Hepatitis C infection at a tertiary hospital in South Africa: Clinical presentation, non-invasive assessment of liver fibrosis, and response to therapy

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Background. Hepatitis C is a viral infection that leads to chronic liver disease, resulting in significant morbidity and mortality. Objectives. To describe the demographic characteristics and clinical presentation of patients with chronic hepatitis C infection. The aspartate aminotransferase-to-platelet ratio index (APRI) and the fibrosis index based on 4 factors (FIB-4) were assessed for prediction of liver fibrosis. Methods. We retrospectively reviewed 87 records of patients who presented to the liver clinic at Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa, from January 2007 to December 2016. Patients’ records were reviewed and analysed using SPSS statistical software version 24. Convenience sampling was used. Results. The patients’ mean (standard deviation (SD)) age was 52.6 (12.3) years. Fifty-four percent were female. Hepatitis C virus genotype 5 was exclusively found in blacks (p<0.001), constituting 60.3% of infections in this ethnic group and 48.7% in the cohort, followed by genotype 1 (21.8%), genotype 3 (15.4%), genotype 4 (10.3%) and mixed-genotype infections (3.8%). Genotype 5 patients were older (mean (SD) age 56.7 (9.8) years) than genotype 1 (46.3 (11.4) years) and genotype 3 (42 (9.8) years) (p=0.002 and p<0.001, respectively). The receiver operating characteristic curve for METAVIR F0 v. APRI (cut-off <0.7) showed a moderate correlation, with an area under the curve (AUC) of 0.349 (p=0.002), sensitivity of 78.8%, specificity of 70.6% and a negative predictive value (NPV) of 63.2%. METAVIR F4 v. APRI (cut-off ≥1.5) showed an AUC of 0.881 (p<0.001) with sensitivity of 85.7%, specificity of 93% and a positive predictive value (PPV) of 67%. METAVIR F0 v. FIB-4 (cut-off <1.45) showed a moderate correlation, with an AUC of 0.332 (p=0.021), sensitivity of 78.3%, specificity of 53.8% and an NPV of 73.7%. METAVIR F4 v. FIB-4 (cut-off >3.25) had a strong correlation, with an AUC of 0.952 (p<0.001), sensitivity of 63.6%, specificity of 100% and a PPV of 100%. Early virological response (EVR) was found to predict sustained virological response (SVR) to therapy (odds ratio 27.8; 95% confidence interval 2.8 - 274.3; p=0.004).

Conclusions. Compared with other genotypes, genotype 5 was predominant in our cohort, particularly in older age groups. Moreover, APRI and FIB-4 scores correlated significantly with advanced fibrosis in HCV patients. Finally, EVR during therapy was found to determine SVR.

Hepatitis C is a viral infection that leads to chronic liver disease resulting in significant morbidity and mortality, with many patients progressing to liver cirrhosis and hepatocellular carcinoma. It tops the list of indications for liver transplantation in Japan, Europe and the USA. Seven major hepatitis C virus (HCV) genotypes have been recognised since the identification of HCV in 1989. These genotypes are one of the most critical factors determining response to therapy. Genotype 5 is reported to be the predominant HCV genotype in South Africa (SA), constituting ~40% of HCV infections, followed by genotype 1 (33%).

