Received: 24 April 2019 | Revised: 3 October 2019 | Accepted: 22 October 2019

DOI: 10.1111/liv.14285

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Clinical outcome indicators in chronic hepatitis B and C: A primer for value-based medicine in hepatology

Mario Strazzabosco[1,2,3] | Paolo A. Cortesi[4] | Sara Conti[4] | Stefano Okolicsanyi[1,2] | Matteo Rota[4,5] | Antonio Ciaccio[1,2] | Paolo Cozzolino[4] | Carla Fornari[4] | Marta Gemma[1,2] | Luciana Scalone[4] | Giancarlo Cesana[4] | Luca Fabris[2,3,6] | Michele Colledan[7] | Stefano Fagiuoli[8] | Gaetano Ideo[9] | Claudio Zavaglia[10] | Giovanni Perricone[10] | Luca M. Munari[9] | Lorenzo G. Mantovani[4] | Luca S. Belli[2,10]

[1]Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy

[2]International Center for Digestive Health, University of Milan-Bicocca, Milan, Italy

[3]Liver Center & Section of Digestive Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA

[4]Research Centre on Public Health (CESP), University of Milan-Bicocca, Milan, Italy

[5]Department of Molecular and Traslational Medicine, University of Brescia, Brescia, Italy

[6]Department of Molecular Medicine, University of Padua School of Medicine, Padua, Italy

[7]Department of Surgery, Papa Giovanni XXIII Hospital, Bergamo, Italy

[8]Department of Gastroenterology, Papa Giovanni XXIII Hospital, Bergamo, Italy

[9]FADE Foundation, Milan, Italy

[10]Hepatology and Gastroenterology Unit - Liver Unit, ASST GOM Niguarda, Milan, Italy

Correspondence
Mario Strazzabosco, Section of Gastroenterology, School of Medicine and Surgery, University of Milan-Bicocca, Via Cadore 48, Milan, Italy.
Department of Internal Medicine, Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar Street LMP 1080, 06520 New Haven, CT, USA.
Emails: mario.strazzabosco@unimib.it; mario.strazzabosco@yale.edu

Funding information
Fondazione FADE amici dell'epatologia ONLUS; Italian Ministry of Health. Decreto Ministeriale 10 luglio 2007, "Progetti attuativi del Piano sanitario nazionale - Linee guida per l'accesso al cofinanziamento alle regioni e alle province autonome di Trento e Bolzano", Gazzetta Ufficiale 10 ottobre 2007, n. 236; Lombardy Region Directorate General for Health. Nota Direzione Generale Sanità del 12.02.2009 prot.

Abstract

Background & Aims: Chronic liver diseases (CLDs) are major health problems that require complex and costly treatments. Liver-specific clinical outcome indicators (COIs) able to assist both clinicians and administrators in improving the value of care are presently lacking. The Value-Based Medicine in Hepatology (VBMH) study aims to fill this gap, devising and testing a set of COIs for CLD, that could be easily collected during clinical practice. Here we report the COIs generated and recorded for patients with HBV or HCV infection at different stages of the disease.

Methods/Results: In the first phase of VBMH study, COIs were identified, based on current international guidelines and literature, using a modified Delphi method and a RAND 9-point appropriateness scale. In the second phase, COIs were tested in an observational, longitudinal, prospective, multicentre study based in Lombardy, Italy. Eighteen COIs were identified for HBV and HCV patients. Patients with CLD secondary to HBV (547) or HCV (1391) were enrolled over an 18-month period and followed for a median of 4 years. The estimation of the proposed COIs was feasible

Abbreviations: AIH, autoimmune hepatitis; CLDs, chronic liver diseases; COIs, clinical outcome indicators; CPT, Child-Pugh-Turcotte; DAAs, direct-acting antivirals; DI, disagreement index; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; HH, hereditary haemochromatosis; MELD, model for end-stage liver disease; MPR, median panel rating; NUCs, nucleoside and nucleotide analogues; PBC, primary biliary cholangitis; peg-IFN, pegylated interferon; PSC, primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis; SVR, sustained virological response; VBMH, value-based medicine in hepatology.

Luca M. Munari, Lorenzo G. Mantovani and Luca S. Belli share last authorship.

H1.2009.0005417; The support of the Yale Liver Center, DK034989 Silvio O. Conte Digestive Diseases Research Core Centers, Clinical Core, is gratefully acknowledged.

Handling Editor: Janus Ong

in the real-word clinical practice and COI values compared well with literature data. Further, the COIs were able to capture the impact of new effective treatments like direct-acting antivirals (DAAs) in the clinical practice.

Conclusions: The COIs efficiently measured clinical outcomes at different stages of CLDs. While specific clinical practice settings and related healthcare systems may modify their implementation, these indicators will represent an important component of the tools for a value-based approach in hepatology and will positively affect care delivery.

KEYWORDS

cirrhosis, clinical outcome indicators, decompensated cirrhosis, hepatocellular carcinoma, hepatology, value-based Medicine

1 | INTRODUCTION

In the last three decades, the science and practice of hepatology have evolved into a highly complex discipline able to offer effective care for most acute and chronic liver diseases (CLDs). Despite the availability of preventative measures and therapeutic treatments, the prevalence of liver disease remains elevated, and in several geographic regions the burden of CLDs will be overwhelming as access to new treatments is limited and not universally sustainable. Treatment of liver cancer, end-stage liver disease or viral hepatitis requires costly surgical procedures and medications[1,2]; unfortunately, healthcare systems worldwide are facing serious sustainability problems that limit the access to these treatments. Several strategies are being followed to improve the sustainability of healthcare, but most of them revolve around cost-containment, reduced coverage and contraction in system capacity.[3]

Due to the necessity to treat a large population of patients with complex and costly therapies, as well as of the human and economic costs generated by negative outcomes,[1,2] hepatologists have become aware of the importance to closely monitor clinical outcomes of liver diseases. The use of systematic measurement of clinical outcome indicators (COIs) over an adequate period of observation would provide the information needed to activate the positive loop that drives practice improvement and cost reduction at the patient level.[4,5] Furthermore, the availability of a comprehensive set of COIs would represent a unique instrument in the set of tools needed for decision-making in the delivery of hepatology care.

A range of process indicators for liver disease is available[6,7]; these are proxy to the outcome, but they do not measure the actual outcomes achieved. The value of care is based on actual outcome metrics. This is becoming a major element in health decision-making, at every level, local practice, hospital, state and nationally. Assessment of the value of care requires several sets of data, that is, COIs, patient-reported outcomes and the cost of providing or failing to provide adequate care.[5]

Key points

- Chronic liver diseases (CLDs) are a major global health problem that requires complex and costly treatments to care for the patient.
- Liver-specific clinical outcome indicators (COIs) able to evaluate the whole cycle of care are needed to assist both clinicians and administrators in improving quality and value of care.
- This study has generated and tested a series of COIs that will be used to implement a value-based approach in hepatology and to guide decision-making for practitioners as well as for health authorities, and ultimately to improve the care of the patients affected by CLDs.

