Meta-analysis

Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection

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Background: **The risk of major hepatic resection in patients with hepatic steatosis remains controversial. A meta-analysis was performed to establish the best estimate of the impact of steatosis on patient outcome following major hepatic surgery.**

Methods: **A systematic search was performed following Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. Risk ratios (RRs) for complication and mortality rates were calculated for patients with no, less than 30 per cent and at least 30 per cent steatosis, and a meta-analysis was carried out.**

Results: **Of six observational studies identified, four including a total of 1000 patients were subjected to meta-analysis; two others were tabulated separately. Compared with patients without steatosis, those with less than 30 per cent and at least 30 per cent steatosis had a significantly increased risk of postoperative complications, with a RR of 1·53 (95 per cent confidence interval (c.i.) 1·27 to 1·85) and 2·01 (1·66 to 2·44) respectively. Patients with at least 30 per cent steatosis had an increased risk of postoperative death (RR 2·79, 95 per cent c.i. 1·19 to 6·51).**

Conclusion: **Patients with steatosis had an up to twofold increased risk of postoperative complications, and those with excessive steatosis had an almost threefold increased risk of death.**

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Introduction

Non-alcoholic fatty liver disease comprises a variety of pathological states ranging from hepatic steatosis to non-alcoholic steatohepatitis, cirrhosis and, ultimately, liver failure[1]. Mostly unrecognized before 1980, it is now estimated that up to 30 per cent of the Western adult population has some degree of steatosis[2]. Today, non-alcoholic fatty liver disease is the most common chronic liver disease in Western countries, and its prevalence has mirrored the increasing epidemic of obesity and the metabolic syndrome[2,3]. The prevalence in non-Western countries is also expected to increase, mainly as a result of globalization of the Western diet.

Hepatic surgery is the only curative treatment option for patients with primary and secondary hepatobiliary malignancies[4–6], and liver resection is increasingly being performed for living donor liver transplantation[7]. Advances in surgical technique and improvements in preoperative evaluation of liver function in selected patients have resulted in a decline in the perioperative mortality rate to as low as zero[8,9]. The risk of morbidity and mortality associated with hepatic surgery, however, is closely related to the volume and function of the remnant liver[10]. It is estimated that about 20 per cent of patients undergoing liver resection and up to 25 per cent of donors for liver transplantation have some degree of steatosis[11]. Extensive surgery can be performed safely on healthy livers, but the risk of major hepatic resection in patients with steatosis remains unclear[12,13].

Although steatosis is an established risk factor for primary non-function of hepatic allografts[11,14,15], the literature with respect to surgical outcome following a major hepatectomy has not been reviewed systematically. The aim of this systematic review was to assess the impact of hepatic steatosis on complications and mortality following major hepatic surgery for either hepatic neoplasms or living liver donation.

Methods

Literature search strategy

A systematic search of PubMed, Embase, Science Citation Index, CINAHL and the Cochrane Library was performed for articles published between January 1994 and May 2009 (cut-off date 1 May 2009) relevant to steatosis as a risk factor in major hepatobiliary surgery for either hepatic neoplasms or living liver donation. Before 1994, the literature offered little to no clinical data on the impact of steatosis on surgical outcome. The MeSH headings 'surgical procedures, operative' and 'fatty liver' were used in PubMed. Keywords used in other databases included 'steatosis' and 'surgery'. Manual reference checks of accepted papers in recent reviews and included papers were performed to supplement the electronic searches.

Literature screening

Studies were evaluated for inclusion by two independent reviewers for relevance to the subject. Study selection was accomplished through three levels of study screening (*Fig. 1*). At level 1, studies were excluded for the following reasons: reviews, letters, case reports, editorials and comments; animal or *in vitro* studies; fewer than ten patients in the study; and languages other than English. At level 2, abstracts of all studies accepted at level 1 were reviewed for relevance. The full text was obtained for relevant papers and any citations for which a decision could not be made from the abstract. For level 3 screening, inclusion required that studies described patients who underwent major hepatobiliary surgery, defined as a resection of at least three liver segments, for either hepatic neoplasms or living liver donation; measured steatosis by histology and assessed the degree of steatosis independently; described surgical outcomes (morbidity and/or mortality) and stratified outcomes by degree of steatosis; and described the outcomes of the donor, not the recipient, in studies of living liver donation. These selection criteria were assessed independently by the reviewers and scored on a standardized form. Any discrepancies in inclusion were resolved by discussion between the reviewers.

