Outcomes following an index emergency admission with cholecystitis: a national cohort study

Jemma Mytton, BSc[1*], Prita Daliya, MRCS[2,3*], Pritam Singh, MA, PhD, FRCS[2], Simon L Parsons, DM, FRCS[2,3], Dileep N Lobo, DM, FRCS, FACS, FRCPE[3,4], Richard Lilford, PhD[5,] Ravinder S Vohra, PhD, FRCS[2,3]

[*] Joint first authors

[1] Department of Health Informatics, University Hospitals Birmingham NHS Foundation Trust, Yardley Court, 11-13 Frederick Road, Edgbaston, Birmingham B15 1JD, UK
[2] Trent Oesophago-Gastric Unit, City Hospital Campus, Nottingham University Hospitals NHS Trust, Hucknall Road, Nottingham NG5 1PB, UK
[3] Gastrointestinal Surgery, Nottingham Digestive Diseases Centre and National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Queen's Medical Centre Campus, Derby Road, Nottingham, NG7 2UH, UK
[4] MRC/ARUK Centre for Musculoskeletal Ageing Research, School of Life Sciences, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, UK
[5] Warwick Medical School, University of Warwick, Coventry CV4 7AL, UK

Correspondence and reprint requests to:
Mr. Ravinder S. Vohra
Trent Oesophago-Gastric Unit,
Nottingham University Hospitals NHS Trust,
City Hospital Campus,
Hucknall Road,
Nottingham, NG5 1PB.
U.K.
Email: ravinder.vohra@nuh.nhs.uk
Tel: +44 1159691169

Keywords: cholecystitis, emergency cholecystectomy, index cholecystectomy

Total word count: 2803 (excluding abstract, tables, figures and references)

No. of figures: 3

No. of tables: 4

Supplementary file: 1

Conflicts of interest: None of the authors has a direct conflict of interest to declare. DNL has received unrestricted research funding from BBraun and speaker's honoraria from Fresenius Kabi, BBraun, Shire and Baxter Healthcare for unrelated work.

Source of funding: This work was supported by the Medical Research Council [grant number MR/K00414X/1]; and Arthritis Research UK [grant number 19891]. RJL is supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) West Midlands. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Author contributions

All named authors have been involved in the planning, conduct, and reporting of the study, and accept full responsibility for the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.
Corresponding author (guarantor): RSV.
Study design: JM, PD, PS, SLP, DNL, RL, RSV.
Data collection: JM, RL, RSV.
Data-analysis: JM, PD, PS, RL, RSV.
Data-interpretation: JM, PD, PS, SLP, DNL, RL, RSV.
Writing of Manuscript: JM, PD, PS, SLP, DNL, RL, RSV.
Creation of figures: JM, PD, DNL, RSV.
Critical review of Manuscript: JM, PD, PS, SLP, DNL, RL, RSV.
Final approval: JM, PD, PS, SLP, DNL, RL, RSV.

This paper was presented at the Annual Meeting of the Society for Academic and Research Surgery, London, January 2019 and has been published in abstract form (Br J Surg 2019; 106 (S3): 13-4).

Structured Abstract

Objective

The objective of this study was to evaluate the differences between patients who undergo cholecystectomy following index admission for cholecystitis, and those that are managed non-operatively.

Summary Background Data

Index emergency cholecystectomy following acute cholecystitis is widely recommended by national guidelines, but its effect on clinical outcomes remains uncertain.

Methods

Data collected routinely from the Hospital Episode Statistics database (all admissions to National Health Service organizations in England and Wales) were extracted between 1st April 2002 and 31st March 2015. Analyses were limited to patients aged over 18-years with a primary diagnosis of cholecystitis. Exclusions included records with missing or invalid datasets, patients who had previously undergone a cholecystectomy, patients who had died without a cholecystectomy, and those undergoing cholecystectomy for malignancy, pancreatitis or choledocholithiasis. Patients were grouped as either 'no cholecystectomy' where they had never undergone a cholecystectomy following discharge, or 'cholecystectomy'. The latter group was then subdivided as 'emergency cholecystectomy' when cholecystectomy was performed during their index emergency admission, or 'interval cholecystectomy' when a cholecystectomy was performed within 12 months following a subsequent (emergency or elective) admission. Propensity Score Matching was used to match emergency and interval cholecystectomy groups. Main outcome measures included 1) One-year total length of hospital stay due to biliary causes following an index emergency admission with cholecystitis. 2) One-year mortality; defined as death occurring within 1-year following the index emergency admission with acute cholecystitis.

Results

Of the 99,139 patients admitted as an emergency with acute cholecystitis, 51.1% (47,626) did not undergo a cholecystectomy within 1-year of index admission. These patients were older, with more co-morbidities (Charlson Comorbidity Score ≥ 5 in 23.5% vs. 8.1%, $p<0.001$) when compared to patients who did have a cholecystectomy. While all-cause 1-year mortality was higher in the non-operated versus the operated group (12.2% vs. 2.0%, $p<0.001$), gallbladder-related deaths were significantly lower than all other causes of death in the non-operated group (3.3% vs. 8.9%, $p<0.001$). Following matching, 1-year total hospital admission time, was significantly higher following emergency compared with interval cholecystectomy (17.7 days vs. 13 days, $p<0.001$).

Conclusions

Over 50% of patients in England did not undergo cholecystectomy following index admission for acute cholecystitis. Mortality was higher in the non-operated group, which was mostly due to non-gallbladder pathologies but total hospital admission time for biliary causes was lower over 12 months. Increasing the numbers of emergency cholecystectomy may risk over-treating patients with acute cholecystitis and increasing their time spent admitted to hospital.

Introduction

The prevalence of gallstones in the global adult population is between 10-15%.[1] While 80% of people do not suffer pain or complications, the most common complication is acute cholecystitis.[2] Laparoscopic cholecystectomy is generally recommended to prevent recurrent episodes of cholecystitis and further complications after the initial admission.[1] Clinical trials have concentrated on the timing of performing cholecystectomy in patients with acute cholecystitis and operative outcomes.[1, 3] Level one evidence advocates index emergency cholecystectomy for the majority of patients presenting with acute cholecystitis when compared with interval cholecystectomy.[3-7] Due to these perceived benefits, financial incentives are being offered to increase the numbers of index emergency operations performed across many healthcare systems, including the National Health Service (NHS) in the United Kingdom (UK).[8-12] Despite this, data from Europe, Asia and North America show that the majority of patients with acute cholecystitis still undergo interval cholecystectomy.[13-16]

An area that is less well studied is the natural history of acute cholecystitis. Early studies showed that recurrent attacks of pain and complications may actually diminish in up to half of initially symptomatic patients.[17, 18] One concern is that patients may be over-treated if policies continue to promote index emergency cholecystectomy. Furthermore, while a non-operative approach would clearly avoid surgery-related complications, it is unclear if delaying cholecystectomy has a detrimental effect on patient outcomes and increases healthcare costs.