COIs should not relate to the single episode of care, but should be measured along the full cycle of treatment for a specific condition.[4,5] Furthermore, indicators should be easy to collect and focused on the outcome to avoid/achieve, rather than the intermediate steps. In order to measure clinical outcomes, properly designed indicators are therefore needed. Unfortunately, a comprehensive set of COIs for liver diseases able to capture the whole cycle of care is presently not available.

The Value-Based Medicine in Hepatology (VBMH) study aims to fill this gap, by devising and testing a set of COIs for several major liver conditions. The present paper focuses on patients with hepatitis B (HBV) and C (HCV) infection. Based on the available literature, current guidelines and the involvement of expert hepatologists, we generated and tested a set of indicators to monitor clinical outcomes for each different stages of CLDs (chronic hepatitis, compensated cirrhosis, decompensated cirrhosis and/or hepatocellular carcinoma (HCC)). While their values change according to local conditions, practices and healthcare systems, these indicators represent a critical tool to begin implementing a value-based approach in hepatology and guide decision-making by practitioners and by healthcare authorities.

2 | METHODS

2.1 | Design

The design of the VBMH study involved two phases. In Phase 1, a set of COIs was devised using a modified Delphi method. In Phase 2, the VBMH indicators were field tested.

2.2 | Generation of clinical outcome indicators

A modified four-step 'Delphi method' was adopted to generate COIs and consisted in a structured process[8,9] for each liver condition considered (chronic hepatitis B, chronic hepatitis C, cirrhosis compensated and decompensated), involving a focus group composed by a panel of hepatologists with proved experience (see Appendix S1 and Tables S1-S3). Focus group discussions took place between 2010 and 2011. A detailed description of the Delphi process adopted for this study is available in the Appendix S2.

2.3 | Assessment of feasibility and values of COIs

In this second phase of the VBMH study, the identified COIs were tested in an observational, longitudinal, prospective, multicentre study involving the liver units of three major healthcare centres located in Lombardy, Italy. The study was conducted in the San Gerardo Hospital – Monza (an academic medical centre), the Papa Giovanni XXIII Hospital – Bergamo (a non-academic centre with an active liver transplant program) and in the Niguarda Ca'Granda Hospital – Milan (non-academic medical centre with an active liver transplant program). These three hospitals serve a population of around 3 million people. The study protocol and informed consent forms were approved by the Ethics Committees of Azienda Ospedaliera – Niguarda Ca'Granda Hospital (Milan-Italy), of San Gerardo Hospital (Monza-Italy), and of Papa Giovanni XXIII Hospital (Bergamo-Italy). The study protocol is in agreement with the principles established by the 18th World Medical Assembly (Helsinki, 1964).

2.4 | Patients

From March 2011 to November 2012, all consecutive subjects carrying an established or new diagnosis of chronic HBV, chronic HCV, cirrhosis, HCC, NAFLD/NASH, hereditary haemochromatosis (HH), autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) were enrolled. Cirrhotic patients were classified as decompensated if they reported an event of decompensation (bleeding, hepatic encephalopathy, ascites) in the past, at enrolment or in the study period. All patients were treated following the Italian, European and American Associations for the Study of the Liver (AISF/EASL/AASLD) guidelines. In other words, patients were considered decompensated, independently of the fact that the episode of decompensation had regressed afterwards. In the present paper, we focus only on patients with HBV infection, HCV infection and related sequelae.

Diagnosis, treatments and follow-up visits were performed according to the local guidelines and standard of care protocols in each centre. In each centre the Section Chief and a Co-principal investigator oversaw the application of the current EASL/AASLD guidelines in the management of liver patients. Patients enrolled were older than 18 years and willing and able to sign an informed consent. Co-infected patients (HIV/HBV, HIV/HCV, HBV/HDV and HBV-DNA positive/HCV-RNA positive) were excluded from the study.

2.5 | Data collection

A web-based electronic medical record database was created and used to collect the clinical variables needed to generate the COIs design in the VBMH study. Information on socio-demographic and clinical data (diagnosis, date of diagnosis, liver functional parameters, diseases aetiology, previous and ongoing treatment, etc) were collected at baseline. Furthermore, during the follow-up period, clinical data, pharmacological treatments, diagnostic tests, surgical procedures and hospitalizations were collected when the patients accessed the centre, as per standard of care. Last extraction and data analysis were performed in March 2017.

2.6 | Statistical analysis

2.6.1 | Phase 1

For each proposed indicator, the level of agreement was assessed by the median panel rating (MPR) and the median disagreement index (DI). DI was computed as IPR/(IPRr + CFAxAI), where IPR is the inter-percentile range computed as the difference between the 75th and 25th percentile of all valid scores, IPRr is the inter-percentile range required for disagreement when perfect symmetry exists, AI is the asymmetry index computed as MPR-5 and CFA is the correction factor for asymmetry.[12] Optimal values for IPRr and CFA of 2.35 and 1.5 have been used in the above formula following empirical work on a 9-point scale.[13] We considered a COI as an appropriate measure of quality of care to be assessed if its median rating after the fourth step was between 7 and 9 without any disagreement, defined as a corresponding DI < 1.0.

2.6.2 | Phase 2

Baseline demographic and clinical characteristics for HCV and HBV patients enrolled in the VBMH study are expressed as percentages (%) for categorical variables and mean ± standard deviation for continuous variables.

The focus groups were tasked to select COIs easy to collect and applicable to every liver unit and based on the current understanding of the natural history of liver disease and evidence-based treatment guidelines.

Each COI was designed to provide information on the rate of occurrence of a single and well-defined outcome, independently from other outcomes. For example, the decompensation rate in

patients with compensated cirrhosis was assessed independently of the eventual development of HCC. Conversely, the incidence of HCC was assessed in all patients with cirrhosis (compensated and decompensated) by means of other outcome indicator. Based on this premise, and because the study aimed at measuring the actual achievement of an outcome, we choose not to adjust for competing outcomes. COIs assessing the probability of survival, viral suppression/eradication and hospitalization at predefined follow-up times were analysed through the Kaplan-Meier estimator, accounting for censoring. COIs focused on rates were estimated accounting for each subject's follow-up time. If required by the expert panel, COIs were also stratified by potential prognostic factors.

After closure of the enrolment period and 3 years into the follow-up, in January 2015 the direct-acting antivirals (DAAs) treatment became available in Italy for the treatment of HCV hepatitis. Therefore, the identified COIs were used to assess the impact of DAAs in HCV-related liver disease. Because of the radical changes in the efficacy and tolerability of HCV treatment, we report here only COI observed in the DAAs era (ie focusing only on HCV-positive patients on 1 January 2015).