Risk factors for hepatitis C infection include blood and blood products transfusion and organ transplantation prior to 1992, intravenous drug use, long-term haemodialysis, multiple sexual partners, tattooing and scarification, unsafe medical practices, HIV infection, and being born to an HCV-infected mother. Interestingly, the ethnic background of patients has also been reported to determine the prevalence of HCV infection. A US study including >5 million individuals reported the highest prevalence of hepatitis C in blacks, followed by Hispanics. Anti-HCV antibodies are used for screening for hepatitis C. Thereafter qualitative and quantitative assays are used to detect the HCV virus RNA and determine the number of existing viral copies. Further tests are done to determine the genotypes and their subtypes. Patients diagnosed with hepatitis C usually require a liver biopsy before starting treatment unless contraindicated, e.g. patients with thrombocytopenia and haemophilia. Liver biopsy is done to assess the degree of fibrosis and detect other liver disorders such as fatty liver and iron overload. According to the 2010 SA hepatitis C guidelines, liver biopsy was not mandatory in HCV genotypes 2 and 3 because of excellent sustained viral response (SVR) rates (90%) with the combination of pegylated interferon and ribavirin (PEG-RBV) in those individuals. The METAVIR score is usually used to report on the liver histology. Recently, non-invasive scores have been introduced as predictors of liver fibrosis. These include...
the aspartate aminotransferase-to-platelet ratio index (APRI) and the fibrosis index based on four factors (FIB-4). The APRI and FIB-4 scores have been reported to identify hepatitis C-related fibrosis in many studies, thus alleviating the need for the invasive liver biopsy. Sonderegger et al. emphasised the importance of these scores in the assessment of liver fibrosis in the context of hepatitis C in sub-Saharan Africa, as they are cheap, available, easy to interpret and can be done in an outpatient setting. However, these scores have not been reported on in HCV-infected individuals in SA or sub-Saharan Africa.

Other useful non-invasive methods for evaluation of liver fibrosis/cirrhosis include computed tomography liver surface nodularity scores, magnetic resonance elastography, and transient elastography (FibroScan). Lack of expertise and the high cost of these methods prevent their regular use. FibroScan uses measurement of liver stiffness to detect cirrhosis. While it is an excellent tool for assessment of liver cirrhosis, it is not readily available, especially in low-income settings.

The standard treatment used for chronically infected patients with hepatitis C in SA was the combination of PEG-RBV for 24 or 48 weeks, with SVR achieved in up to 80% of those treated. However, achievement of an SVR is governed by the HCV genotype along with other factors such as genetic factors, e.g. interleukin (IL)-28B. Hadziyannis et al. showed that patients infected with genotype 1 need standard doses of ribavirin, while those infected with genotypes 2 and 3 are adequately treated with low doses. Given the serious side-effects of such a combination and obstacles to its use among large numbers of HCV patients, deciding whether to use the combination was not always easy. Since the introduction of directly acting antivirals (DAAs) in May 2011, hepatitis C treatment has evolved tremendously, especially with the introduction of pangenotypic regimens that conferred higher SVR rates with shorter duration of therapy.

Several factors are known to predict response to HCV therapy, including: (i) age, with age <40 years associated with a better response; (ii) race (whites do better than blacks in US studies); (iii) body mass index (BMI) (patients with a BMI <25 kg/m² do better than those with higher BMIs); (iv) HCV genotype; (v) viral load; (vi) rapid viral response; and (vii) the degree of liver fibrosis, and alpha-fetoprotein and IL-28B gene polymorphism.

Objectives
Despite the impact of HCV infection on the SA population, especially in view of its frequent coexistence with the highly prevalent HIV infection, there is a lack of published data on HCV. This study therefore aimed to describe the demographic characteristics of patients with chronic hepatitis C, disease presentation, clinical parameters, co-infection with hepatitis B and HIV, and response to therapy. It also aimed to assess the utility of the fibrosis score in detecting liver fibrosis. It is expected that the findings will help to provide data on the spectrum of hepatitis C infection in a referral hospital setting in SA and to shed light on the use of fibrosis scores in the SA setting.

Methods
The research protocol was approved by the Human Research Ethics Committee of the University of the Witwatersrand (ref. no. M170538).

Study population
We retrospectively reviewed 87 records of patients who presented to the liver clinic in the Division of Gastroenterology at Chris Hani Baragwanath Hospital (CHBAH), Johannesburg, between January 2007 and December 2016. No files were excluded. Patients diagnosed with hepatitis C infection were referred from local clinics, the South African National Blood Service, CHBAH and private clinics. Their records were reviewed and analysed. Convenience sampling was used.

