Mortality after extrahepatic gastrointestinal and abdominal wall surgery in patients with alcoholic liver disease. A systematic review and meta-analysis.

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Abstract

Aims: This meta-analysis aimed to define the perioperative risk of mortality in patients with alcoholic liver disease (ALD) undergoing extrahepatic gastrointestinal surgery.

Methods: Systematic searches of Embase, Medline and CENTRAL were undertaken to identify studies reporting about patients with ALD undergoing extrahepatic gastrointestinal surgery published since database inception to January 2019. Studies were only considered if they reported on mortality as an outcome. Pooled analysis of mortality was stratified as benign and malignant surgery; and specific operative procedures where feasible.

Results: Of the 2899 studies identified only five studies met inclusion criteria. The operative procedures undertaken were cholecystectomy($n=1$), umbilical hernia repair($n=1$) and oesophagectomy($n=3$). The total number of patients with ALD studied were 172. Therefore, any study on liver disease patients undergoing extrahepatic surgery that crucially included a subset with alcohol aetiology were included as a secondary analysis even though they failed to stratify mortality by underlying aetiology. The total number of studies that met this expanded inclusion criteria was 62, reporting on 37,703 patients with liver disease of which 1735 (4.5%) had a definite diagnosis of ALD. Meta-analysis of proportions of in-hospital mortality in patients with ALD undergoing upper gastrointestinal cancer surgery (oesophagectomy) was 23% (95% CI 14-35% $I^2=0\%$). In-hospital mortality following oesophagectomy in liver disease patients of all aetiologies was lower, 14% (95% CI 9-21% $I^2=41.1\%$).

Conclusion: Postoperative in-hospital mortality is high in patients with liver disease and ALD in particular. However, the currently available evidence on ALD is limited and precludes definitive conclusions on postoperative mortality risk.

Introduction

Alcoholic liver disease is an increasing global public health problem due to excessive alcohol consumption, especially in European countries.(Marcellin and Kutala, 2018, Byass, 2014)

The incidence of alcoholic liver disease in Europe was estimated as 14-26 per 100, 000 population(Zatonski et al., 2010) and median prevalence estimated as 312 per 100,000 population (Pimpin et al., 2018). However, given significant variation in international reporting global incidence is likely to be underestimated. Instead mortality from alcoholic liver cirrhosis is often used as the proxy for burden of alcoholic liver disease.(Rehm et al., 2013) The World Health Organisation (WHO) recognises alcohol, as one of the major behavioural risk factors driving the global rise of non-communicable diseases.(WHO, 2018, Forouzanfar et al., 2016) Alcohol consumption and alcoholic liver disease are both associated with an increased risk of extrahepatic gastrointestinal cancers such as oesophageal, gastric, pancreatic and colorectal cancer.(Bagnardi et al., 2015, Kalaitzakis et al., 2011, Jepsen et al., 2016) They are also associated with an increased risk of benign conditions such as cholelithiasis and abdominal wall herniae.(Bouchier, 1969, Acalovschi et al., 1991, Acalovschi, 2014, Conte et al., 1999, Gray et al., 2008) The definitive management of these conditions often requires surgical intervention. However, surgery in the population of patients with alcoholic liver disease is reportedly associated with a higher risk of morbidity and mortality.(Garrison, 1984, Mansour et al., 1997)

A review of surgical risk in patients with liver disease published in 1999 suggested that almost all the available data on the risk of surgery in patients with liver disease pertained to liver cirrhosis only, with the risk of mortality in patients with less severe variants of alcoholic liver disease completely unaddressed.(Friedman, 2010) There are even fewer studies

specifically evaluating surgical risk based on the different underlying aetiology such as viral and alcohol related liver disease.(Kalaitzakis et al., 2011) There is global consensus on the rise of alcohol use disorders as well as benign and malignant alcohol related gastrointestinal disease. (WHO, 2018, Forouzanfar et al., 2016) This therefore warrants contemporary surgical risk and outcomes assessment in this particular at risk group.

Studies from the 1980's suggested that the presence of liver cirrhosis was a contraindication to major gastrointestinal surgery such as laparotomy for elective or emergency presentations.(Garrison, 1984) However, with the advent of laparoscopic and minimal access surgery, it is unknown if the postoperative risk of mortality remains the same.(Puggioni and Wong, 2003, Lopez-Delgado et al., 2016) The aim of this systematic review was to identify the available evidence, critically appraise it, synthesis the findings and quantify the mortality risk in patients with alcoholic liver disease undergoing extrahepatic gastrointestinal and abdominal wall surgery.

Methods

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.(Liberati et al., 2009)

Literature search

Systematic searches of Medline, EMBASE, Cochrane Library databases, WHO International Clinical Trials Registry Platform (ICTRP) and Clinical trials.gov were undertaken to identify studies reporting postoperative outcomes in patients with alcoholic liver disease published from database inception to January 25th 2019. Only abdominal wall and extrahepatic gastrointestinal surgical procedures were considered, including oesophagectomy; gastrectomy; cholecystectomy; pancreaticoduodenectomy; appendicectomy and colonic resectional surgery. The abdominal wall procedures were any open or laparoscopic repair of ventral, inguinal, femoral and incisional herniae. The detailed search strategy is presented in **Appendix 1**. The search terms included: [*'alcohol(ic) liver disease' OR 'alcohol(ic) cirrhosis'*] **AND** [(*'umbilical' 'paraumbilical' 'ventral' 'incisional' 'inguinal' 'femoral' - hernia(e)'*) OR ((*'oesophageal' 'pancreas' 'gallbladder' 'colon' 'rectum' - surgery'*))] mapped to corresponding Medline Subject Headings (MeSH). Hand searches of thesis repositories and reference lists of relevant studies were undertaken to ensure comprehensive inclusion.

