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REVIEW

Conceptual framework for outcomes research studies of hepatitis C: an analytical review

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Abstract: Hepatitis C virus infection is one of the main causes of chronic liver disease worldwide. Until recently, the standard antiviral regimen for hepatitis C was a combination of an interferon derivative and ribavirin, but a plethora of new antiviral drugs is becoming available. While these new drugs have shown great efficacy in clinical trials, observational studies are needed to determine their effectiveness in clinical practice. Previous observational studies have shown that multiple factors, besides the drug regimen, affect patient outcomes in clinical practice. Here, we provide an analytical review of published outcomes studies of the management of hepatitis C virus infection. A conceptual framework defines the relationships between four categories of variables: health care system structure, patient characteristics, process-of-care, and patient outcomes. This framework can provide a starting point for outcomes studies addressing the use and effectiveness of new antiviral drug treatments.

Keywords: chronic hepatitis C, humans, treatment outcome, combination drug therapy, antiviral agents

Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide.[1] According to recent estimates, more than 185 million people around the world have been infected with HCV.[2,3] The prevalence of hepatitis C infection varies substantially, with the highest estimated prevalence in Central and East Asia (3.8% and 3.7%, respectively) and in the North Africa/Middle East regions (3.6%) of the world.[4] While an estimated 15%–30% of all HCV infections clear spontaneously, most evolve to chronic hepatitis, which can lead to cirrhosis and hepatocellular carcinoma.[5,6] Progression of liver disease may be influenced by various factors, including the duration of infection, alcohol abuse, and coinfection with hepatitis B virus (HBV) and human immunodeficiency virus (HIV).[7]

Eleven HCV genotypes (designated 1–11) with several distinct subtypes (designated a, b, c, etc) have been identified. Genotypes 1–3 have a worldwide distribution with types 1a and 1b accounting for roughly 60% of global infections.[8] Genotype 1a is most often found in Northern Europe and North America, while genotype 1b is primarily found in Southern and Eastern Europe as well as Japan. Type 3 is endemic in Southeast Asia and is erratically distributed in different countries. Genotype 4 is largely found in the Middle East, Egypt, and Central Africa, while type 5 is almost entirely found in South Africa. Genotypes 6–11 are distributed throughout Asia.[8]

Treatment with antiviral drugs can reduce the hepatitis C viral load in serum to undetectable levels. A sustained viral response (SVR) is defined as undetectable HCV

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RNA at 12 (SVR12) or 24 weeks following completion of drug therapy.[9] Patients who achieve SVR have substantially reduced risk of progression to cirrhosis, development of hepatocellular carcinoma, and both liver-related and all-cause mortality.[10]

Until 2011, the combination of pegylated interferon α-2 (administered weekly by subcutaneous injection) and twice-daily oral ribavirin for either 24 (genotypes 2 and 3) or 48 weeks (genotype 1 and others) was the approved treatment for chronic hepatitis C in both the European Union and the United States.[11] With this regimen, HCV genotype 1-infected patients had SVR rates of approximately 40%–50%.[11] In 2011, the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved two new oral antivirals for HCV genotype 1 infections: the direct-acting antivirals (DAAs), telaprevir and boceprevir. In clinical trials, addition of these DAAs to pegylated interferon α-2 and ribavirin improved SVR rates in treatment-naïve, HCV genotype 1-infected patients.[12–15]

Three new, once-daily oral DAAs were approved by the EMA in 2014: simeprevir, sofosbuvir (both approved by the FDA in 2013), and daclatasvir (approved by the EMA in 2014 and by the FDA in 2015).[11,16–19] When used as a component of a combination regimen, typically with pegylated interferon α-2 and ribavirin, these new DAAs have led to improvements in SVR rates.[11] Such triple regimens have the drawback, however, of increased regimen complexity and the potential for additional adverse effects.

Hepatitis C treatment is rapidly evolving away from interferon- and ribavirin-based therapy.[20] Combinations of DAAs, including simeprevir plus sofosbuvir as well as daclatasvir plus sofosbuvir, have shown great efficacy. New, once-daily fixed-dose combinations of ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir have been formulated, the latter copackaged with twice-daily dasabuvir tablets. Both treatments were approved by the EMA and FDA in late 2014 and are indicated as 12–24-week courses for HCV genotype 1 infections.[21,22] In Phase III clinical trials, treatment with ledipasvir/sofosbuvir resulted in SVR12 rates of 94%–99%.[23] Clinical trials with the four-drug combination (ombitasvir/paritaprevir/ritonavir/dasabuvir) have resulted in SVR12 rates of 90%–100%.[24] In the near future, new, pangenotypic combinations of DAAs are expected to become available, appropriate for all fibrosis stages, with shorter durations of treatment and SVR rates approaching 100%.

In summary, the new DAA-containing regimens are associated with improved SVR rates but bring differing regimen complexities and new spectra of potential side effects and antiviral resistance. These new regimens have been tested in controlled trials, where patients tend to have relatively more favorable outcomes.[25] The effectiveness of these regimens in clinical practice must be determined. Outcomes research studies have shown that patient outcomes are affected by multiple factors, including the health care processes that are recommended in guidelines for the management of HCV infection. Here, we provide a review and analysis of studies of the management of HCV infection in real-world settings. We also summarize the processes-of-care measures recommended in guidelines for the management of HCV infection.

