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REVIEW ARTICLE

Surrogate endpoints in liver surgery related trials: a systematic review of the literature

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Abstract

Background: Although the safety of liver surgery has improved enormously, hepatic surgery continues to face challenging complications. Therefore, improvements supported by evidence-based guidelines are still required. The conduct of randomized controlled trials in liver surgery using dichotomous outcomes requires a large sample size. The use of surrogate endpoints (SEPs) reduces sample size but SEPs should be validated before use.

Aim: The aim of this review was to summarize the SEPs used in hepatic surgery related trials, their definitions and recapitulating the evidence validating their use.

Method: A systematic computerized literature search in the biomedical database PubMed using the MeSH terms 'hepatectomy' or 'liver resection' or 'liver transection' was conducted. Search was limited to papers written in the English language and published between 1 January 2000 and 1 January 2010.

Results: A total of 593 articles met the search terms and 49 articles were included in the final selection. Standard biochemical liver functions tests were the most frequently used SEP (32 of 49 the studies). The used definitions of SEPs varied greatly among the studies. Most studies referred to earlier published material to justify their choice of SEP. However, no validating studies were found.

Conclusion: Many SEPs are used in liver surgery trials however there is little evidence validating them.

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Introduction

In the last decades, liver surgery has been a constantly evolving field and its prominent role in the treatment of primary, secondary, malignant or non-malignant liver diseases has been well established.[1] Although considerable improvements in mortality and morbidity rates have been achieved in many surgical centres, complications as a result of surgically induced liver damage still represent challenging events.[2] Consequently, trials evaluating surgical techniques and therapeutic interventions with appropriate endpoints are still needed in this field.

Randomized controlled trials (RCTs) are considered mandatory in evaluating the significance of clinical interventions and their potential implementation in daily clinical practice.[3] However, conducting adequately powered RCTs is frequently not feasible in many medical fields such as hepatic surgery.[4–6] In spite of calls for more rigorous surgical research trials, the overall number and quality of RCTs in surgery remains suboptimal.[6] The introduction of standards in reporting RCTs such as the Consolidated Standards of Reporting Trials (CONSORT)[7] has led to the necessity of defining primary and, if required, secondary outcomes.[7] Thus, it is imperative to standardize the definitions of the endpoints reported in hepatic surgery trials. Currently, the chosen outcomes are mostly clinical endpoints and can be divided in short- (e.g. peri-operative complications and peri-operative or 30 days mortality) and long-term outcomes (e.g. survival and disease-free survival). Van den Broek *et al.* recently demonstrated that conducting an adequately powered RCT in liver surgery using

the clinical dichotomous outcomes mortality and morbidity was not feasible because of the required large sample size.[8]The introduction of surrogate endpoints (SEPs) in RCTs is considered a potential solution for solving the problems which usually compromise the conduct of a sound trial such as complexity, sample size, long-term follow-up and costs.[9]

A SEP is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives.[10–12] Ideally, changes on a SEP induced by a therapy should reflect a clinically meaningful endpoint. In practice, this requirement frequently fails.[13] Moreover, SEPs should be validated before being used to assess clinical outcomes. Nonetheless, validation is usually overlooked, especially if biologically plausible grounds are given.[14] In practice, a correlation is often considered as validation for a SEP. However, it has been demonstrated that a correlate does not make a surrogate.[13]

Objectives of this paper

The aim of the present systematic review was to summarize the SEPs representing the effect of surgically induced damage used in liver surgery trials. Additionally, this study aimed at finding common definitions of the used SEPs and at recapitulating the evidence or validation justifying the use of those particular endpoints.

Methods

Search strategy

Three authors (K.v.M., D.L. and S.O.D.) performed a systematic computerized literature search according to the methodology recommended by the Cochrane Collaboration. The worldwide database of biomedical literature PubMed was searched using the Medical Subject headings (MeSH) terms: 'hepatectomy' or 'liver resection' or 'liver transection'. Additionally, the three authors (L.M., K.v.M. and D.L.) manually reviewed all the articles' references lists for identification of relevant studies. Search results were stored in an Endnote file (Endnote X2, Philadelphia, PA, USA).