Inclusion criteria

The titles and abstracts of studies identified from the searches were screened for suitability independently by two authors (AA and DJH) and any discordant articles adjudicated by (JW).

For a study to meet the eligibility criteria (Appendix 2), they had to be in adult human subjects, reporting on patients with alcoholic liver disease undergoing extrahepatic gastrointestinal surgery or abdominal wall surgery. The studies had to report on mortality as an outcome. This group of studies formed the primary analysis group. Another group which comprised of all studies reporting on patients with liver disease undergoing extrahepatic surgery but crucially including patients with alcoholic liver disease and reporting on mortality but failing to stratify mortality outcomes by aetiology were included as the secondary analysis group. (See **Appendix 2**) All full text published randomized controlled trials (RCT), nationwide population-based studies and prospective or retrospective observational studies were eligible for qualitative synthesis and quantitative meta-analysis.

Exclusion criteria

Studies reporting liver surgery, liver transplant or shunt related surgery were excluded. Studies on liver disease in children, or with no patients with an alcoholic aetiology, for example reporting on only non-alcoholic fatty liver disease (NAFLD), viral or autoimmune liver diseases were also excluded. Animal studies, case reports and case series (defined as number of study participants <10), meeting abstracts and publications for which the full text was irretrievable (with no full publication available from authors), letters, comments and editorials were excluded. No language limitation were applied.

Data Extraction

Data were extracted by two reviewers independently (AA and LB) into predefined templates and adjudicated by a third reviewer (DJH) to resolve any discrepancies. Data were collected

for type of study, country of origin, number of patients in the respective studies, and separately for the number of the study population with liver disease, and for the number with alcohol aetiology. For population-based studies, data were also collected for the databases used and the years of inclusion.

The primary outcome was 30-day mortality. Secondary outcome was in-hospital mortality. Where feasible this was assessed in the *primary analysis group* of only patients with alcoholic liver disease and in the *secondary analysis group* of all liver disease patients who also included patients with an alcohol aetiology.

Statistical analysis

To quantify 30-day and in-hospital mortality after surgery in alcoholic liver disease we conducted a meta-analysis of proportions based on the number of deaths at 30-days or in-hospital as reported in each study. A Freeman-Tukey transformation was used to establish a variance of the raw proportions of each study.(Nyaga et al., 2014) The transformed proportions were then pooled using a random effects model to account for the anticipated clinical and statistical heterogeneity of the included studies.

It was agreed a priori to divide studies into the broad categories of benign and malignant. Thereafter, studies on benign surgery were subgrouped into their individual procedural types: appendicectomy, cholecystectomy, hernia repair. In pooling of data, the plan was to analyse stratified for the individual operative procedure. However, in the absence of enough data points, studies on benign surgery were pooled together.

For malignant disease, studies were classified and quantitatively analysed as either upper gastrointestinal or lower gastrointestinal. Upper gastrointestinal surgery included

oesophagogastric operations and hepatobiliary pancreatic procedures. Whilst Lower gastrointestinal included surgery for all cancers of the colon. However, to account for studies that did not describe a single type of procedure and or included a mix of benign and malignant conditions – a separate category of mixed gastrointestinal was also reported.

Groups and stratifications for data analysis were:

- Benign
 - Abdominal Wall hernia
 - Appendicectomy
 - Cholecystectomy
 - Hernia repair
- Malignant
 - Upper gastrointestinal
 - Lower gastrointestinal
- Mixed gastrointestinal surgery

The amount of statistical heterogeneity of the included studies was evaluated using the I^2 statistic. An I^2 less than 25% was considered to indicate low heterogeneity and an $I^2 > 75\%$ to indicate high statistical heterogeneity.(Melsen et al., 2014) All analyses were performed using Stata version 15.

Risk of bias

Risk of bias in included RCTs was analysed independently by two review authors (AA and LB) using the Cochrane Collaboration tool for assessing the risk of bias in randomized trials. For

non-randomised studies, the Newcastle-Ottawa Scale quality assessment were used to assess the risk of bias. All studies are reported as low, moderate or high risk of bias.

Publication bias

Publication bias was assessed by visual assessment of asymmetry in the funnel plot of included studies that had a comparator arm (surgical outcomes in liver disease or alcoholic liver disease versus general population).

Protocol registration

The protocol was registered with the PROSPERO database (www.crd.york.ac.uk/prospero)—registration no. CRD42019119903.