Literature search

A search of PubMed was conducted for primary studies of the management of HCV infection using the algorithm: "antiviral agents/therapeutic use"[Mesh Terms] AND "hepatitis c, chronic"[MeSH Terms] AND ("process assessment (health care)"[Mesh terms] OR "preventive health services"[Mesh terms] OR "quality of health care"[Mesh terms] OR "physician's practice patterns"[Mesh terms] OR "quality indicators, health care"[MeSH Terms]) AND (hasabstract[text] AND "2009/12/14"[PDat] : "2014/12/12"[PDat]) NOT review[publication type] NOT "clinical trial"[publication type] NOT "United States"[MeSH terms] NOT polymorphism*[title word] AND English[language] AND has abstract[text]. Bibliographies of articles identified in the search were screened.

Conceptual framework

An outcomes research study typically rests on a hypothesis relating an outcome, eg, a patient free of HCV infection, and a variable or set of variables upon which the outcome is hypothesized to be dependent, eg, antiviral drug treatment. The variables are categorized as either 1) an outcome or dependent variable or 2) an independent or predictor variable, upon which the outcome variable is dependent. Hence, the framework consists of sets of variables and the relationships between them (ie, their designation as outcome or predictor variables). The conceptual framework is shown as a graphical model in Figure 1. It has four domains, ie, categories of variables: 1) health care system structure, 2) patient characteristics, 3) process-of-care, and 4) patient outcomes.

Health care system structure refers to how health care is delivered to the patient and includes clinic and provider characteristics as well as the HCV surveillance system.[26] Surveillance is defined as the "ongoing systematic collection, collation, analysis, interpretation of data; and the

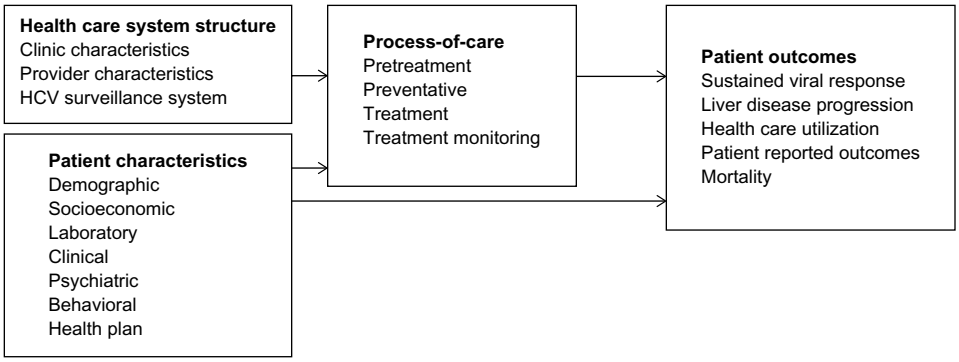

Figure 1 Graphical model of variable relationships in outcomes research studies of management of HCV infection.
Notes: Arrows run left to right from predictor variables to outcome variables. Process-of-care variables may be both predictor and outcome variables. The process-of-care variables are derived from Kanwal et al.[51]
Abbreviation: HCV, hepatitis C virus.

dissemination of information to those who need to know in order that action be taken".[27,28] Process-of-care defines what is being delivered and includes four categories of care: pretreatment, preventative, treatment, and treatment monitoring. Patient characteristics are categorized as demographic, socioeconomic, laboratory, clinical (medical and psychiatric), behavioral, and health plan (health care insurance).

In this framework, the category "patient outcomes" is the ultimate outcome or dependent variable. The other variable categories are directly or indirectly predictors of this outcome variable. Health care system structures and patient characteristics are predictors of the process-of-care, which is a predictor of patient outcomes. Patient characteristics are also direct predictors of patient outcomes. The process-of-care is the most immediate determinant of the effectiveness of management of HCV infection in patients. The optimum process-of-care is set out in clinical practice guidelines from professional societies. Some measures recommended in guidelines are also used as performance measures, also referred to as "quality-of-care measures", which are specific metrics used to monitor the delivery of health care. These guidelines are reviewed below.

HCV management guidelines

Guidelines for the management of HCV infection

Clinical practice guidelines (see list in Table S1), define the best-evidence practices and standards for the prevention and treatment of HCV infection, ie, they relate to the process-of-care.

The populations targeted in guidelines vary. The United States Institute of Medicine's guideline for the prevention of hepatitis and liver cancer targets the general population.[29] Three other US guidelines specifically refer to individuals born between 1945 and 1965 (a population at increased risk of HCV infection).[30–33] Other guidelines focus on persons with chronic HCV infection, with an HIV coinfection, or patients with liver cancer (Table S1).