The objective of this current study was to use the advantages of a large population database to examine the medium-term sequelae following a common entry point of patients admitted with acute cholecystitis. The primary aim was to identify the patient and hospital variables that determine which patients do not undergo a cholecystectomy following index emergency admission for acute cholecystitis, and their 1-year mortality. The secondary aim was to understand if interval cholecystectomy on a subsequent admission had a detrimental effect on patients by comparing 1-year total hospital admission time and mortality with those patients treated with emergency cholecystectomy during index admission.

Methods

Data Sources

Data were extracted from the Hospital Episode Statistics (HES, http://www.hscic.gov.uk/hes) database, which contains patient demographic and clinical information on every admission to an NHS hospital in England. HES is linked to the Office for National Statistics (ONS), which collects data on all registered deaths in the UK, to obtain mortality information. Data were analyzed in line with a data sharing agreement with NHS Digital for HES data.

Inclusion & Exclusion Criteria

Data analyses were limited to a primary diagnosis of acute cholecystitis (K81.0) coded using the ICD-10 (International Classification of Diseases-tenth version) classification, between 1st April 2002 and 31st March 2015. The Office of Population, Censuses and Surveys-fourth revision (OPCS-4) classification of interventions and procedures codes was used to identify all patients who underwent cholecystectomy (J18). Data were extracted for all patients over 18-years of age. Records with missing or invalid datasets (age, gender, or residence outside England) were excluded, as were patients who had previously undergone a cholecystectomy, or died in hospital without a cholecystectomy. Patients undergoing cholecystectomy for malignancy, pancreatitis or choledocholithiasis were also excluded. The remaining patients were grouped as either 'no cholecystectomy' where patients had never had a cholecystectomy following discharge, or 'cholecystectomy'. The latter group was then subdivided as 'emergency cholecystectomy' when cholecystectomy was performed during their index emergency admission, or 'interval cholecystectomy' when a cholecystectomy was performed following a subsequent admission (emergency or elective) within 12 months. Operations were classified as laparoscopic, open, or a laparoscopic converted to open procedure.

Outcomes

The outcome measures monitored were 1-year total hospital admission time for all biliary causes and 1-year mortality; defined as death occurring within 1-year following the index emergency admission with acute cholecystitis. The total hospital admission time for biliary causes was defined as the total number of inpatient days due to a diagnosis of cholelithiasis (ICD-10 K80), cholecystitis (ICD-10 K81) or biliary acute pancreatitis (ICD-10 K851). Deaths from gallbladder pathologies were defined using the following ICD-10 coding for the death record from ONS: K563, K65, K8[0123567], C23, C35.

Variables

To allow comparable risk adjustment, patient and hospital characteristics were defined as explanatory variables. These included patient age, gender, ethnicity, quintiles of Index of Multiple Deprivation (IMD) score,[19] Charlson comorbidity score,[20] trust volume and type of hospital (teaching vs. non-teaching). The IMD score was selected as it uses weighted scores across several domains (crime, living environment, housing & services, income, employment, education & training, and health & disability) to stratify inequality and relative deprivation across neighborhoods in England. A higher state of deprivation has been linked with a negative impact on health.[19, 21] Trust volume was expressed as the average number of emergency procedures per year and was evaluated as a categorical variable after being split into tertiles (low: ≤24 emergency cholecystectomies/year, medium: 25 to 49 emergency cholecystectomies/year, and high: ≥50 emergency cholecystectomies/year).

Statistical Analysis

Results presented here are as described in accordance with the STROBE guidelines for reporting observational studies.[22] Data were analyzed using Stata® version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA). Differences between groups were evaluated using chi-squared tests for categorical variables and t-tests for continuous variables.

Propensity score matching (PSM) was used to select patients with similar characteristics who underwent interval cholecystectomy with those who underwent emergency cholecystectomy. Patients were matched on a one-to-one basis on multiple confounders (age, gender, ethnicity, IMD score, comorbidities, and trust volume). Greedy matching was performed using the nearest neighbor technique within a caliper distance of 0.2 standard deviations, without replacement.[23] Although PSM reduced the total population data available for analysis, this technique provides a more accurate estimate of treatment effect by reducing selection bias in these otherwise heterogeneous groups.[23]

Logistic regression models were used to compare 1-year mortality between the two matched groups. Statistical significance was measured at $p<0.05$, with results expressed as adjusted odds ratios (ORs) or incidence rate ratios (IRR) with 95 per cent confidence intervals (CI). Negative binominal regression was used to compare total length of stay between matched groups. One-year survival following emergency admission for cholecystitis was assessed using the Kaplan-Meier method. The cholecystectomy and no cholecystectomy groups were compared using the log-rank test.

Results

Demographics

A total of 99,139 patients were admitted in England as an emergency, with a primary diagnosis of acute cholecystitis between 2002 and 2015. Of these, 5,964 patients were excluded as demonstrated in Figure 1. Of the remaining 93,175 patients included in the final analysis, 47,626 (51.1%) did not undergo a cholecystectomy within 1-year of the index emergency admission for cholecystitis. A further 3,925 (4.2%) patients subsequently underwent a cholecystectomy when this non-operated group was followed up for a median of 4.8 years.

Cholecystectomy vs. non-operative treatment for acute cholecystitis

There were significant differences in explanatory variables between the non-operated (n=47,626) and operated (n=45,549) patients (Table 1). Patients who did not undergo a cholecystectomy were older (64 vs. 54 years, p<0.001), more likely to be male (42.8% vs. 38.0%, p<0.001), and in particular, had more co-morbidities (Charlson Comorbidity Score of 5 or more in 23.5% vs. 8.1%, p<0.001) when compared with patients who had a cholecystectomy. Cholecystectomy was more likely to be performed in high-volume centers compared with medium- or low-volume centers (48.4% vs. 44.3%, p<0.001). Again, age, deprivation, fewer co-morbidities and higher volume centers were independent predictors of cholecystectomy (Table 2).

At 1-year following emergency admission for acute cholecystitis (Figure 2), all-cause mortality was significantly higher in the non-operated group when compared with those having a cholecystectomy (12.2% vs. 2.0%, p<0.001). When these were separated into gallbladder related and non-gallbladder related deaths at 1-year, patients who did not have a cholecystectomy had more gallbladder related deaths than those who did have a cholecystectomy (3.3% vs. 0.7%, p<0.001), however, gallbladder-related deaths were still significantly lower than all other causes of death in the non-operated group (3.3% vs. 8.9%, p<0.001).

Emergency vs. interval cholecystectomy

Some 45,549 patients underwent a cholecystectomy either as an index emergency cholecystectomy (n=16,448) or an interval cholecystectomy (n=29,101). The median time from emergency admission to cholecystectomy in the emergency group was 3 days (IQR 1-5) compared with 103 days (IQR 56-168) in the interval group (p<0.001). The majority of patients in the interval cholecystectomy group (78.8%) did not require readmission before their interval cholecystectomy. Those that did, had a median of one further emergency admission prior to the admission for interval cholecystectomy.

