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Imaging features for the prediction of clinical endpoints in chronic liver disease: a scoping review protocol

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ABSTRACT

Introduction Chronic liver disease is a growing cause of morbidity and mortality in the UK. Acute presentation with advanced disease is common and prioritisation of resources to those at highest risk at earlier disease stages is essential to improving patient outcomes. Existing prognostic tools are of limited accuracy and to date no imaging-based tools are used in clinical practice, despite multiple anatomical imaging features that worsen with disease severity.

In this paper, we outline our scoping review protocol that aims to provide an overview of existing prognostic factors and models that link anatomical imaging features with clinical endpoints in chronic liver disease. This will provide a summary of the number, type and methods used by existing imaging feature-based prognostic studies and indicate if there are sufficient studies to justify future systematic reviews.

Methods and analysis The protocol was developed in accordance with existing scoping review guidelines. Searches of MEDLINE and Embase will be conducted using titles, abstracts and Medical Subject Headings restricted to publications after 1980 to ensure imaging method relevance on OvidSP. Initial screening will be undertaken by two independent reviewers. Full-text data extraction will be undertaken by three pretrained reviewers who have participated in a group data extraction session to ensure reviewer consensus and reduce inter-rater variability. Where needed, data extraction queries will be resolved by reviewer team discussion. Reporting of results will be based on grouping of related factors and their cumulative frequencies. Prognostic anatomical imaging features and clinical endpoints will be reported using descriptive statistics to summarise the number of studies, study characteristics and the statistical methods used.

Ethics and dissemination Ethical approval is not required as this study is based on previously published work. Findings will be disseminated by peer-reviewed publication and/or conference presentations.

Strengths and limitations of this study

- The findings from the study informed by this protocol will support the ongoing and future development of more accurate prognostication tools to deliver much needed improvements in clinical outcomes of patients with chronic liver disease through understanding of current evidence and methods.
- In an era of growing use of large-volume data-driven artificial intelligence/machine learning model development processes, the findings from the study informed by this protocol will help streamline data generation, collation and validation of key parameters from imaging for models, particularly as generating large-volume chronic liver disease patient data sets is difficult and costly.
- This study protocol is timely as the use of imaging in patients with chronic liver disease has become an integral part of clinical practice and therefore the findings of studies informed by the research identified by this scoping review are likely to be relevant to routine clinical practice.
- Our protocol has been developed in accordance with established guidance and the scoping review that arises will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines.
- Only studies linking imaging features directly to clinical endpoints will be included. Cross-sectional studies linking imaging features with existing invasive and non-invasive non-imaging prognostic factors/scores will be excluded.

INTRODUCTION

The prevalence of liver disease continues to increase in the UK, where it is the third leading cause of premature death in working age and the leading cause of death in 30–49 year-olds.[1] For most patients, liver disease is a chronic and insidious process developing over many years. Diagnosis usually occurs during their first hospital admission with acute decompensation (AD), including symptoms of gastrointestinal haemorrhage, hepatic encephalopathy, jaundice or ascites. Sixty-day mortality for these patients has remained between 30% and 40% over the past 10 years,[2] driven by long-standing preadmission decline in patient functional reserve and lack of access to costly and limited tertiary care services including liver transplant.[3]

Accurate prognostication of patients with liver disease could potentially improve clinical outcomes by informing prioritisation of healthcare resources to those at highest risk at earlier disease stages, when treatments may have better long-term outcomes. Improved prognostication could impact the clinical care pathway at several points, for example, it could empower patients to target improvements in specific prognostic factors through behavioural modification, take the form of more intensive secondary care follow-up/optimisation to avoid AD in those at higher risk with apparently stable disease, inform treatment escalation decisions for acute hospitalised patients, improve end-of-life care quality by avoiding futile intensive care interventions and inform the prioritisation of patients who survive acute admission for liver transplantation.