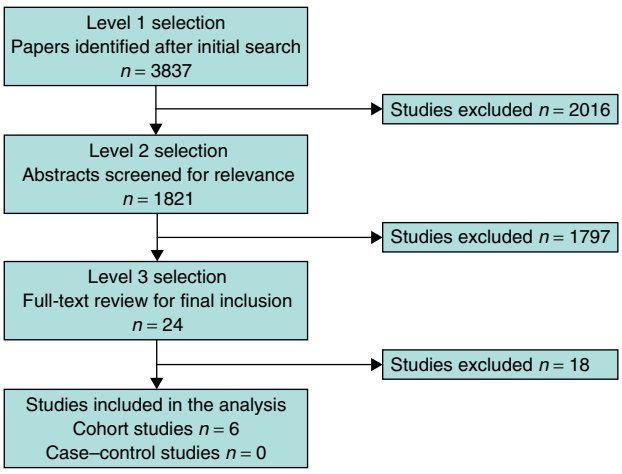

Fig. 1 Flow diagram showing selection of articles

Data extraction and critical appraisal

Data, including study design, study population, presence or not of steatosis and grade if present, and outcomes, were extracted in duplicate from each included article using a standard form. Because differences in underlying parenchymal disease and associated co-morbidities might affect homogeneity, articles that described outcomes for patients who underwent major hepatic resection for either hepatic neoplasms or living liver donation were tabulated separately to allow more accurate risk assessment. Kin relationships, defined as multiple publications describing the same or overlapping series of patients, were identified and the data included only once to avoid double counting of patients. The level of evidence of each article was scored using the Oxford Centre for Evidence-based Medicine Level of Evidence scale[16] and the quality of articles was assessed according to the Newcastle–Ottawa Scale for observational and case–control studies, which scores selection, comparability and outcome[17].

Statistical analysis

Risk ratios (RRs) and 95 per cent confidence intervals (c.i.) were calculated from raw data using patients without steatosis as the reference group. Where possible, outcome data resulting from multivariable analysis were extracted from the identified manuscripts. For univariable analysis, statistical significance between groups was assessed using Fisher's exact test.

A meta-analysis was performed with complications and mortality as outcome measures using Review Manager (RevMan) software (version 5.0.21; The Nordic Cochrane Centre, Copenhagen, Denmark). Each study was weighted by sample size. Studies were not weighed for study quality (quality of allocation concealment). The complications and mortality associated with the

different degrees of steatosis (no steatosis *versus* less than 30 per cent steatosis, and no steatosis *versus* at least 30 per cent steatosis) were estimated as a pooled RR with 95 per cent c.i. using the random-effects model of DerSimonian and Laird[18]. Overall effects were determined using the Z test. Two-sided $P < 0{\cdot}050$ was considered statistically significant. Statistical heterogeneity was explored by inspecting the forest plot, and from χ^2 and inconsistency (I^2) statistics; an I^2 value of 50 per cent or more represented substantial heterogeneity[19].

Sensitivity analysis showed that the overall estimates using the fixed-effects model were virtually identical, indicating relatively little variation between included studies. Other sensitivity analyses included removal of one study at a time to determine whether the conclusion was driven by any single study, cumulative meta-analysis to determine sensitivity to publication date, and assessment of the width of the confidence interval around a summary effect size to determine the robustness of a quantitative estimate. The meta-analysis was carried out in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines[20].

Results

Quantity and quality of evidence

Among 3837 articles identified by the initial search, six fell within the scope of the study (*Fig. 1*)[13,21–25]. Four articles described outcomes for patients who underwent major hepatic resection for hepatic neoplasms (*Table 1*)[21–24], whereas two described patients who underwent major surgery for living liver donation (*Table 2*)[13,25]. All identified studies followed an observational design, scored 7 or more (of 9) on the Newcastle–Ottawa Scale and provided level 2b evidence on the Oxford Level of Evidence scale.

Complications

On univariable analysis, Gomez and colleagues[23], Kooby and co-workers[22] and McCormack *et al.*[24] found that patients with any degree of steatosis had a significantly increased risk of postoperative complications following hepatic surgery ($P < 0{\cdot}001$[22,23] and $P = 0{\cdot}012$[24]). Multivariable analysis revealed that, when adjusted for potential confounders such as presence of co-morbidity, extent of hepatic resection and amount of intraoperative blood loss, any degree of steatosis remained associated with total postoperative complications, with RRs ranging from 1·24 to 3·84[22–24]. In addition, Kooby and colleagues[22] reported that patients with any degree of steatosis were more likely to suffer from infective, wound-related, hepatobiliary and gastrointestinal postoperative complications. Gomez and co-workers[23] also noted that patients with any degree of steatosis had an increased risk of infective complications.

