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Hepatitis C virus infection and hospital-related outcomes: a systematic review protocol

Lianping Ti,[1,2] Michelle Ng,[2] Lindila Awendila,[1] Patrizia Maria Carrieri[3]

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[1]British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Vancouver, British Columbia, Canada
[2]Department of Medicine, University of British Columbia, St. Paul's Hospital, Vancouver, British Columbia, Canada
[3]Faculté de Médecine, Aix Marseille Université, Marseille, France

Correspondence to
Dr Lianping Ti;
mintti@cfenet.ubc.ca

ABSTRACT

Introduction People living with hepatitis C virus (HCV) infection are disproportionately over-represented in the healthcare system due to various individual and contextual circumstances, including comorbidities and socioeconomic marginalisation. With growing trends in morbidity and mortality related to HCV infection, HCV is becoming a significant health and financial burden on the healthcare system, particularly in acute hospital settings. It is noteworthy that with the advent of direct-acting antiviral therapy the increasing number of patients who are cured of HCV could potentially result in different patterns of hospital-related outcomes over time.

Methods and analysis We will conduct a systematic review of published literature to retrieve quantitative research articles pertaining to hospital outcomes among patients living with HCV. Primary outcomes include hospitalisation rates, length of stay, leaving against medical advice, readmission and in-hospital mortality. In total, five databases will be searched (MEDLINE, EMBASE, CINAHL, PsycINFO and Web of Science). Titles, abstracts and full texts will be independently reviewed by two investigators in three separate stages. The methodological quality of included quantitative research studies will be assessed using a validated tool. Data from included articles will be extracted using a standardised form and synthesised in a narrative account.

Ethics and dissemination Results of this systematic review could provide a better understanding on how to optimise health systems and services to improve patient outcomes and care. The results of this study may provide future research with a foundation to guide decision-making and for designing and implementing systems-level interventions to improve treatment and care delivery for people living with HCV. Ethical approval for this study was received by the University of British Columbia/Providence Health Care Research Ethics Board. Findings from this study will be disseminated through peer-reviewed publications, presentations, reports and community forums

PROSPERO registration number CRD42017081082; Pre-results.

Strengths and limitations of this study

- This study will be the first to systematically assess the literature on the impact of hepatitis C virus (HCV) infection on hospital-related outcomes.
- All included articles will be assessed for methodological quality using a validated tool, the Downs and Black checklist.
- There may be some heterogeneity in the way that the main exposure, HCV infection, and the hospital-related outcomes are defined, which may bias individual studies.

INTRODUCTION

The harms associated with hepatitis C virus (HCV) constitute a major public health challenge globally. It is estimated that 71 million people are living with chronic HCV infection, with a significant proportion who are at high risk of developing advanced liver disease, cirrhosis or liver cancer.[1] In fact, a review of the literature revealed that the risk of hepatocellular carcinoma increases up to 17-fold in patients living with chronic HCV compared with their HCV-negative counterparts, and this may persist even after achieving a treatment-induced sustained virological response.[2–5] If left untreated, approximately 399 000 people die annually from consequences associated with HCV, mostly from advanced liver disease and hepatocellular carcinoma.[6–8] According to WHO surveillance data, hepatitis-related deaths are at an all-time high, with an increasing number of individuals dying as a result of viral hepatitis infection compared with HIV, tuberculosis and malaria, which have been declining in recent years.[1]

People living with chronic HCV infection are often over-represented in the healthcare system.[9 10] Previous studies have demonstrated that these individuals are large users of inpatient, emergency department and outpatient health services, which is likely a result of a number of individual and contextual circumstances, including comorbidities and socioeconomic marginalisation.[11 12] For example, a national study conducted in the USA indicated that inpatient admissions among HCV-infected individuals born between 1945 and 1965 (ie, baby boomers) increased by