Study eligibility

The search was limited to patients older than 18 years, and to articles published between 1 January 2000 and 1 January 2010. Exclusion criteria were non-human studies and papers published in languages other than English. Studies were eligible if they used SEPs as primary or secondary outcome measures. They were excluded if they reported only on dichotomous outcomes, such as mortality and morbidity, or only reported on survival. Papers using outcome measures that were not considered as surrogate markers for liver injury, i.e. the need for a blood transfusion, the amount of operative blood loss or transection time, were also excluded as well as studies reporting on surgical procedures other than liver resection or assessing the effects of different therapeutic modalities such as chemotherapy, radio-frequency ablation or liver transplantation. Trials focusing on non-surgical interventions such as imaging, the effect of portal vein embolization as well as on liver regeneration were also excluded.

Search of evidence justifying the use of SEPs

All included studies were further scrutinized for references justifying the choice of the used SEPs. All references related to the endpoints mentioned either in the 'introduction' or in the 'materials and methods' sections were considered as references providing evidence and justification for the choice of the SEP. All references were assessed for compliance with the Boissel criteria for validation of SEPs.[15] Briefly, SEPs were checked upon three criteria: convenience, prediction validity and relationship with clinical endpoint.

Data collection and analysis

Two authors (K.v.M. and L.M.) extracted the data and the results were reviewed independently by two other authors (D.L. and S.O.D.). Disagreements were solved by discussion. The following data were recorded systematically after formation of the final list of studies fulfilling the inclusion criteria: first author, year of publication, study design, number of patients, defined endpoints and the association of defined endpoints with morbidity, mortality or survival. The references given by the authors to explain the choice of the surrogate endpoints were also recorded in a separate Endnote file.

Results

Quality and quantity of evidence

A total of 593 articles met the search terms. Overall, 552 were excluded. Of those, 320 were excluded after reading the abstracts and 232 were excluded after reading the full text. Cross-checking through the references of the included papers delivered an additional 8 studies, resulting in a total of 49 articles being included in this review (Fig. 1). All studies were either RCTs or consecutive case series. The search for references justifying the choice of endpoints delivered 125 articles. These studies were mainly reviews or previously published clinical trials (data not shown).

Used SEPs and their definitions

Several biomarkers of hepatic functions as well as systemic parameters were used as SEPs (Table 1). Standard biochemical liver functions tests to quantify hepatocellular damage [post-operative plasma alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (AP)] were the most frequently used SEPs (32 of the 49 studies). Hepatic synthetic function quantified with various haematological factors such as prothrombin time (PT) and platelets counts was also frequently used (29 studies). Only two studies used a single SEP. The remaining studies examined a combination or two or more SEPs. Eleven studies did not find a correlation between the used SEP and a clinical outcome.

The definitions of the used SEPs varied greatly among studies (Table 2). The most frequently used SEPs (biochemical liver func-