Analyses were performed with SAS 9.4 (SAS Institute) and R-software (R Development Core Team, 2008).

3 | RESULTS

3.1 | Phase 1. Clinical outcome indicators (COIs)

The proposed COIs are presented, following a sequence designed along the progression of liver disease related to HBV or HCV infection, that is, from chronic hepatitis to compensated and decompensated cirrhosis and/or HCC. Each step represents an outcome that should be avoided, but also a condition that requires specific management to prevent further progression. The selected COIs, their internal median score achieved during the rounds of ratings and associated DI value are shown in Table 1. Levels of evidence for each indicator, derived from available published literature according to Oxford Centre for Evidence-Based Medicine,[13] are also reported when available. Indicators are shown following the rank assigned at the conclusive meeting. Tables S4-S12 report all COIs proposed by the focus groups and the formulation of the finally selected ones (Table 1). Each COI selected for the validation study was reviewed and justified based on the current literature and discussed in Appendix S3.

3.2 | Phase 2. Assessment of COIs values

A total of 3182 patients were enrolled in the whole VBMH study. For the purpose of this analysis, 2080 consecutive patients with HBV or HCV infection were analysed. HBV-related liver disease was defined by the presence of HBsAg or HBV-DNA in the serum. According to this definition, 547 patients had HBV-related disease; 234 (42.8%) were cirrhotic and 111 (20.3%) had HCC at the time of recruitment. In 1533 HCV-Ab-positive patients, 1391 also were HCV-RNA-positive (90.7%); 851 (55.5%) were cirrhotic and 336 (21.9%) had HCC at the time of recruitment. At the time of the last analysis, in March 2017, median follow-up time was 4.4 years (Q1-Q3: 2.2-5.0) for the HBV cohort and 3.7 years (Q1-Q3: 1.7 4.8) for the HCV cohort.

The baseline characteristics of HBV and HCV patients are reported in Table 2. The calculated values of each COI related to patients with HBV or HCV infection are reported in Tables 3 and 4 respectively.

4 | HBV

During the study follow-up, 353 HBV patients (64.53%) were treated with nucleoside and nucleotide analogues (NUCs). In HBV patients on treatment with NUCs for at least 12 months, 92.7% achieved viral suppression, (defined as HBV-DNA <12 IU/mL) at 3 years of follow-up (indicator 1) (Table 3).

Yearly incidence rate of HCC (indicator 3) was 1.46 per 100 person-years, which is comparable with literature studies.[14] The estimated cumulative HCC incidence was 2.3% at 1 year, 5.1% after 3 years and 6.3% after 5 years. In the 23 HCC incident cases, 69.6% were diagnosed at an early stage (BCLC 0/A); all of them were being treated with NUCs. In HBV-positive patients group, 79 (14.4%) died and 29 (5.3%) received a liver transplant (indicator 4). As the aim of the treatment is preventing death or transplantation, the yearly incidence rate of negative outcomes in HBV-infected patients was 5.59 per 100 person-years and the estimated cumulative incidence was 9.3%, 18.4% and 22.5% at 1, 3 and 5 years respectively. Among the 79 patients who died without a transplant, 58 had HCC, while in 15 cases the cause of death was not liver-related.

4.1 | Compensated cirrhosis HBV

The yearly decompensation rate in cirrhotic HBV patients (and indicator 11) was 2.24 per 100 person-year, and the estimated cumulative decompensation rate was 1.8% at 1 year, 7.1% at 3 years and 9.9% at 5 years, consistent with the literature[10,14]; of the patients who experienced a decompensation, 84.6% were in treatment with NUCs. Seven patients with cirrhosis had a Child-Pugh-Turcotte (CPT) ≥ B7 and were treated with NUC for a minimum of 6 months; among them, one patient improved his functional status (indicator 2), with at least a two points decrease in CPT score. There were no variceal bleedings (indicator 12) during follow-up.

The indicator 13a reported a yearly HCC incidence rate of 3.73 per 100 person-years, in line with literature.[15,16] Seventy-one per cent of incident HBV-HCC were detected at an early stage (BCLC 0/A) (indicator 13b) and therefore potentially amenable to curative treatment.

4.2 | Decompensated cirrhosis HBV

Cirrhotic patients were classified as decompensated at enrolment if they reported an event of decompensation (bleeding, hepatic

TABLE 1 COIs established by the focus groups

Condition	No	Indicator	Rank	DI	Level of evidence (CEBM-Oxford)
HBV chronic hepatitis	1	Viral suppression rate in HBV-treated patients	9	0	1b
	2	Functional improvement in HBV-treated cirrhotic patients	7	0.37	2b
	3	Incidence of HCC in HBV patients	9	0.12	2a
	4	Rate of mortality or liver transplantation in HBV	9	0.12	2c
HCV chronic hepatitis	5	SVR in HCV patients	9	0.12	2b
	6	SVR in HCV-related compensated cirrhosis	9	0	2b
	7	SVR in HCV-related decompensated cirrhosis	na	na	2b
	8	Functional improvement in HCV-treated cirrhotic patients	na	na	1b
	9	Incidence of HCC in HCV patients	na	na	1a
	10	Rate of mortality or liver transplantation in HCV	na	na	1a
Compensated cirrhosis	11	Rate of decompensation	9	0	1a
	12	Variceal bleeding rate	9	0	1a
	13a	Incidence of HCC in compensated cirrhosis	9	0.12	2b
	13b	Efficacy of surveillance (diagnosis in BCLC tumor stage 0/A)			
Decompensated cirrhosis	14	Overall survival at 1 and 3 y stratified by CPT and MELD score at recruitment and after decompensation among patients without prevalent HCC	9	0	1a
	15	Survival after variceal bleeding	9	0.12	2b
	16	Annual recurrence of variceal bleeding	9	0	1b
	17a	Survival after SBP	9	0.12	1b
	17b	Annual recurrence of SBP	9	0	1b
	18	Hospital readmission rate and length of hospital stay	7	0.37	2b

Abbreviations: BCLC, Barcelona clinic liver cancer; CPT, Child-Pugh-Turcotte; DI, disagreement index; HBV, chronic hepatitis B infection; HCC, hepatocellular carcinoma; HCV, chronic hepatitis C infection; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; SVR, sustained virological response; na, not available: outcome indicators added after the conclusion of the focus groups, following the introduction of new direct-acting antiviral agents.

encephalopathy, ascites) before or at enrolment (therefore, these patients were considered decompensated at enrolment even if the episode of decompensation had regressed), otherwise, patients were considered decompensated from the time the first complication occurred during the study period.

Among the recruited HBV cirrhotic patients, 61 were classified as decompensated without HCC. Table 3 reports the values and the observed survival for the four dimensions of indicator 16. Indicator 14a shows a 3-year survival of 84.7% of patients for CPT A and 66.0% for CPT B, while the indicator 14b shows a 3-year survival of 87.1% for patients with model for end-stage liver disease (MELD) ≤15 and 28.6% for those with MELD >15. Indicator 14c and indicator 14d were not calculated because only a few patients with HBV were reported in CPT B, CPT C and in MELD >15 categories.