These HCV guidelines provide recommendations in the process-of-care categories of pretreatment (surveillance and testing for viral load and genotype), preventative (education, ie, knowledge and awareness of HCV prevention and HBV and hepatitis A virus [HAV] immunization), treatment (antiviral drug and treatment regimen), and treatment monitoring.

Process-of-care measures recommended in guidelines

The specific process-of-care measures recommended in selected US and global guidelines are given in Table S2. The most extensive list is from the American Association for the Study of Liver Diseases and associated bodies (AASLD, IDSA, and IAS-USA).[32] This guideline includes 22 measures in the four categories of care: 1) pretreatment, 2) preventative, 3) treatment, and 4) treatment monitoring and is the only guideline in Table S2 to include measures in the treatment monitoring category. The Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force (USPSTF) guidelines, both of which focus on persons born between 1945 and 1965, each contain only four measures: pretreatment (risk factor assessment, anti-HCV antibody test, and HCV diagnostic test in the USPSTF guideline), preventative (counseling about alcohol use in the CDC guideline), and treatment (antiviral treatment).[30,31] Thus, only two measures are recommended in all four of the guidelines in Table S2: anti-HCV antibody test and antiviral treatment.

The 2015 guideline from the European Association for the Study of the Liver covers most of the items in the AASLD, IDSA, and IAS-USA guidelines, including specific recommendations regarding antiviral drug treatment and

treatment monitoring.[9] Specific drug regimens, including interferon-free regimens, are recommended, taking into account HCV genotype, degree of liver disease progression, potential drug–drug interactions, etc. Dose modification is discussed, and patient counseling regarding the importance of medication adherence is recommended.[9] The World Health Organization's (WHO) guideline includes only five measures in the pretreatment, preventative, and treatment categories.[4]

Process-of-care measures as performance measures

Performance measures, also referred to as "quality-of-care" measures, are specific metrics used to assess the quality of medical care provided to patients with HCV infection. Specific process-of-care measures are used as performance measures in the United States. The specific process-of-care measures proposed by various US governmental and professional entities are listed in Table S3.

The American Medical Association-Physician Consortium for Performance Improvement (AMA-PCPI) work group created a list of 12 performance measures that focus on pretreatment, preventative, treatment, treatment monitoring, and patient outcomes (specifically SVR) to improve outcomes for adult patients with HCV (Table S3).[34] The AMA-PCPI is the only organization listed in Table S3 to include patient outcomes in their list of performance measures. The Centers for Medicare and Medicaid Services' 2014 Physician Quality Reporting System includes five HCV-specific quality indicators: pretreatment (confirmation of hepatitis C viremia and HCV genotyping), preventative (HAV vaccination/immunity and HCV RNA test at treatment week 0), and treatment monitoring (HCV RNA testing between weeks 4 and 12 after initiation of treatment).[35] Finally, the American Gastroenterological Association Institute's measures were adapted from an earlier set of measures from the Centers for Medicare and Medicaid Services.[33]

Three performance measures from the pretreatment and preventative categories were recommended in all of these four documents: 1) HCV genotyping, 2) HAV vaccination/immunity, and 3) HCV RNA testing prior to commencing treatment.

Outcomes research studies of HCV infection

The search of PubMed with key terms for hepatitis C, antiviral agents, and health care process identified 27 unique reports of HCV-specific outcomes research studies conducted in Europe, the United States, and elsewhere. These studies analyzed multiple variables within the domains of health care system structure, patient characteristics, and process-of-care.

Outcome (dependent) variables

In studies conducted in countries outside the United States, initiation of antiviral treatment and treatment monitoring were the only process-of-care outcome variables, and SVR was the only patient outcome variable measured (Table 1). No pretreatment or preventative outcome variables were measured in these studies.

The data source in the majority of US studies was the Veterans Health Administration. Two US studies used health insurance claims data,[36,37] one used data from several HIV clinics,[38] and two were epidemiologic studies (Table 2).[39,40] Antiviral treatment and SVR were the two outcome variables measured most frequently (Table 2). All of the other outcome variables in these US studies fell into the process-of-care category. Among other treatment outcome variables measured were type of antiviral treatment (by genotype), antiviral treatment completion, and whether antiviral treatment was offered. Other dependent variables were in the categories of pretreatment (referral to a specialty clinic, specialist evaluation, etc), preventative (HIV test, HAV serology test, HAV vaccination, etc), and treatment monitoring (HCV test at treatment weeks 0, 12, etc). Kanwal et al[41] used a composite outcome variable – whether the patient received 50% or more of a list of 23 process-of-care measures: seven each in the categories of pretreatment, preventative, and treatment monitoring, and two treatment measures.

Predictor variables

Variables predictive of dependent process-of-care and patient outcome variables are presented in Table 3. A "+" in Table 3 indicates that a statistically significant association was observed (either positive or negative) and a "0" indicates that no statistically significant association was found. The number of "+" or "0" signs for each association indicates the number of studies in which the association was reported.

The studies listed in Table 3 showed that the patient outcome, SVR, (see next-to-last column in Table 3) is affected by some process-of-care measures (optimum preventative care, treatment experience, treatment dose, treatment modification, treatment completion, and combination therapies) and by various patient characteristics – demographic (primarily age), laboratory (primarily HCV genotype), clinical/medical (primarily cirrhosis), clinical/psychiatric (depression), and behavioral (patient adherence and visit frequency).

