Improving surgical outcomes: peri-operative care in patients with cirrhosis

Background

Despite worldwide increases in chronic liver disease, patients with cirrhosis are living longer due to improved medical management [1]. Mortality among hospitalised patients with cirrhosis has fallen steadily despite increasing age and complexity [2]. Improved outcomes are attributed to improved liver specific interventions as the absolute reduction in mortality is greater than those without cirrhosis (eg heart failure). Access to expertise, appropriate choice of interventions & care pathways are needed to improve surgical care of patients with cirrhosis.

Non-hepatic surgery in cirrhosis: why now? Population-based studies report increasing prevalence of patients with cirrhosis undergoing colorectal cancer surgery; Denmark (1996-2009) 0.4% [3], America (1998-2005) 0.8% [4] and UK (2001-2017) 0.7% overall [5]. In 2017, 1.07% of patients undergoing colectomy had cirrhosis suggesting increasing cirrhosis prevalence is reflected in those undergoing surgery [5]. The five-year hip fracture risk (1997-2014) is increased in alcohol-related cirrhosis compared to the general population in both England (2.9% vs 0.8% in controls) and Denmark (4.6% vs 0.9% in controls) [6]. Patients with cirrhosis had 5.5-fold (adjusted HR 5.5; 95% CI 4.3-6.9) and 8.5-fold (adjusted HR 8.5; 95% CI 4.3-6.9) increased rates of hip fracture in England and Denmark respectively [6]. There is extremely limited prevalence data outside that presented, postoperative mortality is high in cirrhosis but current evidence precludes definitive conclusions on surgical risks [7].

In the UK, increasing incidence of cirrhosis is secondary to alcohol misuse and the obesity pandemic [8]. Liver disease is in the top 3 for inequitable healthcare [9]. The median age of death for people with liver disease differs by 9 years in those residing in the most deprived quintile compared to the least deprived [10]. In the UK the commonest reason for alcohol-related admissions are cancer (almost a quarter) and unintentional injuries (almost a quarter) [11]. The prevalence of a BMI $\geq$ 25 is 67% in men, with 26% obese, and 60% in women, with 29% obese [12]. These modifiable risk factors also contribute to several other gastrointestinal diseases, including benign [13] and malignant colonic disease [14, 15] for which colorectal surgery is often indicated. In addition, osteoporosis is an important complication of chronic liver disease which increases the risk of bone fractures [16, 17], particularly in patients with alcoholic cirrhosis [18]. 47.3% of patients with cirrhosis have a first diagnosis during an emergency admission to hospital [19]. 66.7% have entirely normal liver function tests [20]. Patients with risk factors (alcohol dependency, diabetes and obesity) for chronic liver disease should be routinely screened for cirrhosis as reliance on abnormal liver function tests will miss most patients with significant liver injury [21].

What is the problem? Mortality after abdominal surgery was historically high enough to preclude surgery in all patients with cirrhosis [22], with morbidity rates up to 77% and mortality rates up to 50% [23]. Peri-operative care and surgical techniques have evolved [24], leading to an uptake of surgery in higher risk groups [25, 26]. The increased mortality risk is poorly defined. Published data is predominantly single-centre retrospective observational studies focusing on short-term outcomes [5]. Population-based studies suffered similar shortcomings, with inadequately defined surgery details (elective, emergency, site), with medium and long-term mortality risk unaddressed which likely significantly underreports the true surgical risk. Recent UK data showed 90-day mortality following elective colectomy of 7% in compensated cirrhosis and 10% in decompensated cirrhosis both of which were substantially less than 35% and 41%, respectively, following emergency colectomy [5]. UK cholecystectomy data showed a 3-fold (OR 3.22, IQR 1.72-6.02) and a 4.5-fold (OR 4.52, IQR 2.46-8.33) increased odds of 90-day mortality in patients with cirrhosis following elective & emergency cholecystectomy

[27]. The 30-day mortality of patients with cirrhosis undergoing orthopaedic surgery is 11.1% compared to 5.0% without liver disease (HR 2.8, 95% CI 1.9 – 3.9) [6].