The datasets used and/or analysed during the study are available from the corresponding author (WBA) on reasonable request.

Data collection
A standardised data collection sheet was used. Data were extracted from records of all patients who attended the clinic. The results of baseline investigations, including a full blood count, liver function tests, urea and electrolytes, hepatitis C viral load and genotype, hepatitis B serology and HIV serology, were recorded. Liver biopsy results, where available, were extracted. A liver biopsy was performed in all consenting patients except where it was contraindicated or was not part of the treatment protocol (it was not done in patients with genotype 3). Patients eligible for treatment were treated with PEG-RBV. Hepatitis C viral load levels measured during treatment and at 24 weeks after treatment completion to determine SVR were extracted.

Definitions
Treated patients were deemed to have achieved a rapid virological response if they had an undetectable HCV viral load at week 4 of therapy. Early virological response (EVR) was defined as complete when viral load was undetectable at 12 weeks of treatment or as partial when there was a 2-log drop in viral load at 12 weeks of treatment. SVR was defined as an undetectable HCV viral load 24 weeks after completion of treatment.

Statistical analysis
All data were analysed using SPSS statistical software, version 24.0 for Windows (SPSS Inc., USA). Categorical data such as gender, ethnicity and symptoms were analysed using Pearson’s χ² test or Fisher’s exact test when >20% of cells had an expected frequency <5. Continuous data such as age and viral load were analysed using parametric methods and presented as means and standard deviations (SDs) or medians and percentiles for non-normally distributed data. The geometric mean was used to analyse BMI and viral load. The t-test was used in the analysis of normally distributed continuous data, and one-way analysis of variance with Dunnett’s correction was used to compare the ages of patients with the different genotypes; otherwise the Mann-Whitney U-test was used. Multinomial logistic regression was used to determine the risk factors for HCV infection in the study cohort after calculating their univariate logistic regression. The Wilcoxon signed-rank test was used for analysis of treatment effect on viral load and liver enzymes. Eta correlation was used to assess the correlation between the METAVIR, APRI and FIB-4 scores, while Spearman’s correlation was used for the correlation between APRI and FIB-4 scores. The receiver operating characteristic (ROC) curve was also used to compare APRI and FIB-4 with the gold standard METAVIR. A p-value of <0.05 was considered statistically significant.

Results
Demographics
Eighty-seven patients’ records were identified (Fig. 1). The mean (SD) age of the cohort at presentation was 52.6 (12.3) years. Female patients constituted 53.5% of the group. There were 71 blacks (81.7%), 9 Asians (10.3%) and 7 whites (8.0%). Black HCV-infected patients tended to be older compared with other ethnic groups, with a mean (SD) age of 55.7 (10.6) years, which was statistically significant (p=0.001) (Table 1).
Risk factors
Twenty-three of the black patients had a history of blood transfusion, but this was not statistically significant. Five individuals had haemophilia. There was no statistically significant difference in the prevalence of haemophilia between the different ethnic groups. White patients had more tattooing and history of intravenous drug use than blacks and Asians, which was statistically significant ($p<0.001$) (Table 1). Histories of previous surgery and scarification were not significantly different between the ethnic groups. Data for men who have sex with men were not available.

Clinical presentation
Thirty-one patients (35.6%) were incidentally diagnosed. Forty-seven (60.3%) were symptomatic. In 9 patients (10.3%), presentation was

