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Optimising the clinical strategy for autoimmune liver diseases: Principles of value-based medicine☆

Marco Carbone[a,b,1], Laura Cristoferi[a,b,1], Paolo Angelo Cortesi[d], Matteo Rota[b], Antonio Ciaccio[a,b], Stefano Okolicsanyi[a,b], Marta Gemma[a,b], Luciana Scalone[d], Giancarlo Cesana[d], Luca Fabris[b,c,e], Michele Colledan[f], Stefano Fagiuoli[g], Gaetano Ideo[i], Luca Saverio Belli[b,h], Luca Maria Munari[h], Lorenzo Mantovani[d], Mario Strazzabosco[a,b,c,*,2]

[a] Division of Gastroenterology, Department of Medicine and Surgery, University of Milan-Bicocca, Milan, Italy
[b] International Center for Digestive Health, University of Milan-Bicocca, Milan, Italy
[c] Liver Center & Section of Digestive Diseases, Department of Internal Medicine, Yale University School of Medicine, New Haven, CT, USA
[d] Research Centre on Public Health (CESP), University of Milan-Bicocca, Milan, Italy
[e] Department of Molecular Medicine, University of Padua School of Medicine, Padua, Italy
[f] Department of Surgery, Papa Giovanni XXIII Hospital, Bergamo, Italy
[g] Department of Gastroenterology, Papa Giovanni XXIII Hospital, Bergamo, Italy
[h] Department of Hepatology and Gastroenterology, Liver Unit, Niguarda Hospital, Milan, Italy
[i] FADE Foundation, Milan, Italy

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ABSTRACT

Background: Autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis represent the three major autoimmune liver diseases (AILDs). Their management is highly specialized, requires a multidisciplinary approach and often relies on expensive, orphan drugs. Unfortunately, their treatment is often unsatisfactory, and the care pathway heterogeneous across different centers. Disease-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. Aim of our study was to generate a set of COIs for the three AILDs. We then prospectively validated these indicators based on a series of consecutive patients recruited at three tertiary clinical centers in Lombardy, Italy.

Methods: In phase I using a Delphi method and a RAND 9-point appropriateness scale a set of COIs was generated. In phase II the indicators were applied in a real-life dataset.

Results: Two-hundred fourteen patients were enrolled and followed-up for a median time of 54 months and the above COIs were recorded using a web-based electronic medical record program. The COIs were easy to collect in the clinical practice environment and their values compared well with the available natural history studies.

Conclusions: We have generated a comprehensive set of COIs which sequentially capture different clinical outcome of the three AILDs explored. These indicators represent a critical tool to implement a value-based approach to patients with these conditions, to monitor, compare and improve quality through benchmarking of clinical performance and to assess the significance of novel drugs and technologies. This article is part of a Special Issue entitled: Cholangiocytes in Health and Diseaseedited by Jesus Banales, Marco Marzioni, Nicholas LaRusso and Peter Jansen.

Abbreviation: AASLD, American Association for the Study of Liver Diseases; AIH, autoimmune hepatitis; AILDs, autoimmune liver diseases; BMD, bone mineral densitometry; CCA, cholangiocarcinoma; COIs, clinical outcome indicators; CRC, colorectal cancer; DAAs, direct acting agents; DI, disagreement index; EGDS, esophagogastroduodenoscopy; EQ-5D, EuroQol five dimensions questionnaire; EASL, European Association for the Study of the Liver; HRQoL, health related quality of life; IPR, inter-percentile range; LT, liver transplantation; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; RAS, RAND/UCLA appropriateness scale; UDCA, ursodeoxycholic acid; ULN, upper limit of normal; VAS, visual analogue scale; VBHC, value-based healthcare; VBMH, value-based medicine in hepatology

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* Corresponding author at: Section of Gastroenterology, School of Medicine and Surgery, University of Milan-Bicocca, Via Cadore 48, Milan, Italy.
E-mail address: mario.strazzabosco@yale.edu (M. Strazzabosco).
[1] Joint first authors.
[2] Dept. of Internal Medicine, Section of Digestive Diseases, Yale University School of Medicine, 333 Cedar Street LMP 1080, 06520 New Haven, CT USA.

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1. Introduction

Primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) represent the three major autoimmune liver diseases (AILDs). They are all complex disorders resulting from the effects of multiple genes in combination with as yet unidentified environmental factors. Their clinical manifestations and pathogenesis are quite different, but they are usually grouped together. Unfortunately, for all three disorders, treatment is unsatisfactory and a significant number of patients eventually progress to end-stage liver disease requiring liver transplantation (LT) [1]. With the introduction of direct acting agents (DAAs) for the treatment of HCV hepatitis, the landscape of clinical hepatology has changed enormously and in this scenario, AILDs are fast becoming a major clinical challenge.

Over the last decade the practice of hepatology has moved into a highly complex discipline that is no more dominated by supportive treatments, but is actually able to offer prevention and effective care for most liver diseases. The management of patients with AILDs is highly specialized, requires a multidisciplinary approach and often relies on expensive, orphan drugs. However, healthcare systems are facing problems to sustain and support the continuing new therapies for liver disease and a significant number of patients may not receive appropriate treatments. Different strategies are being followed to improve the sustainability of healthcare; unfortunately, most of them revolve around cost-containment, reduced coverage and contraction in system capacity [2].