The pathophysiology of cirrhosis, portal hypertension and sarcopaenia [28] predisposes patients to complications following surgery. The risk of bleeding is increased due to the collateral circulation and varices (eg in the abdominal cavity). The haemostatic balance is disrupted in cirrhosis and difficult to predict on routine laboratory testing [29]. Patients with cirrhosis also have an inappropriate response to surgical stress and are predisposed to develop postoperative hepatic decompensation, especially after emergency operations (emergency umbilical hernia repairs OR 13.29 compared to elective repair, resulting in increased length of stay, 7 vs 3 days, $p<0.01$) [30]. The decision to perform surgery in patients with cirrhosis requires careful consideration and stringent preoperative assessment with risk stratification is essential to inform individualised approaches but is not standardised and poorly evidenced [25, 31]. Some miss out on critical surgery whereas others are subjected to harms leading to an unacceptable variability in practice that must change for the benefit of patients.

What is the current standard of care? Cirrhosis is frequently a barrier to surgery, with variable approaches to individual risk assessment, patient pathways & service provision. The severity of the liver disease using Child-Turcotte-Pugh (CTP) & Model for End Stage Liver Disease (MELD) scores were used to risk stratify patients with cirrhosis undergoing surgery (based on clinical evaluation &/or routinely accessible laboratory tests). In abdominal surgery, two studies 13-years apart reported near-identical perioperative mortality rates of 10%, 30% and 80% in CTP A, B and C respectively [22, 32]. Recently, however, CTP scores correlated poorly with surgical outcomes [33], likely due to avoidance of surgery in decompensated cirrhosis. MELD score, based solely on objective laboratory values, is utilised to prioritise liver transplantation. Increasing MELD score was associated with worse surgical outcomes, with 1% increase in mortality/MELD point < 20 and 2% increase/MELD point $\geq$20 [34].

In a retrospective study of carefully selected cirrhosis patients undergoing surgery, MELD score, American Society of Anaesthesiologists (ASA) class and age were significant predictors of mortality, used to derive the Mayo Postoperative Surgical Risk Score [35]. Recently, the VOCAL-Penn model was developed [36]. However, VOCAL-Penn model is applicable only to those with compensated cirrhosis (CTP A cirrhosis & MELD $\leq$9) [31]. In 50-75% of hospitalised patients with decompensated cirrhosis, liver disease would not have been detected beforehand [19, 37]. In addition, while different factors may be considered in the risk assessment of patients with cirrhosis, none of these are reversible or modifiable in the short term in the preoperative period to improve post-operative outcomes.

Role of Clinically Significant Portal Hypertension (CSPH) The development of portal hypertension in cirrhosis is associated with marked systemic and splanchnic haemodynamic changes, which impact on the cardiopulmonary and renal circulation and consequently contribute to post-surgical complications. Transjugular hepatic venous pressure gradient (HVPG) is the only validated technique currently available to accurately evaluate portal pressure [38]. HVPG has been an important prognostic marker for surgical resection of hepatocellular carcinoma [39]. In a prospective study, HVPG was shown to predict survival in patients with cirrhosis undergoing elective extrahepatic surgery, CTP and MELD scores were not related to survival [40]. The placement of transjugular intrahepatic portosystemic shunt (TIPSS) is an effective intervention to reduce portal pressure [41] with the potential to reduce the risks of perioperative complications. However, transjugular measurement of HVPG is invasive and only available in tertiary centres [42]. This has precluded the use of HVPG in routine clinical practice. Even when available, HVPG measurements are not widely established in the preoperative assessment.

Non-invasive alternatives Baveno VII criteria suggest patients can be stratified with advanced liver disease with a transient elastography (TE) measurement of ≥10kPa [43]. In aetiologies other than NASH, CSPH may be ruled out with by TE ≤15kPa and a platelet count ≥150x10^9/L (sensitivity and negative predictive value >90%). Excluding obese patients, a TE of ≥25 kPa is sufficient to rule in CSPH (specificity and positive predictive value >90%). Quantitative MRI provides a surrogate measure of portal pressure over a wide range of HVPG [44]. MRI outperforms TE particularly in patients with CSPH (portal pressure >10mmHg). At this range of portal pressure the risk of decompensation steadily increases. MR elastography (MRE) requires additional expensive hardware but MRE estimation of liver (r^2 = 0.92; p<0.001) or spleen (r^2 = 0.94; p<0.001) stiffness also correlates with HVPG over a broad spectrum of disease in selected patients without malignancy using abbreviated protocols [45].