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**Table 1. Hepatitis C infection: Cohort characteristics according to ethnicity**

| Characteristics                  | Black (N=71) | White (N=7) | Asian (N=9) |
|----------------------------------|-------------|-------------|-------------|
| Age (years), mean (SD)           | 55.7 (10.6) | 33.1 (3.9)  | 43.6 (11.6) |
| Gender, n (%)                    |             |             |             |
| Male                             | 33 (46.5)   | 3 (42.9)    | 4 (44.4)    |
| Female                           | 38 (53.5)   | 4 (57.1)    | 5 (55.6)    |
| Comorbidities, n (%)             |             |             |             |
| DM                               | 8 (11.3)    | 0           | 2 (22.2)    |
| CKD                              | 8 (11.3)    | 0           | 0           |
| Haemophilia                      | 4 (5.65)    | 1 (14.3)    | 0           |
| Chronic hepatitis B              | 2 (2.83)    | 0           | 1 (11.1)    |
| HIV                              | 16 (22.6)   | 1 (14.3)    | 0           |
| BMI, mean (SD)                   | 25.1 (1.2)  | 24 (1.2)    | 26.3 (1.15) |
| Risk factors, n (%)              |             |             |             |
| Blood transfusion                | 23 (32.4)   | 1 (14.3)    | 2 (22.2)    |
| Tattoo                           | 0           | 3 (42.9)    | 0           |
| Scarification                    | 1 (1.4)     | 0           | 0           |
| IV drug use                      | 0           | 3 (42.9)    | 0           |
| Surgery                          | 11 (15.5)   | 0           | 2 (22.2)    |
| GTs (N=78), n (%)                |             |             |             |
| GT 1                             | 63 (80.8)   | 6 (7.7)     | 9 (11.5)    |
| GT 3                             | 11 (17.5)   | 2 (33.3)    | 4 (44.4)    |
| GT 4                             | 3 (4.8)     | 4 (66.6)    | 5 (55.6)    |
| GT 5                             | 8 (12.7)    | 0           | 0           |
| >1 GT                            | 38 (60.3)   | 0           | 0           |
| VL, mean (SD)                    | Log 5.8 (0.8)| Log 5.6 (1.2)| Log 5.5 (1.2)|
| Total treated (N=48), n (%)      | 37 (52.1)   | 5 (71.4)    | 6 (66.7)    |
| Response/non-response to treatment, N | 34   | 5           | 5           |
| SVR, n (%)                       | 27 (79.4)   | 5 (100)     | 2 (40.0)    |
| Non-responders, n (%)            | 5 (14.7)    | 0           | 2 (40.0)    |
| Relapse, n (%)                   | 2 (5.9)     | 0           | 1 (20.0)    |

SD = standard deviation; DM = diabetes mellitus; CKD = chronic kidney disease; BMI = body mass index; IV = intravenous; GT = genotype; VL = viral load; SVR = sustained virological response.
not documented. Of symptoms and signs, the most frequent was joint pain (n=11; 12.8%). This was followed in frequency by ascites (n=6; 6.9%), lower limb oedema (n=5; 5.7%) and jaundice (n=5; 5.7%). Of the 78 patients for whom the information was available, 9 were smokers; 13/81 patients consumed alcohol. The geometric mean (SD) BMI was 25.12 (1.2).

Comorbidities
Comorbidities in this cohort included diabetes mellitus (n=10 patients), chronic kidney disease (n=8 black patients) and cardiovascular disease (n=7). There was no statistically significant difference in the prevalence of comorbidities between the different ethnic groups. Of the 87 patients, 3 (2 blacks and 1 Asian) had chronic hepatitis B, while 17 patients had HIV infection (n=16 (22.5%) black and n=1 (14.3%) white patients). The median (interquartile range) CD4+ count for the HIV co-infected patients was 448 (283 - 900) cells/µL.

Genotypes
Genotypes were available for 78 patients. Genotype 5 was exclusively found in blacks. It constituted 60.3% of infections in this ethnic group and 48.7% in the cohort, followed by genotype 1 (21.8%), genotype 3 (15.4%), genotype 4 (10.3%) and mixed-genotype infection (3.8%). When genotype 5 was compared with HCV genotypes in other ethnic groups, a statistically significant difference was evident (p<0.001). Genotype 5 patients were found to be older, with a mean (SD) age of 56.7 (9.8) years, compared with genotype 1 (46.3 (11.4) years) and genotype 3 (42 (9.8) years) (p=0.002 and p<0.001, respectively).

