

Missed Opportunities for HCV Treatment WJH Submission Response to Revision Requests

REVIEWERS COMMENTS AUTHORS RESPONSES

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: I would like to congratulate the authors on their manuscript titled 'Missed Opportunities for Hepatitis C Treatment at a Tertiary Care Hospital in South Australia'. This manuscript focuses on the referral of patients with HCV at a tertiary care center. I enjoyed reading this study and the manuscript is overall well written; however, I do have a few comments:

1. Please add an abstract to the manuscript. It is missing from the manuscript file.

Completed

2. Please address what 'PBS scheme' means in the introduction/background section. World Journal of Hepatology has a broad readership around the world and the readers may not be familiar with these terms. Please explain region specific terms in the manuscript.

Australia's initial success were facilitated by the landmark decision to provide DAA therapy to individuals through the Pharmaceutical Benefit Scheme (PBS) scheme. The Australian PBS scheme is a state sponsored program subsidising prescription medication for Australian citizens and permanent residents. PBS subsidisation ensures that patients with HCV only pay a dispensing fee for DAA prescriptions which equates to \$AUD38.30 for general patients and \$AUD6.20 for concessional patients. This has significantly reduced financial barriers to accessing DAA therapy for Australians with HCV.

3. How did the authors account for bias within the admitting teams? Differences in training can account for differences in referral rate. Was there a standard protocol in place for referral at the start of the study? Was it a single provider on the teams or were all the providers trained under the same setting? The authors should mention this in the manuscript.

Our study was a retrospective cohort study of referrals for Hepatitis C treatment at a tertiary hospital in South Australia. No specific protocols or training pertaining to hepatitis C referral pathways were delivered to healthcare providers working on each of the units. During our study period, patients diagnosed with hepatitis C in

the tertiary care setting would typically be referred directly to either gastroenterology or infectious diseases units for consideration of treatment. Assessing differences in referral rates between medical, surgical, emergency and psychiatric services was one objective of our retrospective study. We have used the findings of our study to identify areas of educational need and to inform protocol design for standardising hepatitis C referral pathways including automatic notifications to providers on electronic medical record applications

4. It would be interesting to know the reason for low attendance at the GI or ID clinic after the referral? Do the authors have information on this? Of the referred patients, we they all counseled in a similar fashion about their diagnosis and need for referral?

Our study findings demonstrate that identification of HCV patients is necessary but not in itself sufficient to achieve cure of HCV. 13 of the 28 patients referred to gastroenterology or Infectious diseases clinic commenced treatment. 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, and similar socioeconomic factors that may have predisposed them to HCV infection. As a retrospective study, there was no process for standardisation of the referral process and patient counselling. Given the significant differences in referral rates between specialties and variable awareness of HCV treatment advances, it would be unlikely that patients were counselled in a similar fashion across different admitting units.

5. The readers would like to know the author's take on referral to a sub-specialist vs primary care provider with respect to commencing treatment for HCV.

Based on our study outcomes, which demonstrated limited attendance of referred patients at sub-speciality clinics, we advocate an integrated approach to HCV treatment that utilises both subspecialty viral hepatitis units and primary care providers. In line with international trends, prevalence of HCV in Australia is greater in marginalised and vulnerable groups such as persons who inject drugs, homeless persons and prisoners. Current specialist centric treatment models are not well suited to engaging these “hard to reach” groups with prolonged treatment plans. Despite small sample size, our study indicates that a centralised model of care has significant limitations. Less than half of referred patients attended clinic appointments, let alone commenced treatment.

Australian prescribing guidelines now accommodate for non-specialist prescriptions. Primary health physicians and authorised nurse practitioners can now prescribe DAA therapy in Australia. At the time period covered by the study, uptake of hepatitis C treatment by general practitioners in our state was mostly in its infancy apart from a few GPs with an interest in hepatitis C. GP prescribers accounted for less than 20% of DAA prescriptions. Most GPs were still consulting with Gastroenterologist or ID physicians through shared care type arrangements or community hepatitis C nurses).

Primary care providers are ideally placed to leverage long term relationships with patients to ensure successful commencement and completion of treatment and monitor adherence for HCV patients. Correspondingly, progressively increasing proportions of HCV treatment prescriptions in Australia are being provided by primary care providers.