Results

Characteristics of studies reporting on only Alcoholic Liver disease

Of the 2899 studies identified, 97 full text articles were evaluated of which 5 studies met the inclusion criteria and formed the primary analysis group (appendix 2) Three studies included patients with alcoholic liver disease (Belghiti, 1990, Fekete, 1987, Pescovitz, 1984). Two additional studies included patients with all cause liver disease but reported mortality outcomes for patients with alcoholic liver disease separately.(Thulstrup, 2001, Lu et al., 2005) Two studies originated from France (Belghiti, 1990, Fekete, 1987) and there was a single study each from Denmark, (Thulstrup, 2001), Taiwan(Lu et al., 2005) and the United States of America.(Pescovitz, 1984) The studies spanned a 21-year period from 1984 to 2005.

Patient characteristics

The total number of patients studied were 172, number of men 117 (77.0%) and women 55(33.0%). The mean age was 56.3 years. The operative procedures undertaken in these studies were cholecystectomy (n=1), umbilical hernia repair (n=1) and oesophagectomy (n=3). The three studies on oesophagectomy reported only in-hospital mortality. The two studies on benign surgery reported 30-day mortality with the study by Pescovitz also reporting a mean 18-month follow-up. The latter also reported early minor complications such as ascites fluid leak, and wound infections following umbilical hernia repair, with one mortality within the 90-day follow-up secondary to bleeding varices. The nationwide study by Thulstrup et al reported four deaths at the 30-day follow-up, from the 52 patients with

alcohol cirrhosis undergoing cholecystectomy compared to the 11 deaths in 1204 patients without cirrhosis. (Appendix 5-Table 2)

Characteristics of studies in “all cause liver disease”

The total number of studies meeting the secondary inclusion criteria (**Appendix 2**), that is studies on liver disease patients including alcohol aetiology but not reporting mortality outcomes stratified by aetiology was 62 from the original 2899 studies identified. (**Table 1**). The studies originated from 16 countries across 4-continent with a widely different pattern of harmful alcohol consumption. Characteristics of the included studies are summarised in **Table 1**.

The majority of the included studies 80.6% (n=50/62) were single centre observational studies, 17.8% (n=11) were nationwide population-based reports and a single RCT (1.6%) was identified.(Ji, 2005) The majority of studies 90.3% (n=56) were of moderate to high risk of bias. Reasons for high risk of bias included a lack of randomisation and a failure to describe adequately the methods of cohort identification. Only 15 studies (24.2%) were assessed as moderate risk of bias, and fewer still, 9.7% (n=6) were classified as low risk.

The surgical procedures undertaken in the 62 included studies were open and laparoscopic cholecystectomy 34.9% (n=22), abdominal wall hernia repair 12.7% (n=8), appendicectomy 1.6% (n=1), upper gastrointestinal surgery 15.9% ((n=10), which included oesophagogastrectomy (n=5), peptic ulcer surgery (n=1) and pancreaticoduodenectomy (n=4)), lower gastrointestinal surgery for cancer 9.5% (n=6). The number of studies that described a mixed variety of surgical procedures without separating out the individual procedures types were 15 (25.3%).

Patient characteristics

The total number of patients in this expanded criteria of studies were 3.6-million, and this included 37,703 patients with liver disease. Only 56 studies reported details on aetiology of liver disease and in these studies, 1735 (4.6% of the total liver disease patients) were reported to have a definitive diagnosis of alcoholic liver disease. The mean age of patients with liver disease from all the included studies was 58.7 years. (10, 12, 19-78) In the studies that supplied gender distribution of their included patients, 20,086 patients were male in and 17, 312 were female.

Crude Mortality risk in alcoholic liver disease patients

A single study in the primary analysis group reported mortality at 30-days. (Thulstrup, 2001) They included 52 patients with alcoholic cirrhosis versus 1204 patients without liver disease. In the group with alcoholic cirrhosis mortality at 30-days was 7.7% (4/52) it was lower in the general population without liver disease 0.9% (11/1204). They also did an additional analysis of 58 patients with non-alcohol related cirrhosis who had a mortality rate of 1.7% (1/58).

Crude Mortality risk in all cause liver disease patients

A total of 7 studies provided data on mortality at 30-days in patients with liver disease (secondary analysis group). The crude mortality at 30-days after benign surgery in patients with liver disease was 3.9% (30/763) and was 0.7% (434/62323) in the general population without liver disease. After malignant surgery, crude mortality at 30-days was 17.8%

(824/4624) in patients with liver disease and 5.3% (28397/539074) in the general population without liver disease.

Meta-analysis

There was insufficient studies to undertake meta-analysis of 30-day mortality for benign or malignant surgery in patients with alcoholic liver disease. Pooled analysis of in-hospital mortality in this patient group was only possible for those undergoing upper gastrointestinal cancer surgery (oesophagectomy). (**Figure 1**). Pooled 30-day and in-hospital mortality for the secondary analysis group (all cause liver disease) are summarised in **Figure 2, Figure 3 and Figure 4**.

Heterogeneity

There is an expectation of clinical and statistical heterogeneity given the varying complexity of the surgical procedures undertaken, as well as the individual patients' degree of underlying liver disease. This influenced the decision to employ a random effects model for this meta-analysis. Overall, the quantity of statistical heterogeneity was low to moderate for benign conditions and for upper gastrointestinal cancers. For lower gastrointestinal cancer, the high statistical heterogeneity precluded quantitative pooling.