As concerns indicators 15 and 16, only three patients experienced variceal bleeding during follow-up and mortality was absent at 6 weeks, indicating that when international guidelines for prevention and treatment are followed and patients undergo aetiological treatment of the underlying liver disease, the incidence of complications that were once considered life threatening can be successfully controlled. Regarding the efficacy of the acute management of spontaneous bacterial peritonitis (SBP), the indicators tested (indicators 17a and 17b) compared favourably with the literature[17,18] although the number of events was low (Table 3). The indicator examining the probability of readmission at 1 year was 43.8% (indicator 18), better than the results reported in the latest literature,[19-21] although median time of hospitalization was longer.[22]

5 | HCV

Among 1391 patients with positive HCV-RNA at enrolment, 353 patients (23.0%) died and 102 (6.7%) received a liver transplant with a yearly rate of mortality or liver transplantation of 9.43 per 100 person-years. Of the 353 patients who died without a transplant, 239 had HCC, and for 61 (17%) the cause of death was not liver-related. Finally, in 1197 HCV patients who were HCC-negative at enrolment, 138 incident cases of HCC were subsequently registered, and 135 of them (98%) were diagnosed in patients with an established diagnosis of cirrhosis. Seventy-seven per cent were diagnosed at an early stage (BCLC 0/A). The yearly incidence rate of HCC was 3.62 per 100 person-year. These figures, however, include two distinct periods in the history of HCV treatment. In fact,

TABLE 2 Descriptive statistics of patients selected for the analysis

	All patients	HBV	HCV
Patients enrolled	2080	547	1533
Follow-up time in years			
Mean (STD)	3.37 (1.79)	3.66 (1.79)	3.27 (1.77)
Median (Q1-Q3)	3.94 (1.84-4.94)	4.39 (2.21-5.04)	3.74 (1.73-4.83)
Age, years			
Mean (STD)	60 (13)	59 (12)	61 (13)
Median (Q1-Q3)	61 (50-71)	60 (51-67)	62 (50-72)
Missing	2 (0.10%)	0 (0.00%)	2 (0.13%)
Sex			
M	1325 (63.70%)	409 (74.77%)	916 (59.75%)
F	755 (36.30%)	138 (25.23%)	617 (40.25%)
BMI, kg/m^2 at inclusion in the study			
Mean (STD)	25.43 (3.91)	25.44 (3.96)	25.42 (3.90)
Median (Q1-Q3)	25.16 (22.83-27.58)	25.34 (23.03-27.47)	25.14 (22.77-27.64)
Missing	5 (0.24%)	0 (0.00%)	5 (0.33%)
HBsAg-positive at inclusion in the study			
Yes	—	512 (93.60%)	—
No	—	35 (6.40%)	—
HCVRNA-positive at inclusion in the study			
Yes	—	—	1391 (90.74%)
No	—	—	142 (9.26%)
HCV Genotype			
1	—	—	671 (43.77%)
2	—	—	276 (18.00%)
3	—	—	129 (8.41%)
4	—	—	115 (7.50%)
Not typed	—	—	342 (22.31%)
Patients with cirrhosis			
Prevalent cases at inclusion in the study	1085 (52.16%)	234 (42.78%)	851 (55.51%)
Incident cases during follow-up	118 (5.67%)	18 (3.29%)	100 (6.52%)
Aetiology of cirrhosis			
HBV	200 (9.62%)	200 (79.37%)	—
HBV + alcohol	52 (2.50%)	52 (20.63%)	—
HCV	758 (36.44%)	—	758 (79.71%)
HCV + alcohol	193 (9.28%)	—	193 (20.29%)
Patients with HCC			
Prevalent cases at inclusion in the study	447 (21.49%)	111 (20.29%)	336 (21.92%)
Incident cases during follow-up	161 (7.74%)	23 (4.20%)	138 (9.00%)
Patients with CC			
Prevalent cases at inclusion in the study	716 (34.42%)	152 (27.79%)	564 (36.79%)
Incident cases during follow-up	110 (5.29%)	17 (3.11%)	93 (6.07%)
CPT of CC patients at inclusion in the study[a]			
A	789 (95.52%)	165 (97.63%)	624 (94.98%)
B	35 (4.24%)	4 (2.37%)	31 (4.72%)
C	1 (0.12%)	0 (0.00%)	1 (0.15%)

(Continues)

TABLE 2 (Continued)

	All patients	HBV	HCV
Missing	1 (0.12%)	0 (0.00%)	1 (0.15%)
Patients with DC[b]			
Prevalent cases at inclusion in the study	369 (17.74%)	82 (14.99%)	287 (18.72%)
Incident cases during follow-up	167 (8.03%)	14 (2.56%)	153 (9.98%)
CPT of DC[b] patients at inclusion in the study[c]			
A	200 (37.31%)	44 (45.83%)	156 (35.45%)
B	260 (48.51%)	36 (37.50%)	224 (50.91%)
C	59 (11.01%)	15 (15.63%)	44 (10.00%)
Missing	17 (3.17%)	1 (1.04%)	16 (3.64%)
MELD of DC[b] patients at inclusion in the study[c]			
≤15	402 (75.00%)	69 (71.88%)	333 (75.68%)
>15	71 (13.25%)	13 (13.54%)	58 (13.18%)
Missing	63 (11.75%)	14 (14.58%)	49 (11.14%)

Abbreviations: BMI, body mass index; CC, compensated cirrhosis; CPT, Child-Pugh-Turcotte; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; Q1-Q3, 1st quartile – 3rd quartile; STD, standard deviation.

[a]% computed on patients with CC.

[b]Cirrhotic patients were classified as decompensated if they reported a decompensation event (bleeding, hepatic encephalopathy, ascites) in the past, at enrolment or in the study period.

[c]% computed on patients with DC.

in 2015, the highly effective and tolerable DAA treatments became available in Italy and radically changed the management and the expected outcome of patients with HCV-related liver disease. The HCV COIs estimated referring to the entire observation period (interferon and DAAs eras combined) are shown in Table S13. Here we will focus on COIs data acquired from January 2015 onward. (Table 4) Among 725 patients with positive HCV-RNA present in January 2015, 35.9% achieved a sustained virological response (SVR) (by 2 years from DAA approval) (Indicator 5a) and this figure quickly rose to 68.0% by the end of the study (by 2 years and 3 months of follow-up) (Figure 1A), as access to DAA increased. Of the treated patients, 89.7% achieved an SVR (Indicator 5b). Among the 369 patients with positive HCV-RNA and compensated cirrhosis (CC), 45.8% achieved a SVR by 2 years of the DAA approval (Indicator 6a) and 73.0% by the end of the study (after 2 years and 3 months of follow-up) (Figure 1B); 90.4% of treated patients achieved an SVR (Indicator 6b). Among 151 patients with positive HCV-RNA and decompensated cirrhosis (DC), 45.0% achieved a SVR by 2 years of DAA approval (Indicator 7a) and 53.0% achieved SVR by the end of the study (Figure 1C); 88.7% of treated patients achieved (Indicator 7b). Since 2015, the yearly HCC incidence rate (x100 person-years) was 5.25 (3.91-6.90) (Indicator 9) and the yearly rate of mortality or liver transplantations (x100 person-years) was 8.39 (6.85 - 10.18) (indicator 10).