The use of prognostic factors and models for the evaluation of chronic liver disease has been established for some time. The use of Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores and their variants have been incorporated into clinical pathways,[4] but both are of limited value in the prediction of long-term clinical outcomes. More recently, development of acute-on-chronic liver failure (CLIF)/AD CLIF scores and their variants have been established for the assessment of patients with organ failure/in the critical care setting, but these result in area under receiver operating characteric(AUROC) values around 0.75 for the prediction of mortality.[5] Invasive measurements such as the hepatic venous pressure gradient (HVPG) also have established prognostic value in patients with stable cirrhosis, but are invasive and require specialist centre expertise.[6]

Patients with chronic liver disease are routinely imaged electively and in the emergent setting with ultrasound (US), CT and MRI. Abnormal structural features are known to worsen with increasing liver disease severity. Macroscopic changes occur both within the liver and outside the liver, affecting organs such as the spleen, splanchnic vasculature, kidneys, gastrointestinal tract, peritoneal space, abdominal musculature and axial skeleton,[7] all of which have the potential to help inform better prognostic modelling for chronic liver disease. Such structural changes, however, are not quantified during routine diagnostic reporting, although the development of new machine learning-based tools for quantification of such features from standard anatomical imaging (such as automated measures of organ volume[8]) has the potential to change this. The combination of these new tools with appropriate selection of anatomical imaging features could yield multivariable imaging-based models that could add to existing prognostic models and help improve clinical outcomes in patients with chronic liver disease.

STUDY RATIONALE

Adequately powered studies for the development and validation of multivariable imaging-based models in chronic liver disease are difficult because of the range of potential relevant but differing clinical endpoints, and the need for appropriately sized data sets with event rates of the clinical endpoint of interest to support the number of variables used in the model being developed. The sheer number of variables evaluated in radiomics and/or artificial intelligence (AI)-based approaches, for example, would require sample sizes that could only be generated from costly large-scale multicentre studies.[9] An evidence-based approach, however, could provide a more streamlined method for preselection of specific imaging-based variables that would be more likely to contribute to a useful prognostic model.

Initial PubMed and Embase searches by the authors using generic search terms such as 'liver' AND 'imaging' AND 'prediction' demonstrate that existing literature on the use of imaging features for the prediction of clinical endpoints in chronic liver disease is varied. There are differences in the imaging modalities used (eg, US, CT and MRI); the structural features that have been studied (eg, organ size, vessel size, radiomic features, sarcopenia measures, etc); the liver disease endpoints that have been selected for prediction (eg, survival, AD, development of hepatocellular carcinoma, etc); and the maturity of the prognostic models that are proposed (ie, the extent to which a model has been developed/validated and how clinically usable it is).

A scoping review as proposed initially by Arksey and O'Malley,[10] with subsequent refinements,[11 12] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews[13] is an appropriate approach to appraise evidence in this area. It will enable knowledge and concepts in the field to be mapped, establish the value of undertaking a full systematic review and identify gaps in the existing knowledge base.

The scoping review protocol presented here will provide an important summary of the literature pertaining to the imaging modalities used, structural features measured, choice of clinical endpoints studied, their reported associations and the current landscape of imaging-based prognostic models in chronic liver disease. This review will also form a basis for future systematic reviews and meta-analyses and for informing future primary research into the development of imaging-based multivariable prognostic models.

STUDY OBJECTIVES

The aim of this scoping review will be to map the literature describing anatomical imaging features that may have prognostic value for relevant clinical endpoints in chronic liver disease, specifically:

- To provide an overview of prognostic factors and models that have linked anatomical imaging features with clinical endpoints in chronic liver disease.
- To define the clinical population that has been investigated by these studies.

- To assess the maturity of evidence for prognostic factors and models derived/investigated within published studies.
- To identify studies for potential inclusion into a future systematic review/meta-analysis.

METHODS AND DESIGN

The protocol was developed in accordance with the stages defined by Arksey and O'Malley[10] and subsequent enhancements defined by Levac *et al*.[11] Protocol development was driven by the lead author collaborating closely with experienced statisticians for methodological guidance (authors TP and SM). The drafted protocol was then refined by input from authors with specialist clinical and research expertise (SAT, YH, DB, DY, RPM and SH).