Publication bias

All the studies with a comparison group (alcoholic liver disease/all cause liver disease versus general populations) were included in the analysis of publication bias. It demonstrated that

the odds ratio of mortality in patients with liver disease was higher in every study and every procedure considered, however the magnitude of the risk reported differed. (**Appendix 4**)

The significant asymmetry seen even of studies of similar procedures suggests the possibility of underlying bias – pertaining not only to publication bias, but likely influenced by selection bias and confounding bias which are all drawbacks identified in observational studies.

Discussion

What this review found?

There is a significant lack of evidence regarding the surgical outcomes of patients with alcoholic liver disease undergoing extrahepatic gastrointestinal surgery. We identified five studies reporting outcomes on 172 patients. Following expansion of the inclusion criteria to contain all studies where some patients had an alcohol aetiology, the total number of eligible studies increased but the total number with an alcoholic aetiology was small 1735 out of 37,703 patients (4.6%). Alcoholic liver disease spans a spectrum of disease severity from simple steatosis to decompensated cirrhosis. However, in the currently available literature on surgery in this population, the range of alcoholic liver disease is not represented, with the majority of studies focusing solely on patients with cirrhosis.

Mortality risk (Meta-analysis of proportions)

In the primary analysis group (studies reporting only alcoholic liver disease), it was not possible to determine 30-day mortality risk. In-hospital mortality could only be assessed in patients undergoing upper gastrointestinal cancer surgery, where the pooled mortality was 23% (95% CI 14-35% $I^2=0\%$). In the secondary analysis group, 30-day mortality was reported by less than a third of the included studies with the remainder reporting in-hospital mortality. Quantitative pooling of 30-day mortality risk could only be determined for those patients undergoing benign surgery and not for the individual procedural types.

With regards the secondary outcome of in-hospital mortality, it was feasible to assess this for the majority of procedures. Specifically regarding cholecystectomy, the in-hospital mortality risk differed based on the patients studied. For example in studies where there

was selection of only patients with Child-Pugh A and B grade cirrhosis, the in-hospital mortality was 0% ($I^2=0\%$). However, in those that also included Child-Pugh C patients, or did not select out patients the in-hospital mortality was 3% (95% CI 1-6, $I^2=61.66\%$). The in-hospital mortality risk after upper gastrointestinal cancer was much higher at 14% (95% CI 9-21% $I^2=41.1\%$), reflecting the added complexity of these operations.

What is already known?

[Postoperative mortality in patients with liver disease and alcoholic liver disease](#) *Cholecystectomy*

A Swedish nationwide population based study, which evaluated all cholecystectomies performed between 2007 and 2010 reported a 30-day mortality of 0.15% following the procedure in the general population.(Sandblom, 2015) They also reported a 2.2 fold increased risk of mortality in those undergoing an open cholecystectomy. Only one study reported 30-day mortality in patients undergoing cholecystectomy, and in that study crude mortality at 30-days was 7.7% in patients with alcoholic liver disease (Appendix 5-Table 2). In-hospital mortality, however, was 0% for those patients with Child-Pugh A and B cirrhosis, supporting the findings that laparoscopic cholecystectomy is feasible for these patients. The in-hospital mortality for studies that included Child C patients was 3%, which represents a 20-fold increased risk of death when compared to the quoted mortality risk of 0.15% in the general adult population.(Sandblom, 2015)

Hernia repair

Elective hernia repair is overall a low risk procedure, where mortality risk is not raised above that of the background population.(Nilsson et al., 2007) Emergency surgery may increase the risk after hernia repair.(Basta et al., 2016) In this review, the individual studies reported 30-day mortality risk that ranged from 1% (0-4%, Gray et al(Gray et al., 2008)) to 7%(5-9%, Saleh et al(Saleh et al., 2015)), Figure 1. The in-hospital mortality risk was lower at 2%(1-2%). These findings are important as it reiterates the importance of understanding the consequences of surgery in patients with liver disease, beyond the initial in-hospital post-operative period.

Upper Gastrointestinal Surgery

Morbidity and mortality after upper gastric cancer surgery is high even in patients who are fundamentally fit and well. The in-hospital mortality risk in this meta-analysis was 14% in the secondary analysis group, which is expectedly higher than was seen for patients undergoing benign surgery. The in-hospital mortality in those patients with alcoholic liver disease was higher still at 23%. No study provided data on 30-day mortality risk for this procedure.

Lower Gastrointestinal Surgery

The mortality risk after lower gastrointestinal cancer surgery, could not be formally pooled due to the high I^2 -values signifying significant statistical heterogeneity. However, in the individual studies, mortality at 30-days ranged from 1.8% to 16%. These mortality risk

identified in the individual studies are consistent with mortality risk published in the literature which suggest postoperative mortality of 1-5% in patients without liver disease and 6-41% in those with underlying liver disease.(Montomoli, 2013)

Severity of alcoholic liver disease.

Several studies in liver disease have suggested poor outcomes in patients with an alcohol aetiology when compared to patients with other causes of liver disease. It would appear the same phenomenon is also present in patients with an alcohol aetiology of liver disease undergoing general surgical procedures. Two population-based studies (Thulstrup, 2001, Montomoli, 2013), reported a much higher risk of mortality in patients with alcoholic liver disease undergoing cholecystectomy and colectomy when compared to patients with other aetiological causes of liver disease. This was further demonstrated in the meta-analysis of proportions, where patients with alcohol aetiology undergoing upper gastrointestinal cancer surgery had a higher rate of mortality of 23% compared to 14% in the “all liver disease” population. These findings of poorer postoperative prognosis of patients with an alcohol aetiology remains interesting but it would need further investigation and dedicated studies that are adequately powered to examine any true differences in outcomes for alcohol versus non-alcohol related liver disease.