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>60% (2.6% in 2001 to 4.2% in 2010, p<0.001) over a 9-year period.[12] The health burden on patients living with HCV infection is also increasing due to the advancing age of this population, where most were infected as a result of nosocomial or iatrogenic practices in healthcare settings prior to the introduction of blood and organ screening.[13] Furthermore, an advancing age coincides with the slow progression of the infection's clinical manifestations.[14] There are also significant healthcare costs associated with increasing chronic HCV severity, with acute inpatient costs being the largest contributor to the financial burden on the health system.[11 15 16]

In recent years, the advent of direct-acting antiviral (DAA)-based therapies has made controlling the HCV epidemic a realistic probability.[17 18] By extension, this would result in a significant reduction in hospital and health service utilisation and would likely have a beneficial effect on the resource burden currently imposed on the health system. To date, there has been no explicit systematic review that has examined the impact of HCV infection on hospital-related outcomes, including hospital admission rates, length of stay, leaving hospital against medical advice, readmissions and in-hospital mortality, and the potential impact of DAAs on these outcomes. Most of the previously reviewed literature has been focused on hospital outcomes among people living with HIV/AIDS, a population that overlaps significantly with people living with HCV infection due to shared transmission routes.[19] Therefore, the purpose of this systematic review is to comprehensively assess the literature on this topic to provide a better understanding on how to optimise health systems and services to improve patient outcomes and care.

METHODS AND ANALYSIS

Protocol and registration

This systematic review protocol conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist (online supplementary additional file 1), and we will adhere to the PRISMA guidelines for the development of this systematic review.[20 21] This protocol has been registered in the PROSPERO database (CRD42017081082).

Research question

The proposed systematic review will aim to answer the following research question: what is the impact of HCV infection on hospital-related outcomes among adults?

Patient and public involvement

No patients were involved in the design of the study. However, results will be disseminated to appropriate patient groups as described in the discussion section.

Eligibility

The research question being addressed is best described by the population, exposure and outcomes (PEO) framework: the population of interest will include adults ≥18 years of age (at baseline); the exposure of interest will be acute or chronic HCV infection; the outcome of interest will be hospital-related outcomes, which will include the following: proportion or rates of hospitalisation; length of stay; proportion or rates of leaving hospital against medical advice; proportion or rates of readmission and proportion or rates of in-hospital mortality. While the introduction of DAAs has been relatively recent, efforts will also be made to examine the potential impact of expanded access to DAAs on these hospital-related outcomes.

For the present study, only original quantitative research studies that report on HCV and hospital-related outcomes will be included. Commentaries, letters to the editors, editorials and other types of opinion pieces will be excluded. We will also exclude literature reviews, but will conduct back referencing to ensure that all relevant studies from the literature review are captured. The search will be restricted to publications in English, but in order to capture a comprehensive list of relevant articles, will not be restricted to setting or publication date; however, these will be recorded during data extraction and synthesis. The planned start date for this study is February 2018.

Information sources and search strategy

We will conduct a comprehensive search strategy to identify articles that meet the eligibility criteria. Specifically, we will search the following databases: MEDLINE, EMBASE, CINAHL, PsycINFO and Web of Science. As indicated above, search terms will be based on the PEO framework, and these terms will be mapped to database-specific medical subject headings and controlled vocabulary terms when available (online supplementary additional file 2). Additionally, we will search reference lists of research articles and systematic reviews to identify relevant articles not otherwise captured in the search strategy. To ensure the robustness of the search strategy, we have consulted with a medical reference librarian with expertise in systematic reviews and population and public health at the University of British Columbia (U. Ellis, personal communication, October 5, 2017).

Study records

We will conduct database searches and import the full-text articles from the search strategy into Endnote X8. Then, we will remove any duplicates prior to reviewing the titles, abstracts and full-text articles. This will be conducted independently in three separate stages by two investigators. At each review stage, studies clearly not meeting the inclusion criteria will be excluded from further review and the reason for exclusion will be recorded. If the two investigators are not able to come to a consensus regarding the inclusion or exclusion of an article, this will be resolved by discussion with a third investigator.

