piecemeal necrosis was present in 79 (40%) samples, although the majority were mild (53/79). The presence of portal tract inflammation with lymphoid aggregates or follicles, together with fatty change and/or lobular activity constitutes a very characteristic and easily recognisable appearance (fig 1). However, all four features were found together only in a small minority of specimens. Thirty one (16%) patients had stage 0 liver fibrosis, 27 (14%) had stage 1, 69 (35%) had stage 2 (fig 3), 43 (22%) had stage 3, 16 (8%) had stage 4, and 12 (6%) had stage 5. Thus, 31 patients had no evidence of fibrosis whilst 12 patients (6%) had established cirrhosis.

STATISTICAL ANALYSIS

The mean (SD) of each component of inflammatory activity and scores for fibrosis by

subgroups are shown in table 2. Univariate analysis of each individual component of inflammation in relation to fibrosis with $\chi^2$ test for trend applied to fibrosis classified as a four category variable (0 = normal, 1/2 = mild, 3 = moderate, 4/5 = severe) showed a highly significant association with fibrosis ($p < 0.0005$).

MODELLING OF INTERACTIONS

Figure 4 shows the model derived from hierarchical log linear analysis of the results. Direct lines between variables indicates significant interactions (strengths indicated by p values). This model reveals that there is a strong relation between liver fibrosis and piecemeal necrosis, lobular inflammatory activity ($p < 0.001$), and fatty change ($p < 0.0001$). This last strong relation, between fat and fibrosis, was not expected. Portal tract inflammation was strongly correlated with the presence of lymphoid aggregates or follicles ($p < 0.0001$), but this relation might be at least partly explained by practical difficulties associated with separately grading these two entities. Not unexpectedly, the presence of lymphoid aggregates was associated with bile duct damage ($p = 0.001$).

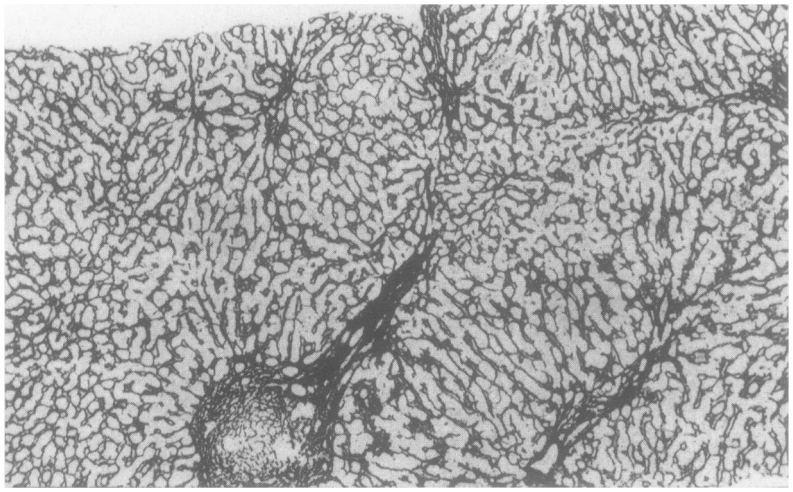

*Figure 3 Chronic HCV infection. Reticulin stain showing the distinctive pattern of fibrosis (stage 2) with short fibrous spurs radiating into the parenchyma from portal tracts. The portal tract to the lower left of centre also includes a lymphoid aggregate.*

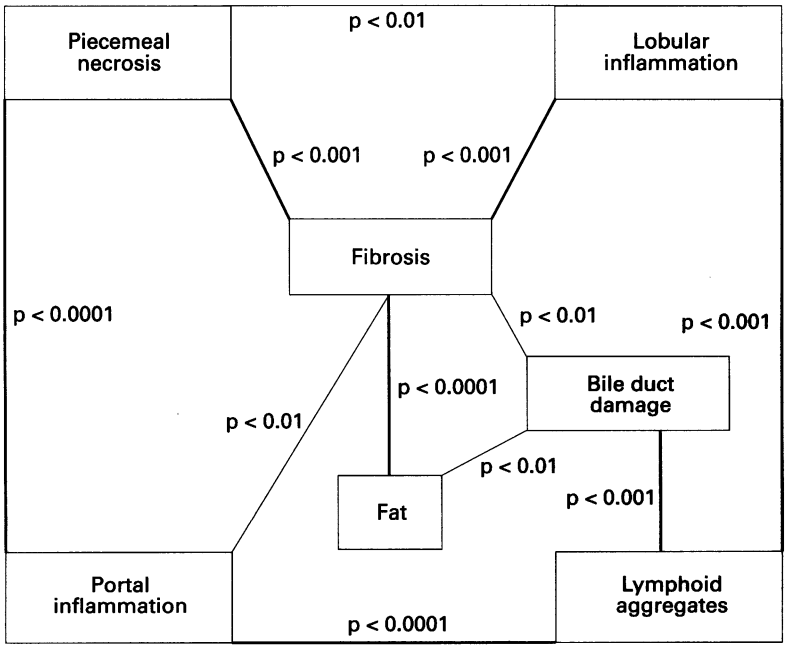


*Figure 4 Graphical representation of the best log linear model of the inter-relation between inflammatory features and liver fibrosis (see appendix for generating class).*

