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Retrospective Cohort Study

Missed opportunities for hepatitis C treatment at a tertiary care hospital in South Australia

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Abstract

BACKGROUND

Hepatitis C is a global epidemic and an estimated 230 000 Australians were living with chronic hepatitis C in 2016. Through effective public health policy and state commitment, Australia has utilised the advent of direct acting antiviral (DAA) therapy to transform the therapeutic landscape for hepatitis C virus (HCV). However, treatment rates are falling and novel public health approaches are required to maintain momentum for HCV elimination. Contemporary discourse in cascades of care have focused on expanding testing capabilities but less attention has been given to linking previously diagnosed patients back to care. Our simple and focused study rests on the premise that hospital admissions are an excellent opportunity to identify and refer previously diagnosed patients for HCV treatment.

AIM

To assess whether inpatients with HCV are appropriately referred on for treatment.

METHODS

We conducted a retrospective single centre cohort study that examined all patients with HCV presenting to The Queen Elizabeth Hospital (QEH) inpatient service between January 1 and December 31, 2017. QEH is a tertiary care hospital in South Australia. The main inclusion criteria were patients with active HCV infection who were eligible for DAA therapy. Our study cohort was identified using a comprehensive list of diagnosis based on international classification of diseases-10 AM codes for chronic viral hepatitis. Patients were excluded from the analysis if they had previously received DAA therapy or spontaneously cleared HCV. Patients presenting with decompensated liver cirrhosis or other systemic

medical conditions conferring poor short-term prognosis were also excluded from the analysis. The primary outcome of our study was referral of patients for HCV treatment. Secondary outcomes included assessment of factors predicting treatment referral.

RESULTS

There were 309 inpatients identified with hepatitis C as a principal or additional diagnosis between January 1 and December 31, 2017. Of these patients, 148 had active HCV infection without prior treatment or spontaneous clearance. Overall, 131 patients were deemed eligible for DAA treatment and included in the main analysis. Mean patient age was 47.75 ± 1.08 years, and 69% of the cohort were male and 13% identified as Aboriginal or Torres Strait Islander. Liver cirrhosis was a complication of hepatitis C in 7% of the study cohort. Only 10 patients were newly diagnosed with HCV infection during the study period with the remainder having been diagnosed prior to the study.

CONCLUSION

Under 25% of hepatitis C patients presenting to an Australian tertiary hospital were appropriately referred for treatment. Advanced age, cirrhosis and admission under medical specialties were predictors of treatment referral.

Key Words: Hepatitis C; Viral hepatitis; Treatment cascade; Hepatology; Public health; Missed opportunities

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Core tip: Hepatitis C virus (HCV) treatment in Australia has undergone a major paradigm shift since the advent of direct acting anti-viral (DAA) therapy. Uptake of DAA therapy for HCV is falling despite universalisation of access through pharmaceutical benefit scheme listing. In our study, 26% of chronic hepatitis C patients presenting to a tertiary hospital were referred for treatment. Hospital admissions constitute an excellent opportunity to identify and treat patients with chronic hepatitis C. Extrapolating this study, both nationally and internationally, would serve to supplement treatment numbers in the goal of HCV eradication.

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INTRODUCTION

Globally, over 70 million people are infected with hepatitis C virus (HCV)[1]. While usually asymptomatic initially, chronic HCV infection can result in the development of cirrhosis and hepatocellular carcinoma over the course of a few decades[2,3]. HCV is primarily spread through use of shared needles in either healthcare or recreational drug use settings. Viral transmission can also occur through exchange of bodily fluids and blood transfusions. Contemporary therapeutic advances in the treatment of HCV have rendered the virus essentially curable within 30 years of its first identification. This has been lauded as a major scientific landmark[4].

Historically, HCV treatment had revolved around lengthy interferon-based regimens. These treatment courses were poorly tolerated and had limited efficacy. The major shift in the treatment paradigm for HCV has been fuelled by the development of highly effective oral direct acting antiviral (DAA) agents. Sustained virological response (SVR) rates have continued to improve with the introduction of pan-genotypic DAA regimens such as sofosbuvir/velpatasvir and glecaprevir/pibrentasvir. These oral treatment regimens have excellent side-effect profiles and SVR rates > 95% across all genotypes in both trial and real world settings[5,6]. The emergence of DAAs has resulted in the World Health Organization ambitiously targeting 2030 for the elimination of HCV as a public health threat. This ambitious target encompasses a 90% decline in new infections, a reduction in HCV-related mortality by 65% and treatment provision for 80% of those infected[7].