Viral loads
The mean (SD) viral load for the cohort was log 5.7 (0.9). There was no statistical difference between the different ethnic groups or different genotypes in terms of viral load levels.

METAVIR and fibrosis scores
Fifty-nine patients, of whom 10 were known to be HIV-positive, had liver biopsy results. The mean (SD) platelet count for patients with HIV was 297 (92) × 10^9/L. Metavir and APRI scores and FIB-4 and APRI scores were found to be strongly correlated (r=1, 0.997 and 0.817, respectively). The ROC curve for METAVIR F0 and APRI (cut-off <0.7) showed a moderate correlation, with an AUC of 0.349 (p<0.002), sensitivity of 78.8%, specificity of 70.6% and a negative predictive value (NPV) of 63.2%, and that for METAVIR F4 v. APRI (cut-off ≥1.5) had an AUC of 0.881 (p<0.001) with sensitivity of 85.7%, specificity of 93% and a positive predictive value (PPV) of 67% (Fig. 2). METAVIR F0 v. FIB-4 (cut-off <1.45) had a moderate correlation, with an AUC of 0.332 (p=0.021), sensitivity of 78.3%, specificity of 53.8% and an NPV of 73.7%. METAVIR F4 v. FIB-4 (cut-off >3.25) had a strong correlation, with an AUC of 0.952 (p<0.001), sensitivity of 63.6%, specificity of 100% and a PPV of 100% (Fig. 3).

Treatment
All treated patients received pegylated interferon α-2a (Pegasys) and ribavirin. Of 48 patients who were treated, 44 completed treatment; 34 patients achieved SVR while 9 did not, and in 1 case results were not available (Fig. 1). All but 1 of the patients developed side-effects secondary to treatment. Anaemia was the most common side-effect (n=33; 68.8%), followed by leukopenia (n=31; 65%) and fatigue (n=27; 56.2%). Growth factors (erythropoietin and granulocyte-colony stimulating factor) were used in 17 (35.4%) and 6 (12.5%) patients, respectively, during treatment.

Both alanine aminotransferase and aspartate aminotransferase showed a statistically significant decline post treatment (p<0.001). EVR was found to predict SVR to therapy (odds ratio 27.8; 95% confidence interval 2.8 - 274.3; p=0.004) (Table 2).

Discussion
Chronic HCV infection causes significant morbidity and mortality, as it remains asymptomatic for prolonged periods of time until the individual develops chronic liver disease and/or HCC, yet it is potentially curable.[1]

As HCV has the same mode of transmission as HIV, and the prevalence of HIV in SA is high, SA would be expected to have a large burden of patients with HCV infection. There is a paucity of data on HCV infection in SA. We describe the clinical characteristics of our cohort of 87 patients, with specific emphasis on genotype 5. This genotype is endemic in SA, but there is a paucity of literature on it worldwide.[24] Genotype 5 was seen in 48.7% of the patients in our cohort; this is similar to what Smuts et al.[35] described in a sample of 79 patients. On the other hand, Prabdial-Sing et al.[24] described a slightly lower proportion of genotype 5 infections (36%) in a larger cohort studied at the National Health Laboratory Service. Ethnic groups were not identified in their study. In the present study, genotype 5 was found exclusively in SA