Limitations

There is a lack of dedicated studies evaluating alcoholic liver disease patients undergoing gastrointestinal surgery. Only three studies contained a full cohort of patients with an alcohol aetiology and a further two had separated out outcomes based on aetiologies. Given the paucity of studies we had to accept all studies that included a subset of patients with an alcohol aetiology. However, even amongst these patients with liver cirrhosis those with an alcohol aetiology are few. Considering alcoholic cirrhosis accounts for the majority of cases of cirrhosis (approx. 60%) and contributes to 48% of deaths due to liver cirrhosis (Rehm et al., 2013), the small proportion currently studied may underestimate the true mortality risk after surgery in patients with alcoholic cirrhosis. Additionally, the currently available evidence focuses on liver cirrhosis which means the mortality risk in less severe alcoholic liver disease could not be explored.

The studies included in this meta-analysis encompassed a wide window from 1980's to 2018, the evolution of surgical practice and 30-day mortality outcomes over this time period could not be explored meaningfully due to the lack of relevant studies per individual procedure type and this is a potential bias in our mortality estimates. Additional confounding which could not be explored due to lack of patient level data is the potential of co-existent risk such as overall comorbidity and lifestyle risks such as obesity and smoking which are known to affect surgical outcomes.

The lack of dedicated studies also meant that for patients with alcoholic liver disease, we could only undertake pooling of mortality data for those undergoing upper gastrointestinal cancer surgery, but not for benign or lower gastrointestinal cancer surgery. For certain procedures, we could not undertake formal meta-analysis of the data due to the high

degree of statistical and plausibly clinical heterogeneity. Medical practices may vary regionally and the population characteristics, proportion with alcohol aetiology, the stage and grade of cancers (for malignant surgery) were all likely to vary and could have contributed to the heterogeneity. However, in the studies where pooling could be undertaken, patients undergoing surgical intervention had a demonstrable increased risk of mortality when compared to reported mortality risk in general populations.

Conclusion

Patients with alcoholic liver disease undergoing surgery have a high risk of in-hospital and 30-day mortality. The currently available evidence is of low quality and are mostly single centre retrospective studies with an inherently higher risk of bias. Alcoholic liver disease is increasing, and trial data are scarce, it therefore necessitates large population based studies to assess the risk of morbidity and mortality following gastrointestinal surgery and provide the much-needed evidence to inform practice.

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Table 1

Author (Year)	Country	Types of Surgery included		Total number of patients in the study	Grade of liver disease	Child-Pugh Classification	Definition of mortality	Number of centres	Risk of bias
				Number of Liver disease	Chronic LD	A			
					Cirrhosis	B			
				Number with alcohol aetiology		C			
						Meld Score			
RCT									
Ji et al. 2005	China	Cholecystectomy		Total = 80 LD = 80 ETOH = 9	Cirrhosis	Child A (41) Child B (32) Child C (7) Meld = nr		SC	Moderate
Nationwide database study									
		Type of surgery	Database used and years included						
Carbonell et al. 2005	USA	Ventral Hernia	UHC Database	Total =32,033	Cirrhosis	Nr	In-hospital mortality	MC	Moderate

			(1999-2004)	LD = 1197 ETOH = nr		Meld = nr			
Chmielecki et al. 2012	USA	Cholecystectomy	NIS (2003-2006)	Total = 3240 LD = 3240 ETOH = 320	Cirrhosis	Nr Meld = nr	In-hospital mortality	Nationwide	Moderate
Csikesz et al. 2009	USA	Cholecystectomy; Colectomy	NIS (1998-2005)	Total = 2.8 million LD = 22569 ETOH = nr	Cirrhosis	Nr Meld = nr	In-hospital mortality	Nationwide	Moderate
Ecker et al. 2014	USA	Hernia	ACS – NSQIP (2009-11)	Total = 138,366 LD = 778 ETOH = 58	Ascites (including cirrhosis patients)	Nr Meld range = 12.9 (10.2-15.1)	30-day mortality	Nationwide	low
Gray et al. 2008	USA	Hernia	VA NSQIP (1998-2002)	Total = 1421 LD = 127 ETOH = 24	Cirrhosis	Nr Meld = nr	30-day mortality	MC	low
Hansen et al. 2002	Denmark	Hernia	DNHR (1993-1997)	Total = 1300 LD = 457 ETOH = nr	Cirrhosis	Nr Meld = nr	30-day mortality	Nationwide	low
Montomoli et al. 2013	Denmark	Colectomy for colorectal cancer	DNRP (1996-2009)	Total = 39840 LD = 527 ETOH = 60	LD, cirrhosis	Nr Meld = nr	30-day mortality	Nationwide	low