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Risk of bias in individual studies

The methodological quality, including risk of bias, of included quantitative research studies will be assessed using the Downs and Black checklist for the reporting of healthcare studies.[22 23] This 27-item checklist has been shown to be a valid and reliable tool in assessing the quality of research studies. Higher scores represent higher overall methodological quality. Each article will be independently scored by two investigators. If the two investigators are not able to come to a consensus regarding the inclusion or exclusion of an article, this will be resolved by mutual consent and discussion with a third investigator.

Data synthesis

A PRISMA flow chart will be created to outline the article selection process.[24] Data from included studies will be extracted using a standardised form developed to capture study characteristics and main findings and summarised in a table. Specifically, information on study characteristics (eg, geographical setting, study design, study period (including therapeutic periods, ie, interferon-based therapy era, first-generation DAA-based therapy era, second-generation DAA-based therapy era), study population), participant characteristics (eg, age, sex/gender); study objectives; outcome variable(s) and main study findings will be extracted from individual studies. Should there be multiple articles pertaining to the same study population and setting, we plan to extract comprehensive data across the articles but they will be linked together as one unique study. Findings from the included studies will then be synthesised in a narrative account that addresses the objectives of this systematic review.

ETHICS AND DISSEMINATION

The proposed systematic review will be the first to synthesise the literature to identify the burden of HCV infection on the healthcare system, particularly as it pertains to acute inpatient hospital care. The results from this review will provide evidence to help health system leaders and policymakers develop effective health policies and strategies that will positively influence how care is delivered to patients living with HCV. Additionally, these findings may reveal efficient models of treatment and care that would promote retention and continuity of care for patients and minimise any gaps in the healthcare system.

We plan to conduct a comprehensive and reproducible search and analysis of the available literature while recognising that there may be some limitations. First, the investigators are aware that biases may be present even in studies that have been well designed. To address this, the proposed review will be evaluated on its risk of bias using a validated tool and will be conducted independently by two investigators. Second, there may be some heterogeneity in the way that the main exposure and outcomes are defined, which may bias individual studies. While we plan to include all studies that fit the eligibility criteria with no restrictions on measurement, we plan to record and report these in our data extraction table. Third, it is possible that some eligible studies may be missed in our search strategy, though we have sought expert advice from an experienced librarian to ensure that our search strategy is as inclusive as possible.

On completion of the proposed systematic review, a robust knowledge dissemination and exchange strategy will be implemented. We plan to submit the findings of this review for publication in a peer-reviewed open access journal to ensure that the results are accessible to the appropriate scientific and clinical audiences. We also plan to present the results at relevant scientific conferences and meetings both nationally and internationally (eg, Conference on Retroviruses and Opportunistic Infections, The Liver Meeting, The Canadian Network on Hepatitis C Meeting). Recognising that the publication of research findings through scientific avenues may not necessarily be easily accessible to public and community end users, our findings will also be disseminated through newsletters and plain language summaries throughout local hospitals and clinical programmes for timely and effective uptake of the research findings.

In sum, the proposed systematic review will examine and quantify the effect of HCV infection on hospital-related outcomes, and, whenever possible, the effect of expanded access to DAAs on these outcomes. Findings from this review may lead to the identification of current gaps in the literature regarding this topic and the development of new research questions to be answered. In addition, this review may discover effective quality improvement strategies in an effort to minimise the health, societal and financial burden imposed on the hospital and healthcare system.

Contributors LT led the development of the protocol and planned and designed the systematic review protocol. LT prepared the first draft. MN, LA and PMC reviewed and critically revised the first and successive draft of the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval The study was approved by the Ethical Committee of University Hospital of Larissa.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1. World Health Organization. *Global hepatitis report, 2017*. Geneva: World Health Organization, 2017.