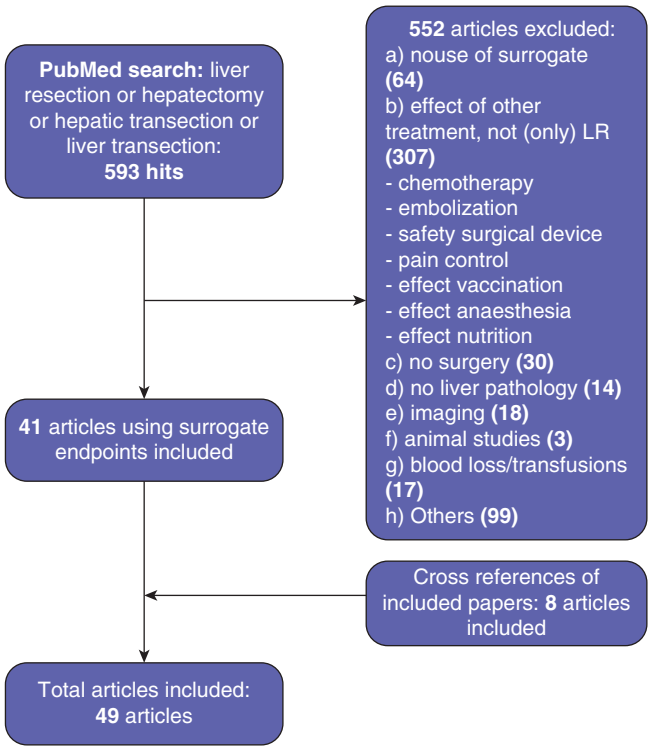

Figure 1 Flowchart selection articles. LR, liver resection

tion tests) were often defined as plasma peak values over a period of 3 to 7 days post-operatively. These discrepancies in definitions and timing of measurement of the SEPs were seen throughout the studies included in this review (Table 2). Authors aimed at showing a correlation between clinical outcomes (mortality and/or morbidity) or an independent predictor factor of these dichotomous outcomes.

Evidence justifying the choice of SEPs

A total of 26 studies referred to earlier published studies to support their choice of SEP (Table 3). From the retrieved studies justifying the SEP, 46% were experimental studies and 77% were clinical studies. Only 6 studies used RCTs as a reference for the selection of their endpoint. Of these none was a validating study for a SEP.

Validation of the SEPs using the three criteria defined by Boissel *et al*.

The used SEPs occurred more often than clinical endpoints, therefore complying to the first criteria described by Boissel *et al*.[15] The two other criteria of Boissel *et al*. could not be verified in this review as they required full insight of the original data and potential follow-up of the patients.

Discussion

The present systematic literature review is an attempt at a comprehensive and critical evaluation of surrogate endpoints used in liver surgery-related clinical trials. The majority of studies used biological plausible, though not validated, surrogate outcomes. As the liver is involved in a multitude of processes, many functions could serve as surrogate endpoints. In line with this, many surrogate outcomes have been used in reporting the results of trials in hepatic surgery. However, there was a lack in standardized definitions of the most commonly used SEPs.

Liver surgery has been a subject of extensive research in the past two decades.[16] As a result, the safety and efficacy of surgical interventions have increased substantially while the indications for performing a liver resection are continuously extending.[17–20] In spite of a decrease in mortality and morbidity rates, there is still a need for standardized outcome parameters to evaluate therapeutic efficacy or hazards of liver operations.[21] Composite and surrogate outcomes are considered as statistically adequate alternatives for replacing the standard short-term dichotomous outcome of mortality and morbidity in many medical fields.[21–25] Formulation of surrogate outcomes requires, first and foremost, standardization of definitions of the used SEPs. The lack of adequate definitions of outcomes impairs comparison and evaluation of diagnostic and therapeutic trials. Recently, van den Broek *et al*.[21] conducted a survey among hepato-biliary surgeons to reach a consensus on definitions of complications after liver surgery. These definitions were extracted from the currently available literature and standardized by the authors before being subjected to discussion by experts. The need for the aforementioned survey on the definitions was because of the lack of uniformity on definitions as shown in the present review. To reach a consensus on the definitions of the SEPs frequently used in liver surgery related trials, a questionnaire similar to the survey above stated should be designed. Defining SEPs for hepatic surgery trials should take into account the numerous targets of interventions in liver surgery-related trials. As all the currently used SEPs are yet to be validated, many definitions can be proposed and adapted to the different effects expected from various interventions.