Nguyen et al. 2009	USA	Colectomy for colorectal cancer	Nationwide Inpatient Sample (1998-2005).	Total = 503,583 LD = 4042 ETOH = nr	Cirrhosis	Nr Meld = nr	In-hospital mortality	Nationwide	low
Saleh et al. 2015	Canada	Umbilical hernia	ACS NSQIP (2005-2011)	Total = 688 LD = 688 ETOH =51	Cirrhosis	Nr Meld = 13.9(SD 4.9)	30-day mortality	Nationwide	low
Thulstrup et al. 2001	Denmark	Cholecystectomy	Danish National registry (1977-1994)	Total = 1314 LD = 110 ETOH =52	Cirrhosis	Nr Meld = nr	30-day mortality	Nationwide	low
Poulsen et al. 2000	Denmark	Appendectomy	Danish National registry (1977-1993)	Total = 59051 LD = 69 ETOH = nr	Cirrhosis	Nr Meld = nr	30-day mortality	Nationwide	Moderate
Observational Studies									
Befeler et al. 2005	USA	Intra-abdo surgery -cholecystectomy -exploratory laparotomy		Total = 53 LD = 53 ETOH =10	Cirrhosis	A (21) B (27) C (5) Meld = nr	90-day mortality	SC	Moderate
Belghiti et al, 1990	France	Oesophagectomy		Total = 32 LD = 32 ETOH =32	Cirrhosis	A (30) B (2) Meld = 12 (IQR 8-16)	In-hospital mortality	SC	High

Binger et al, 2008	USA	Laparoscopic cholecystectomy	Total = 99 LD = 99 ETOH =38	Cirrhosis	Nr Meld =10.9 Women = 10.7 Men	In-hospital mortality	SC	High
Busquets et al. 2016	Spain	Pancreaticoduodenectomy	Total = 45 LD = 15 ETOH =6	Cirrhosis	A (n=15) Meld = nr	In-hospital mortality	SC	High
Cappellani et al, 2008	Italy	Laparoscopic cholecystectomy	Total = 40 LD = 40 ETOH =7	Cirrhosis	A (20) B (10) C (10) Meld = nr	In-hospital mortality	SC	High
Cobb et al. 2004	USA	Laparoscopic cholecystectomy, colectomy, splenectomy	Total = 50 LD = 50 ETOH =3	Cirrhosis	A (39) B (10) C (1) Meld = 8.9	In-hospital mortality	SC	High
Cucinotta et al. 2003	Italy	Cholecystectomy	Total = 22 LD = 22 ETOH =3	Cirrhosis	A(12) B(10) Meld = nr	In-hospital mortality	SC	High
Curro et al. 2005	Italy	Cholecystectomy	Total = 42 LD = 42 ETOH =7	Cirrhosis	A (22) B (16) C (4)	In-hospital mortality	SC	High

					Meld = nr			
Curro et al. 2007	Italy	Cholecystectomy	Total = 50 LD = 50 ETOH =11	Cirrhosis	A (32) B (18) Meld = nr	In-hospital mortality	SC	High
Da Silveira et al. 2006	USA	Cholecystectomy	Total = 99 LD = 33 ETOH =7	Cirrhosis	A(22) B(11) Meld = nr	In-hospital mortality	SC	High
D'Albuquerque et al. 1995	Brazil	Cholecystectomy	Total = 12 LD = 12 ETOH =1	Cirrhosis	A(8) B(4) Meld = nr	In-hospital mortality	SC	High
Delis et al. 2010	USA	Cholecystectomy	Total = 220 LD = 220 ETOH =93	Cirrhosis	A(194) B(26) Meld range = 8-27	In-hospital mortality	SC	High
Del Olmo et al. 2003	Spain	Intra-abdominal surgery, hernia	Total = 221 LD = 135 ETOH = nr	Cirrhosis	A (83) B (41) C (11) Meld = nr	30-day mortality	SC	Moderate
Dunnington et al. 1987	USA	Cholecystectomy	Total = 32 LD = 32 ETOH =22	Cirrhosis	A (6) B (14) C (2) Meld = nr	In-hospital mortality	SC	High

Eker et al. 2011	Netherlands	Umbilical hernia	Total = 30 LD = 30 ETOH =7	Cirrhosis	A (6) B (19) C (5) Meld = 12 (IQR 8-16)	In-hospital mortality	SC	High
Farnsworth et al. 2004	USA	Abdominal and others	Total = 40 LD = 40 ETOH =10	Cirrhosis	A (13) B (22) C (5) Meld = nr	30-Day & 90-Day mortality	SC	Moderate
Fekete et al. 1987	France	Oesophago-gastrectomy	Total = 23 LD = 23 ETOH =23	Cirrhosis	A (21) B (2) Meld = nr	In-hospital mortality	SC	High
Fernandes et al. 2000	USA	Cholecystectomy	Total = 235 LD = 48 ETOH =26	Cirrhosis	A (38) B (10) Meld = nr	In-hospital mortality	MC	High
Franzetta et al, 2003	Italy	Extrahepatic surgery (cholecystectomy/colectomy)	Total = 40 LD = 40 ETOH =7	Cirrhosis	A (14) B (13) C (13) Meld = nr	In-hospital mortality	SC	High