There were significant differences in explanatory variables between the unmatched emergency and interval cholecystectomy groups (Table 3). Patients undergoing emergency cholecystectomy were more likely to be female (63.1% vs. 61.4%, p<0.001), less deprived (IMD score of 4 or more in 36.2% vs. 34.8%, p=0.002), and had more co-morbidities (Charlson Comorbidity Score of 5 or more in 9.7% vs. 7.2%, p<0.001) when compared with interval cholecystectomy. Emergency cholecystectomy was more likely to be performed in high volume hospitals (45.3% vs. 33.5% vs. 19.4%, p<0.001) when compared with medium- and low-volume hospitals (Figure 3). Similarly, emergency cholecystectomy was more likely to be performed in teaching (38.3% vs. 35.0%, p=0.001) compared with non-teaching hospitals. The total hospital admission time in the year following index emergency admission for cholecystitis was significantly longer for those having emergency cholecystectomy compared with interval cholecystectomy (9 days (IQR 5-18) vs. 8

days (IQR 4-15), p<0.001). All-cause mortality following index emergency cholecystectomy was higher when compared at 1-year (3.8% vs. 1.0%, p<0.001).

A matched one-to-one dataset was created of 15,675 patients undergoing emergency cholecystectomy and 15,675 undergoing interval cholecystectomy. Patient age, gender, ethnicity, IMD scores, and Charlson comorbidity scores were similar between these matched groups (Supplementary Table 1). The standardized percentage bias across covariates for these matched groups can be seen in Supplementary Figure 1.

Total hospital admission time in this matched dataset was lower in the interval cholecystectomy group 13.0 days (95% CI 12.8-13.2) compared with 17.7 days (95% CI 17.4-17.9) in the emergency group (p<0.001). Multivariable analysis of these matched cohorts (Table 4) demonstrated significantly higher risk of all-cause mortality at 1-year following emergency cholecystectomy when compared with interval cholecystectomy (OR 3.3, 95% CI 2.7-3.9, p<0.001).

Discussion

This population-based study demonstrates that 51% of patients in England did not undergo a cholecystectomy within the first year following an index emergency admission with acute cholecystitis. Even when followed up for nearly 5-years, 47% of patients did not undergo a cholecystectomy. Non-operative management of acute cholecystitis is influenced by patient factors (age and co-morbidities) and hospital factors (low and medium volume centers). This non-operated group had a higher 1-year all-cause and non-gallbladder related mortality consistent with the hypothesis they are a frail patient group. In the 12 months following the index admission, this non-operated group spent less time admitted to hospital (7 days vs 8 days $p<0.001$) with biliary causes than the cholecystectomy group. When only patients undergoing a cholecystectomy are considered, those undergoing an emergency operation spend an extra 4.7 days in hospital over a period of 12 months after the first emergency admission when compared with those undergoing interval cholecystectomy in a propensity score matched dataset. This finding was made despite the interval cholecystectomy group including any emergency readmissions prior to the planned admission for surgery. Patients undergoing emergency cholecystectomy were older with more co-morbidity and had higher mortality than those undergoing interval cholecystectomy. The higher mortality was observed both in an unmatched and matched analysis. The current study would suggest default policies of emergency cholecystectomy for all patients during an index emergency admission with acute cholecystitis may result in increased patient harm by over-treatment, when watchful waiting or judicious interval cholecystectomy may be more appropriate.

Cholecystectomy remains the treatment of choice for patients with symptomatic gallstones[24, 25] despite natural history studies suggesting recurrent pain may only affect half of initially symptomatic people.[17] A recent systematic review identified only two randomized controlled trials from Norway comparing the clinical and cost effectiveness of cholecystectomy with conservative management in people presenting with uncomplicated symptomatic gallstones or cholecystitis.[26] Fifty-five percent of this heterogeneous cohort randomized to conservative treatment did not undergo a cholecystectomy during the 14-year follow-up period. This trend favoring continued non-operative management is similar to that observed in the current study. Most of the surgical procedures in this systematic review were performed during the first 5 years and virtually no operations occurred after 5 years.[26] The current data seems to suggest more than 95% of cholecystectomies are performed in the first year in the NHS.

In the current study, patients who did not progress to cholecystectomy were older, with more co-morbidities. This may simply reflect that either emergency or interval cholecystectomy was deemed inappropriate due to fitness for surgery. A key limitation of the current study is the lack of quality of life data or patient reported outcomes and it is unclear if these non-operated patients suffered from recurrent symptoms or complications. However, total hospital admission time for biliary causes was actually lower in the non-operated group over the 12 months following the index admission (7 days vs 8 days $p<0.001$). Natural history studies[17, 27] and more recent observational and population-based studies,[18, 28] suggest nearly half of initially symptomatic patients were relieved of symptoms within the first year of an observation period.

Clearly, there is a group of patients with recurrent symptoms or complications following the index admission with acute cholecystitis. Many clinical trials have concentrated on the timing of cholecystectomy. Index emergency cholecystectomy is reportedly associated with less gallbladder-specific morbidity,[29-33] a shorter total length of hospital stay,[30-43] lower hospital costs,[30, 32, 34, 40] and fewer lost work days,[30, 35, 39, 44] without increased operative mortality when compared with interval cholecystectomy.[30, 36-39, 41, 45] In contrast, the current population based study, demonstrated significantly lower total hospital admission time in the interval group and mortality was three-fold higher following index emergency cholecystectomy when compared with interval cholecystectomy.

There is an issue of external validity in these non-pragmatic randomized clinical trials.[46, 47] With respect to the current analysis, it should be realized both the patient populations and healthcare systems studied in the clinical trials are different. Patients having index emergency cholecystectomy were older with more co-morbidities than those that had interval cholecystectomy. Furthermore, they have waited a median of three days before an operation suggesting they may have failed antibiotics and conservative treatment. There are also likely to be system processes including the availability of resources in specialty units, and a variation in clinical decision making by subspecialty surgeons with expertise in upper gastrointestinal or hepatobiliary surgery.[48]

The results presented here support a strategy to improve pathways to enable more efficient interval cholecystectomy. There are valid concerns of waiting for an interval cholecystectomy following an acute admission with cholecystitis. Some of these patients are likely to suffer gallstone-related complications, and recurrent admissions.[3-7] However, the current study suggests nearly 80% of the patients in the interval group do not have another hospital admission prior to cholecystectomy, and currently wait a median of 103 days.

Although HES provides robust datasets on medical diagnoses, interventions, outcomes and explanatory variables, careful analysis and interpretation is required due to the retrospective, observational nature of data collection. HES data do not include detailed information on patient physiology, investigative findings, disease severity or patient reported outcomes. Patients admitted as an emergency have a higher risk of poorer outcomes. HES data unfortunately lacks the availability of comprehensive patient, disease or operative data to allow for risk stratification. Factors such as operative time, and case difficulty, can influence the outcomes studied here. Emergency cholecystectomies can be complex operative cases, with longer operative times,[35, 38, 39, 49, 50] and greater intra-operative blood loss,[35, 37] when compared with interval cholecystectomies.[35, 37, 50] HES does not provide information on the impact on quality of life, patient attitudes and patient satisfaction. In other studies, patient preference was predictably for emergency cholecystectomy,[41] but analgesic use and pain score were not statistically significant when emergency and interval cholecystectomy were compared.[37, 38, 43, 50, 51] There is also some evidence that emergency cholecystectomy may cause more pain in the early postoperative period.[35]

The current study did not review any detail on temporizing interventions such as percutaneous gallbladder drainage procedures, or the influence of disease severity in the surgical decision-making process. Whilst radiological drainage procedures are coded for in the HES database, it is unclear whether these are for the drainage of collections for unrelated reasons, or specifically cholecystostomy drains. These factors together with patient choice can play a large part in influencing case selection for and against index emergency cholecystectomy, and consequently operative outcomes. Future guidelines supporting index emergency cholecystectomy should therefore consider these factors, together with the availability of and access to appropriate radiological, endoscopic and specialist biliary resources.