![Fig. 2. ROC curve showing correlation between APRI and METAVIR scores. (ROC = receiver operating characteristic; APRI = aspartate aminotransferase-to-platelet ratio index; AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value.)](image-url)
The major strength of this study is that it is a multicentre study that included 125 chronic hepatitis C patients. Conventional cut-offs for these scores cannot be used to detect cirrhosis before initiation of therapy. While liver biopsy has been deemed the gold standard, implementing it in all settings can be difficult owing to high cost, lack of expertise and cultural unacceptability. Several non-invasive methods of liver fibrosis assessment have been studied and developed. These include the APRI and FIB-4, which have not been studied previously in our setting. In our cohort, scores for liver fibrosis such as the APRI and FIB-4 correlated significantly with an advanced METAVIR score of fibrosis (METAVIR F3 and F4). Similar results have been reported by others. Implementing these scores in clinical practice can reduce the need for invasive liver biopsies. Interestingly, the same fibrosis scores have been found to have limitations when used in hepatitis B patients. Conventional cut-offs for these scores cannot be used to detect cirrhosis in the setting of hepatitis B, owing to high misclassification rates.

Various factors have been found to affect clearance of the virus, but in our cohort week 12 EVR was the only predictor of SVR. Rao et al. came to a similar conclusion in their multicentre study that included 125 chronic hepatitis C patients.

**Study strengths and limitations**

The major strength of this study is that it adds significant information on the clinical characteristics of patients with HCV in SA.

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**Table 2. Predictors of SVR**

| Variables | SVR | No SVR | p-value |
|-----------|-----|--------|---------|
| Age (years), mean (SD) | 47.2 (11.8) | 54.7 (9.9) | 0.103  |
| Gender, n | | | |
| Male (N=19) | 15 | 4 | 0.889  |
| Female (N=24) | 18 | 6 | |
| Ethnicity, n | | | |
| White (N=5) | 5 | 0 | |
| Black (N=34) | 27 | 7 | |
| Asian (N=4) | 2 | 2 | |
| HIV (N=4), n | 4 | 0 | 0.999  |
| GTs, n | | | |
| GT 1 | 5 | 3 | |
| GT3 | 5 | 1 | |
| GT4 | 1 | 3 | |
| GT5 | 20 | 2 | |
| >1 GT | 3 | 0 | |
| RVR (N=27), n | 23 | 4 | 0.211  |
| EVR week 12 (N=43), n | 34 | 9 | 0.004*  |
| FIB-4 (N=40), n | 33 | 7 | 0.036  |
| APRI (N=40), n | 33 | 7 | 0.079  |

SVR = sustained virological response; SD = standard deviation; GT = genotype; RVR = rapid virological response; EVR = early virological response; FIB-4 = fibrosis index based on 4 factors; APRI = aspartate aminotransferase-to-platelet ratio index; PPV = positive predictive value; NPV = negative predictive value.

*On univariate analysis EVR week 12 was found to be the only significant factor determining response, with a p-value of 0.004.

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**Fig. 3**. ROC curve showing correlation between FIB-4 and METAVIR scores. (ROC = receiver operating characteristic; FIB-4 = fibrosis index based on 4 factors; AUC = area under the curve; NPV = negative predictive value; PPV = positive predictive value.)
with assessment of the utility of fibrosis scores, even though it was a retrospective single-centre study and did not include patients who had been treated with DAAs. However, this situation has since changed, and DAAs are going to be the standard of care for HCV patients in SA.

**Conclusions**

The current study concludes that genotype 5 is the predominant genotype in a single SA centre. It is more common than other genotypes among older SA blacks. Moreover, the APRI and FIB-4 had sufficient power to diagnose advanced fibrosis in HCV patients, alleviating the need for liver biopsy in selected individuals. Despite their shared modes of transmission, hepatitis B and HIV infections were not commonly encountered in HCV patients in this cohort. Finally, EVR was found to determine who is likely to have an SVR.

**Declaration.** The research for this study was done in partial fulfilment of the requirements for WBA’s MMed (Med) degree at the University of the Witwatersrand.

**Acknowledgements.** None.

**Author contributions.** WBA wrote the manuscript. GIG analysed the patient data and assisted in writing the manuscript. RA and CM assisted in writing the manuscript. All authors read and approved the final manuscript.

**Funding.** Privately funded.

**Conflicts of interest.** None.

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Accepted 3 March 2020.