Aims and objectives

Overarching aim: to tackle inequalities of access, research and national variability in surgery provision to patients with cirrhosis. We will develop a sustainable multidisciplinary partnership focused on increasing inclusivity, diversity & improving outcomes of all patients with cirrhosis. Objectives are:

- Establish the partnership infrastructure with key contacts within each region
- Map, support and build partnership readiness to deliver meaningful impact on patient care with robust and improved evidence-based care pathways.
- Work with diverse and inclusive PPIE partners to identify methods & teams to expand under-represented groups in surgical research of patients with cirrhosis
- Through collaboration with professional and diverse public stakeholders, identify 10-12 key research questions
- Co-design and submit at least 3 high-quality competitive research proposals to future NIHR calls on identification and optimised peri-operative care of patients with cirrhosis

Plans of activities

1. Research capacity & capability building

Initially we will establish the partnership & create a diverse & inclusive multidisciplinary research network of patients, clinicians and methodologists with relevant expertise & lived experience representing multiple institutions. Working together the research network will help with all partnership activities, prioritise participatory action, learning, workforce development, community engagement and knowledge sharing using a community of practice model [46].

Mapping current services and research capacity (months 2 - 3)

The expert management group (EMG) with our PPIE steering committee will co-produce an electronic survey of all partnership members to map patient pathways, service provision, research capacity and barriers to surgical care (elective, emergency and cancer) of patients with cirrhosis. We will map research activity across these services, through examination of NIHR and Clinical Research Network portfolio, and scope a funding proposal (NIHR RfPB) to do qualitative interviews to help understand variability in service provision with stakeholders.

Structured training

The research partnership will offer flexible funding for structured training & development opportunities to build research capacity, with focused learning that builds on NIHR's Good Clinical Practice, Associate Principal Investigator Scheme & online courses "Improving Healthcare Through Clinical Research" and "What is Health Research?". Based on brief needs assessment with collaborators & leveraging courses from co-applicants, these will include:

- Cultural Competence Training: offered by the Centre for Ethnic Health Research
- Trial design: (i) Complex Intervention Development or (ii) Surgical Trials Research: courses by Leeds CTRU
- How to be a good Chief Investigator: by the Trials Methodology Research Partnership
- Access to partnership seminars and events to support skills development
- Nottingham's Research Hub Research Futures School and Citizen Panel registry

Knowledge exchange (month 1)

The partnership will provide mechanisms for members to exchange knowledge, mentoring & develop skills to improve access, research & surgical outcomes of patients with cirrhosis:

- A digital portfolio of members expertise, interests and collation of existing big datasets
- A virtual workspace for partnership members to facilitate information sharing & queries
- A dedicated webpage and accompanying mailing list for sharing news and resources
- A single point of contact facilitated by a partnership coordinator to seek advice/support.

2. Research proposal development

Partnership existing data informatics (months 1 – 12)

The research network will utilise all expertise with statistical and clinical support from experienced partners to undertake preliminary analysis of existing datasets (2017 BASL Emergency Hepatology services data, Prof Deehan's Newcastle & Prof Ollivere's Nottingham orthopaedic datasets) to inform crucial incidence, clinical outcomes, and feasibility data to strengthen co-produced (clinician, methodologist and PPIE) partnership proposals prepared for stage 2. Preliminary data will be disseminated in month 5 and published by month 12.

Research question generation (months 2-3):

We will lead a research question generation exercise, through a modified version of the Child Health & Nutrition Research Initiative (CHNRI) methodology [47]. Using our partnership PPIE steering committee & the EMG, we will work together with "Expert Stakeholders" (people with relevant professional or personal experience within & beyond our partnership) to collate & prioritise two research questions from all members relating to improving access, research and outcomes to patients with cirrhosis who need surgery. It will comprise 5 key stages:

1. Defining the scope and prioritisation criteria within the EMG.
2. Sourcing potential research questions from Expert Stakeholders.
3. Synthesising proposed research questions within the EMG.
4. Scoring of the proposed research questions by the Expert Stakeholders.
5. Analysis and dissemination of the top priority research questions (anticipate ~ 10-12).