Table 1 Outcome (dependent) variables reported in studies performed outside of the United States

Outcome variable	France		Italy			Hungary	Australia		Switzerland	Denmark	UK	Japan
	Bourliere et al[54]	Winnock et al[63]	Angeli et al[64]	Borroni et al[53]	Giannelli et al[65]	Gazdag et al[66]	Deborah Friedman et al[25]	Gidding et al[67]	Bruggmann et al[68]	Hansen et al[69]	Harris et al[70]	Tanioka et al[55]
Process-of-care												
Pretreatment												
Preventative												
Treatment												
Antiviral treatment		✓	✓			✓		✓				
Treatment monitoring												
Treatment modification				✓								
Patient outcomes												
SVR	✓			✓	✓		✓		✓	✓	✓	✓

Abbreviation: SVR, sustained viral response.

Antiviral treatment, the most frequently measured process-of-care outcome variable, is predicted by health care system structure variables, process-of-care variables, and by patient characteristics. The health care system structure variables influencing antiviral treatment were clinic characteristics (treatment facility) and provider characteristics (weekly patient N, years at HIV clinic, and experience). The process-of-care measures were optimum pretreatment care and optimum preventative care. The patient characteristics were demographic (primarily age and race), laboratory (alanine aminotransferase level, hemoglobin, CD4 count, and genotype), clinical/medical (coronary artery disease/cardiovascular disease, cirrhosis, and pulmonary disease), clinical/psychiatric (bipolar disorder and depression), and behavioral (primarily alcohol or illicit drug use) variables (Table 3).

Discussion

Outcomes research studies have analyzed dozens of variables in multiple categories within the domains of health care system structure, patient characteristics, and process-of-care (Table 3). The results of these studies indicated that some patient characteristics, eg, demographic (race) and behavioral (illicit drug use), were predictive of the process-of-care variable, antiviral treatment. Other patient characteristics, eg, demographic (age) and laboratory (HCV genotype), were predictive both of receiving antiviral treatment and of SVR (a patient outcome). In addition, some health care system structure variables were predictive of receiving antiviral treatment, and optimum preventative care (a process-of-care variable) was predictive of SVR.

The majority of the published outcomes research studies were conducted in the era of pegylated interferon/ribavirin as the standard for antiviral treatment, and so there are few published observational studies of the new DAAs and new DAA combinations. HCV-TARGET is an international consortium of HCV investigators who have established a common research database and are conducting a longitudinal observational study of the treatment of HCV therapy with DAAs.[40] PITER is an ongoing longitudinal study of the impact of DAAs on the natural course of infection and long-term clinical outcomes.[42] Clinical trials of multiple interferon-free combinations of DAAs have been completed or are ongoing.[43–45] Outcomes research studies will be needed to clarify for which patient groups, and in which clinical settings, these new regimens are most effective. In the United States, the patient's health plan type may influence whether they receive the new DAAs. Most Medicaid plans currently limit access to sofosbuvir in

Table 2 Outcome (dependent) variables in US observational studies

Outcome variable	Veterans Health Administration										Health claims		HIV clinic	Epidemiologic	
	Brau et al[52]	Butt et al[50]	Huckans et al[71]	Kanwal et al[48]	Kanwal et al[51]	Kanwal et al[a,41]	Kramer et al[47]	Rongey et al[72]	Rousseau et al[73]	Shim et al[49]	Kanwal et al[b,36]	Mitra et al[37]	Wagner et al[c,38]	Evon et al[39]	Sterling et al[40]
Process-of-care															
Pretreatment															
Referral to a specialty clinic									✓[d]						
GI/hepatologist specialist evaluation								✓							
HCV viremia confirmation						✓					✓				
HCV specialist evaluation				✓		✓									
HCV genotyping						✓			✓		✓				
Liver biopsy if genotype 1						✓			✓[e]						
Exclude liver disease/HBV						✓									
Exclude liver disease/autoimmune						✓									
Exclude liver disease/iron-overload						✓									
Laboratory evaluation									✓						
Preventative															
HIV test						✓									
HAV serology test						✓	✓								
HAV vaccination						✓	✓	✓		✓	✓				
HBV serology test						✓	✓								
HBV vaccination						✓	✓	✓			✓				
Depression treatment						✓									
Substance abuse disorder treatment						✓									
HIV screening								✓							
HCC screening								✓[f]							
Treatment															
Antiviral treatment		✓[g]		✓	✓			✓	✓		✓		✓		
Antiviral treatment/ genotype 1						✓									
Antiviral treatment/ nongenotype 1						✓									
Antiviral treatment completion	✓				✓										
Antiviral treatment offered													✓		
Antiviral treatment modification	✓														
Treatment monitoring															
HCV test W0						✓					✓				
HCV test W12 (genotype 1)						✓					✓				
HCV test W24 (genotype 1)						✓									
HCV test W48 (genotype 1)						✓									
HCV test W24 posttreatment end						✓									
Reduce ribavirin dose for anemia						✓									