Stage 1: identifying the research question

The following research questions were defined to guide our review:

- What structural imaging features have been linked prognostically with clinical endpoints in chronic liver disease?
- What clinical endpoints have been used in these studies?
- What imaging modalities have been used to obtain the anatomical imaging features studied?
- What aetiologies of liver disease have been studied?
- To what extent has the model presented been developed/validated?
- How was the study designed—prospective/retrospective, setting, sample sizes, follow-up interval, number of institutions/scanners?
- What statistical methods have been to generate or test the model?
- How usable do the prognostic models appear to be?

Stage 2: identifying relevant studies

Inclusion/exclusion criteria were developed iteratively over a series of meetings between the lead author and statisticians (TP and SM) and with input from subspecialist experts (DY and RPM) and are listed in table 1.

Stage 3: study selection

Search strategies for MEDLINE and Embase (OvidSP) were refined over the course of several meetings between the lead author and statistician coauthors (TP and SM) to ensure appropriate publications were identified.

MEDLINE and Embase will be searched using a search strategy targeting titles, abstracts and Medical Subject Headings and be defined to include four key terms. The first, defining the target population, will be constructed to capture variations of the terms 'liver disease', 'liver fibrosis' and 'cirrhosis'. The second will be constructed to capture variations of 'imaging', 'US', 'CT' and 'MRI'. The third will be constructed to capture variations of potential references to prognostic studies. The final term will specify exclusions of publication types. Studies after 1980 will be included to ensure the imaging technology used is relevant to currently used methods and studies will be manually limited to English to facilitate review. The formal search strategy can be found in online supplemental material 1.

Identified records from search results will be screened using the Rayyan web/mobile application in blinded mode.[14] The Rayyan deduplication tool will be used to remove any duplicate references that may have been identified by both databases. The final deduplicated reference list will undergo initial screening of titles and abstracts by two independent reviewers (MDC and TP). Any duplicate references not removed by the Rayyan tool will also be removed at the time of manual screening. Uncertainties or disagreements will be resolved by discussion between both reviewers, with escalation to the coauthors with expertise in the area when appropriate.

For studies that meet the inclusion criteria, full texts will be obtained with relevant authors contacted to request these if required. Studies that evaluate the combinations of parameters that meet both inclusion and exclusion criteria are likely. These studies will be screened in greater depth to assess if there are sufficient data to separate the assessment of parameters meeting the inclusion criteria, so that these data can still be included in the review. Finally, the reference list of identified full-text studies will not be checked as this scoping review aims to provide an overview of the literature structure, as a step towards a more comprehensive systematic review. The study selection process is summarised in figure 1. Initial searches performed in February 2021 identified 3079 records.

Stage 4: data extraction

A data charting proforma was drafted to include key manuscript details such as author, year of publication, country of origin, but also specific questions designed to address the research questions, including the imaging modalities investigated, recruitment setting/context, the prognostic study phase, sample sizes, the liver disease aetiologies studied, anatomical features investigated, clinical endpoints used, the statistical analysis methods used and the derived prognostic model usability. The proforma draft (online supplemental material 2) was arranged to align with the order in which such information was likely to be extracted from a full-text manuscript.

All reviewers will undergo training using specially designed training materials tailored to the data charting proforma (online supplemental material 3). The data charting proforma will then be piloted between three designated reviewers (AB, CM and MAP) using five potential studies. The pilot will enable the proforma and instructions to be refined to ensure that all relevant results are extracted, that all reviewers understand the charting process and that there is a level of consensus between the reviewers on how to approach the review process, thereby reducing inter-rater variability. Final data extraction will be performed independently by the three reviewers (figure 1). Workflow will be tracked using the Rayyan web/mobile application[14] and any uncertainties,