Gervaz et al. 2003	USA	Colectomy	Total = 72 LD = 72 ETOH =35	Cirrhosis	A (31) B (30) C (11) Meld = nr	In-hospital mortality	SC	High
Gil et al, 2003	Argentina	Cholecystectomy	Total = 15 LD = 15 ETOH =7	Cirrhosis	A (14) B (1) Meld = nr	In-hospital mortality	SC	High
Guo et al. 2014	China	Gastrectomy	Total = 58 LD = 58 ETOH =1	Cirrhosis	A (25) B (31) C (2) Meld = nr	In-hospital mortality	SC	High
Han et al. 2017	South Korea	Colectomy for colorectal cancer	Total = 275 LD = 55 ETOH =8	Cirrhosis	A (46) B (9) Meld = range	30-day mortality	SC	Moderate
Hotiet et al. 2007	USA	Mixed surgical procedures	Total = 195 LD = 195 ETOH =35	Cirrhosis	A (41) B (115) C (39) Meld = 14.2(SD 6.3)	30-day mortality	SC	High
Jang et al. 2008	South Korea	Gastrectomy	Total = 57 LD = 57 ETOH =22	Cirrhosis	A (46) B or C(11) Meld = nr	In-hospital mortality	MC	High

Lehnert et al. 1993	Germany	Laparotomy for peptic ulcer	Total = 69 LD = 69 ETOH =32	Cirrhosis	Nr Meld = nr	In-hospital mortality	SC	High
Leonie et al. 2001	Italy	cholecystectomy	Total = 96 LD = 24 ETOH =3	Cirrhosis	A (19) B (5) Meld = nr	In-hospital mortality	SC	High
Levente et al. 2008	Belgium	cholecystectomy	Total = 52 LD = 52 ETOH =6	Cirrhosis	A (36) B (14) C (2) Meld = nr	In-hospital mortality	SC	High
Lledo et al. 2011	Spain	cholecystectomy	Total = 503 LD = 43 ETOH =6	Cirrhosis	A (20) B (15) C (2) Meld = nr	In-hospital mortality	SC	High
Lu et al, 2005	Taiwan	Oesophagectomy	Total = 16 LD = 16 ETOH =13	Cirrhosis	A (12) B (2) C (2)	In-hospital mortality	SC	High
Mansour et al. 1997	USA	Intra-abdo surgery	Total = 92 LD = 92 ETOH =44	Cirrhosis	A (48) B (33) C (11)	In-hospital mortality	SC	High

					Meld = nr			
Metcalfe et al. 1987	USA	Colectomy for colorectal cancer	Total = 54 LD = 54 ETOH =17	Cirrhosis	Nr Meld = nr	In-hospital mortality	SC	Moderate
Meunier et al. 2008	France	Colectomy for colorectal cancer	Total = 43 LD = 43 ETOH =39	Cirrhosis	A (17) B (21) C (5) Meld = nr	In-hospital mortality	SC	High
Morino et al. 2000	Italy	cholecystectomy	Total = 33 LD = 33 ETOH =14	Cirrhosis	A (27) B (4) C (2) Meld = nr	In-hospital mortality	SC	High
Neeff et al. 2014	Germany	Intra abdominal surgery	Total = 204 LD = 204 ETOH =109	Cirrhosis	A (79) B (78) C (47) Meld = reported as Categories only	30-day & 90-day mortality	SC	Moderate
Northup et al. 2005	USA	Non-transplant surgery	Total = 140 LD = 140 ETOH =39	Cirrhosis	Nr Meld = 18.0 (SD7.8)	30-day mortality	SC	Moderate

Oh et al, 2011	South Korea	Hernia repair	Total = 780 LD = 129 ETOH =15	Cirrhosis	A (45) B (66) C (18) Meld = nr	In-hospital mortality	SC	High
Pescovitz et al. 1984	USA	Umbilical hernia repair	Total = 22 LD = 22 ETOH =22	Cirrhosis	Nr Meld = nr	30-day mortality, late mortality >30-days	SC	High
Poggio et al. 2000	USA	Lap cholecystectomy	Total = 50 LD =50 ETOH =13	Cirrhosis	A (39) B (11) Meld = nr	In-hospital mortality	SC	High
Ramesh et al. 2008	India	Pancreas surgery for chronic pancreatitis	Total = 57 LD = 57 ETOH =28	Steatosis, Cirrhosis	Nr Meld = nr	In-hospital mortality	SC	High
Regimbeau et al. 2015	France	Pancreaticoduodenectomy	Total = 105 LD = 35 ETOH =22	Cirrhosis	A (24) B (11) Meld range = 10 (4-36)	In-hospital mortality	MC	High

Song et al. 2011	South Korea	Intra-abdominal surgery	Total = LD = 98 ETOH = 22	Cirrhosis	A (45) B (66) C (18) Meld = 10.82 +/- 3.84	30-day and 90-day mortality	SC	High
Tachibana et al. 2000	Japan	Oesophagectomy	Total = 245 LD = 18 ETOH =14	Cirrhosis	A (11) B (7) Meld = nr	In-hospital mortality	SC	High
Teh et al. 2007\$	USA	Small and large bowel and spleen	Total = 214 LD = 214 ETOH =42	Cirrhosis	Nr Meld range = 8 (5– 11)	30-day, 90- day and 1- year mortality	SC	High
Telem et al. 2010	Canada	Intra-abdominal operations	Total = 100 LD = 100 ETOH =18	Cirrhosis	A (50) B (33) C (17) Meld = 12.4	nr	SC	Moderate
Tuech et al. 2002	France	Lap cholecystectomy	Total = 26 LD = 26 ETOH =14	Cirrhosis	A (22) B (4) Meld = nr	Long-term mortality	SC	Moderate
Warnick et al. 2011	Germany	Pancreaticoduodenectomy	Total = 1649	Cirrhosis	A (30)	In-hospital mortality	SC	High