Not prescribing growth-stimulating factors for leucopenia			✓			
Patient outcomes						
SVR	✓	✓	✓[h]		✓	✓
Health care utilization				✓		

Notes: [a]The main outcome measure was a composite score (≥50% of all indicated care).[36] [b]The outcome variable in the primary analysis was the receipt of any of the seven quality indicators in Medicare's 2009 Physician Quality Reporting Initiative.[36] [c]The main outcome variable was offering HCV antiviral treatment in HIV-coinfected patients.[38] [d]Defined as the scheduling of an appointment to see a specialist in gastroenterology or infectious disease, whether or not the patient attended. [e]Liver biopsy not limited to patients with genotype 1. [f]Hepatocellular carcinoma and endoscopic variceal screening of patients with cirrhosis. [g]Prescription for antiviral treatment. [h]Sustained viral response analysis limited to patients who completed antiviral treatment.

Abbreviations: GI, gastrointestinal; HAV, hepatitis A virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained viral response; W, week.

patients with advanced cirrhosis.[46] Thirty-eight percent of patients in the HCV-TARGET had cirrhosis,[40] whereas much lower percentages of patients treated with interferon regimens had cirrhosis, eg, 7%–14% in Veterans Health Administration populations.[41,47–52]

Regarding monitoring of antiviral treatment, there are only two studies of the modification of the antiviral regimen during treatment,[53,54] only one of optimal treatment monitoring,[51] and no studies of switching or adjustments of antiviral regimens in response to treatment ineffectiveness (eg, due to the development of tolerance). Future analyses will be required to determine outcomes of new DAA therapies based on the intensity of monitoring.

Studies of patient outcomes have focused on SVR. There are no observational studies with patient reported outcomes, eg, health-related quality of life, as dependent variables and no studies of long-term clinical outcomes, eg, all-cause mortality, liver-related death, hepatocellular cancer, and others (liver decompensation, variceal bleeding, encephalopathy). The above end points should be incorporated into observational studies to show the extent of the benefits of antiviral treatment in clinical practice. In addition, the patient populations should include patient groups normally underrepresented in clinical trials settings, eg, patients with multiple comorbidities or injection drug users, as well as patients with minimal or mild fibrosis. Incorporating quality of life and work-productivity parameters into observational studies would also be relevant to documenting the potential benefits of SVR. Finally, studies are needed to determine the health care resource use in real-life settings in order to estimate costs associated with the process-of-care measures being recommended in guidelines (the only study of the determinants of health care utilization or costs examined the effects of patient nonadherence).[37]

Medication adherence is included in the framework as a predictor variable – a patient behavioral characteristic – shown to be predictive of SVR. However, there are other studies in which adherence is the outcome variable. Variables predictive of adherence fall in the domains of process-of-care (treatment regimen), health care system structure (clinic characteristics), and patient characteristics (demographic, behavioral, laboratory, and clinical/psychiatric).[55–57] Adherence rates in these studies of interferon-based regimens were relatively low – 38% to 72%. Outcome studies will be needed to confirm that rates of adherence to the new DAA regimens, which have simplified dosing and shorter treatment durations, are improved as expected when delivered in tertiary or community settings. Also, other variables such as reinfection rate

Table 3 Variables predictive of dependent process-of-care and patient outcome variables in observational studies

Predictor variables	Dependent process-of-care variables					Dependent patient outcome variables	
	Pretreatment[48,72]	Preventative[47,49]	Treatment[a,38,48,50,51,63,64,66,67,72,73]	Treatment monitoring[b]	Process composite[c,36,41]	SVR[25,39,40,51–55,65,68–71]	Health care utilization[37]
System structure							
Clinic characteristics							
Clinic number							
Clinic type (GI)		+					
HCV patient load					0		
HCV provider availability							
Quality measures					0		
Treatment facility	+		+				
Treatment facility factor[d]					+		
Provider characteristics							
Provider sex			0				
Weekly patient, N			+				
Annual patient, N							
Threshold[e]			0				
Years at HIV clinic			+				
Specialty					+		
Experience			+				
Process-of-care							
Pretreatment							
Specialist evaluation		+					
Optimum pretreatment care			+			0	
Preventative							
Optimum preventative care			+			+	
Treatment/treatment monitoring							
Optimum treatment monitoring						0	
Treatment for HCV		+					
Treatment experience[f]						0, +/0[g]	
Treatment dose						+,+[h]	
Treatment modification						+[i],0[i]	
Treatment completion						+,0	
Combination therapies						+	
Patient characteristics							
Demographic							
Age		+,+	+,+,+		+,+	+,+,+,+,0,0,0	
Sex		0	0		0	+,+/0[k],0,0/0[g]	
Marital status			+				
Nationality						+	