Table 1 Inclusion/exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	► Adult humans (≥18 years) with liver disease (of any aetiology)/cirrhosis/chronic liver disease.	► Animal studies. ► Paediatric studies. ► Liver disease where hepatocellular carcinoma (HCC), transplant or transjugular intrahepatic portosystemic shunts (TIPSS) are criteria for inclusion into the study. ► Studies pertaining to focal liver lesions, including liver metastases or benign liver lesions. ► Studies pertaining to acute liver failure.
Concept	► Prognostic evaluation using CT, MRI or US. ► Imaging measures derived from anatomical features (eg, organ size, liver segment size ratios, organ contour, surface nodularity, vessel size, vessel-related parameters, including the presence of thrombus, increased periportal space, ascites, body composition features derived from area-based measures such as fat, muscle, sarcopenia). ► Imaging measures derived from non-contrast enhanced, non-quantitative imaging signal (eg, CT density, MR signal intensity, radiomics/textural measures, etc). ► Clinical endpoints including (but not limited to): – Mortality/survival, acute decompensation, variceal bleed, portal venous thrombosis, ascites, transplant-free survival, organ failure, infection/sepsis, development of acute-on-chronic liver failure. – HCC-related endpoints where the presence of HCC is not a criterion for inclusion into the study. – Studies evaluating the association with established prognostic markers (including but not limited to invasive markers such as HVPG and endoscopic variceal grade and non-invasive markers such as CTP and MELD scores).	► Diagnostic evaluation using CT, MRI or US. ► Prognostic studies using: – Other imaging modalities (including functional nuclear medicine studies such as positron emission tomography). – Non-binary anatomical features assessed subjectively by study readers (eg, subjective categorisation of the severity of liver surface nodularity). – Non-radiomic quantitative imaging methods. – Postcontrast enhancement ratios. – Biomechanical imaging methods (ie, elastography US/MRI; acoustic radiation force impulse (ARFI) US; shear wave US). – Doppler US. – Quantitative MRI methods (eg, perfusion MRI, diffusion-weighted imaging, T1 mapping, etc). – Quantitative CT methods (eg, perfusion, dual energy, iodine mapping). – Histology/microscopy studies. ► Clinical endpoints: – HCC-related endpoints, where HCC is a criterion for inclusion into the study. – Post-transplant endpoints. – Post-TIPSS endpoints. – Liver fibrosis. ► Studies pertaining to image reconstruction. ► Studies pertaining to the development of methods for quantifying anatomical features.
Context	► Studies from any country. ► Studies where recruitment has taken place in primary or secondary care (inpatient or outpatient setting), to avoid selection bias arising from the recruitment setting.	► Studies published prior to 1980 to ensure the imaging technology reviewed is relevant to modern imaging methods. ► Studies published in non-English languages.
Source type	► Prognostic model development and validation of primary research studies, including prospective/retrospective cohort and case–control studies, at any stage/phase.	► Diagnostic studies. ► Case studies/case series; editorials; letters; conference proceedings; reviews/narrative studies; systematic reviews/meta-analyses; book chapters; grey literature.

CTP, Child-Turcotte-Pugh; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; US, ultrasound.

controversies or conflicts will be resolved by discussion between review team members.

Stage 5: collating, summarising and reporting the results

Descriptive data analysis will be structured to address the research questions established previously. Data extracted by reviewers will be collated, related factors will be grouped into categories and simple frequency counts will be presented. Analysis will include grouping of potential prognostic anatomical imaging features into categories, presented alongside the clinical endpoints (also grouped into categories) that they have been associated with. Potential prognostic anatomical imaging