In contrast, Behrns and colleagues[21], Cho and co-workers[13] and Nagai *et al.*[25] did not find a significant association between overall complications and steatosis

Table 1 Characteristics, outcome measures and major findings of studies describing patients who underwent major hepatic surgery for benign or malignant neoplasms

Reference	Year	Country	Study type	Steatosis	*n*	NOS	Evidence	Primary outcome	Major findings
Behrns *et al.*[21]	1998	USA	Retrospective cohort	No steatosis Total steatosis < 30% ≥ 30%	72 63 56 7	7	2b	Complications/death within 30 days or before discharge	Patients with steatosis: Complication rate↑ Bilirubin leak↑
Kooby *et al.*[22]	2003	USA	Prospective cohort	No steatosis Total steatosis < 30% ≥ 30%	160 325 223 102	9	2b	Complications/death within 60 days or before discharge	Patients with steatosis: Complication rate↑ Mortality not↑
Gomez *et al.*[23]	2007	UK	Prospective cohort	No steatosis Total steatosis < 30% 30–60% > 60%	192 194 122 60 12	8	2b	Complications/death before discharge; blood loss; length of ICU stay; liver failure	Patients with steatosis: Complication rate↑ Mortality not↑ Blood loss↑ Length of ICU stay↑
McCormack *et al.*[24]	2007	USA	Prospective cohort (matched)	No steatosis Total steatosis 10–30% > 30%	58 58 44 14	9	2b	Complications/death within 90 days; blood loss; length of ICU stay	Patients with steatosis: Complication rate↑ Mortality not↑ Blood loss↑ Length of ICU stay↑

NOS, Newcastle–Ottawa Scale; ICU, intensive care unit; ↑, increased.

Table 2 Characteristics, outcome measures and major findings of studies describing patients who underwent major hepatic surgery for living related liver donation

Reference	Year	Country	Study type	Steatosis	*n*	NOS	Evidence	Primary outcome	Major findings
Cho *et al.*[13]	2006	Korea	Prospective cohort	No steatosis Total steatosis 5–30%	36 18 18	7	2b	Complications/death	Patients with steatosis: Complication rate not↑ Mortality not↑ Early regeneration impaired Long-term regeneration not impaired
Nagai *et al.*[25]	2009	Japan	Prospective cohort	No steatosis Total steatosis 5–20%	31 10 10	8	2b	Complications/death; liver regeneration; liver function	Patients with steatosis: Complication rate↑ Long-term regeneration not impaired Hyperbilirubinaemia↑

NOS, Newcastle–Ottawa Scale; ↑, increased.

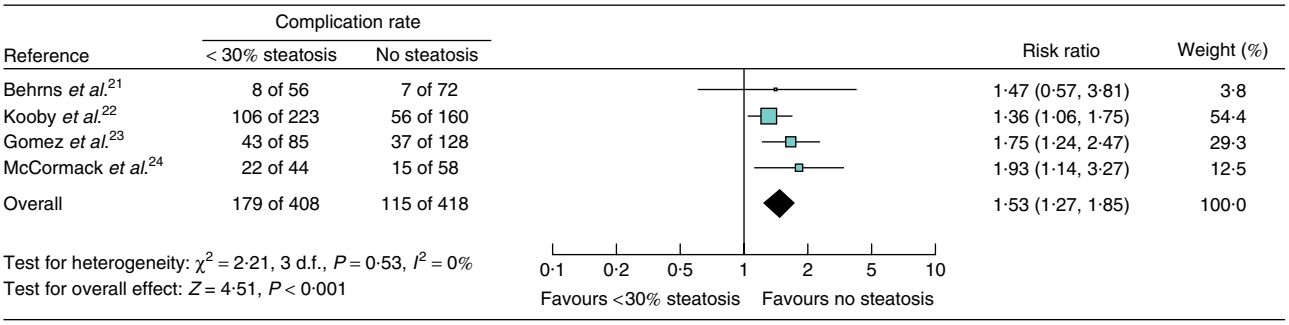

Fig. 2 Forest plot of complication rates in patients with less than 30 per cent steatosis *versus* those with no steatosis. Risk ratio estimates, shown with 95 per cent confidence intervals, were calculated using the random-effects model. The diamond represents the overall treatment effect from the pooled studies spanning the 95 per cent confidence interval. No steatosis was defined as no hepatocytes containing fat infiltration[21–23] and less than 10 per cent of hepatocytes with fat droplets[24]