While uptake of DAAs around the world has been variable, Australia has been in the vanguard of nations on the path to HCV elimination. DAA therapy is expensive with a 12-wk course of sofosbuvir/velpatasvir costing over \$US 75000. Australia's initial success was facilitated by the landmark decision to provide DAA therapy to individuals through the pharmaceutical benefit scheme (PBS) scheme[8]. The Australian PBS scheme is a state sponsored programme subsidising prescription medications for

Australian citizens and permanent residents. PBS subsidisation ensures that patients with HCV only pay a dispensing fee for DAA prescriptions which equates to \$AUD 38.30 for general patients and \$AUD 6.20 for concessional patients. This has significantly reduced financial barriers to accessing DAA therapy for Australians with HCV. Universalisation of DAA therapy in March 2016 resulted in > 44 000 Australians, approximately 20% of the total estimated population with chronic HCV, being initiated on treatment by June 2017.

However treatment uptake has consistently fallen in Australia since the introduction of DAAs[9]. Eliminating barriers to treatment has supplanted improving SVR as the dominant issue in the current HCV therapeutic landscape[10]. Novel approaches are required to ensure that Australia can meet the aforementioned elimination targets. Modelling has suggested that testing needs to be increased by 50% to achieve this[11]. To this end, recent studies have advocated programmes aimed at identifying and treating HCV in prisons and needle and syringe exchange programmes[12,13].

One area that is often overlooked is the opportunistic identification of untreated patients within hospital inpatient cohorts. Patients with HCV often have complex medical and social situations that necessitate frequent presentations to hospital. Additionally, a significant proportion of patients diagnosed with HCV prior to DAA therapy have been lost to follow up. Hospital admissions thus represent an excellent opportunity to identify both newly and previously diagnosed HCV patients. Our study aims to assess the extent to which current practices ensure that patients with HCV presenting to tertiary hospitals are referred on for DAA therapy.

MATERIALS AND METHODS

Setting

The Queen Elizabeth Hospital (QEH) is a tertiary hospital in Northwest Adelaide with 35 000 inpatient admissions *per annum*. Northwest Adelaide has the highest prevalence of HCV in South Australia[14].

Study cohort

Our single-centre retrospective study included all patients with a principle or secondary diagnosis of HCV presenting to any QEH inpatient service between January 1 and December 31, 2017. The study cohort was identified using a comprehensive list of diagnosis based on international classification of diseases-10 AM codes for chronic viral hepatitis. These codes included B17.1, B18.2, B18.8, B18.9 as either principal or additional diagnosis.

Data ascertainment/collection

De-identified data for our patients were collated from electronic medical records and stored on secure hospital databases. Data collated included demographic data, HCV antibody and RNA status, unit of admission, prior treatment information, presence of complications such as liver cirrhosis or, referral to specialist service, attendance at specialist clinic, initiation of DAA therapy and completion of DAA therapy.

We excluded patients who had previously been successfully treated for HCV and those who had spontaneously cleared the virus. Patients were defined as having active HCV on the basis of their most recent polymerase chain reaction study. Successful treatment was defined as achievement of SVR at 12 wk post-treatment (SVR12).

The primary study outcome was referral of patients to gastroenterology or infectious diseases services for treatment of HCV by the admitting team. For the purposes of this study, admitting hospital teams were divided into four subdivisions: Medical, Surgical, Mental Health and Emergency Departments. Referral to specialist service for the purpose of HCV treatment had to be clearly documented in electronic medical records to satisfy our inclusion criteria. Attendance at a clinic and initiation and completion of treatment were determined through electronic medical records and cross-referencing with local HCV treatment databases.

Statistical analysis

Statistical analysis was performed using GraphPad Prism for Windows. Parametric data are presented as mean $\pm$ SEM. Categorical variables were compared using the χ^2 and Fisher's exact tests. Quantitative variables were analysed by *t*-test and, when the assumption for normality was not met, the Mann-Whitney *U* test. Univariate binary logistic models were performed to investigate the association between HCV treatment referral and five predictors: clinical unit, age, gender, Aboriginal or Torres Strait Islander status and cirrhosis status.