However, experience with HCV management and DAA prescriptions remains variable amongst primary care providers. Moreover, Australian prescribing guidelines stipulate that primary care providers must initially consult with specialists (gastroenterologists or infectious diseases specialists) to treat HCV until sufficient experience to prescribe independently. Therefore, in the Australian context an ideal “hub and spoke” treatment model would take advantage of both the enhanced patient accessibility of primary care providers as well as the knowledge and treatment experience of sub-specialists. The role of sub-specialists in this model is long-term capacity strengthening of primary care providers as well as providing an easily accessible consult service for difficult cases. Viral hepatitis nurses are uniquely positioned to connect sub-specialty expertise hubs with community-based treatment spokes both in conjunction with and independently of primary care providers. At our unit, experienced viral hepatitis nurses perform an integral outreach role in ensuring referred patients remain engaged with treatment protocols. Ensuring community treatment links is a vital step to ensure sustained engagement of HCV patients with treatment courses and blood testing.

6. The readers would like to the deficits in the structure of management, based on the author's findings, and areas which can be improved upon to increase follow-up and treatment for these patients. Identifying the deficits in how these referral are handled from admission to discharge has widespread implications on a global scale and correcting them could significantly improve compliance. Adding this would greatly enhance the quality of this manuscript.

The focus of our study was on whether current practices in an Australian tertiary hospital ensure that patients with either new diagnoses or existing diagnosis of HCV were appropriately identified and referred for treatment. Over 75% of hospital inpatients with chronic HCV were not referred on for treatment. This suggests that current hospital practices are not adequately identifying patients with HCV. Performing this retrospective cohort study has provided our unit with an insight into where management structures for identification and treatment of HCV can be optimised. This study also confirmed our research hypothesis, namely that inpatient hospital admissions constitute an excellent opportunity to engage patients with HCV treatment.

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 study findings also demonstrate that identification of HCV patients is necessary but not in itself sufficient to achieve cure of HCV. 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 and low prioritisation of health needs in the context of the same socioeconomic factors that predisposed them to HCV infection.

Proactive measures are required to ensure that identified patients successfully commence and complete treatment courses. Hospitals thus require comprehensive multi-faceted approaches to ensure opportunities for 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.

Firstly, educational initiatives and protocol development can enhance screening and diagnosis of HCV for those specialties or departments that frequently encounter at risk patients. Our study demonstrated lower referral rates from surgical, emergency department and mental health units. Succinctly, the insidious nature of HCV and limited inter-disciplinary professional awareness constituted the major treatment barriers in the context of our study. There is a pressing need to integrate HCV screening and treatment with routine medical and psychiatric pro-active for at risk individuals. Knowledge of HCV treatment advances can be variable and educational and awareness raising measures are an important avenue to augment identification and treatment of patients with HCV.

Secondly, our hospital utilises electronic medical record systems for routine inpatient and outpatient care. Ensuring electronic systems appropriately and automatically notify healthcare professionals can help minimise the risk of missing opportunities for HCV treatment.

Thirdly, strengthening community links are important to ensure that HCV patients engage with treatment courses after being discharged. This is especially pertinent in the Australian context given financial barriers to inpatient treatment of HCV. Current prescribing guidelines stipulate that treatment courses of DAAs are only subsidised for outpatient prescriptions. Viral hepatitis nurses are uniquely positioned to continue to engage with HCV patients and ensure adherence to outpatient treatment regimens. At our unit, experienced viral hepatitis nurses perform an integral outreach role in ensuring referred patients remain engaged with treatment protocols and post treatment Sustained Virological Response (SVR) testing.

7. The authors should expand on the limitation section. This study has numerous limitations which were not addressed in this section.

Our study has a number of limitations. Firstly, our study is limited by a small sample size as a single centre study. Secondly, the use of hospital coding to identify HCV patients introduces a sampling bias by systematically excluding patients with HCV without known or recorded diagnosis from the analysis. Our study does not specifically address assess the extent to which current hospital practices ensure that at risk patients are investigated for and diagnosed with HCV.

8. The sample size for the study is too small to draw out definite conclusions. The authors should try to re-frame the study to include a larger sample size.

Our study methodology provides a template for systematically identifying HCV patients from inpatient cohorts. Although the study number is small, it still serves to highlight an area of concern. We identified a large number of number of missed opportunities for hepatitis C treatment in our inpatient hospital cohort. The sample size was adequate the identify the sub-specialties to target additional education and protocols for referral and treatment. 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.

(1) Science editor:

Authors showed outcomes of inpatients with HCV. As the results, DAAs treatment could not be appropriately introduced. This study was interesting, but several issues remained to be addressed. Authors should revise according to reviewer's comments. Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

(2) Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before its final acceptance, the author(s) must provide the Institutional Review Board Approval Form or Document, Signed Informed Consent Form(s) or Document(s). For example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.