in patients who underwent hepatic resection. Behrns and colleagues[21] described patients who underwent hepatic resection for hepatic neoplasms, whereas Cho and co-workers[13] and Nagai *et al.*[25] described the outcome of living liver donation. On univariable analysis, Behrns and colleagues[21] found that patients with steatosis were more likely to develop hyperbilirubinaemia and increased aspartate aminotransferase levels following hepatic surgery. Logistic regression analysis by Nagai and co-workers[25] corroborated this result by demonstrating that steatosis was associated with the development of hyperbilirubinaemia in living liver donors with mild steatosis (5–20 per cent) following hepatectomy (odds ratio 7·94, 95 per cent c.i. 1·17 to 54·03; $P = 0·034$). In contrast, Cho *et al.*[13] found that biliary leakage was the most common major complication among living liver donors following hepatectomy, although rates for patients with and without steatosis were not significantly different (RR 1·27, 95 per cent c.i. 0·94 to 1·72; $P = 0·100$).

A meta-analysis was subsequently conducted to investigate steatosis as a risk factor for complications following major hepatic resection (at least three segments). Four studies were included in the meta-analysis[21–24], all of which examined patients who underwent hepatic resection for primary or secondary malignancies. For studies that also included patients having resection of fewer than three segments, only data for those who underwent resection of at least three segments were included in the meta-analysis. A total of 1000 patients was analysed, including 418 patients with no steatosis, 408 with less than 30 per cent steatosis and 174 with at least 30 per cent steatosis. Two studies[13,25] were excluded to avoid introduction of heterogeneity because the authors studied living liver donors who, by definition, did not have underlying liver pathology. There was no substantial heterogeneity when comparing complication

rates in patients with either less than or at least 30 per cent steatosis with patients without steatosis ($I^2 = 0$ per cent). The summary RR of patients with less than 30 per cent steatosis compared with patients without steatosis was 1·53 (95 per cent c.i. 1·27 to 1·85; $P < 0·001$) (*Fig. 2*). The summary RR of patients with more severe steatosis (at least 30 per cent) compared with patients without steatosis was 2·01 (95 per cent c.i. 1·66 to 2·44; $P < 0·001$) (*Fig. 3*).

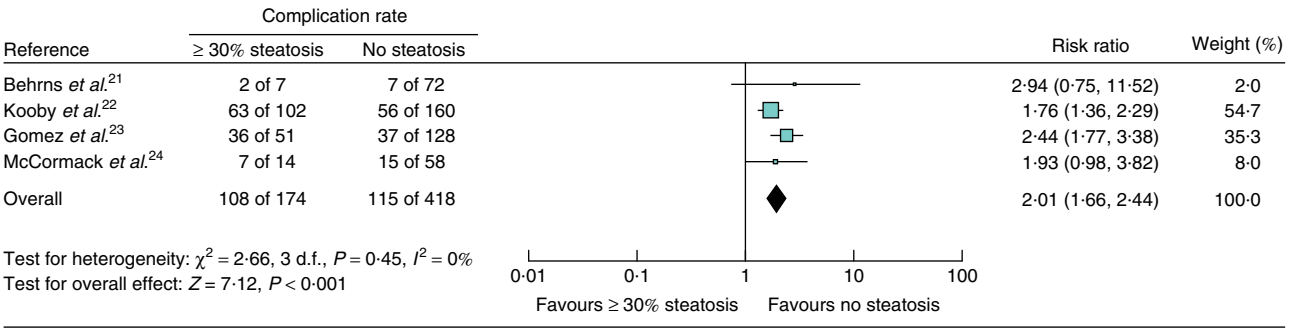

Fig. 3 Forest plot of complication rates in patients with at least 30 per cent steatosis *versus* those with no steatosis. Risk ratio estimates, shown with 95 per cent confidence intervals, were calculated using the random-effects model. The diamond represents the overall treatment effect from the pooled studies spanning the 95 per cent confidence interval. No steatosis was defined as no hepatocytes containing fat infiltration[21–23] and less than 10 per cent of hepatocytes with fat droplets[24]