Ethics

This study was completed in accordance with the guidelines set by the SA Health Research Governance Policy Directive.

RESULTS

A total of 309 inpatients were identified as having HCV as a principal or additional diagnosis between January 1 and December 31, 2017. On further inspection, 96 of these patients had previously received treatment and had successfully been cleared of the virus. Forty-two patients had successfully cleared the virus spontaneously without evidence of treatment. Twenty-five patients had been erroneously labelled as having HCV despite negative serological results. Of the 148 patients with active HCV, 17 were either admitted under palliative care or died within 6 mo of admission. Consequently, 131 patients of our study cohort were deemed eligible for treatment and included in the main analysis (Table 1).

The mean age of eligible patients was 47.75 ± 1.08 years, and 69% of the cohort were male and 13% identified as Aboriginal or Torres Strait Islander. Liver cirrhosis was a complication of HCV in 7% of the study cohort. Only 10 patients were newly diagnosed with HCV during the study period with the remainder of patients having been diagnosed prior to the study. In terms of admitting unit, the majority of patients were admitted under medical specialties (41/131). A substantial proportion of patients were also admitted under surgical specialties (37/131) and mental health (38/131). The remaining 15 patients were admitted as short stay patients by the Emergency Department.

Overall, 32 patients (24%) were referred on for treatment of their HCV and 51% of patients admitted by medical teams were referred. Mental health and surgical teams referred 18% and 11% of patients, respectively. None of the patients admitted under the Emergency Department were referred. The odds ratio (OR) for appropriate referral for medical specialties *versus* nonmedical specialties was 7.20 [95% confidence interval (CI): 3.0–17.1; $P < 0.0001$]. There was a significant association between referral status and age [odds ratio (OR): 1.05, 95% CI: 1.01–1.08, $P = 0.0097$]. Those with liver cirrhosis were also significantly more likely to be referred on for treatment (OR: 19.0, 95% CI: 3.7–96.3, $P = 0.0004$). Neither gender (male *vs* female, OR: 1.3, 95% CI: 0.5–3.0, $P = 0.62$) nor Aboriginal status (OR: 1.1, 95% CI: 0.3–3.7, $P = 0.85$) were predictors of treatment referral.

Referral was necessary but not sufficient to ensure successful treatment of HCV in the context of our study. Four patients were referred to their GP for treatment with none of these patients commencing treatment. Thirteen of the 28 patients referred to the gastroenterology or infectious diseases clinic commenced treatment. Eight patients were documented to have completed treatment and achieve SVR12.

DISCUSSION

Our study found that 76% of inpatients with chronic hepatitis C were not referred on for treatment. This suggests that current hospital practices are not adequately addressing the issue of HCV elimination. Low referral rates can be traced back to two main factors.

Firstly, HCV can often be overlooked in the face of more acutely pressing medical and social issues that precipitated hospital admission in the first place. This is unsurprising given that, until late stage hepatological complications arise, HCV is often asymptomatic. This notion would appear to be supported by the fact that presence of cirrhosis was a strong predictor for treatment referral. Secondly, knowledge of HCV treatment advances may be limited outside of gastroenterological and physician spheres[15]. This assertion would appear to be supported by the significantly higher referral rates for patients admitted under the care of physicians. Succinctly, the insidious nature of HCV and limitations of professional awareness constituted the major treatment barriers in the context of our study. Thus, proactive measures are required to ensure that HCV patients are first identified and subsequently treated. Comprehensive multifaceted approaches are required to ensure that opportunities for inpatient HCV treatment are taken advantage of. These approaches should focus on educational initiatives for healthcare professionals and patients, optimisation of electronic medical records notifications and ensuring community outreach initiatives for HCV patients on discharge.