Parental status[l]			+		
Race		+,+	+,+,+,+,+	0	0,+
Rural residence	+		+		
Socioeconomic					
Annual income <$30K	+				
Homeless		0			
Social support					0
Laboratory					
ALT ≥40 IU/mL	+	0	+,+	+	0
Low hemoglobin			+,+		0/+[g]
CD4 <200 cells/mm^3			+,+		
Hepatic dysfunction			+		
HCV genotype 1		+	+		+,+,+,+,0/+[g]
HCV genotype 2/3		+	+,+		+,+,+,+,+
HCV genotype 4		+			
HCV RNA					+,0, 0/0[g]
HIV viral load					+[m]
HIV diagnosis		+	0	0	
HIV RNA, mean					
Neutrophils <2,000/mm^3					0
Clinical/medical					
Anemia					
BMI					+
CAD/cardiovascular disease			+,+		
Cirrhosis	+	+,0	+,+	+,+	+,+,+,+,+/+[g]
Comorbidity, N				+,+	
Comorbidity, physical			+		0
Diabetes			+		0,+[k,] +/0[g]
End-stage renal disease		+			
Fibrosis					+[i],+[n]
Hepatitis B			+		
Pulmonary disease			+,+		
Stroke			+		
Time since infection			0		0
Clinical/psychiatric					
Bipolar disorder			+		
Depression			+°,0	+	+
Psychosis		+,+		0	
PTSD			+		
Schizophrenia			+		

(*Continued*)

Table 3 (*Continued*)

Predictor variables	Dependent process-of-care variables					Dependent patient outcome variables	
	Pretreatment[43,67]	Preventative[42,44]	Treatment[a,33,43,45,46,58,59,61,62,67,68]	Treatment monitoring[b]	Process composite[c,31,36]	SVR[20,34,35,46–50,60,63–66]	Health care utilization[32]
Behavioral							
Adherence[p]			+			+,+/+[k],+	+[q]
Alcohol/drugs			+,+		+,+	0	
Alcohol use		+,0	+[r]			0,0	
Drugs, illicit		+,0	+[r],+,+,+			0[s]	
Drugs, treatment (dependency)			+				
HAART regimen			+				
HCV knowledge			+				
PCP care, continuity	0						
Prior STD		0					
Sex with same-sex		0					
Treatment for depression			+				
Visit frequency		+	+		+	+	
Commercial plan							
Geographic region					+,0		
Health plan type					0		
Years in health plan					0		
Annual claims					0		

Notes: The "+" sign represents a statistically significant association (positive or negative) with the outcome variable, while "0" indicates no significant association. The number of "+" signs for each association indicates the number of studies in which the association was reported. The predictor variables listed are those included in multivariate analyses in the various studies (not every variable measured in univariate analyses). [a]Wagner et al[38] focuses on predictors of being offered HCV treatment. [b]There were no studies that exclusively looked at treatment monitoring (all of the listed studies looked at treatment monitoring as the composite of individual process-of-care measures). [c]Composite(s) of individual process-of-care measures. [d]Treatment facility factor was presented as "number of weekly half-day clinics" (capturing how frequently clinics were available for access to specialty care) and "administrative location of HCV clinic" in two separate models. Kanwal et al[41] presented two multilevel logistic regression analyses in which the first analysis included the number of weekly half-day clinics and the second analyses replaced the number of weekly half-day clinics with the administrative services of the HCV program. The weekly half-day clinics variable was statistically significant when there were 13 or more dedicated clinics while the administrative location variable was statistically significant. [e]Threshold for assessing patient readiness which assessed the likelihood that a provider would prescribe HCV treatment to a patient with various conditions that could affect the patient's readiness or appropriateness for treatment. Providers responded on a 5-point Likert scale, ranging from "very likely" to "very unlikely".[38] [f]Refers to round of treatment (treatment naïve versus retreatment). [g]Presented multivariate analyses for chronic HCV patients with genotype 1 treated with boceprevir and telaprevir. Also found albumin levels and total bilirubin to be significantly associated with SVR in patients treated with telaprevir (association was not significant among patients treated with boceprevir). IL28B genotype was found to be significantly associated with SVR among patients treated with boceprevir and telaprevir.[40] [h]Treatment dose referred to the average dose of pegylated interferon and ribavirin for patients with chronic HCV infection treated with pegylated interferon/ribavirin.[53] [i]Refers to patients with prior treatment failure.[54] [j]Dose reduction referred to ribavirin dose reduction for patients with chronic HCV infection treated with pegylated interferon/ribavirin.[53] [k]Study reported data for genotype 1 and genotypes 2/3 in separate multivariate analyses. Sex, adherence, and early viral response were found to be significantly associated with SVR in genotype 1 infected patients. In genotype 2/3 patients, diabetes, adherence, and early viral response were found to be significantly associated with SVR. Sex was not associated with SVR in genotype 2/3 infected patients.[65] [l]Parental status defined as being a patient with children.[58] [m]Viral load was a predictive factor for SVR in both treatment naïve and treatment-failure patients.[54] [n]Found advanced fibrosis to be significantly associated with SVR.[52] [o]Depression reported as "major" and "mild" depression.[50] [p]Adherence to HIV drugs/HCV treatment. [q]Adherence was measured using the medication possession ratio.[37] [r]Presented as "alcohol abuse or dependence" and "drug abuse or dependence".[50] [s]Presented as intravenous drug use mode of acquisition.[25]

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CAD, coronary artery disease; GI, gastrointestinal; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PCP, primary care provider; PTSD, posttraumatic stress disorder; RNA, ribonucleic acid; STD, sexually transmitted disease; SVR, sustained viral response.

in high risk groups, eg, persons with injecting drug use, and the effect on prevalence and incidence in these groups will need to be captured in the future. Likewise, the dependency of SVR on baseline resistance associated variants may become important in some subgroups, and the prevalence of these variants after treatment failure will require scrutiny.