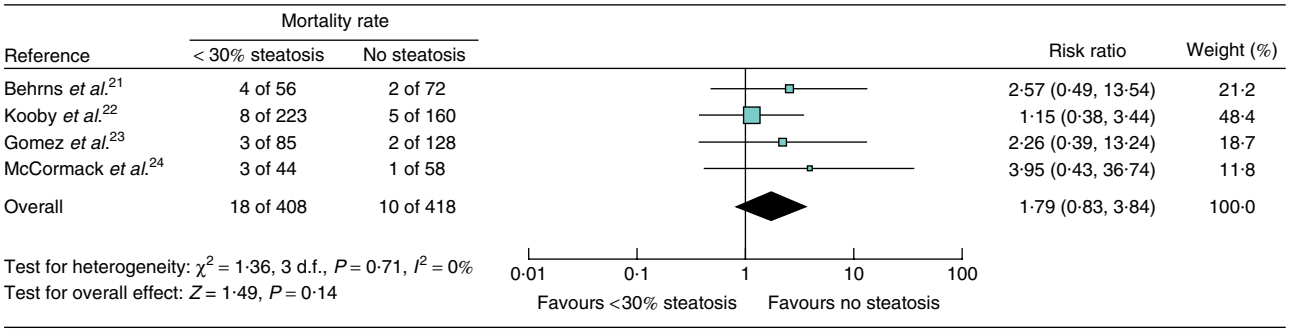

Fig. 4 Forest plot of mortality rates in patients with less than 30 per cent steatosis *versus* those with no steatosis. Risk ratio estimates, shown with 95 per cent confidence intervals, were calculated using the random-effects model. The diamond represents the overall treatment effect from the pooled studies spanning the 95 per cent confidence interval. No steatosis was defined as no hepatocytes containing fat infiltration[21–23] and less than 10 per cent of hepatocytes with fat droplets[24]

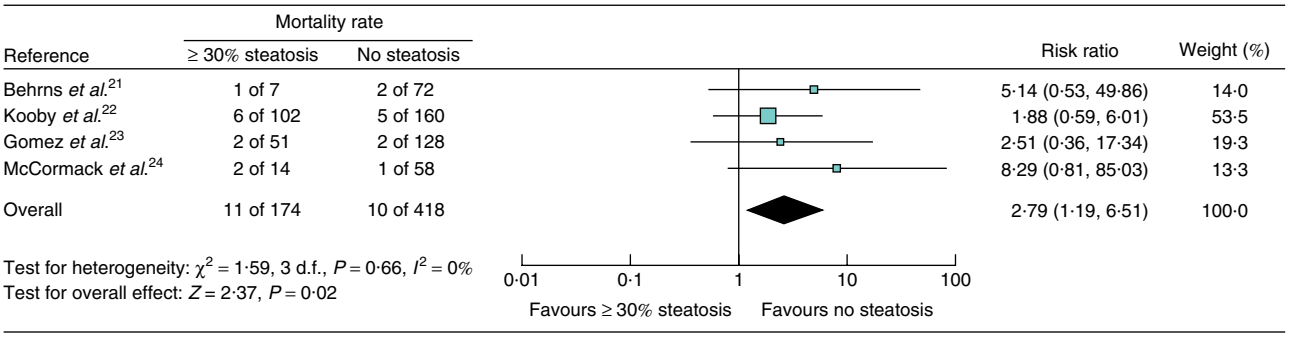

Fig. 5 Forest plot of mortality rates in patients with at least 30 per cent steatosis *versus* those with no steatosis. Risk ratio estimates, shown with 95 per cent confidence intervals, were calculated using the random-effects model. The diamond represents the overall treatment effect from the pooled studies spanning the 95 per cent confidence interval. No steatosis was defined as no hepatocytes containing fat infiltration[21–23] and less than 10 per cent of hepatocytes with fat droplets[24]

Mortality as an outcome

None of the six studies in the systematic review found a significant difference in mortality rates between patients with or without any degree of steatosis on univariable analysis, with RRs ranging from 1·00 to 1·08[13,21–25].

The meta-analysis of steatosis as a risk factor for mortality following major hepatic resection (at least three segments) was limited to four studies[21–24]. There was no substantial heterogeneity when comparing mortality rates in patients with either less than or at least 30 per cent steatosis with rates in patients without steatosis ($I^2 = 0$ per cent). The summary RR for mortality in patients with less than 30 per cent steatosis compared with that in patients without steatosis was increased, but not significantly, to 1·79 (95 per cent c.i. 0·83 to 3·84; $P = 0·14$) (*Fig. 4*). The summary RR, however, increased significantly when patients with more severe steatosis (30 per cent or more) were compared with those without steatosis (RR 2·79, 95 per cent c.i. 1·19 to 6·51; $P = 0·02$) (*Fig. 5*).

Discussion

Obesity, diabetes mellitus, the metabolic syndrome and associated non-alcoholic fatty liver disease are reaching epidemic proportions throughout the world, but the full impact of hepatic steatosis on postoperative outcome is only beginning to be understood. Although the scientific evidence is relatively scarce, steatosis is commonly considered as a significant risk factor in hepatic surgery[1,12,26,27]. The results of the present systematic review and meta-analysis revealed a significant association between degree of steatosis and increased risk of postoperative complications and mortality.