Conclusion

Strict oversight needs to be considered when financially incentivizing index emergency cholecystectomy. The current study would suggest default policies of emergency cholecystectomy for all patients during an index emergency admission with acute cholecystitis may risk over-treatment, when watchful waiting or judicious interval cholecystectomy may be more appropriate.[26]

References

1 Gurusamy KS, Davidson BR. Gallstones. *BMJ.* 2014; 348: g2669.
2 Halldestam I, Enell EL, Kullman E, Borch K. Development of symptoms and complications in individuals with asymptomatic gallstones. *Br J Surg.* 2004; 91: 734-738.
3 Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of randomized controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg.* 2010; 97: 141-150.
4 Zhou MW, Gu XD, Xiang JB, Chen ZY. Comparison of clinical safety and outcomes of early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a meta-analysis. *Sci World J.* 2014; 2014: 274516.
5 Menahem B, Mulliri A, Fohlen A, Guittet L, Alves A, Lubrano J. Delayed laparoscopic cholecystectomy increases the total hospital stay compared to an early laparoscopic cholecystectomy after acute cholecystitis: an updated meta-analysis of randomized controlled trials. *HPB.* 2015; 17: 857-862.
6 Cao AM, Eslick GD, Cox MR. Early cholecystectomy is superior to delayed cholecystectomy for acute cholecystitis: a meta-analysis. *J Gastrointest Surg.* 2015; 19: 848–857.
7 Wu XD, Tian X, Liu MM, Wu L, Zhao S, Zhao L. Meta-analysis comparing early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg.* 2015; 102: 1302-1313.
8 Bokhari S, Walsh U, Qurashi K, et al. Impact of a dedicated emergency surgical unit on early laparoscopic cholecystectomy for acute cholecystitis. *Ann R Coll Surg Engl.* 2016; 98: 107-115.
9 Cubas RF, Gomez NR, Rodriguez S, Wanis M, Sivanandam A, Garberoglio CA. Outcomes in the management of appendicitis and cholecystitis in the setting of a new acute care surgery service model: impact on timing and cost. *J Am Coll Surg.* 2012; 215: 715-721.
10 Shakerian R, Skandarajah A, Gorelik A, Thomson B. Emergency management of gallbladder disease: are acute surgical units the new gold standard? *World J Surg.* 2015; 39: 2636-2640.
11 Agrawal S, Battula N, Barraclough L, Durkin D, Cheruvu CV. Early laparoscopic cholecystectomy service provision is feasible and safe in the current UK National Health Service. *Ann R Coll Surg Engl.* 2009; 91: 660-664.
12 National Institute for Health and Care Excellence. NICE Costing statement: Gallstone disease. Implementing the NICE guideline on gallstone disease (CG188). London: National Institute for Health and Care Excellence, 2014. Available at: https://www.nice.org.uk/guidance/cg188/resources/costing-statement-pdf-193298365 (Accessed 1 January 2019).
13 Lee SW, Yang SS, Chang CS, Yeh HJ. Impact of the Tokyo guidelines on the management of patients with acute calculous cholecystitis. *J Gastroenterol Hepatol.* 2009; 24: 1857-1861.
14 Casillas RA, Yegiyants S, Collins JC. Early laparoscopic cholecystectomy is the preferred management of acute cholecystitis. *Arch Surg.* 2008; 143: 533-537.
15 Riall TS, Zhang D, Townsend CM, Jr., Kuo YF, Goodwin JS. Failure to perform cholecystectomy for acute cholecystitis in elderly patients is associated with increased morbidity, mortality, and cost. *J Am Coll Surg.* 2010; 210: 668-679.
16 Greenstein AJ, Moskowitz A, Gelijns AC, Egorova NN. Payer status and treatment paradigm for acute cholecystitis. *Arch Surg.* 2012; 147: 453-458.
17 McSherry CK, Ferstenberg H, Calhoun WF, Lahman E, Virshup M. The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. *Ann Surg.* 1985; 202: 59-63.

18 Festi D, Reggiani ML, Attili AF, et al. Natural history of gallstone disease: Expectant management or active treatment? Results from a population-based cohort study. *J Gastroenterol Hepatol.* 2010; 25: 719-724.
19 English Index of Multiple Deprivation (IMD) 2015. London: Ministry of Housing, Communities and Local Government, 2015. Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (Accessed 31 January 2019).
20 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987; 40: 373-383.
21 The English Indices of Deprivation 2015 – Frequently Asked Questions (FAQs) 2015. London: Ministry of Hosuing, Communities and Local Government, 2015. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/579151/English_Indices_of_Deprivation_2015_-_Frequently_Asked_Questions_Dec_2016.pdf. (Accessed 8 June 2019).
22 von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet.* 2007; 370: 1453-1457.
23 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res.* 2011; 46: 399-424.
24 Guidelines for the treatment of gallstones. American College of Physicians. *Ann Intern Med.* 1993; 119: 620-622.
25 Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland & Royal College of Surgeons of England. Commissioning Guide: Gallstone Disease. London: Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland & Royal College of Surgeons of England, 2016. Available at: http://www.augis.org/wp-content/uploads/2014/05/Gallstone-disease-commissioning-guide-for-CONSULTATION-020816-to160916.pdf (Accessed 20 September 2018).
26 Brazzelli M, Cruickshank M, Kilonzo M, et al. Clinical effectiveness and cost-effectiveness of cholecystectomy compared with observation/conservative management for preventing recurrent symptoms and complications in adults presenting with uncomplicated symptomatic gallstones or cholecystitis: a systematic review and economic evaluation. *Health Technol Assess.* 2014; 18: 1-101, v-vi.
27 Ransohoff DF, Gracie WA. Treatment of gallstones. *Ann Intern Med.* 1993; 119: 606-619.
28 Larsen TK, Qvist N. The influence of gallbladder function on the symptomatology in gallstone patients, and the outcome after cholecystectomy or expectancy. *Dig Dis Sci.* 2007; 52: 760-763.
29 Faizi KS, Ahmed I, Ahmad H. Comparison of early versus delayed laparoscopic cholecystectomy: choosing the best. *Pak J Med Health Sci.* 2013; 7: 212-215.
30 Gutt CN, Encke J, Koninger J, et al. Acute cholecystitis: early versus delayed cholecystectomy, a multicenter randomized trial. *Ann Surg.* 2013; 258: 385-393.
31 Mare LD, Saadi A, Roulin D, Demartines N, Halkic N. Delayed versus early laparoscopiuc cholecystectomy for acute cholecystitis: A prospective randomized study. *HPB.* 2012; 14(Suppl): 130.
32 Roulin D, Saadi A, Di Mare L, Demartines N, Halkic N. Early versus delayed cholecystectomy for acute cholecystitis, are the 72 hours still the rule?: A randomized trial. *Ann Surg.* 2016; 264: 717-722.