In the present comprehensive literature review, we were able to retrieve references rationalizing the selection of SEPs used in the majority of the studies. These references were studies using similar endpoints either in clinical trials or in experimental settings. Unfortunately, no study using validated SEPs was found. Validation and value of SEPs has been, and still is, a matter of debate.[13,26] Prentice[12] developed four criteria that are sufficient to validate a SEP in phase three clinical trials. However, these criteria have been considered too stringent and difficult to verify.[27,28] In a comprehensive review, Boissel *et al*.[15] redefined the three main criteria that a SEP must meet to be considered as valid surrogate for a clinical endpoint. First, a surrogate should be convenient, i.e. it should occur more often than the corresponding clinical point. The time course of the SEP should precede that of the clinical endpoint so that disease or its progression can be recognized or predicted quicker than the actual clinical endpoint using the SEP.[25] Second, the relationship between the surrogate and the clinical endpoint should be established both quantitatively and qualita-

Table 1 Functions and events used as surrogate endpoints (SEPs)

Function and/or event measured	Surrogate endpoints	Number of papers using SEPs
• Hepatic parameters		
Hepatocellular damage	ALT, AST, GGT, AP	32
Uptake, conjugation, excretion	Serum (total or conjugated) bilirubin	29
Cholestasis	Alkaline phosphatase	2
Hepatic synthetic function	Coagulation factors, platelets, INR, PT, glycogen content, albumin	23
Hepatic perfusion, anion excretion	ICG (k), ICG-PDR	6
Hepatic anaerobe metabolism	Transhepatic oxygen pressure gradient, hepatic oxygenation, transhepatic lactate gradient	2
Hepatocyte urea synthesis capacity	Ammonia	1
• Systemic parameters		
Oxidative stress	SOD, MDA, MPO, gluthatione, gluthatione disulfide	6
Anaerobe metabolism	Lactate, pyruvate	6
Inflammation	Cytokines, PMNL activation, CRP	12
Apoptosis	Caspases, Bcl2, beclin-1	1

ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase; AP, alkaline phosphatse; INR, international normalized ratio; PT, prothrombin time; ICG, indocyanine green; SOD, superoxide dismutase; MDA, malondialdehyde; MPO, myeloperoxidase; PMNL, polymorphonuclear leucocyte; CRP, C-reactive protein.

tively through relevant epidemiological and clinical studies. The nature of this relationship should be understood in terms of pathophysiology or in terms of an expression of joint risk.[25] Lastly, a surrogate endpoint should produce parallel estimates of risks and benefits as the clinical endpoints. The endpoints selected by the authors in the last 10 years all seemingly comply to the first criterion as they describe alterations either in hepatic or systemic parameters. However, we were not able to verify if the other criteria were met challenging the validity of the obtained results in the studies included in this review. The complexity of validation is perhaps clearly illustrated by two elegant studies which attempted to validate surrogates for mortality following post-resectional liver failure.[29,30] Balzan *et al.* prospectively evaluated 704 patients undergoing hepatic resection.[29] They were able to show that the 50-50 criteria (PT <50% and serum total bilirubin >50 μmol/l on day 5 post-operatively) were an accurate predictor of liver failure and death after a hepatectomy. However, their findings were soon contested by Mullen *et al.*[30] who conducted a similar study in 1059 patients undergoing major hepatectomy in which the 50-50 criteria could not be reproduced. The authors therefore introduced a new criterion (peak bilirubin >7.0 mg/dl) that should be considered as a more reliable marker predicting post-resectional liver failure and mortality.

Several other medical fields have been trying to standardize the outcomes that are used in clinical trials. Recently, the National Institutes of Health (NIH) and the Agency for Healthcare Research and Quality in the United Kingdom convened an expert group to propose which biomarkers should be assessed as standardized asthma outcomes in future clinical research studies.[31–33] The challenging task of validating SEPs in liver surgery related trials should follow a similar design and start by assessing and standardizing the definitions of the most commonly used SEPs. It could be achieved either by the conduct of a survey among worldwide HPB surgeons or the formation of an experts panel as demonstrated by the NIH. As a result, a common international prospective database with clear definitions of SEPs could be established. This database would allow the conduct of multicentre trials validating the SEPs in liver surgery. Alternatively, a large multi-centre, multi-national prospective study could be designed to validate the potentially most valuable SEPs. As an example, the Medical Research Council (UK) recently funded a prospective validation study of a combination of the SEPs dimethyl-arginine and ischaemia modified albumin (DASIMAR; MRC 08/H0714/8) in decompensated cirrhosis. Moreover, a recently published study presented an international, multicentre, external validation analysis of the utility interval to biochemical failure (IBF) in predicting prostate cancer mortality at the time of biochemical failure.[34] IBF was chosen as prostatic cancer progression defined by prostate-specific antigen, otherwise known as biochemical failure (BF), is almost always the earliest sign of recurrent prostate cancer and can predate clinical manifestations of disease by months to years. Earlier, a large study of 221 men who experienced BF after radiotherapy, a shorter time interval between the completion of treatment and BF [i.e. interval to BF (IBF)] had been shown to be related to the development of distant metastasis and prostate cancer mortality.[35] Thereafter the extensive validation study was designed to substantiate IBF as a SEP for identification of the potentially lethal prostate cancer. These studies are solid examples liver surgery researchers can follow.