In the systematic review, four publications reporting on patients undergoing hepatic resection for benign or malignant neoplastic disease and two reporting outcome of living liver donors following resection were identified[13,21–25]. Because differences in underlying parenchymal disease and associated co-morbidities could possibly affect homogeneity, studies of living liver donors were excluded from the meta-analysis. Interestingly, Cho and colleagues[13] demonstrated that living liver donors with less than 30 per cent steatosis did not have increased postoperative complication and mortality rates; more importantly, long-term regeneration was not impaired. Nagai and co-workers[25] also demonstrated that liver regeneration was not impaired; however, mild steatosis (5–20 per cent) was associated with hyperbilirubinaemia.

As the severity of steatosis and extent of resection appeared to be important predictors of postoperative complications in patients undergoing hepatic resection for benign or malignant neoplastic disease[21–24], data for those who had a resection of at least three segments were extracted for meta-analysis. It was demonstrated that the risk of developing postoperative complications and of death increased in parallel with the severity of steatosis. Several potential limitations of this study, however, warrant discussion.

This meta-analysis was limited by the availability of observational studies only, which are more prone to confounding factors and bias[28]. Therefore, explicit inclusion and exclusion criteria were applied and study quality was analysed strictly, focusing on extracting the best available. In the systematic review process, many papers were excluded because of limitations in study design, most commonly because of poor definition of complications or degree of steatosis. As a result of these rigorous selection criteria, the review was limited to a disappointing number of six studies with level 2b evidence. However, all studies scored at least 7 of 9 points on the Newcastle–Ottawa Scale, indicating good quality[17]. This resulted in not incorporating study quality as a weighting factor in the meta-analysis; furthermore, such weighting by study quality remains controversial[29].

Although only papers assessing degree of steatosis according to the current 'gold standard' were included, recent evidence suggests that the histological evaluation of steatosis, even when performed on large wedge biopsies and assessed by expert pathologists, may be unreliable[30]. This inconsistent assessment of hepatic steatosis may be worrisome; however, until alternatives such as computerized analysis are validated to assess degree of steatosis, liver biopsy and subsequent histological evaluation remain the standard.

All postoperative complications were included in the analysis and no attempt was made to classify outcomes according to validated complication classification systems, such as the Clavien–Dindo classification or the Accordion severity grading system[31,32]. There was a lack of uniformity in presentation and definition of complications among the studies. Furthermore, the appropriate format of a scoring system to classify surgical complications is still under debate[33].

Selective use of Pringle's manoeuvre (inflow clamping of the porta hepatis)[34] may predispose the remnant liver to an additional ischaemic insult that by itself may be a factor for complications[26]. It has been proposed that steatotic liver may be more vulnerable to temporary interruption of blood flow[26,27]; however, a recent Cochrane meta-analysis concluded that vascular occlusion did not significantly affect morbidity and mortality following major hepatic resection[35]. Behrns and colleagues[21] reported that the

inflow occlusion time was shorter in patients with at least 30 per cent steatosis, whereas it was comparable between groups in two other reports[22,24]. The use of inflow occlusion was not related to postoperative outcome in these three papers. The use of vascular occlusion was not mentioned specifically in the other three reports[13,23,25].

Co-morbidities, such as diabetes mellitus, may have confounded the results, as this risk factor is independently related to poor surgical outcome[36]. Studies examining the impact of obesity on surgical outcomes have yielded conflicting results, although the two largest studies concluded that obesity is not a risk factor for death or complications in patients undergoing elective general surgery[37,38]. Two studies[23,24] demonstrated significant correlations between the presence of steatosis and diabetes and obesity, whereas the presence of steatosis was related only to obesity in three reports[13,21,22]. Multivariable analysis in two of the studies[22,24], however, did not show an association between body mass index and presence of diabetes and surgery-related morbidity and mortality.

Preoperative chemotherapy is linked to the development of hepatic steatosis, and translates into increased postoperative infection rates[39,40]. Of the four studies in which patients were treated for hepatic malignancies, only Kooby and colleagues[22] reported that patients with steatosis were more likely to have received preoperative chemotherapy. As the other studies did not find a significant association between preoperative chemotherapy and presence of steatosis, the effects of preoperative chemotherapy as a potential confounder may be negligible, but cannot be ruled out.

Substantial heterogeneity between studies may preclude a pooled comparison. The preformulated hypothesis and comprehensive search of multiple biomedical databases minimized the presence of publication bias[41]. In addition, a clinically meaningful patient group was selected and the degrees of steatosis were clearly defined. In exploring heterogeneity using funnel plots and χ^2 and inconsistency (I^2) statistics, significant heterogeneity was not observed.