Only 10% of our cohort were newly diagnosed with HCV during the study period. The majority of our patients had been diagnosed with HCV in the pre-DAA era and had been lost to follow-up. This finding is in keeping with a recent population level Swedish study demonstrating that 61% of patients diagnosed with hepatitis C in 2013 were lost to follow-up[16]. Contemporary hepatitis C cascade of care discourse has focused on expanding testing capabilities as a means of targeting resistant pockets of the virus[11]. Linking previously diagnosed patients back with treatment pathways should also form an integral component of the multifaceted public health approach to hepatitis C elimination. Performing this study provided our gastroenterology and infectious diseases units with a database of additional HCV patients to contact and initiate on treatment. Our viral hepatitis nurses were able to successfully treat 27% of patients in whom earlier treatment opportunities were missed. Moreover, our study methodology provides a template for systematically identifying HCV patients from inpatient cohorts in order to link patients to care. Extrapolating this study to other health networks across Australia, and indeed internationally, would supplement overall treatment numbers in the pursuit of HCV elimination.

Table 1 Baseline characteristics

Total number of patients	131
Age, yr	47.75 ± 1.08
Gender, n (%)	
Male	90 (69)
Female	41 (31)
Aboriginal or Torres Strait Islander, n (%)	17 (13)
Presence of cirrhosis, n (%)	
Cirrhosis	9 (6.9)
No clinical evidence of cirrhosis	122 (93.1)
New diagnosis of HCV, n (%)	
Yes	10 (7.6)
No	121 (92.4)
Unit of admission, n (%)	
Medical	41 (31)
Surgical	37 (28)
Mental health	38 (29)
Emergency department	15 (11)
Referral for DAA treatment, n (%)	
Yes	32 (24.4)
No	99 (75.6)
Outcome after referral, n (%)	
Attendance at specialist clinic	14 (10.6)
Initiation of DAA treatment	13 (9.9)
Achievement of SVR12	8 (6.1)

HCV: Hepatitis C virus; DAA: Direct acting anti-viral.

It is important to note that appropriate identification and referral of patients is necessary but not sufficient for treatment of hepatitis C. In the context of our study, 50% of referred patients did not attend clinic appointments and were subsequently lost to routine follow-up. Moreover, only 25% of patients referred for treatment of hepatitis C achieved SVR12 by the end of the study period. This equates to 6% of the total cohort of hepatitis C patients presenting to the QEH being cleared of the virus during the study period. Low clinic attendance rates of referred patients can be traced back to a combination of institutional and patient-related factors. Institutional factors included variable levels of patient counselling and deficits in community engagement with either patients or primary care providers after hospital discharge. Patient-related factors contributing to loss to follow-up included poor health literacy, low prioritisation of health needs, and adverse socioeconomic circumstances that may have predisposed them to HCV infection.

Our findings highlight the limitations of centralised specialist services in treating poorly engaged patients and the need for greater emphasis on community treatment. From our experience, viral hepatitis nurses were ideally placed to identify these hitherto missed opportunities for treatment and ensure sustained linkage of patients to HCV care. Furthermore, primary health physicians play a vital role in achieving HCV elimination given their unparalleled access to patients. These realities have been recognised in Australia with updated guidelines permitting both experienced hepatitis nurse practitioners and primary care physicians to prescribe DAA therapy. Early successes of these policy updates are evidenced by recent data from the Kirby Institute, Sydney showing that primary care prescribers had overtaken their specialist counterparts[9]. Nevertheless, specialist hepatitis treatment centres have an important role in treating complex HCV patients as well as providing training for and longitudinal capacity strengthening of community DAA prescribers.

Our study had a number of limitations. Firstly, our study was limited by a small sample size and being a single centre study. Although the study number was small, it still highlighted an area of concern. We identified a large number of missed opportunities for hepatitis C treatment in our inpatient cohort. The sample size was adequate to identify the subspecialties to target additional education and protocols for referral and treatment. Secondly, the use of hospital coding to identify hepatitis C patients introduced a sampling bias by systematically excluding from the analysis patients with HCV without known or recorded diagnosis. Our study did not specifically address assess the extent to which current hospital practices ensure that at-risk patients are investigated for and diagnosed with HCV. Furthermore, given that PBS listing, and thus universalisation, of DAA therapy was only initiated in March 2016, we were only able to study a short time-frame.