33 Wiggins T, Markar SR, Mackenzie H, et al. Optimum timing of emergency cholecystectomy for acute cholecystitis in England: population-based cohort study. *Surg Endosc.* 2019: 1-8.
34 Chandler CF, Lane JS, Ferguson P, Thompson JE, Ashley SW. Prospective evaluation of early versus delayed laparoscopic cholecystectomy for treatment of acute cholecystitis. *Am Surg.* 2000; 66: 896-900.
35 Gul R, Dar RA, Sheikh RA, Salroo NA, Matoo AR, Wani SH. Comparison of early and delayed laparoscopic cholecystectomy for acute cholecystitis: experience from a single center. *N Am J Med Sci.* 2013; 5: 414-418.
36 Johansson M, Thune A, Blomqvist A, Nelvin L, Lundell L. Management of acute cholecystitis in the laparoscopic era: results of a prospective, randomized clinical trial. *J Gastrointest Surg.* 2003; 7: 642-645.
37 Kolla SB, Aggarwal S, Kumar A, et al. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a prospective randomized trial. *Surg Endosc.* 2004; 18: 1323-1327.
38 Lai PB, Kwong KH, Leung KL, et al. Randomized trial of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg.* 1998; 85: 764-767.
39 Lo CM, Liu CL, Fan ST, Lai EC, Wong J. Prospective randomized study of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Ann Surg.* 1998; 227: 461-467.
40 Ozkardes AB, Tokac M, Dumlu EG, et al. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a prospective, randomized study. *Int Surg.* 2014; 99: 56-61.
41 Saber A, Hokkam EN. Operative outcome and patient satisfaction in early and delayed laparoscopic cholecystectomy for acute cholecystitis. *ISRN Minim Invasive Surg.* 2014; 2014: 162643.
42 Serralta AS, Bueno JL, Planells MR, Rodero DR. Prospective evaluation of emergency versus delayed laparoscopic cholecystectomy for early cholecystitis. *Surg Laparosc Endosc Percutan Tech.* 2003; 13: 71-75.
43 Yadav RP, Adhikary S, Agrawal CS, Bhattarai B, Gupta RK, Ghimire A. A comparative study of early vs. delayed laparoscopic cholecystectomy in acute cholecystitis. *Kathmandu Univ Med J (KUMJ).* 2009; 7: 16-20.
44 Khan SSA. Early versus delayed cholecystectomy for acute cholecystitis, a prospective randomized study. *Pak J Gastroenterol.* 2002; 16: 30-34.
45 Ghani AA, Jan WA, Haq A. Acute cholecystitis: immediate versus interval cholecystectomy. *J Postgrad Med Inst.* 2005; 19: 192–195.
46 Grapow MT, von Wattenwyl R, Guller U, Beyersdorf F, Zerkowski HR. Randomized controlled trials do not reflect reality: real-world analyses are critical for treatment guidelines! *J Thorac Cardiovasc Surg.* 2006; 132: 5-7.
47 Rothwell PM. External validity of randomised controlled trials: "To whom do the results of this trial apply?". *Lancet.* 2005; 365: 82-93.
48 Boddy AP, Bennett JM, Ranka S, Rhodes M. Who should perform laparoscopic cholecystectomy? A 10-year audit. *Surg Endosc.* 2007; 21: 1492-1497.
49 CholeS Study Group. Population-based cohort study of outcomes following cholecystectomy for benign gallbladder diseases in the UK and Ireland. *Br J Surg.* 2016; 103: 1704-1715.
50 Verma S, Agarwal PN, Bali RS, Singh R, Talwar N. Early versus delayed laparoscopic cholecystectomy for acute cholecystitis: a prospective randomized trial. *ISRN Minim Invasive Surg.* 2013; 2013: 486107.

51 Macafee DA, Humes DJ, Bouliotis G, Beckingham IJ, Whynes DK, Lobo DN. Prospective randomized trial using cost-utility analysis of early versus delayed laparoscopic cholecystectomy for acute gallbladder disease. *Br J Surg.* 2009; 96: 1031-1040.

Legends for figures

Figure 1: Study flow diagram.

Flow diagram demonstrating the identification of patients for analyses.

* All emergency admissions presenting to hospitals in England between 1st April 2002 and 31st March 2015.

** Patients excluded from analyses may have been excluded for multiple reasons.

Figure 2: One-year survival following emergency admission for cholecystitis.

Kaplan Meier curve demonstrating one-year survival following admission with acute cholecystitis in emergency cholecystectomy, and no cholecystectomy groups.

Figure 3: Number of cholecystectomies performed in high, medium, and low volumes trusts.

Bar chart demonstrating variation in number of cholecystectomies performed in centers of different volumes.

Table 1: Patient characteristics and explanatory variables in all groups.

		Cholecystectomy *n*=45,549	**No Cholecystectomy** *n*=47,626	***p*-value**
Age mean years (SD)		54.30 (17.11)	64.06 (19.96)	<0.001
Gender	**Male**	17,311 (38.01)	20,393 (42.82)	<0.001
	Female	28,238 (61.99)	27,233 (57.18)	
Ethnicity	**White**	36,317 (79.73)	37,803 (79.37)	<0.001
	Non-white	3,205 (7.04)	3,963 (8.32)	
	Unknown	6,027 (13.23)	5,860 (12.30)	
Index of Multiple Deprivation Score	**5** (least deprived)	7,678 (16.86)	7,500 (15.75)	<0.001
	4	8,396 (18.43)	8,502 (17.85)	
	3	9,261 (20.33)	9,238 (19.40)	
	2	9,538 (20.94)	10,295 (21.62)	
	1 (most deprived)	10,578 (23.22)	11,852 (24.89)	
	Unknown	98 (0.22)	239 (0.50)	
Charlson Comorbidity Score	**0**	35,038 (76.92)	28,559 (59.97)	<0.001
	1 to 4	6,813 (14.96)	7,893 (16.57)	
	≥5	3,698 (8.12)	11,174 (23.46)	
Trust Volume	**High**	22,066 (48.44)	21,092 (44.29)	<0.001
	Medium	13,489 (29.61)	14,328 (30.08)	
	Low	9,994 (21.94)	12,206 (25.63)	
Type of Hospital	**Teaching**	13,988 (30.71)	14,742 (30.95)	0.444
	Non-teaching	31,552 (69.27)	32,893 (69.07)	
Total LOS within a year for all causes median (IQR)		13 days (6-22)	14 days (8-28)	<0.001
Total LOS within a year for biliary causes (K80, K81, K851) median (IQR)		8 days (4 -16)	7 days (3-18)	<0.001

Values expressed as number (%), unless otherwise stated.
SD: Standard Deviation. LOS: Length of Stay. IQR: Inter-Quartile Range.