This is the first systematic review and meta-analysis to investigate steatosis as a risk factor in hepatic resection. In a previous narrative review, data were summarized from experimental and clinical studies regarding steatosis as a risk factor in liver surgery[12]. The authors concluded that steatosis was a major determinant of patient outcome after hepatic surgery. However, only two of the five clinical studies included in the previous review remained after applying rigorous selection criteria in the present analysis[21,22]. The other three papers were excluded because of poor definition of steatosis and because the papers used overlapping patient populations (kin relationships). In the present paper, four other articles that have been published since publication of the earlier review were identified and included. Another narrative review summarized the literature regarding liver surgery in the presence of cirrhosis and steatosis, but no attempt was made to establish an effect estimate of steatosis as a risk factor following hepatic surgery[27].

Given the increased risk of complications and death in patients who underwent a major hepatic resection in parallel to the severity of steatosis, and with the rising prevalence of steatosis in patients undergoing liver resection, surgeons should be aware of the potential risks, inform their patients and, if feasible, intervene before surgery.

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References

1 Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med* 2002; **346**: 1221–1231.
2 Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC *et al*. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387–1395.
3 Bellentani S, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F *et al*. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med* 2000; **132**: 112–117.
4 Al-Asfoor A, Fedorowicz Z, Lodge M. Resection *versus* no intervention or other surgical interventions for colorectal cancer liver metastases. *Cochrane Database Syst Rev* 2008; (2)CD006039.
5 Verslype C, Van Cutsem E, Dicato M, Arber N, Berlin JD, Cunningham D *et al*. The management of hepatocellular carcinoma. Current expert opinion and recommendations derived from the 10th World Congress on Gastrointestinal

Cancer, Barcelona, 2008. *Ann Oncol* 2009; **20**(Suppl 7): vii1–vii6.
6 Aljiffry M, Abdulelah A, Walsh M, Peltekian K, Alwayn I, Molinari M. Evidence-based approach to cholangiocarcinoma: a systematic review of the current literature. *J Am Coll Surg* 2009; **208**: 134–147.
7 Petrowsky H, Busuttil RW. Evolving surgical approaches in liver transplantation. *Semin Liver Dis* 2009; **29**: 121–133.
8 Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K *et al*. One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 2003; **138**: 1198–1206.
9 Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C *et al*. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. *Ann Surg* 1999; **229**: 322–330.
10 Yamanaka N, Okamoto E, Oriyama T, Fujimoto J, Furukawa K, Kawamura E *et al*. A prediction scoring system to select the surgical treatment of liver cancer. Further refinement based on 10 years of use. *Ann Surg* 1994; **219**: 342–346.
11 Selzner M, Clavien PA. Fatty liver in liver transplantation and surgery. *Semin Liver Dis* 2001; **21**: 105–113.
12 Veteläinen R, van Vliet A, Gouma DJ, van Gulik TM. Steatosis as a risk factor in liver surgery. *Ann Surg* 2007; **245**: 20–30.
13 Cho JY, Suh KS, Kwon CH, Yi NJ, Lee KU. Mild hepatic steatosis is not a major risk factor for hepatectomy and regenerative power is not impaired. *Surgery* 2006; **139**: 508–515.
14 Angulo P. Nonalcoholic fatty liver disease and liver transplantation. *Liver Transpl* 2006; **12**: 523–534.
15 Adam R, Hoti E. Liver transplantation: the current situation. *Semin Liver Dis* 2009; **29**: 3–18.
16 Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B *et al*. Oxford Centre for Evidence-based Medicine, Levels of Evidence (March 2009). http://www.cebm.net/index.aspx?o=1025 [accessed 9 June 2009].
17 Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M *et al*. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. Ottawa Health Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm [accessed 9 June 2010].
18 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.
19 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–1558.
20 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D *et al*. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008–2012.
21 Behrns KE, Tsiotos GG, DeSouza NF, Krishna MK, Ludwig J, Nagorney DM. Hepatic steatosis as a potential risk factor for major hepatic resection. *J Gastrointest Surg* 1998; **2**: 292–298.
22 Kooby DA, Fong Y, Suriawinata A, Gonen M, Allen PJ, Klimstra DS *et al*. Impact of steatosis on perioperative outcome following hepatic resection. *J Gastrointest Surg* 2003; **7**: 1034–1044.
23 Gomez D, Malik HZ, Bonney GK, Wong V, Toogood GJ, Lodge JP *et al*. Steatosis predicts postoperative morbidity following hepatic resection for colorectal metastasis. *Br J Surg* 2007; **94**: 1395–1402.
24 McCormack L, Petrowsky H, Jochum W, Furrer K, Clavien PA. Hepatic steatosis is a risk factor for postoperative complications after major hepatectomy: a matched case–control study. *Ann Surg* 2007; **245**: 923–930.
25 Nagai S, Fujimoto Y, Kamei H, Nakamura T, Kiuchi T. Mild hepatic macrovesicular steatosis may be a risk factor for hyperbilirubinaemia in living liver donors following right hepatectomy. *Br J Surg* 2009; **96**: 437–444.
26 Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med* 2007; **356**: 1545–1559.
27 McCormack L, Capitanich P, Quiñonez E. Liver surgery in the presence of cirrhosis or steatosis: is morbidity increased? *Patient Saf Surg* 2008; **2**: 8.
28 Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ* 1998; **316**: 140–144.
29 Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'Abbé KA. Incorporating variations in the quality of individual randomized trials into meta-analysis. *J Clin Epidemiol* 1992; **45**: 255–265.
30 El-Badry AM, Breitenstein S, Jochum W, Washington K, Paradis V, Rubbia-Brandt L *et al*. Assessment of hepatic steatosis by expert pathologists: the end of a gold standard. *Ann Surg* 2009; **250**: 691–697.
31 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD *et al*. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; **250**: 187–196.
32 Strasberg SM, Linehan DC, Hawkins WG. The Accordion severity grading system of surgical complications. *Ann Surg* 2009; **250**: 177–186.
33 Clavien PA, Strasberg SM. Severity grading of surgical complications. *Ann Surg* 2009; **250**: 197–198.
34 Pringle JH. Notes on the arrest of hepatic hemorrhage due to trauma. *Ann Surg* 1908; **48**: 541–549.
35 Gurusamy KS, Kumar Y, Ramamoorthy R, Sharma D, Davidson BR. Vascular occlusion for elective liver resections. *Cochrane Database Syst Rev* 2009; (1)CD007530.
36 Little SA, Jarnagin WR, DeMatteo RP, Blumgart LH, Fong Y. Diabetes is associated with increased perioperative mortality but equivalent long-term outcome after hepatic resection for colorectal cancer. *J Gastrointest Surg* 2002; **6**: 88–94.
37 Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. *Ann Surg* 2009; **250**: 166–172.