			LD = 32 ETOH =27		B (2) Meld = 11+/-5			
Yoshida et al. 2012	Japan	Lap Splenectomy	Total = 60 LD = 60 ETOH =2	Cirrhosis	A (24) B (33) C (3) Meld = 12.4	30-day mortality	SC	Moderate
Zarski et al, 1988	France	Mixed Gastrointestinal surgery	Total = 67 LD = 67 ETOH =48	Cirrhosis	Child-Pugh scores Meld = nr	In-hospital mortality	SC	High
Ziser et al. 1999	USA	Multitude of operations	Total = 733 LD = 733 ETOH =224	Cirrhosis	Child-Pugh Scores Meld = nr	30-day mortality	SC	High

Legend

UHC - University Health-System Consortium (UHC), formed in 1984, is an alliance comprised of 129 academic medical centers.

NIS - Nationwide Inpatient Sample (United States of America) The NIS is the largest all-payer inpatient care database in the US, collecting information

on all discharges from approximately 20% of the nation's hospitals every year. It is supported by the Healthcare Cost and Utilization Project and contains all-payer discharge information for 100% of patient discharges from participating hospitals.

DNHR – Danish National Hospital Registry, contains information on all hospital admissions since 1977

DNRP - Danish National Registry of Patients. The DNRP includes information on all nonpsychiatric hospitalizations since 1977 and on outpatient contacts since 1995

nr – not reported

SC – single centre

MC – multicentre

NW – Nationwide population based

Veterans Affairs NSQIP - Veterans' Affairs National Surgical Quality Improvement Program at 16 hospitals

AICP – Alcohol induced chronic pancreatitis

\$ - STUDY Provided data on hepatic resection, and other procedures which were not part of this study inclusion

Fekete/PESCOVITCH/ BELGHITI - 100% alcoholics

GI – gastrointestinal

Saleh study – ascites but including patients with alcohol cirrhosis as well as congestive cardiac failure etc

NEEF – is one of the few retrospective studies that included a follow-up longer than a year, indeed he covered a 5yr follow-up.

In patients with a CTP C the survival fell to 20% at one year, it was 50% at one year in CTP B and 70% in CTPA patients undergoing gastrointestinal surgery. Montomoli and Muenier analysed patients as either alcohol cirrhosis and cirrhosis of any other cause and both concluded that patients with alcohol cirrhosis had worse outcomes

(Ji, 2005, Carbonell et al., 2005, Chmielecki, 2012, Csikesz, 2009, Ecker, 2014, Gray et al., 2008, Hansen et al., 2002, Montomoli, 2013, Nguyen, 2009, Saleh et al., 2015, Thulstrup, 2001, Poulsen et al., 2000, Befeler et al., 2005, Belghiti, 1990, Bingener, 2008, Busquets, 2016, Cappellani, 2008, Cobb et al., 2005, Cucinotta, 2003, Curro, 2005, Curro et al., 2007, da Silveira, 2006, D'Albuquerque, 1995, Delis, 2010, del Olmo et al., 2003, Dunnington, 1987, Eker et al., 2011, Farnsworth et al., 2004, Fekete, 1987, Fernandes et al., 2000, Franzetta, 2003, Gervaz, 2003, Gil, 2003, Guo, 2014, Han, 2017, Hoteit et al., 2008, Jang, 2008, Lehnert and Herfarth, 1993, Leone, 2001, Dery, 2008, Lledo, 2011, Lu et al., 2005, Mansour et al., 1997, Metcalf, 1987, Meunier, 2008, Morino, 2000, Neeff et al., 2014, Northup et al., 2005, Oh et al., 2011, Pescovitz, 1984, Poggio, 2000, Ramesh, 2008, Regimbeau et al., 2015, Song, 2011, Tachibana, 2000, Teh, 2007, Telem et al., 2010, Tuech, 2002, Warnick et al., 2011, Yoshida, 2012, Zarski, 1988, Ziser et al., 1999).

Figure 1

Legend: Meta-analysis of proportions of in-hospital mortality after upper gastrointestinal cancer surgery –(all oesophagectomy) in only patients with definitive diagnosis of alcoholic liver disease.

Figure 2

Legend: Meta-analysis of proportions of 30-day mortality after benign gastrointestinal surgery, including abdominal wall (Hansen, Ecker, Gray and Saleh); appendicectomy (Poulson) and cholecystectomy (Thulstrup).

Figure 3

Legend: Meta-analysis of proportions of in-hospital mortality after benign gastrointestinal surgery. Cholecystectomy – includes studies where all child's grade of cirrhosis are included. Cholecystectomy A&B refers to studies which included only Childs A and B grade cirrhosis.

Figure 4

Legend: Meta-analysis of proportions of in-hospital mortality after upper gastrointestinal cancer surgery – including pancreaticoduodenectomy, gastrectomy and oesophagectomy.