5.1 | Compensated cirrhosis HCV

The yearly decompensation rate in patients with compensated HCV cirrhosis (indicator 11) was 4.74 per 100 person-year, and the estimated cumulative decompensation rate was 4.4% at 1 year, and 7.7% at 2 years. Eight patients with cirrhosis had a CPT ≥ B7 and initiated a treatment; among them 25.0% improved their functional status (indicator 8), with at least a two points decrease in CPT score. The yearly rate of first variceal bleeding (x100 person-years) was1.62 (0.33-4.74) (indicator 12). Indicator 13a reported a yearly HCC incidence rate of 8.05 per 100 person-years. Eighty-eight per cent of incident HCV-HCC were detected at an early stage (BCLC 0/A) (indicator 13b) and therefore potentially amenable to curative treatment.

5.2 | Decompensated cirrhosis HCV

In patients with decompensated HCV cirrhosis, indicator 14a shows a 2-year survival of 86.4% in patients for CPT A and of survival 79.1% for CPT B; while indicator 14b shows a 2-year survival of 83.1% for patients with MELD ≤15 and 57.1% for those with MELD >15. Indicator 14c and indicator 14d reported no informative results because of the low number of patients who developed a decompensated cirrhosis during the follow-up.

As concerns indicators 15 and 16, only four patients experienced variceal bleeding during follow-up and mortality was absent at 6 weeks, again indicating that when international guidelines for prevention and treatment are followed and patients undergo aetiological treatment of the underlying liver disease, the incidence of complications that were once considered life threatening can be successfully controlled. Regarding the efficacy of the acute management of SBP, the indicators tested (indicators 17a and 17b) were not calculated because only one patients reported SBP (Table 3). The indicator examining the probability of readmission at 1 year was 39.8% (indicator 18).

TABLE 3 Outcome indicators measured in the VBMH study on HBV patients

Condition	No		Description			Value (95% CI)	No of patients involved
HBV	1		Probability of viral suppression* (from treatment initiation)		1 y	53.5% (42.4%-65.4%)	76[a]
					2 y	85.5% (75.8%-92.8%)	
					3 y	92.7% (83.4%-97.8%)	
	2		Patients under treatment for at least 6 mo, with CPT score ≥ B7 at enrolment, showing an improvement of CPT score of at least two points within 1 y			14.29%	7
	3		Yearly HCC incidence rate x100 person-years			1.46 (0.92-2.19)	436[b]
			Patients diagnosed with BCLC 0/A among incident cases			69.57%	23
	4		Yearly rate of mortality or liver transplantation x100 person-years			5.59 (4.59-6.75)	547
HBV + Compensated cirrhosis	11		Yearly decompensation rate (x100 person-years)			2.24 (1.19-3.84)	169
	12		Yearly rate of first bleeding (x100 person-years)			0.00 (0.00-0.00)	57[c]
	13	13a	Yearly HCC incidence rate (x100 person-years)			3.73 (2.04-6.25)	107[d]
		13b	Patients diagnosed with BCLC 0/A among incident cases			71.43%	14
HBV + Decompensated cirrhosis	14	14a[e]	Survival probability (from enrolment)	CPT A	1 y	91.2% (75.0%-97.1%)	35
					3 y	84.7% (67.0%-93.4%)	
				CPT B	1 y	66.0% (41.6%-82.2%)	22
					3 y	66.0% (41.6%-82.2%)	
				CPT C	1 y	71.4% (25.8%-92.0%)	7
					3 y	71.4% (25.8%-92.0%)	
		14b[e]	Survival probability (from enrolment)	MELD ≤15	1 y	92.4% (78.3%-97.5%)	40
					3 y	87.1% (71.6%-94.4%)	
				MELD >15	1 y	28.6% (4.1%-61.2%)	7
					3 y	28.6% (4.1%-61.2%)	
		14c[f]	Survival probability (from decompensation)[g]	CPT A	1 y	NA	3
					3 y	NA	
				CPT B	1 y	NA	3
					3 y	NA	
				CPT C	1 y	NA	0
					3 y	NA	
		14d[f]	Survival probability (from decompensation)[g]	MELD ≤15	1 y	100.0% (100.0%-100.0%)	4
					3 y	100.0% (100.0%-100.0%)	
				MELD >15	1 y	NA	1
					3 y	NA	
	15		Survival probability at 6 wks (from the first episode of bleeding)			100.0% (100.0%-100.0%)	3[h]
	16		Probability of bleeding recurrence at 1 y (from the first episode of bleeding)			0.0% (0.0%-0.0%)	
	17	17a	Survival probability at 6 wks (from the first episode of SBP)			100.0% (100.0%-100.0%)	3[i]
		17b	Probability of SBP recurrence at 1 y (from the first episode of SBP)			0.0% (0.0%-0.0%)	

(Continues)

TABLE 3 (Continued)

Condition	No	Description	Value (95% CI)	No of patients involved
	18	Probability of re-admission at 1 y (after the first hospitalization, excluding DH)	43.8% (22.4%-72.8%)	20
		Median length of stay per admission (excluding DH) (IQR)	15.5 (8-21.5)	

Abbreviations: BCLC, Barcelona clinic liver cancer; CC, compensated cirrhosis; CPT, Child-Pugh-Turcotte score; DH, Day Hospital; MELD, model for end-stage liver disease; NA, Not Applicable; SBP, spontaneous bacterial peritonitis.
[a]All HBV patients with HBVDNA ≥12 IU/mL at enrolment and starting a treatment during the study time.
[b]All HBV patients without HCC at the beginning of the observation.
[c]All HBV-CC patients with varices at the beginning of the observation.
[d]All HBV-CC patients without HCC at the beginning of the observation.
[e]All HBV-DC patients without HCC at the beginning of the observation.
[f]All HBV-DC patients with the episode of decompensation during the study time and no HCC at decompensation.
[g]Child/MELD registered at the first visit after decompensation.
[h]All HBV-DC patients with at least one episode of variceal bleeding.
[i]All HBV-DC patients with at least one episode of SBP.
*The date of viral suppression is considered at the time of the follow-up visit when it was first registered.