38 Dindo D, Muller MK, Weber M, Clavien PA. Obesity in general elective surgery. *Lancet* 2003; **361**: 2032–2035.
39 Aloia T, Sebagh M, Plasse M, Karam V, Lévi F, Giacchetti S *et al*. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. *J Clin Oncol* 2006; **24**: 4983–4990.
40 Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg* 2007; **94**: 274–286.
41 Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994; **309**: 1286–1291.

Commentary

Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection (*Br J Surg* 2010: 97: 1331–1339)

A public health crisis is now present in North America and Western Europe, where up to 40 per cent of the population is obese, diabetes mellitus is increasing and a variety of chemotherapeutic regimens used in the treatment of colorectal cancer have resulted in an alarming increase in the rates of non-alcoholic fatty liver disease (NAFLD). The presence of NAFLD and hepatic steatosis in the livers of patients requiring resection as part of a treatment plan for benign and malignant liver disease can significantly complicate their postoperative course, may limit the extent of resection and, finally, make them ineligible for further cycles of chemotherapy.

In this systematic review and meta-analysis the authors address an increasingly common issue in the planning of liver resection in this patient population. This paper attempts to answer two very important questions that must be addressed when the hepatobiliary surgeon is discussing the risks and benefits of liver surgery with the patient. What is the risk of morbidity and mortality in patients undergoing hepatic resection who have steatotic livers?

A comprehensive review of all the literature was carried out with screening at three levels by two of the authors. Starting with 3837 articles, the final analysis was carried out on six observational studies: two papers from the living related liver donation literature and four studies in which a major liver resection (defined as three or more segments) was carried out. All had steatosis defined by histology rather than through imaging, and patients were divided into three groups: no steatosis, less than 30 per cent steatosis and at least 30 per cent steatosis. The authors found a significantly increased risk of postoperative complications in those with any degree of steatosis, and that this risk increased with the degree of steatosis. The postoperative mortality risk increased significantly in patients with at least 30 per cent steatosis.

As the analysis of morbidity and mortality in this patient set is not amenable to the ‘gold standard’ of a multicentre randomized controlled study, observational studies with their inherent limitations are all that we may hope to use to answer these questions. The authors address all the limitations in their data set, and their conclusion should be considered valid. This paper will allow hepatobiliary surgeons to have a truly informed discussion with their patients about the risks of major hepatic surgery in those with steatotic livers.

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