This prompts the change of the paradigm of the healthcare delivery that we are witnessing: a system focused on the volume of care delivered is reorienting towards one looking at clinical outcomes that matter to patients per cost sustained to deliver the care, i.e. value-based healthcare (VBHC) [3]. A value-based clinical approach to liver disease, with outcome measures reflecting the entire cycle of care, is needed to assist both clinicians and administrators in improving the quality and the value of care [4]. The application of systematic measurement of clinical outcome indicators (COIs) over an adequate period of observation would provide information needed to activate the positive loop that drives practice improvement and cost reduction at the patient level. A comprehensive set of outcome measures for liver conditions, and specifically for AILDs, however is not currently available.

Aim of this study was to develop and validate outcome indicators in AILDs. These represent tools to implement a value-based medicine in hepatology (VBMH) for patients with AILDs to compare results and value of care between referral centers, to perform health technology assessment and to guide decision-making process for health authorities.

The Value-Based Medicine in Hepatology (VBMH) study was designed to generate COIs for several major liver conditions, including viral hepatitis, hepatocellular carcinoma (HCC), liver cirrhosis, AILDs and metabolic liver diseases. Here we will report the results of the study for AILDs.

2. Methods

2.1. Design

The design of VBMH is composed by two phases. In phase I using a Delphi method a set of COIs was generated; in phase II the indicators were applied in a real-life dataset.

2.2. Generation of clinical outcome indicators (COIs)

We adopted a modified four-step Delphi method to generate a set of COIs for AIH, PBC, and PSC, that consisted in a structured process involving a Focus Group for the three AILDs composed by a panel of experts (Supplementary Table S1) [5–7]. To generate a preliminary list of COIs, focus Group discussion took place between 2010 and 2011. Experts were called in a one-day-meeting for each AILDs and instructed to identify indicators that: I. were highly correlated to the most relevant clinical outcomes, II. were able to capture the full cycle of care, and that III. could be easily collected during the normal clinical practice. “Process indicators” were proposed only when COIs were not available or were considered too weak to be used to measure the outcome of cares. All the identified COIs were subsequently reviewed in order to create a first list of indicators.

In the second step, the list of COIs was sent to all participants of the Focus Group for validation. Then, the indicators were assessed to reach the consensus within all expert involved in the Focus Groups. The COIs assessment was carried out within the third and fourth step. These two steps were used to assess the value of the proposed COIs and the agreement within the expert, using the RAND/UCLA appropriateness scale (RAS) [8]. While in the first two steps of the Delphi process we involved 8 experts in the management of the AILD (Supplementary Table S1) other 38 experts in hepatology and familiar with VBMH methodology were included in the third and fourth step (final panel of 46 experts involved in the COIs assessment). These expert were members of focus groups of other VBMH studies that we have conducted during the same time period to identified COIs in other liver conditions (e.g. HCV, HBV, Compensated Cirrhosis, Decompensated Cirrhosis, HCC, Liver transplant and NAFLD/NASH) [*Generation and Performance of Outcome Indicators in Liver Disease: The Value Based Medicine in Hepatology Study*. *Abstract 2067*, *Hepatology*, *volume 58*, *number 4* (*suppl*)]. Based on the value reported in the RAS by each expert for each COI, we calculated the median panel rating (MPR) and the RAND “Disagreement Index” (DI) for each proposed indicator. A COI with a MPR between 1 and 3 was classifying as “definitely not appropriate”, between 4 and 6 as “uncertain or equivocal appropriateness”, and equal or higher than 7 as “definitely appropriate”. The DI is based on the distribution and symmetry of the scores across the 9-point RAS, and has been externally validated as a measure of variation in provider beliefs. The DI is calculated using a standard published equation [8]. A higher DI indicates wider spread across the 9-point scale, while lower values indicate increasing consensus. If the DI is < 1.0, then the distribution meets criteria for no extreme variation in ratings. For each liver condition, the indicators with the highest MPR and a DI < 1 were considered for the subsequent validation study.

In the final extra round all the expert hepatologists involved in the Focus Group were called in a face-to-face meeting to generate a ranking of the previously identified COIs based on their significance, importance and potential clinical impact. Finally, each indicator was reviewed based on the current literature, and a level of evidence was applied based on the Oxford Evidence-based Medicine Levels of Evidence [9].

2.3. Assessment of feasibility and values of COIs

In the second phase of the VBMH study, the identified indicators were tested in an observational, longitudinal, prospective, multicenter study involving the Liver Units of three major Health Care Centers located in Lombardy, Italy: 1. the “San Gerardo Hospital” in Monza (an academic medical Center north of Milan), 2. the “Papa Giovanni XXIII Hospital” in Bergamo (a non-academic center with an active liver transplant program, east of Milan), and 3. the “Niguarda Ca'Granda Hospital”, in Milan (non-academic medical center in Milan, with an active liver transplant program). These three hospitals serve a population of approximately three million people. The study protocol and informed consent forms were approved by the Ethical Committees of the participating centers. The study protocol is in agreement with the principles established by the 18th World Medical Assembly [28].

2.4. Patients

From March 2011 to November 2012, all consecutive subjects carrying an established or new diagnosis of AIH, PBC and PSC were