Proposal development workshops on priority research questions:

The proposal development workshops are aimed at shaping competitive research proposals with multidisciplinary expertise focused on the identified top priority research questions. The EMG & PPIE Steering committee will compile a comprehensive list of participants with the Expert Stakeholders, the Nottingham Citizen Panel registry (to include charity partners and targeted diverse populations) and partner PPIE panels (Figure 2). The EMG will convene three proposal development workshops (hybrid events) bringing together the whole network with aligned training opportunities to benchmark progress, disseminate work & seek network expertise and opinions to overcome critical decisions or pinch points to assist ongoing work.

Workshop 1: Shaping the proposal *(months 4 – 6)*

The EMG will present the top 10-12 research questions (e.g. should we introduce routine screening to individuals at risk? Who should be included? What tests, where, what order and how?) and summary of feedback from the Expert Stakeholder group. Objective: to launch the partnership, discuss how questions will be structured within a proposal, define appropriate funding streams and identify multidisciplinary teams needed to answer them & do ongoing work to develop a proposal. Particular attention will be paid to the involvement of study sites with low levels of research activity & involvement of sectors outside traditional research environments (eg alcohol services, patient safety, surgery, anaesthetic teams). Attendees will be encouraged to ask difficult questions, identify issues around delivery, identify expertise needed to answer the research question, formulate plans for multi-site involvement, identify key stakeholders not already part of the partnership & how they can be involved. This will be achieved through a facilitated discussion & break out groups. PPIE members (including from the Citizen Panel) & network partners will input on shaping research proposals, building on their involvement in formulating the priority research questions.

Key deliverable: Focus order of research priority, select teams within the network to address specific trials or projects for a targeted funder. 3 – 6 two-page outline proposals developed by multidisciplinary teams with aims & objectives that map onto the priority research questions. We anticipate developing proposals around NIHR fellowships, NIHR EME Programmes & HTA Programmes testing interventions to improve research, access and outcomes of patients with cirrhosis who require surgery. *Estimated timing:* Disseminated prior to workshop 2.

Workshop 2: Strengthening the methodology *(months 7 - 9)*

The EMG & Research Design Service (RDS) will lead a learning opportunity for network partners on how to write successful grant applications, funding panels criteria & experiences.

Objective: to update the whole partnership, refine study design of $\geq$3 proposals developed from workshop 1 in first (funded) year (an additional 3 identified for development in the subsequent year) including data access & management, methodologies to be employed (qualitative/quantitative/mixed methods/implementation science), outcomes to be measured (primary and secondary outcomes, process evaluation, health economics), interventions, study design, analysis plans etc. Identified small working groups will develop the detailed grant proposals with multidisciplinary leads; including clinicians, methodologists, PPIE focus groups & Trial Managers (mapping pathways & variability, defining trial pathways and starting costings) with an identified sponsor & targeted funding stream. Partnership PPIE members (including from the Citizen Panel) will input on the feasibility, recruitment, inclusion of minority groups, ethics and other practical considerations of the methodology to be employed. Common issues will be discussed in larger groups.

Key deliverable: Plans for proposal design (feasibility, acceptability, efficacy, effectiveness testing), with a formulated study outline (Following the PICOT format; participants, intervention, control, outcome(s), timing). *Estimated timing:* six months after prioritisation 3 proposals will be circulated to the whole of the partnership in advance of workshop 3.

Workshop 3: Refining the proposals *(months 10 – 12)*

Objective: to provide independent peer review and opportunity to act on feedback in advance of submission for at least three draft proposals. Draft proposals will be submitted in advance and reviewed by independent experts from partner universities who have experience of reviewing grants for NIHR. Proposals and feedback will be presented to the whole partnership

before small working multidisciplinary groups (including PPIE focus groups) will work to strengthen identified weaknesses by reviewers to further refine and improve the proposals.

Key deliverable: Feedback provided from independent review, helping to improve the writing of the final bids for stage 2. *Estimated timing:* Three months after workshop 2. RDS will provide additional written feedback outside of the workshop (eg through proposal feedback form comprising methodologists, qualitative experts and public members).

Dissemination Stakeholder Event

The event at the end of the partnership was requested by all stakeholders within the EMG, including our PPIE steering group. The purpose will be to update the partnership on shared learning, activities completed, ongoing and planned opportunities for future work.

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