6 | DISCUSSION

To our knowledge, this is the first study aimed at generating and testing a comprehensive set of indicators able to capture COIs at different stages of CLDs caused by viral hepatitis. COIs were generated through a modified Delphi method and a RAND 9-points appropriateness scale. These COIs were then tested in practice in a large cohort of patients with CLDs related to HCV or HBV infection enrolled in a multicentre prospective observational study. About half of these patients were cirrhotic (43% in HBV and 55% in HCV), reflecting the case mix of hepatology referral centres. The study shows that the majority of proposed COIs were easy to collect and their values compared well with the available literature data. The actual values of the VBMH COIs measured in this work will eventually change according to local conditions, practices, healthcare systems and development of new treatments. It is therefore important to create a reference value for each COI, specific for each specific healthcare systems and local context.

These indicators represent a necessary tool to implement a value-based approach to patients with CLDs, improve quality and value of care and eventually to guide the decision- and policy-making process. This methodology can also be applied with ad hoc modifications to other progressive CLDs.

The approach of our study is novel, as currently available studies focus on process indicators,[6,7] rather than on strong clinical outcomes associated with the progression of liver disease. To have an impact on quality of clinical care and on decision-making, COIs should be generated from data obtained during the real-life practice; they should also be easy to collect and measure. The COIs should also capture the whole cycle of care.[4,5] Focus groups were charged with the challenge to suggest COIs that responded to the above criteria and to avoid excessive granularity in outcomes. Each hepatology centre can further stratify the reported COI according to local epidemiology, practice and interests. For example, the PAGE-B score may predict the risk of HCC development in the HBV population and could be a reference to compare the measured COI value for indicator 3. Age and other comorbidities, such as obesity or diabetes, may increase the risk, and again may be used to more thoroughly stratify the COI. It is important to underline that the COIs do not predict the risk in an individual patient, but simply measure the outcomes in a population of patients.

There are several obstacles in generating COIs for CLDs, mainly due to the long clinical course of the diseases. The ideal approach would be to measure only hard outcomes, such as HCC incidence, transplantation or death, but given the slow progression of CLDs, surrogate endpoints with a proven ability to predict hard outcomes, such as SVR and viral suppression, were an inescapable choice. We generated COIs for each defined stage of CLDs: chronic hepatitis, compensated cirrhosis and decompensated cirrhosis[23,24]; this represents a simpler model than the recent more complex model proposed by D'Amico et al[25]; however, it serves our purpose of collecting real-life rates of specific outcomes in the field.

One of the aims of the VBMH study was to assess the feasibility of collecting the data necessary to calculate the COIs in the clinical practice. Collecting outcome data for the prospective study required the following: all physicians were instructed about the elements to be included in their clinical reports; in each unit, a research assistant transferred the relevant data into the electronic database specifically created for the study. Being this a research study, physicians also acquired the informed consent at enrolment. We expect this effort will become much less significant because of the widespread and increasing use of electronic medical records (EMR). Once the EMR is adjusted to collect the relevant information, these will be built in the practice routine and for the major part, the database will self-populate. Based on the result of our study, the collection of data was feasible for many COIs, although in the setting of HBV patients with advanced cirrhosis some of the COIs could not work due to the

TABLE 4 Outcome indicators measured in the VBMH study on HCV patients in the DAAs era (from January 1, 2015)

Condition	No		Description			Value (95% CI)	No of patients involved
HCV	5	5a	Probability of achieving SVR* among the whole HCV cohort (from January 01, 2015)		2 y	35.9% (30.7%-41.7%)	725
		5b	Probability of achieving SVR* in treated HCV patients			89.7% (83.7%-94.2%)	226
	6	6a	Probability of achieving SVR* among HCV patients with CC (from January 01, 2015)		2 y	45.8% (38.2%-54.3%)	369
		6b	Probability of achieving SVR* in treated HCV patients with CC			90.7% (83.6%-95.6%)	159
	7	7a	Probability of achieving SVR* among HCV patients with DC (from January 01, 2015)		2 y	45.0% (32.2%-60.2%)	151
		7b	Probability of achieving SVR* in treated HCV patients with DC			88.7% (73.8%-97.1%)	44
	8		Patients starting treatment, with CPT score ≥ B7 at enrolment, showing an improvement of CPT score of at least two points within 1 y			25.00%	8
	9		Yearly HCC incidence rate (x100 person-years)			5.25 (3.91-6.90)	679[a]
			Patients diagnosed with BCLC 0/A among incident cases			84.31%	138
	10		Yearly rate of mortality or liver transplantations (x100 person-years)			8.39 (6.85-10.18)	836
HCV + Compensated cirrhosis	11		Yearly decompensation rate (x100 person-years)			4.74 (3.07-7.00)	365
	12		Yearly rate of first bleeding (x100 person-years)			1.62 (0.33-4.74)	132[b]
	13	13a	Yearly HCC incidence rate (x100 person-years)			8.05 (5.54-11.31)	291[c]
		13b	Patients diagnosed with BCLC 0/A among incident cases			87.88%	33
HCV + Decompensated cirrhosis	14	14a[d]	Survival probability (from January 01, 2015)	CPT A	6 mo	94.4% (79.5%-98.6%)	39
					1 y	91.2% (75.0%-97.1%)	
					2 y	86.4% (66.6%-94.9%)	
				CPT B	6 mo	90.2% (75.9%-96.2%)	45
					1 y	82.2% (66.2%-91.1%)	
					2 y	79.1% (62.4%-89.0%)	
				CPT C	6 mo	NA[g]	2
					1 y	NA[g]	
					2 y	NA[g]	
		14b[d]	Survival probability (from January 01, 2015)	MELD ≤15	6 m	93.5% (83.6%-97.5%)	67
					1 y	88.0% (76.4%-94.1%)	
					2 y	83.1% (69.5%-91.0%)	
				MELD >15	6 mo	71.4% (25.8%-92.0%)	8
					1 y	57.1% (17.2%-83.7%)	
					2 y	57.1% (17.2%-83.7%)	

(Continues)

TABLE 4 (Continued)

Condition	No		Description			Value (95% CI)	No of patients involved
		14c[e]	Survival probability (from decompensation)[f]	CPT A	6 mo	100.0% (100.0%-100.0%)	7
					1 y	100.0% (100.0%-100.0%)	
					2 y	NA	
				CHILD B	6 mo	100.0% (100.0%-100.0%)	7
					1 y	66.7% (5.4%-94.5%)	
					2 y	NA	
				CHILD C	6 mo	NA[g]	0
					1 y	NA[g]	
					2 y	NA[g]	
		14d[e]	Survival probability (from decompensation)[f]	MELD ≤15	6 mo	100.0% (100.0%-100.0%)	12
					1 y	100.0% (100.0%-100.0%)	
					2 y	NA	
				MELD >15	6 mo	NA[g]	2
					1 y	NA[g]	
					2 y	NA[g]	
	15		Survival probability at 6 wks (from the first episode of bleeding)			100.0% (100.0%-100.0%)	4[h]
	16		Probability of bleeding recurrence at 1 y (from the first episode of bleeding)			0.0% (0.0%-0.0%)	
	17	17a	Survival probability at 6 wks (from the first episode of SBP)			NA[i]	1[j]
		17b	Probability of SBP recurrence at 1 y (from the first episode of SBP)			NA[i]	
	18		Probability of re-admission at 1 y (after the first hospitalization, excluding DH)			39.8% (17.8%-73.3%)	25
			Median length of stay per admission (excluding DH) (IQR)			12.5 (9.5-18)	

Note: The COIs in the table were estimated in the patients with HCV-RNA-positive when DAAs become available in Italy (January 01, 2015). The COIs were estimated considering as baseline January 01, 2015. The follow-up time considered for estimating COIs was from January 01, 2015 to March 31, 2017.