Because the conceptual framework applies to outcomes research studies, it does not include societal policy, whether specific to hepatitis or blood borne viral infection or targeted more generally to population health.[58–60] Neither does the framework incorporate concepts such as education, social position, cultural, and societal norms, which are included in the CDC/WHO conceptual model of the social determinants of health, in which many of the relationships between parameters are cyclic.[61] A framework with cyclic and bidirectional relationships is described by Rongey et al,[62] who present a conceptual model to identify variables important in implementing a program of health care for chronically HCV-infected US veterans. In contrast, the relationships between the four variable categories in Figure 1 are directed and acyclic, reflecting the analytical approach in outcomes research studies.

Conclusion

This analytical review shows that multiple variables in the domains of health care system structure, patient characteristics, and process-of-care affect SVR, virtually the only patient outcome variable studied to date. Future studies should address which among these factors influence treatment with the new antiviral drugs, the optimum antiviral drug regimens for individual patients, the effectiveness and health care costs of recommended process-of-care measures, and overall patient outcomes in clinical practice.

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Disclosure

The coauthors report the following conflicts of interest: Urbano Sbarigia, Tom Denee, and Norris Turner are employees of Janssen Pharmaceutica. At the time of the development of this article, George J Wan was an employee of Janssen Global Services. Gary Rice has participated in advisory boards for AbbVie, Biogen Idec, Novartis, Janssen Global Services, and Pfizer Inc., has served as a consultant for Gilead, and is a member of speakers' bureaus for Novartis. Gary Rice received financial remuneration from Janssen Global Services for his participation in the study. Geoffrey Dusheiko is a consultant for Janssen Global Services and received financial remuneration from Janssen Global Services for his participation in the study.

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Supplementary materials

Table S1 Guidelines/recommendations for the management of HCV

Agency[a]	Year	Title	Subjects	Recommendation
United States				
AASLD, IDSA, IAS-USA[1]	2014	Recommendations for testing, managing, and treating hepatitis C	Persons at increased risk of HCV infection and adults born between 1945 and 1965	Screening/testing, management, treatment
CDC[2]	2012	Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965	Persons born between 1945 and 1965	Testing, preventative measures (alcohol screening and intervention), treatment[b]
IOM[c,3]	2010	Hepatitis and liver cancer: a national strategy for prevention and control of hepatitis B and C	General population[d]	Surveillance, education, immunization
USPSTF[4]	2013	Screening for hepatitis C virus infection in adults: US Preventive Services Task Force recommendation statement	Persons at high risk of HCV infection and adults born between 1945 and 1965	Risk assessment, screening,[e] treatment
Canada				
CASL[5]	2015	An update on the management of chronic hepatitis C: consensus guidelines from the Canadian Association for the Study of the Liver	Persons with chronic HCV infection	Assessment, treatment, monitoring
CIHR[6]	2014	CIHR Canadian HIV Trials Network Coinfection and Concurrent Diseases Core: Updated Canadian guidelines for the treatment of hepatitis C infection in HIV-hepatitis C coinfected adults	HIV-hepatitis C coinfected adults	Treatment
Europe				
EASL[7]	2015	EASL recommendations on treatment of hepatitis C	Persons with acute and chronic HCV infections	Testing, treatment, monitoring
NICE[f,8]	–	–	–	–
Asia Pacific				
APASL[9]	2012	APASL consensus statements and management algorithms for hepatitis C virus infection	General population[d]	Surveillance, preventative measures, testing, treatment
Latin America				
LAASL[10]	2014	Latin American Association for the Study of the Liver (LAASL) Clinical Practice guidelines: management of hepatocellular carcinoma	Persons with liver cancer	Prevention, immunization, management, surveillance, treatment
Global				
WGO[11]	2013	Diagnosis, management, and prevention of hepatitis C	Children and adults with, or exposed to, HCV infection	Screening, testing, diagnosis, referral, treatment, care, follow-up
WHO[12]	2014	Guidelines for the screening, care and treatment of persons with hepatitis C infection	Persons with HCV infection	Screening, testing, care, treatment

Notes: [a]Government agency, quasiautonomous nongovernmental organization, professional society, or other entity. [b]Refers to the American Association for the Study of Liver Diseases 2011 guidelines for treatment recommendations.[13] The 2011 guidelines have since been updated and have been replaced by the 2014 guidelines.[1] [c]Guidelines are for Hepatitis B and C. [d]General population and/or various or unspecified target populations. [e]Screening tests include antibody testing followed by a confirmatory PCR. [f]Guidelines by NICE have been paused.[8]

Abbreviations: AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; CASL, Canadian Association for the Study of the Liver; CDC, Centers for Disease Control and Prevention; CIHR, Canadian Institutes of Health Research; EASL, European Association for the Study of the Liver; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IAS-USA, International Antiviral Society-USA; IDSA, Infectious Diseases Society of America; IOM, Institute of Medicine; LAASL, Latin American Association for the study of the Liver; NICE, National Institute for Health and Care Excellence; PCR, polymerase chain reaction; USPSTF, US Preventive Services Task Force; WGO, World Gastroenterology Organization; WHO, World Health Organization.