Table 2: Regression analysis table

		Odds Ratio (95% ci)	***p*-value**
Age		0.98 (0.97 to 0.98)	<0.001
Gender	**Male**	1	
	Female	0.99 (0.96 to 1.02)	0.471
Ethnicity	**White**	1	
	Non-white	0.74 (0.70 to 0.77)	<0.001
	Unknown	0.95 (0.91 to 0.99)	<0.001
Index of Multiple Deprivation Score	**5** (least deprived)	1	
	4	0.98 (0.92 to 1.02)	0.303
	3	0.97 (0.93 to 1.02)	0.230
	2	0.86 (0.82 to 0.90)	<0.001
	1 (most deprived)	0.78 (0.75 to 0.82)	<0.001
Charlson Comorbidity Score	**0**	1	
	1 to 4	0.82 (0.79 to 0.85)	<0.001
	≥5	0.41 (0.39 to 0.43)	<0.001
Trust Volume	**High**	1	
	Medium	0.73 (0.70 to 0.76)	<0.001
	Low	0.86 (0.83 to 0.89)	<0.001
Type of Hospital	**Teaching**	1	
	Non-teaching	1.08 (1.05 to 1.12)	<0.001

ci: confidence interval.

Table 3: Patient characteristics and explanatory variables in unmatched cholecystectomy groups.

		Emergency Cholecystectomy n=16,448	Interval Cholecystectomy n=29,101	***p*-value**
Age mean years (SD)		54.59 (17.89)	54.13 (16.65)	0.006
Gender	**Male**	6,071 (36.91)	11,240 (38.62)	<0.001
	Female	10,377 (63.09)	17,861 (61.38)	
Ethnicity	**White**	12,880 (78.31)	23,437 (80.54)	<0.001
	Non-white	1,022 (6.21)	2,183 (7.50)	
	Unknown	2,546 (15.48)	3,481 (11.96)	
Index of Multiple Deprivation Score	**5** (least deprived)	2,923 (17.77)	4,755 (16.34)	<0.001
	4	3,025 (18.39)	5,371 (18.46)	
	3	3,362 (20.44)	5,899 (20.27)	
	2	3,275 (19.91)	6,263 (21.52)	
	1 (most deprived)	3,817 (23.21)	6,761 (23.23)	
	Unknown	46 (0.28)	52 (0.18)	
Charlson Comorbidity Score	**0**	12,379 (75.26)	22,659 (77.86)	<0.001
	1 to 4	2,476 (15.05)	4,337 (14.90)	
	≥5	1,593 (9.69)	2,105 (7.23)	
Trust Volume	**High**	9,987 (60.72)	12,079 (41.51)	<0.001
	Medium	4,525 (27.51)	8,964 (30.80)	
	Low	1,936 (11.77)	8,058 (27.69)	
Type of Hospital	**Teaching**	5,352 (32.54)	8,636 (29.68)	<0.001
	Non-teaching	11,096 (67.46)	20,456 (70.29)	

Values expressed as number (%), unless otherwise stated. SD: Standard Deviation.

Table 4: Adjusted all-cause mortality following emergency and interval cholecystectomy at 1-year.

		Odds Ratio (95% ci)	*p*-value
Age		1.08 (1.07-1.09)	<0.001
Gender	**Male**	1	
	Female	1.03 (0.88-1.20)	0.713
Ethnicity	**White**	1	
	Non-white	0.79 (0.54-1.15)	0.219
	Unknown	1.07 (0.86-1.34)	0.532
Index of Multiple Deprivation Score	**5** (least deprived)	1	
	4	1.40 (1.08-1.82)	0.012
	3	1.49 (1.15-1.92)	0.002
	2	1.57 (1.21-2.04)	0.001
	1 (most deprived)	1.63 (1.26-2.11)	<0.001
Charlson Comorbidity Score	**0**	1	
	1 to 4	1.77 (1.43-2.18)	<0.001
	≥5	4.30 (3.60-5.12)	<0.001
Trust Volume	**High**	1	
	Medium	1.13 (0.94-1.36)	0.19
	Low	1.27 (1.03-1.56)	0.024
Interval Cholecystectomy		1	
Emergency Cholecystectomy		3.26 (2.74-3.89)	<0.001

ci: confidence interval.