Abbreviations: BCLC, Barcelona clinic liver cancer; CC, compensated cirrhosis; CPT, Child-Pugh-Turcotte score; DC, decompensated cirrhosis; DH, day hospital; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; SVR, sustained virological response.

[a]All HCV patients without HCC at January 01, 2015.

[b]All HCV-CC patients with varices at January 01, 2015.

[c]All HCV-CC patients without HCC at January 01, 2015.

[d]All HCV-DC patients without HCC at January 01, 2015.

[e]All HCV-DC patients with the episode of decompensation during the study time and no HCC at the moment of decompensation.

[f]Child/MELD registered at the first visit after decompensation.

[g]Not Applicable because only two patients can be included in the COI estimation.

[h]All HCV-DC patients with at least one episode of variceal bleeding.

[i]Not applicable because only one patient can be included in the COI estimation.

[j]All HCV-DC patients with at least one episode of SBP.

*The date of SVR is considered to be the date of the follow-up visit where the suppression is noted for the first time.

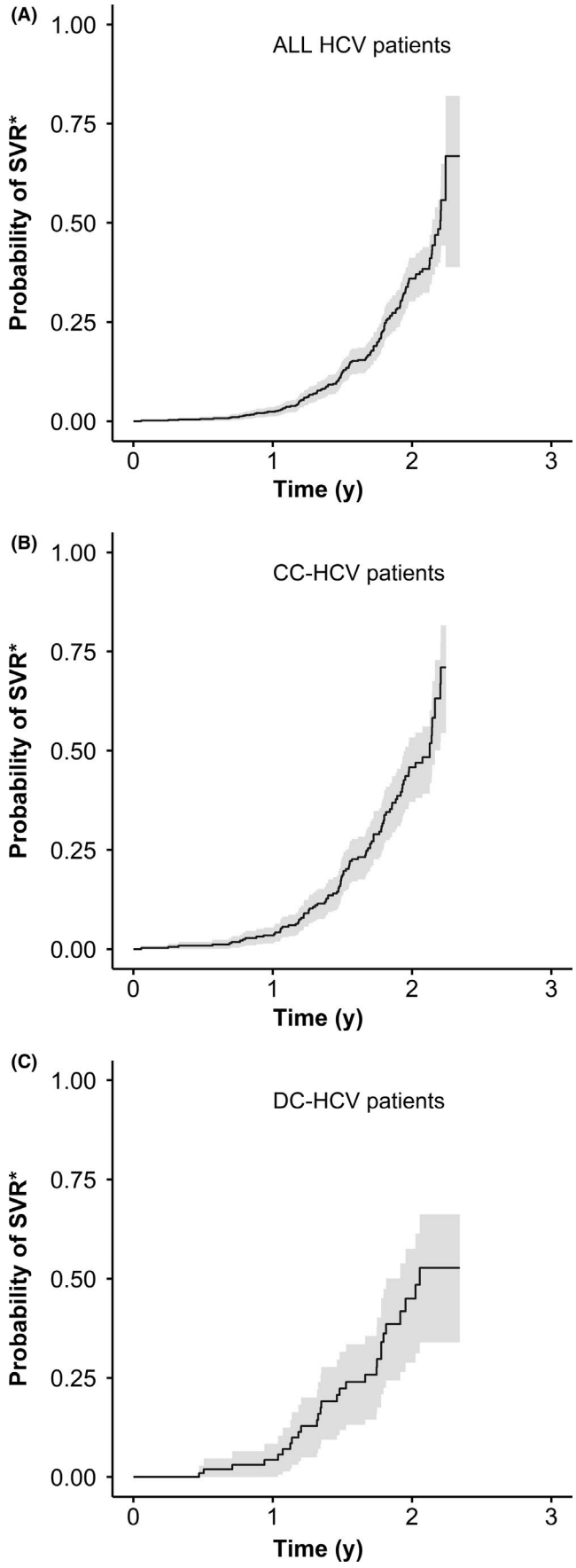

FIGURE 1 Probability of SVR among HCV patients during the DAA era (From January 01, 2015 to March 31, 2017): A, all patients (indicator 5a), B, compensated cirrhotic patients (indicator 6a), C, decompensated cirrhotic patients (indicator 7a). The light grey represent the confidence intervals. *The date of SVR is considered to be the date of the follow-up visit in which viral suppression is noted for the first time

very low number of clinical events. This is to be related to the high efficacy of NUC which have been able to prevent the progression of HBV to a more advanced stage.

COIs should also be sensible to novel treatment opportunities. For example, in chronic viral hepatitis related to HBV and HCV infection, aetiological treatment is effective and determines a significant reduction in the progression to cirrhosis and its complications.[26-28] Our data show that following the introduction of the DAAs, the proposed COIs were sensitive to the new therapeutic scenario and they could rapidly capture the impact of DAAs treatment on the clinical outcomes of patients with HCV infection. For example, the percentage of the whole population of HCV-RNA-positive patients achieving SVR was 3.9% before introduction of DAAs, while it significantly and very rapidly increased to 35.9% (indicator 5) by 2 years after DAAs became available. This percentage would be higher if not for the initial restriction to access. In fact, during the time of the observation, the regulatory agency only allowed DAA treatment for patients with cirrhosis. Clearly, with the new eradication policies, the value of indicators 5 and 10 will significantly improve. This example underscores an important concept: the value of each COI changes with time, therapeutic improvements, regulatory landscape. It is therefore important to monitor and revise them continuously. Our study demonstrates that even with a relatively short follow-up, the COIs were able to easily capture the strong impact of treatment innovation on the decompensation rate, the overall incidence of HCC in patients with cirrhosis and most importantly on the overall probability of death or liver transplantation of patients with HCV. These results will further improve over time, similar to what happened for patients with HBV cirrhosis after the introduction of NUC therapy.[10,11] Again, this demonstrates that COIs can be adapted to capture the impact of advances in treatments. It is important to underline again that while the formulation of the different COIs remains valid at least in Europe and USA (as they have been derived based on the guidelines of EASL and AASLD), their actual numeric value will be influenced by the local conditions and healthcare policies. Having said that, it is reassuring that the values we measured were very close to those expected from the literature.