Table S2 Process-of-care measures in selected guidelines

Measure	Guideline			
	AASLD, IDSA, IAS-USA[1]	CDC[2]	USPSTF[4]	WHO[12]
Pretreatment				
Evaluation by HCV practitioner[a]	✓			
Risk factor assessment	✓	✓[b]	✓	
Anti-HCV antibody test	✓	✓[b]	✓	✓[c]
HCV RNA diagnostic test	✓		✓	✓
HCV genotyping	✓			
Referral of decompensated cirrhosis patients	✓			
Preventative				
HAV vaccination/immunity	✓			
HBV vaccination/immunity	✓			
Evaluation for advanced hepatic fibrosis	✓			✓
Counseling regarding preventing HCV transmission	✓			
Counseling regarding contraception				
Counseling regarding alcohol use	✓	✓		✓
Assessment for potential antiviral drug–drug interactions	✓			
Laboratory tests at treatment W0[d]	✓			
HCV RNA test at treatment W0[d]	✓			
Treatment				
Antiviral treatment	✓[e]	✓[f]	✓	✓
Treatment monitoring				
HCV RNA test at treatment W12	✓			
HCV RNA test at treatment W4, W12, and at treatment end	✓			
Laboratory testing periodically during treatment	✓			
Ongoing assessment liver disease[g]	✓			
Retreatment if prior antiviral therapy failed	✓			
Liver disease progression assessment if antivirals failed	✓			
Monitoring for pregnancy-related issues if ribavirin used	✓			

Notes: [a]Evaluation by a practitioner who is prepared to provide comprehensive management, including consideration of antiviral therapy.[1] [b]Guidelines provide data on different testing methods (HCV antibody testing, HCV RNA testing, HCV viral load testing, and liver enzyme tests). [c]Guidelines recommend that HCV serology testing be offered to screen and identify persons with HCV infection and that nucleic acid testing for the detection of HCV RNA be performed directly following a positive HCV serological test to establish the diagnosis of chronic HCV. [d]W0: treatment week 0, ie, prior to commencement of antiviral treatment. [e]Multiple treatment recommendations depending on patient category. [f]Refers to the American Association for the Study of Liver Diseases 2011 guidelines for treatment recommendations.[13] The 2011 guidelines have since been updated and have been replaced by the 2014 guidelines. [g]In persons for whom antiviral treatment is deferred.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CDC, Centers for Disease Control and Prevention; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; IAS-USA, International Antiviral Society-USA; IDSA, Infectious Diseases Society of America; RNA, ribonucleic acid; USPSTF, US Preventive Services Task Force; W, week; WHO, World Health Organization.

Table S3 US performance measures

Performance measure	AMA-PCPI[14]	2014 PQRS[15]	AGA[16]
Pretreatment			
Confirmation of hepatitis C viremia	✓	✓[a]	
HCV genotyping	✓	✓	✓
Preventative			
HAV vaccination/immunity	✓	✓	✓
HBV vaccination/immunity	✓		✓
Counseling regarding contraception			✓
Counseling regarding alcohol use	✓		✓
HCV RNA test at treatment W0[b]	✓	✓	✓
One-time screening for HCV for patients at risk	✓[c]		
Annual HCV screening for patients who are active injection drug users	✓[c]		
Referral to treatment for patients identified with HCV infection	✓[c]		
Treatment			
Antiviral treatment	✓		✓
Treatment monitoring			
HCV RNA test at treatment W12			✓
HCV RNA testing between weeks 4 and 12 after initiation of treatment	✓	✓	
Discontinuation of antiviral therapy for inadequate viral response	✓		
Discussion and shared decision making surrounding treatment options	✓		
Patient outcomes			
SVR	✓		

Notes: [a]The performance measure's title is "Confirmation of Hepatitis C Viremia"; however, the description states, "percentage of patients aged 18 years and older who are hepatitis C antibody positive seen for an initial evaluation for whom HCV RNA testing was ordered or previously performed". [b]W0: treatment week 0, ie, prior to commencement of antiviral treatment. [c]Presented as one measure with three parts.

Abbreviations: AGA, American Gastroenterological Association; AMA, American Medical Association; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; PCPI, Physician Consortium for Performance Improvement; PQRS, Physician Quality Reporting System; RNA, ribonucleic acid; SVR, sustained viral response; W, week.

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