Figure 1

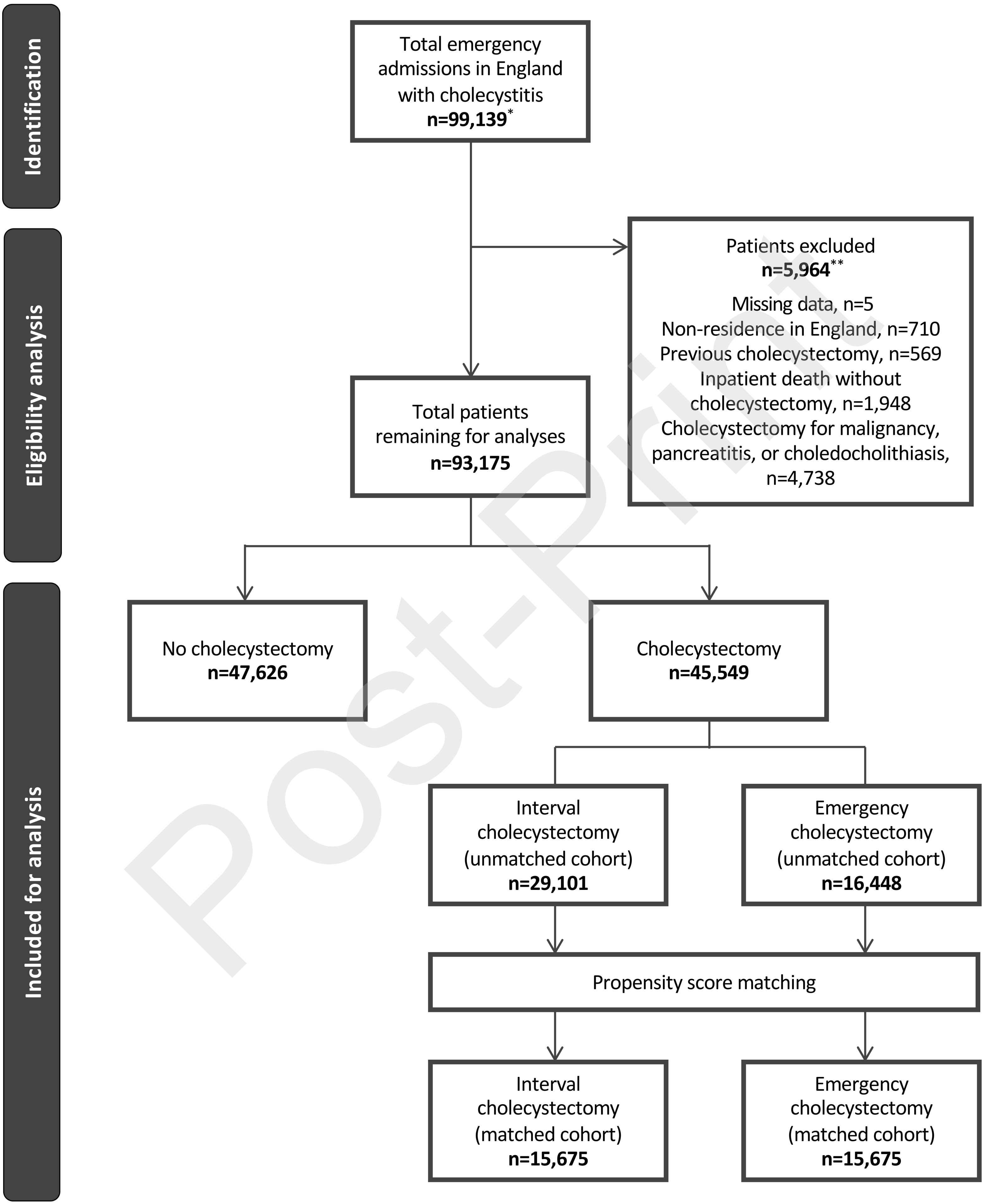

Identification
Eligibility analysis
Included for analysis
Total emergency admissions in England with cholecystitis
n=99,139*
Patients excluded
n=5,964**
Missing data, n=5
Non-residence in England, n=710
Previous cholecystectomy, n=569
Inpatient death without cholecystectomy, n=1,948
Cholecystectomy for malignancy, pancreatitis, or choledocholithiasis, n=4,738
Total patients remaining for analyses
n=93,175
No cholecystectomy
n=47,626
Cholecystectomy
n=45,549
Interval cholecystectomy (unmatched cohort)
n=29,101
Emergency cholecystectomy (unmatched cohort)
n=16,448
Propensity score matching
Interval cholecystectomy (matched cohort)
n=15,675
Emergency cholecystectomy (matched cohort)
n=15,675

Figure 2

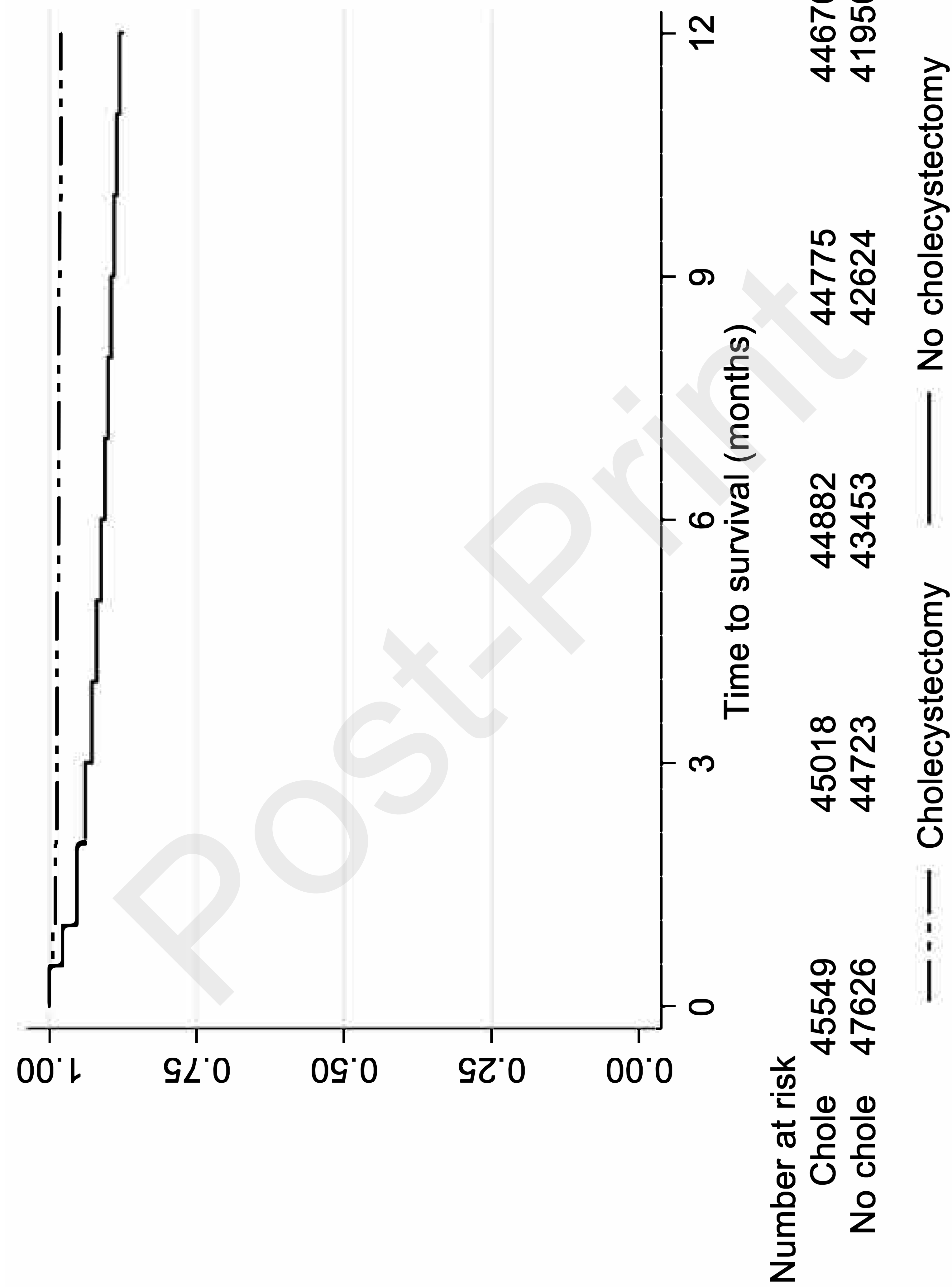
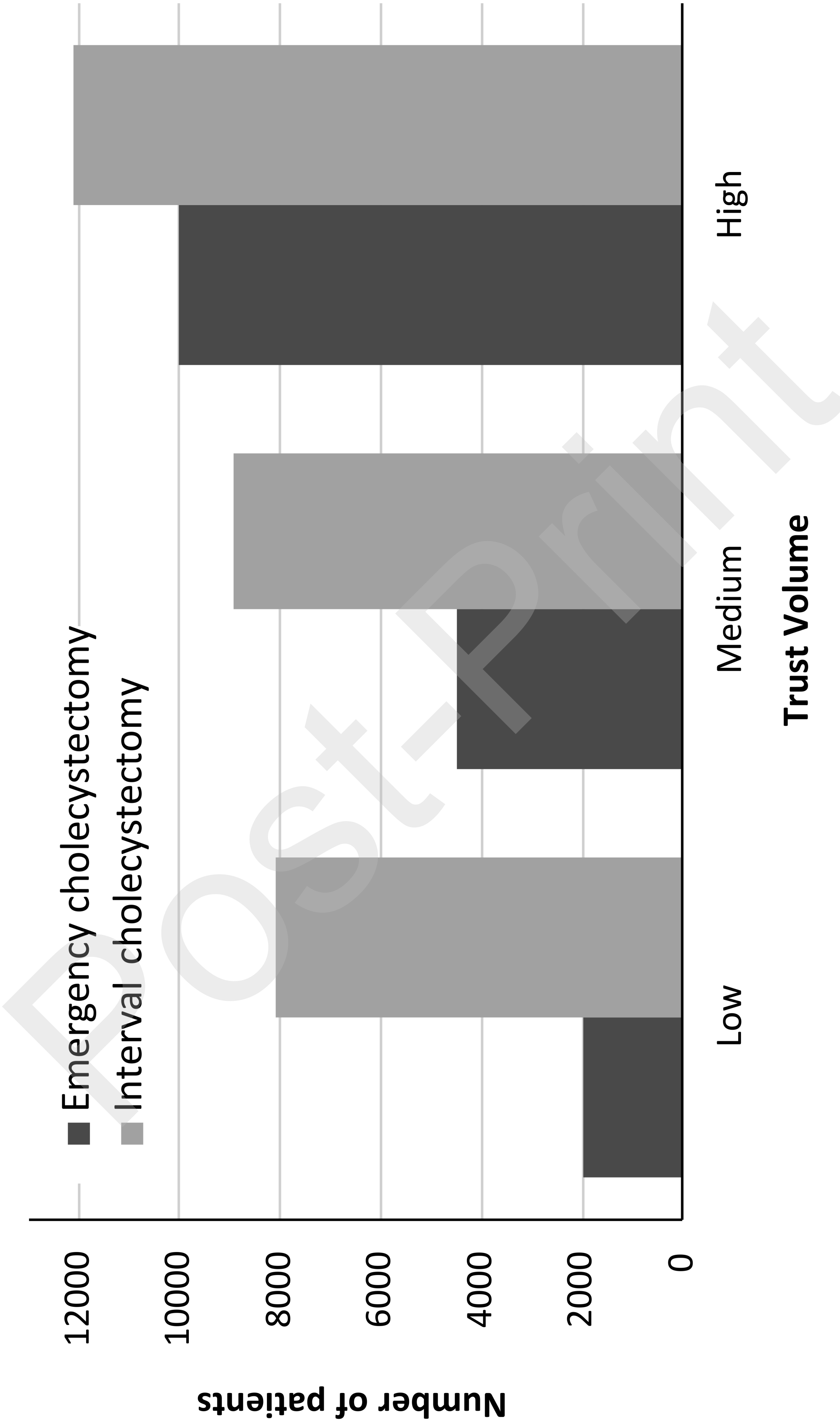
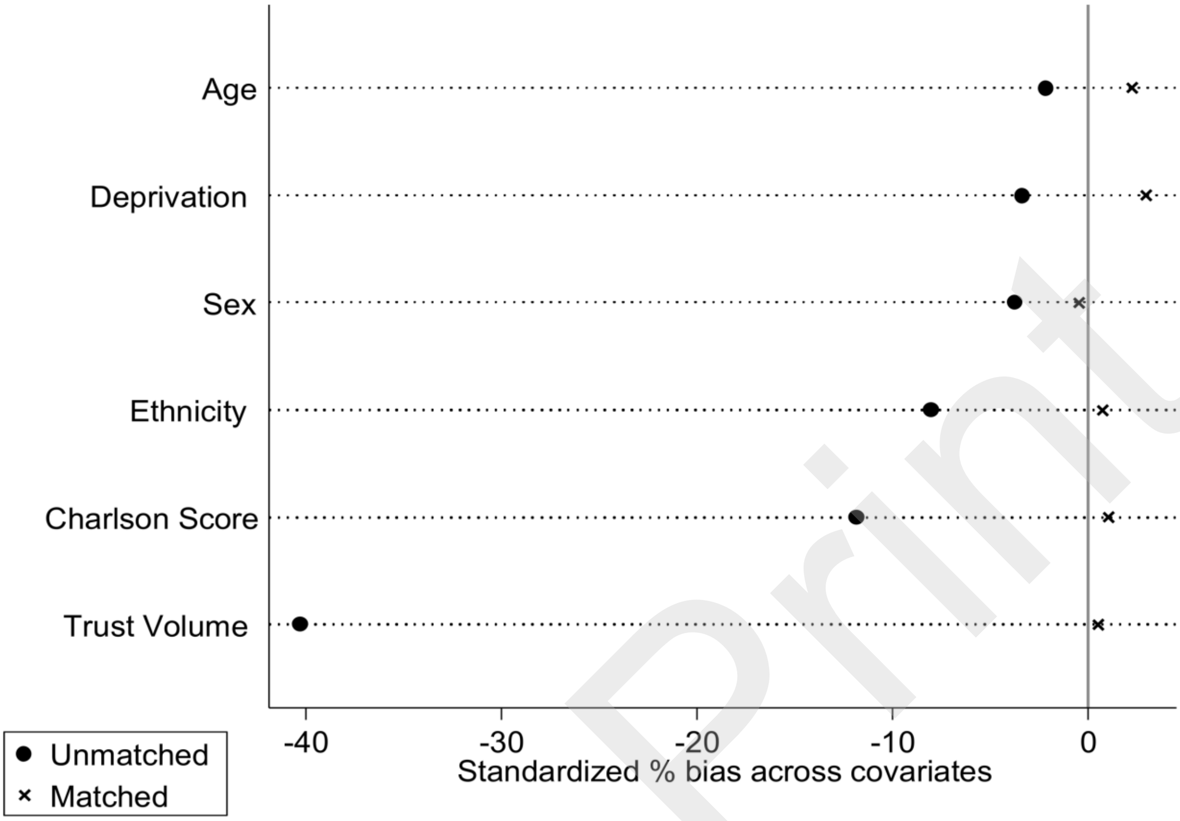