Table 2 Surrogate endpoints and definitions used

First author, year	Liver-related SEP (primary or secondary)	Timepoints of measurement and definition endpoint
Taura, 2010[36]	Portal and hepatic veins pressures; hepatic artery and portal vein blood flow; lactate; bilirubin, INR	Haemodynamic, oxygenation and liver functions at the time of abdominal closure, liver function also peak value over PODs 1, 2 and 4
Pietsch, 2010[37]	Lactate and pyruvate levels in arterial and hepatic venous blood and hepatic oxygenation	Values during liver manipulation, 15 min after hilus occlusion, 10 min after end of LR, at the time of abdominal closure and on POD 1
Domart, 2009[38]	Caspases 3,8,9, Bcl2, beclin-1, light chain type II expressions, vacuoles; ALT, AST, bilirubin, AP, GGT, PT	Values just prior to IP and after liver reperfusion and liver function on POD 7
Xia, 2009[39]	ALT, AST, bilirubin, HA, IL-6	Peak values over 1, 3 and 7 PODs
de Liguori, 2009[40]	ICG PDR, PLF; AST, ALT, bilirubin	Correlation between ICG PDR and onset PLF; correlation ICG PDR and AST, ALT, bilirubin on PODs 1, 5, 10
Arkadopoulos, 2009[41]	AST, bilirubin, PT, IL-6, IL-8, MDA	Liver function: daily till discharge; IL: at 12, 24 and 48 h after LR; MDA: 5 min prior to occlusion and 1 h after reperfusion
Wen, 2009[42]	ALT, T-bilirubin	Values over postoperative course
Beck-Schimmer, 2008[43]	AST and ALT	Peak AST and ALT over 7 PODs
Akita, 2008[44]	ICG-R15 and T-bilirubin	ICG-R15 (after opening abdomen, during clamping phase and at abdomen closure) and peak T-bil over hospitalization period
Ko, 2008[45]	TLV, graft volume, RLV, AST, ALT, T-Bil, PT, albumin, blood urea nitrogen	Values after closure abdomen and over PODs 1, 2, 3, 5, 7 and 30
Scheingraber, 2008[46]	ICG PDR, PT and bilirubin	Peak over 7 PODs
Kim, 2007[47]	ALT, AST, Tbil, IL-6	IL-6: values before and after 30 min Pringle, and liver function tests: values over postoperative course
Pulitano, 2007[2]	PT-INR, AT III, mean platelet count, fibrinogen, D-dimer, platelets count; IL-6, TNF-a	Values over PODs 1, 2 and 5
Tang, 2002[48]; 2007[49]	Glycogen, MDA and ATP content, SOD activity; AST, ALT, AKP	Glycogen content: before occlusion, ATP, MDA and SOD: after occlusion and after 1 hr reperfusion, Liver functions: PODs 1 and 5
Brooks, 2007[50]	Partial pressure carbon dioxide in liver tissue, partial pressure oxygen, bilirubin, ALT	Pressures after 10 min clamping and 5 min reperfusion or 10 min clamp and 20 min reperfusion, Liver function: POD 2
Mullen, 2007[30]	Bilirubin, INR	Peak bilirubin and INR over 90 days
Kostopanagiotou, 2007[51]	Fibronectin	Concentration on POD 1
Schmidt, 2007[52]	IL-6, IL-8, IL-10, TNF-a*, HLA-DR, LPS-induced TNF-a, CRP*	Mean values over PODs 1, 2, 3 and 7
Petrowsky, 2006[53]	AST, ALT, bilirubin and PT	Peak values and area under the curve over 5 PODs
Kostopanagiotou, 2006[54]	MDA AST, PT and bili	MDA: values 5 min after reperfusion, at the end of LR and on PODs 1, 3 and 6, Liver function: On PODs 1, 3 and 6
Theodoraki, 2006[55]	Lactate, transhepatic lactate gradient, transhepatic oxygen pressure gradient	Values 50 min after reperfusion
Dunschede, 2006[56]	Lactate, CHE, AST, ALT and ATP content	Lactate, CHE, ATP content, ALT and AST: opening abdomen, 30 min ischaemia, 30 min reperfusion, POD1, AST, ALT: peak PODs 1–3
Esaki, 2006[57]	Bilirubin ration calculated as serum T-bil on POD2 divided by preoperative level; PT, AST, ALT	Values over 10 PODs
Azoulay, 2006[58]	AST, ALT, T-bil, GST, PT	ALT: peak over PODs 1, 7, 30 (primary endpoint), GST, AST (peak), PT, T-bil: values over PODs 1, 7 and 30
Kim, 2006[59]	IL-6; AST, ALT, PT, Tbil, ICG R15	IL-6: after LR but before reperfusion, at closure abdomen and on POD1, Liver function: Peak over PODs 1, 3 and 7
Sugimoto, 2006[60]	ICG-K values, T-bil, albumin	Values over PODs 1, 2, 3, 5 and 7, Liver function: on POD1