In conclusion, using a well-structured scientific method, we tested a comprehensive set of COIs that represent a critical tool to implement a value-based approach in patients with CLDs. Monitoring outcomes at a specific centre is necessary to implement programs of quality improvement and clinical redesign projects, but also for clinical practice. It enables clinicians to learn

from their own results. Only by regularly measuring these results, clinicians can understand in an objective way if appropriate and effective care is being delivered and where and how to implement quality or effectiveness improvement cycles. As underlined by Porter and Teisberg, the mere collection of the data is enough to jump-start the improvement cycle. Or, in other words, you cannot improve what you do not measure. We believe these COIs will prove to be a useful clinical tool. In time and with their use they will be modified, adapted and improved, but hopefully these changes will be promoted by clinicians.

This work is also preparatory to the implementation for the value-based medicine principles in the field of hepatology. Proposed by Porter and Teisberg,[4] this approach re-orients competition and decision-making in healthcare along its most important aspect: the 'value' of the care for the patient. No matter how simple and obvious this statement may seem, its implications are enormous for the patients, for physicians and for the society. Implementation of value-based hepatology requires data. Hepatologists can do little to provide data for the costs analysis, the denominator of the 'value' equation,[5] but they are instrumental to generate and monitor the outcomes that represent the numerator of the value medicine formula.

CONFLICT OF INTEREST

Mario Strazzabosco reports Advisory Boards rds dor Bayer, Esiai/Merk and Engitix; Dr Fagiuoli reports speaker's bureau for Gilead science, Merck-Sharp & Dome, Abbvie Janssen, and Bristol-Meyer-Squibb, outside the submitted work. The other authors declare no conflict of interest.

ORCID

Mario Strazzabosco https://orcid.org/0000-0002-1995-6331
Paolo A. Cortesi https://orcid.org/0000-0001-5241-4473
Stefano Okolicsanyi https://orcid.org/0000-0003-1189-5631
Luca Fabris https://orcid.org/0000-0001-8538-6317
Luca S. Belli https://orcid.org/0000-0001-8714-2439

REFERENCES

1. Mantovani LG, Strazzabosco M. Healthcare costs associated with hepatocellular carcinoma and the value of care. *Hepatology*. 2013;58(4):1213-1214.
2. Mantovani LG, Cortesi PA, Strazzabosco M. Effective but costly: how to tackle difficult trade-offs in evaluating health improving technologies in liver diseases. *Hepatology*. 2016;64(4):1331-1342.
3. Strazzabosco M, Allen JI, Teisberg EO. Value based care in hepatology. *Hepatology*. 2017;65(5):1749-1755.
4. Porter ME, Olmsted-Teisberg E. *Redefining Health Care: Creating value-based competition on results*. Boston: Harvard Business School Press; 2006.
5. Porter ME. What is value in health care? *N Engl J Med*. 2010;363(26):2477-2481.
6. Kanwal F, Schnitzler MS, Bacon BR, Hoang T, Buchanan PM, Asch SM. Quality of care in patients with chronic hepatitis C virus infection: a cohort study. *Ann Intern Med*. 2010;153(4):231-239.
7. Kanwal F, Kramer J, Asch SM, et al. An explicit quality indicator set for measurement of quality of care in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2010;8(8):709-717.
8. Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. *PLoS ONE*. 2011;6(6):e20476-e20479.
9. Rowe G, Wright G. The Delphi technique as a forecasting tool: issues and analysis. *Int J Forecasting*. 1999;15:353-375.
10. Zoutendijk R, Reijnders JGP, Zoulim F, et al. Virological response to entecavir is associated with a better clinical outcome in chronic hepatitis B patients with cirrhosis. *Gut*. 2013;62(5):760-765.
11. Shim JH, Lee HC, Kim KM, et al. Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol*. 2010;52(2):176-182.
12. Fitch K, Bernstein SJ, Aguilar MD, et al. *The RAND/UCLA Appropriateness Method User's Manual*. Santa Monica: RAND; 2001.
13. Oxford Centre for Evidence Based Medicine. Levels of Evidence and Grades of Recommendation; updated March 2009. http://www.cebm.net/index.aspx?o=1025.
14. Papatheodoridis GV, Chan HL-Y, Hansen BE, Janssen HLA, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J Hepatol*. 2015;62(4):956-967.
15. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004;127(5 Suppl 1):S35-S50.
16. Santi V, Buccione D, Di Micoli A, et al. The changing scenario of hepatocellular carcinoma over the last two decades in Italy. *J Hepatol*. 2012;56(2):397-405.
17. Chalasani N, Kahi C, Francois F, et al. Improved patient survival after acute variceal bleeding: a multicenter, cohort study. *Am J Gastroenterol*. 2003;98(3):653-659.
18. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341(6):403-409.
19. Bajaj JS, Reddy KR, Tandon P, et al. The 3-month readmission rate remains unacceptably high in a large North American cohort of patients with cirrhosis. *Hepatology*. 2016;64(1):200-208.
20. Morando F, Maresio G, Piano S, et al. How to improve care in outpatients with cirrhosis and ascites: a new model of care coordination by consultant hepatologists. *J Hepatol*. 2013;59(2):257-264.
21. Singal AG, Rahimi RS, Clark C, et al. An automated model using electronic medical record data identifies patients with cirrhosis at high risk for readmission. *Clin Gastroenterol Hepatol*. 2013;11(10):1335-1341.e1.
22. Bini EJ, Weinshel EH, Generoso R, et al. Impact of gastroenterology consultation on the outcomes of patients admitted to the hospital with decompensated cirrhosis. *Hepatology*. 2001;34(6):1089-1095.
23. Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. *Aliment Pharmacol Ther*. 2010;32(3):344-355.
24. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. *Hepatology*. 2010;51(4):1445-1449.
25. D'Amico G, Morabito A, D'Amico M, et al. New concepts on the clinical course and stratification of compensated and decompensated cirrhosis. *Hepatol Int*. 2018;12(Suppl 1):34-43.
26. Feld JJ, Wong DK, Heathcote EJ. Endpoints of therapy in chronic hepatitis B. *Hepatology*. 2009;49(5 Suppl):S96-S102.
27. Marcellin P, Boyer N, Gervais A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with

chronic hepatitis C and sustained response to interferon-alpha therapy. *Ann Intern Med*. 1997;127(10):875-881.
28. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcome after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology*. 2009;49(3):729-738.

How to cite this article: Strazzabosco M, Cortesi PA, Conti S, et al. Clinical outcome indicators in chronic hepatitis B and C: A primer for value-based medicine in hepatology. *Liver Int*. 2019;00:1–14. https://doi.org/10.1111/liv.14285

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.