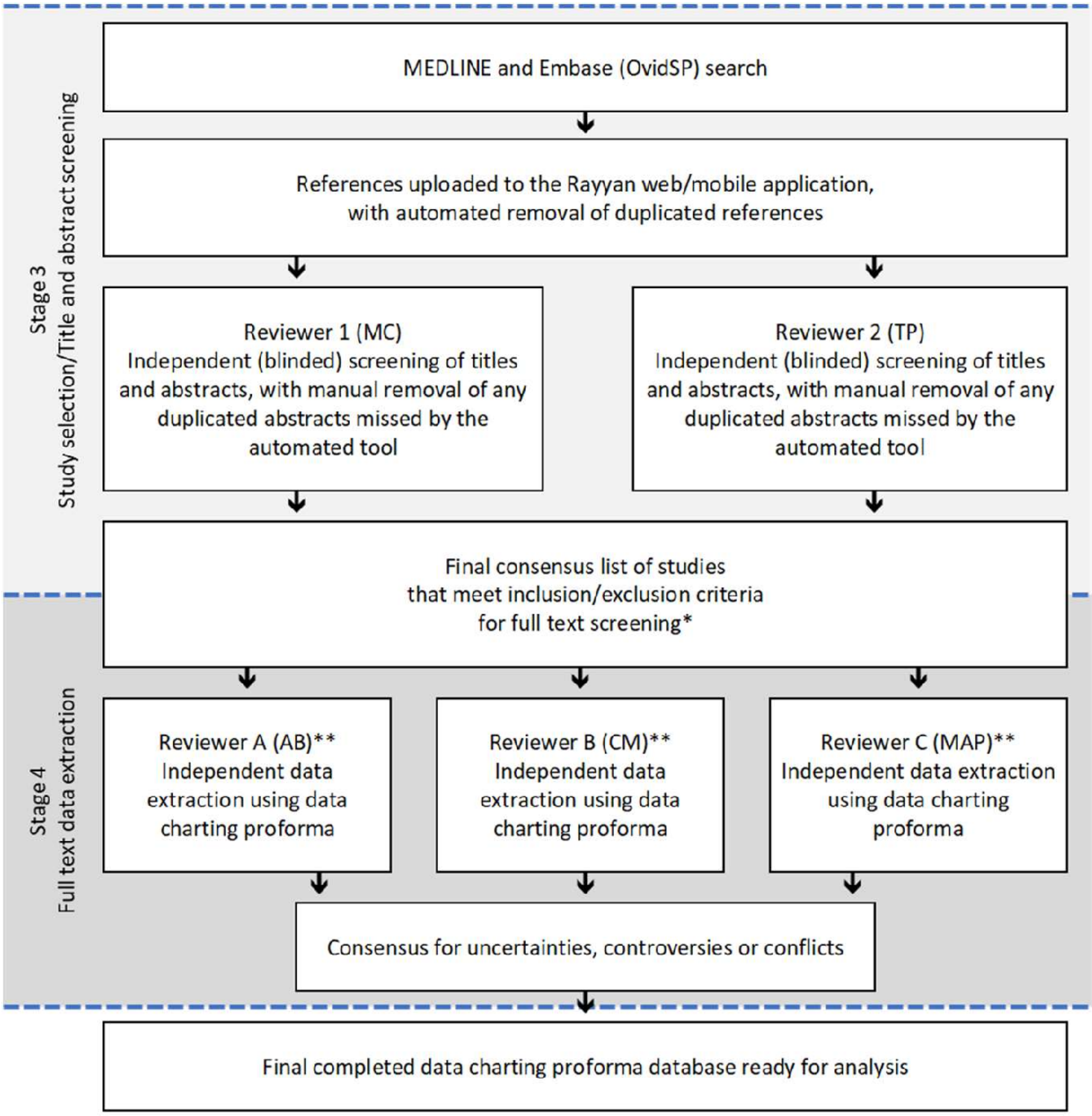

Figure 1 Study selection and data extraction process. *The reference list of identified full-text studies will not be checked as this scoping review aims to provide an overview of the literature structure, as a step towards a more comprehensive systematic review. **Final list of full-text references to be divided equally between each of the three stage 2 reviewers.

features will also be reported by imaging modalities used. Clinical endpoints will be grouped and linked with the disease aetiologies studied. Frequency of study design and characteristics, including the study phase, will be presented. Sample and clinical endpoint sample sizes will also be presented. Finally, the frequency of different statistical methods used to develop the model will also be presented, including an overall assessment of potential prognostic model usability.