1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Time to survival (months)
Number at risk
Chole 45549 45018 44882 44775 44670
No chole 47626 44723 43453 42624 41950
Cholecystectomy
No cholecystectomy
Post-Print

Figure 3



Number of patients
0
2000
4000
6000
8000
10000
12000
Emergency cholecystectomy
Interval cholecystectomy
Low
Medium
High
Trust Volume

Supplementary Document



Supplementary Figure 1: Standardized percentage bias across covariates. Graph demonstrating the variation in explanatory variables between matched and unmatched cholecystectomy groups.

Supplementary Table 1: Patient characteristics and explanatory variables in matched cholecystectomy groups.

		Emergency Cholecystectomy *n*=15,675	**Interval Cholecystectomy** *n*=15,675	***% bias***
Age mean years (SD)		54.51 (17.91)	54.89 (16.59)	2.20
Gender	**Male**	5,803 (37.02)	5,840 (37.26)	-0.50
	Female	9,872 (62.98)	9,835 (62.74)	
Ethnicity	**White**	12,327 (78.64)	12,336 (78.70)	2.90
	Non-white	1,001 (6.39)	904 (5.77)	
	Unknown	2,347 (14.97)	2,435 (15.53)	
Index of Multiple Deprivation Score	**5** (least deprived)	2,749 (17.54)	2,810 (17.93)	1.00
	4	2,890 (18.44)	3,036 (19.37)	
	3	3,215 (20.51)	3,172 (20.24)	
	2	3,150 (20.10)	3,203 (20.43)	
	1 (most deprived)	3,671 (23.42)	3,454 (22.04)	
Charlson Comorbidity Score	**0**	11,884 (75.81)	11,485 (73.27)	0.70
	1 to 4	2,352 (15.00)	2,674 (17.06)	
	≥5	1,439 (9.18)	1,516 (9.67)	
Trust Volume	**High**	10,177 (64.93)	9,683 (61.77)	0.50
	Medium	3,572 (22.79)	3,465 (22.11)	
	Low	1,926 (12.29)	2,527 (16.12)	

Values expressed as number (%), unless otherwise stated. SD: Standard Deviation.

High resolution image from supplementary document