Table 2 *Continued*

First author, year	Liver-related SEP (primary or secondary)	Timepoints of measurement and definition endpoint
Balzan, 2005[29]	Bilirubin and PT	Values at over 7 PODs
Figueras, 2005[61]	ALT, AST, lactate, PT, bilirubin	Liver function: over PODs 1, 2, 3, 5 and 6, Lactate: at the beginning of mobilization, after 10 min reperfusion
Chouker, 2005[62]	PMNL activation, MPO, IL-6, IL-8, ALT	PMNL: 3, 15, 30, 120 min after LR, POD1, MPO: 30 min after LR, ALT: on PODs 1, 2; IL-6, IL-8: 30, 60 min after LR and POD1
Chouker, 2005[63]	ALT, AST, a-GST	Values at 3, 15, 30, 60 min, 24 h and 48 h after LR
Kaiho, 2005[64]	Ammonia	Values over 5 PODs
Bartels, 2004[65]	ALT, AST	Values over PODs 1, 10, 30 min after reperfusion, 6, 12 h after ICU admission, PODs 1, 2, 4 and 6
Li, 2004[66]	AST, ALT, T-bil, albumin, caspase-3 activity, TUNEL assay	Values over PODs 1, 3 and 7
Nishiyama, 2004[67]	ALT, AST, T-bil, albumin, AKP, CHE, PT and platelet count	Values over PODs 1, 3 and 7
Nuzzo, 2004[68]	AST, ALT, bilirubin, PT	Values over PODs 1, 3 and 7
Clavien, 2003[69]	AST, ALT, bilirubin, PT, hepatic ATP	Peak AST and ALT over 7 PODs; ATP: 30 min after reperfusion
Smyrniotis, 2003[70]	PT, bilirubin, AST, ALT; IL-6, IL-8; MDA	Liver function : Peak over PODs 1 to 6; Cytokines: 3, 12, 24 and 48 h after LR; MDA: 30 min after reperfusion
Wu, 2003[71]	IL-6, endostatin	Values over 2, 4, 8 h and PODs 1, 3, 5, 7, 9
Capussotti, 2003[72]	AST, ALT, Tbil	Peak over PODs 1, 3 and 7
Man, 2003[73]	ET1 expression, eNOS and iNOS activity	Correlation between ET-1 and eNOS activity with hepatic ultrastructural changes
Muratore, 2003[74]	IL-6, AST, ALT	IL-6: 1, 4 and 24 h after LR; Liver function: 1, 4 and 24 h after LR
Tang, 2002[48]	Glycogen, ATP and MDA contents, SOD activity, AST, ALT, AKP	At the end of the vascular occlusion and 1 h after reperfusion; Liver function: values over PODs 1 and 5
Vriens, 2002[75]	MDA, glutathione, glutathione disulfide, vitamin C liver enzymes and blood clotting factors	–
Kim, 2002[76]	ALT, AST, bilirubin, TNF-α, IL-1b, IL-6	Liver function: values over PODs 1, 3 and 7; Cytokines: laparotomy, at completion of parenchymal transection, 1 h post reperfusion
Okochi, 2002[77]	T-bil, platelet, AST, ALT, PT, ICGk	Values over PODs 1, 2, 3, 5 and 7
Wiezer, 2001[78]	Plasma amino acid patterns, coagulation and fibrinolytic cascade systems and neutrophil functions	–
Orii, 2001[79]	ALT, AST, ICGk, lactate	Values just after reperfusion and 1 h after reperfusion; Liver function: values over 1 h after LR, PODs 1 and 3
Noie, 2001[80]	AST, Tbil, alb, PT; UTI-urinary trypsin inhibitor in plasma pUTI and urine uUTI, CRP	Values over postoperative course
Yamashita, 2001[81]	IL-6, IL-10 peritoneal and venous	Values over 0, 6, 12 h after reperfusion and on PODs 1, 3 and 7

ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transpeptidase; AP, alkaline phosphatse; INR, international normalized ratio; PT, prothrombin time; ICG, indocyanine green; ICG PDR, indocyanine green plasma disappearance rate; SOD, superoxide dismutase; MDA, malondialdehyde; MPO, myeloperoxidase; PMNL, polymorphonuclear leucocyte; CRP, C-reactive protein; IL, interleukin; HA, hyaluronic acid; LR, liver resection; POD, postoperative day; IP, intermittent pringle manoeuver; PLF, post-resectional liver failure; TLV, total liver volume; RLV, rest liver volume; CHE, cholinesterase.

In an attempt to define and validate SEPs in hepatic surgery trials, caution should be taken in the choice of SEPs considering the different types of hepatic surgery that can be studied and the patient population that is being investigated.

Conclusions

The present systematic review showed that many SEPs are used in hepatic surgery related research. Although these endpoints are

Table 3 Studies used as references for the choice of the surrogate endpoints (SEPs)

First author, year	References for validation of SEPs	Characterization of studies used as references
Taura, 2010[36]	No specific mention of validating studies	No specific mention of validating studies
Pietsch, 2010[37]	No specific mention of validating studies	No specific mention of validating studies
Domart, 2009[38]	No specific mention of validating studies	No specific mention of validating studies
Xia, 2009[39]	No specific mention of validating studies	No specific mention of validating studies
de Liguori, 2009[40]	SEPs adopted from an earlier trial	RCT
Arkadopoulos, 2009[41]	No specific mention of validating studies	No specific mention of validating studies
Wen, 2009[42]	No specific mention of validating studies	No specific mention of validating studies
Beck-Schimmer, 2008[43]	SEPs adopted from clinical and experimental studies	RCTs and experimental studies
Akita, 2008[44]	No specific mention of validating studies	No specific mention of validating studies
Ko, 2008[45]	No specific mention of validating studies	No specific mention of validating studies
Scheingraber, 2008[46]	No specific mention of validating studies	No specific mention of validating studies
Kim, 2007[47]	No specific mention of validating studies	No specific mention of validating studies
Pulitano, 2007[2]	SEPs adopted from earlier trials	RCT and consecutive case series
Tang, 2007[49]	SEP adopted from earlier trials	Experimental studies
Brooks, 2007[50]	SEPs adopted from earlier trials	Observational clinical studies and experimental studies
Mullen, 2007[30]	SEP initially adopted an earlier trial	RCT
Kostopanagiotou, 2007[51]	SEP adopted from a review	Review
Schmidt, 2007[52]	No specific mention of validating studies	No specific mention of validating studies
Petrowsky, 2006[53]	SEPs adopted from earlier trials	RCTs
Kostopanagiotou, 2006[54]	No specific mention of validating studies	No specific mention of validating studies
Theodoraki, 2006[55]	No specific mention of validating studies	No specific mention of validating studies
Dunschede, 2006[56]	SEPs adopted from earlier trials	Experimental study and clinical study
Esaki, 2006[57]	SEPs adopted from clinical experience	No study was used but clinical experience