CONCLUSION

Hepatitis C remains an important public health issue. The advent of state subsidised DAA therapy has transformed the therapeutic landscape of hepatitis C in Australia. Despite this, patient engagement and social issues remain important barriers to the elimination of hepatitis C. Our study found that 24% of hospital inpatients with hepatitis C were referred for DAA therapy. Less than half of referred patients initiated DAA therapy. Our study methodology provides a template for systematically identifying HCV patients from inpatient cohorts in order to link patients to care. Extrapolating this study to other health networks across Australia, and indeed internationally, would supplement overall treatment numbers in the pursuit of HCV elimination.

ARTICLE HIGHLIGHTS

Research background

An estimated 230 000 Australians were living with hepatitis C virus (HCV) in 2006. The advent of direct acting antiviral (DAA) therapy has revolutionized treatment paradigms and greatly improved rates of sustained virological response. Nevertheless, several challenges remain in striving for the goal of HCV elimination by 2030.

Research motivation

Multifaceted interventions and approaches are required to maintain momentum in order to achieve HCV elimination by 2030. Contemporary discourse in cascades of viral hepatitis care focus on expanding testing as the primary means for identifying and treating remaining HCV patients. Enhancing testing infrastructure and introducing systematic viral assessments in correctional facilities, needle exchange programmes, homeless shelters and in high-risk communities are examples of initiatives currently being undertaken. Less attention has been given to linking patients with pre-existing diagnoses of HCV back to care. Inpatient hospital admissions represent an excellent opportunity to identify and treat both newly and previously diagnosed HCV patients.

Research objectives

To assess whether patients with HCV admitted to a tertiary Australian hospital were appropriately referred on for treatment. Our study was designed to assess the extent to which current hospital practices maximise opportunity for identifying and treating patients with HCV.

Research methods

Our study constituted a retrospective cohort study that assessed patients with HCV admitted to The Queen Elizabeth Hospital, Adelaide in 2017. The primary outcome of our study was referral of patients for HCV treatment. Secondary outcomes included assessment of factors predicting treatment referral.

Research results

There were 148 patients with active hepatitis C. Overall, 131 patients of our study cohort were deemed eligible for DAA treatment and included in the main analysis. Thirty-two patients (24%) were referred on for treatment of their HCV infection. The odds ratio (OR) for appropriate referral for physician specialties *versus* nonphysician specialties was 7.2 (95% CI: 3.0–17.1, $P < 0.0001$). Older patients (OR: 1.05, 95% CI: 1.05–1.08, $P = 0.097$) and those with liver cirrhosis (OR: 19.0, 95% CI: 3.7–96.3, $P = 0.0004$) were significantly more likely to be referred on for treatment. Thirteen patients referred to gastroenterology or infectious diseases clinics commenced treatment.

Research conclusions

Hepatitis C remains an important public health issue. The advent of state subsidised DAA therapy has

transformed the therapeutic landscape of hepatitis C in Australia. Despite this, patient engagement and social issues remain important barriers to the elimination of hepatitis C. Our study found that 76% of chronic hepatitis C patients presenting to the inpatient services of our tertiary hospital were not referred on for treatment. Furthermore, DAA treatment was initiated in less than half of referred patients. This suggests that current hospital practices are not adequately identifying patients with HCV. Hospital admissions constitute an excellent opportunity to identify and treat patients with chronic hepatitis C. Extrapolating this study across tertiary healthcare institutions in Australia and overseas would facilitate re-engagement of previously diagnosed HCV patients with care cascade and supplement overall treatment numbers.

Research perspectives

Our study has internationally relevant implications as our methodology provides a template for systematically identifying HCV patients from inpatient cohorts. Extrapolating this across other national and international tertiary healthcare institutions will serve to supplement treatment rates of HCV as we strive to achieve goals of HCV elimination. Our findings also demonstrate that identification of HCV patients is necessary but not in itself sufficient to achieve cure of HCV. Proactive measures are required to ensure that identified patients successfully commence and complete treatment courses. Hospitals thus require comprehensive multifaceted approaches to ensure opportunities for treatment are taken advantage of.

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FOOTNOTES

Author contributions: Raja SS contributed to study conception and design, also contributed to data collection and analysis as well as drafting and revision of the manuscript; Huyn D contributed to study design, supervision, data analysis and manuscript preparation; Stewart J contributed to data collection and analysis; Edwards S performed statistical analysis.

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