Categories emerging from the analysis will be used to demonstrate knowledge and knowledge gaps, and to identify current research status. As the aim of this scoping review is to map knowledge and not to identify the weight of evidence for a particular prognostic estimate, risk of bias assessment will not be undertaken. Data collected on study maturity, study methodology, sample sizes and prognostic model usability will be used to make inferences on overall limitations of existing literature in the area. We will use the scoping review results to inform the design of future primary prognostic studies that include anatomical imaging features, and to provide a foundation for future systematic reviews and meta-analyses in this area.

STUDY LIMITATIONS

Although this study protocol has been designed to deliver robust, meaningful and reproducible scoping review findings, we acknowledge limitations that have been introduced to ensure that this study protocol is practical and deliverable.

First, we have restricted our searches to MEDLINE and Embase, two online databases likely to include most of all significant published work in this area. Our search, however, excludes prepublished work on databases such as medRxiv/bioRxiv or conference proceedings/abstracts that may be of value in this area. We have chosen to exclude the latter on the grounds that even if conference proceedings/abstracts met the inclusion/exclusion criteria, they would be unlikely to report all the information required to accurately complete the proforma (and the posters/talks they pertain to might not be available or accessible online). We have also chosen to exclude paediatric studies because of major differences in liver disease aetiology and disease course.

Studies published in languages other than English will also be excluded due to resource limitations.

We have aimed to exclude studies that evaluate the association between established prognostic markers (such as HVPG, endoscopic variceal grade, CTP and MELD scores), as such studies may adopt a more diagnostic-type study design (eg, a cross-sectional study correlating an anatomical imaging feature with contemporaneous CTP scores), and are therefore unlikely to be identified by the search strategy used. This limitation is deliberate as these studies will have been conducted without the a priori objective of determining the prognostic value of the anatomical imaging features investigated and are therefore less likely to yield meaningful data for a future systematic review/meta-analysis.

The development of macroscopic parenchymal changes detectable on imaging (ie, increased parenchymal heterogeneity) with the advancement of liver disease is a well-recognised phenomenon and has driven our decision to include studies that evaluate tissue textural/radiomic features. While textural measures rely on complex post-processing and are therefore arguably quantitative, where imaging is purely for anatomical assessment, the application of textural quantification is to quantify a structural change and therefore qualifies as assessment of an anatomical imaging feature. Of note, although acquisition parameters have major effects on quantified US echogenicity, CT density, MR signal intensity and subsequently derived textural measures—scoping the application of texture-derived parameters in the literature still aligns with the objective of providing an overview of imaging features that have been linked with clinical endpoints in chronic liver disease.

Finally, in line with established scoping review guidance,[10 11] the use of risk-of-bias tools to appraise the quality of the studies included in the scoping review will not be performed, with the implicit risk of inclusion of flawed study data in the overall study findings. The inclusion of risk-of-bias assessment will however require significant additional resources from the reviewer team and on balance will not provide any additional information contributory to the stated scoping review objectives.

PATIENT AND PUBLIC INVOLVEMENT

Patients and the public were not involved in the development of this scoping review protocol.

ETHICS AND DISSEMINATION

This scoping review protocol is based on secondary data obtained from published manuscripts in scholarly journals and therefore does not require ethical approval. Findings from this scoping review will be disseminated by peer-reviewed publication and/or conference presentations. It is anticipated that the literature gaps identified by this study will help stimulate more clinically useful research in this area and inform the conduct of systematic reviews/meta-analyses for better preselection of anatomical imaging-derived parameters for potential inclusion into prognostic models for chronic liver disease.

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Contributors MDC wrote the manuscript and developed the protocol. SAT edited the manuscript and provided guidance on protocol development. AB, CM, MAP, TP, SH and SM edited the manuscript and developed the protocol. YH, DB, DY and RPM provided guidance on protocol development.

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