Azoulay, 2006[58]	SEPs adopted from earlier studies	Clinical studies and an experimental study
Kim, 2006[59]	SEP adopted from earlier studies	Experimental and clinical studies
Sugimoto, 2006[60]	SEPs adopted from earlier trials	Several clinical studies (RCTs and consecutive case series)
Balzan, 2005[29]	SEPs adopted from two trials	RCTs
Figueras, 2005[61]	SEPs adopted from earlier trials	Clinical studies
Chouker, 2005[62]	No specific mention of validating studies	No specific mention of validating studies
Chouker, 2005[63]	SEPs adopted from earlier studies	Clinical trials and experimental studies
Kaiho, 2005[64]	No specific mention of validating studies	No specific mention of validating studies
Bartels, 2004[65]	No specific mention of validating studies	No specific mention of validating studies
Li, 2004[66]	SEPs adopted from an earlier trial	RCT
Nishiyama, 2004[67]	No specific mention of validating studies	No specific mention of validating studies
Nuzzo, 2004[68]	SEPs adopted from an earlier trial	RCT
Clavien, 2003[69]	SEP adopted from an earlier trial	Non-randomized pilot study
Smyrniotis, 2003[70]	SEP adopted from earlier studies	Experimental and clinical studies
Wu, 2003[71]	SEPs adopted from earlier trials	Experimental studies
Capussotti, 2003[72]	No specific mention of validating studies	No specific mention of validating studies
Man, 2003[73]	SEPs adopted from earlier studies	Experimental and clinical studies
Muratore, 2003[74]	SEPs adopted from earlier studies	Experimental and clinical studies
Tang, 2002[48]	No specific mention of validating studies	No specific mention of validating studies
Vriens, 2002[75]	No specific mention of validating studies	No specific mention of validating studies
Kim, 2002[76]	SEPs adopted from earlier studies	Experimental studies
Okochi, 2002[77]	SEP adopted from an earlier trial	Clinical study
Wiezer, 2001[78]	No specific mention of validating studies	No specific mention of validating studies
Orii, 2001[79]	SEPs adopted from earlier studies	Several clinical studies in the transplantation setting
Noie, 2001[80]	No specific mention of validating studies	No specific mention of validating studies
Yamashita, 2001[81]	SEPs adopted from an earlier trial	Clinical trial

RCT, randomized controlled trial.

biologically plausible, there is little evidence on their validity as true surrogates of clinical endpoints. It is important to standardize SEPs definitions and validate the SEPs used in liver surgery trials as the safety is steadily increasing making the differences between interventions smaller and therefore leading to enormous sample sizes. Validated SEPs could be reliable surrogates of clinical endpoints.

Conflicts of interest

None declared.

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Authors' contributions

Liliane Mpabanzi: manuscript writing, retrieval of data, analysis of results and critical review of the final manuscript.

Kim van Mierlo: search and retrieval of data.

Massimo Malago: critical review of the manuscript.

Cornelis Dejong: critical review of the manuscript.

Dimitrios Lytras: search, retrieval of data and critical review of the final manuscript.

Steven Olde Damink: original idea, search and critical review of the final manuscript.

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