## Discussion

This prospective study of a series of 200 consecutive liver samples from patients with chronic HCV infection shows that the presence of portal tract inflammation with lymphoid aggregates or follicles, fatty change, lobular activity including acidophil formation and bile duct damage form a common histological pattern. This is comparable with other series which have reported similar findings of lymphoid aggregates (45–78%), fatty change (31–72%) and bile duct damage (22–91%).[14-16 20-22] Although the degree of inflammatory activity and liver fibrosis in this series is relatively mild, a proportion of patients will probably progress to cirrhosis (12 patients in this series). These data suggest that the presence of piecemeal necrosis, fat and lobular inflammation may identify those at risk of developing fibrosis, but prospective longitudinal studies must be carried before this can be confirmed.

The single most characteristic feature was the lymphoid aggregate, which varied from loose aggregates of lymphocytes to well-defined structures with germinal centres. They were easily recognised in reticulin preparations. Similar follicles are also seen in primary biliary cirrhosis and chronic hepatitis B infection, but at lesser frequency.[15 16 23 24] The presence of lymphoid follicles in chronic liver diseases with no obvious cause should alert a pathologist to the possibility of HCV infection. The reason for the formation of lymphoid follicles remains obscure but their presence supports the participation of the patient's immune system in the pathogenesis of the liver lesions. Bile duct damage in 16% of patients in this series is in agreement with published data of variable frequencies (5–91%).[15 22] The extraordinarily high frequencies (76–91%) reported in two series may mean that those authors have a lower threshold for the detection of minor degrees of damage.[15 20] The mechanism of bile duct injury in chronic HCV infection is unclear but seems to differ from other liver diseases that express HLA-DR antigen, such as primary biliary cirrhosis, primary sclerosing cholangitis, graft versus host disease, and allograft rejection. HLA-DR was not detected in any of 30 liver biopsy specimens from patients with chronic HCV in a study by Danque *et al.*[25] The lobular activity in HCV infection, as observed in this study, tends to be more focal than in autoimmune hepatitis,[15] which might be compatible with a direct cytopathic effect of HCV,[3] in contrast to the immune mediated injury of autoimmune hepatitis. Fatty change is also a common finding, but whether this is directly related to the HCV infection or secondary to another predisposing factor is not clear.

Fibrosis is the progressive component of the disease process because it is the fibrous scarring that leads to architectural distortion

and the final irreversible stage of cirrhosis. The relative importance of the different types of hepatocellular damage in the pathogenesis of cirrhosis remains uncertain. Using log linear analysis of our data, we have developed a model based on fibrosis demonstrating some important though not necessarily causal relations. Overall, the various inflammatory components are related to fibrosis but piecemeal necrosis, lobular inflammation, steatosis, and portal inflammation are directly linked to fibrosis (fig 4). This is in accordance with the concept, in chronic hepatitis in general, that piecemeal necrosis and bridging necrosis are associated with progressive disease and a worse prognosis.[26 27] This suggests a possible role for these changes in the development of fibrosis and ultimately cirrhosis. The pathology of the cirrhosis is often not characteristic, but lymphoid aggregates and follicles—together with fatty change—were seen in some of these patients; hence, this should alert the pathologist to the possibility of HCV infection as in non-cirrhotic livers.

We recognise the limitations of a single biopsy specimen. The potential sampling error, dependent on the size and quality of the sample, and the fact that the histopathological changes are part of a dynamic process mean that the links demonstrated here may not be causal. Nevertheless, the close inter-relation between the necro-inflammatory activity and fibrosis helps us understand the underlying mechanism in the pathogenesis of cirrhosis in chronic HCV infection. This is part of an ongoing study investigating the natural history of chronic HCV.

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## Appendix

*Generating class for best hierarchical log linear model*

| | *DF* | *Change in likelihood ratio* | *p value* |
|---|---|---|---|
| Fat*fibrosis | 6 | 28.78 | 0.0001 |
| Fibrosis*Piecemeal necrosis | 6 | 25.32 | 0.0003 |
| Fibrosis*Lobular inflammation | 6 | 25.12 | 0.0003 |
| Bile duct damage*Fibrosis | 3 | 11.39 | 0.0076 |
| Portal inflammation*Lymphoid aggregate | 4 | 26.28 | 0.00001 |
| Piecemeal necrosis*Portal inflammation | 4 | 33.11 | 0.00001 |
| Bile duct damage*Fat | 2 | 10.39 | 0.0055 |
| Bile duct damage*Lymphoid aggregate | 2 | 13.47 | 0.0012 |
| Fibrosis*Portal inflammation | 6 | 17.90 | 0.0065 |
| Lymphoid aggregate*Lobular inflammation | 4 | 21.40 | 0.0003 |