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2. de Oliveria Andrade LJ, D'Oliveira A, Melo RC, *et al*. Association between hepatitis C and hepatocellular carcinoma. *J Glob Infect Dis* 2009;1:33–7.
3. Goossens N, Hoshida Y. Hepatitis C virus-induced hepatocellular carcinoma. *Clin Mol Hepatol* 2015;21:105–14.
4. Conti F, Buonfiglioli F, Scuteri A, *et al*. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol* 2016;65:727–33.
5. El-Serag HB, Kanwal F, Richardson P, *et al*. Risk of hepatocellular carcinoma after sustained virological response in Veterans with hepatitis C virus infection. *Hepatology* 2016;64:130–7.
6. World Health Organization. Hepatitis C: fact sheet. 2016 http://www.who.int/mediacentre/factsheets/fs164/en/ (cited 6 Jul 2016).
7. Grebely J, Raffa JD, Lai C, *et al*. Impact of hepatitis C virus infection on all-cause and liver-related mortality in a large community-based cohort of inner city residents. *J Viral Hepat* 2011;18:32–41.
8. Kielland KB, Skaug K, Amundsen EJ, *et al*. All-cause and liver-related mortality in hepatitis C infected drug users followed for 33 years: a controlled study. *J Hepatol* 2013;58:31–7.
9. Xu F, Tong X, Leidner AJ. Hospitalizations and costs associated with hepatitis C and advanced liver disease continue to increase. *Health Aff* 2014;33:1728–35.
10. Goodkin DA, Bieber B, Jadoul M, *et al*. Mortality, hospitalization, and quality of life among patients with hepatitis c infection on hemodialysis. *Clin J Am Soc Nephrol* 2017;12:287–97.
11. Katrak S, Park LP, Woods C, *et al*. Patterns of healthcare utilization among veterans infected with Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) and coinfected with HIV/HCV: unique burdens of disease. *Open Forum Infect Dis* 2016;3:ofw173.
12. Galbraith JW, Donnelly JP, Franco RA, *et al*. National estimates of healthcare utilization by individuals with hepatitis C virus infection in the United States. *Clin Infect Dis* 2014;59:755–64.
13. Joy JB, McCloskey RM, Nguyen T, *et al*. The spread of hepatitis C virus genotype 1a in North America: a retrospective phylogenetic study. *Lancet Infect Dis* 2016;16:698–702.
14. McDonald SA, Hutchinson SJ, Bird SM, *et al*. Hospitalisation for an alcohol-related cause among injecting drug users in Scotland: increased risk following diagnosis with hepatitis C infection. *Int J Drug Policy* 2011;22:63–9.
15. Gordon SC, Pockros PJ, Terrault NA, *et al*. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. *Hepatology* 2012;56:1651–60.
16. Younossi ZM, Otgonsuren M, Henry L, *et al*. Inpatient resource utilization, disease severity, mortality and insurance coverage for patients hospitalized for hepatitis C virus in the United States. *J Viral Hepat* 2015;22:137–45.
17. Martin NK, Vickerman P, Dore G, *et al*. The HCV epidemics in key populations (including PWID, prisoners, and MSM): the use of DAAs as treatment for prevention. *Curr Opin HIV AIDS* 2015;10:374–80.
18. Maan R, van Tilborg M, Deterding K, *et al*. Safety and effectiveness of direct-acting antiviral agents for treatment of patients with chronic hepatitis C virus infection and cirrhosis. *Clin Gastroenterol Hepatol* 2016;14:1821–30.
19. Ford N, Shubber Z, Meintjes G, *et al*. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. *Lancet HIV* 2015;2:e438–e444.
20. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
21. Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
22. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377–84.
23. Marshall BD, Werb D. Health outcomes associated with methamphetamine use among young people: a systematic review. *Addiction* 2010;105:991–1002.
24. Preferred reporting items for systematic reviews and meta-analyses. PRISMA flow diagram. http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx (cited 9 Oct 2017).

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