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Complete List of Authors:	Enochsson, Lars; Umea University, Surgical and Perioperative Sciences Blohm, My; Karolinska institutet Department of Clinical Sciences Intervention and Technology, Division of Surgery, CLINTEC Sandblom, Gabriel; Karolinska Institute, Center for Digestive Diseasee; Karolinska Institutet Department for Clinical Intervention and Technology, Jonas, Eduard; University of Cape Town, Health Sciences Faculty Hallerbäck, Bengt; Goteborgs Universitet, Department of Surgery Lundell, Lars; Karolinska institutet Department of Clinical Sciences Intervention and Technology, Division of Surgery, CLINTEC Österberg, Johanna; Karolinska institutet Department of Clinical Sciences Intervention and Technology
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The completeness of follow-up, a previously unrecognized quality indicator for outcome analyses in registry-based studies?

Lars Enochsson[1], My Blohm[2,3], Gabriel Sandblom[2,4], Eduard Jonas[5], Bengt Hallerbäck[6], Lars Lundell[2], Johanna Österberg[2,3]

[1]Department of Surgical and Perioperative Sciences, Sunderby Research Unit, Umeå University, Sweden

[2]Division of Surgery, CLINTEC, Karolinska Institutet, Stockholm, Sweden

[3]Department of Surgery, Mora Hospital, Mora, Sweden

[4]Center for Digestive Diseases, Karolinska University Hospital, Huddinge, Stockholm, Sweden

[5]Surgical Gastroenterology Unit, Department of Surgery, Groote Schuur Hospital, University of Cape Town Health Sciences Faculty, Cape Town, South Africa

[6]Department of Surgery, Norra Älvsborg County Hospital, Trollhättan, Sweden

Correspondence to:

Lars Enochsson, MD, PhD
Department of Surgical and Perioperative Sciences, Umeå University, Umeå,
Sunderby Hospital
97180 Luleå,
Sweden
E-mail: lars.enochsson@umu.se
Phone: +46 920 28 31 05
Fax: +46 920 28 33 20

ABSTRACT

OBJECTIVE

To analyse factors that may affect the validity of follow-up data in a national quality registry.

DESIGN

Population-based register study.

SETTING

Data from the Swedish national registry of gallstone surgery and endoscopic retrograde cholangiopancreatography (ERCP), GallRiks.

POPULATION

All cholecystectomies and ERCPs recorded in GallRiks between 1 Jan 2006 and 31 Dec 2014.

MAIN OUTCOME MEASURES

Outcomes for intra- as well as post-procedural adverse events between units with either a 30-day follow-up of ≥90% compared to those with a less frequent follow-up (<90%).

RESULTS

Between 2006 and 2014, 162 212 cholecystectomies and ERCP procedures were registered in GallRiks. After the exclusion of non-index procedures and those with incomplete data 152 827 procedures remained for final analyses. In patients having a cholecystectomy, there were no differences regarding the adverse event rates, irrespective of the follow-up frequency. However, in the more complicated endoscopic ERCP procedures, the postoperative adverse event rates were significantly higher in those with a more frequent and complete 30-day follow-up (OR 1.92; 95% CI 1.76-2.11).

CONCLUSIONS

Differences in the follow-up frequency in registries affects the reported outcomes as exemplified by the complicated endoscopic ERCP procedures. A high follow-up rate shall serve as an additional quality indicator for surgical registries.

Strengths and limitations of this study

-The prospectively collected data from over 90% of the registered cholecystectomies and ERCP in nearly all Swedish hospitals is a major strength of this study.

-Self-reported data always have the inherent risk of being subjected to certain bias.

-Another limitation of this study is that it presents data from a period of nine years (2006-2014) where the national coverage rate increased from 73% to 90%.

Funding

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No competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement

There is no additional unpublished data from this study. The data in this study are taken from Swedish registry of Cholecystectomy and ERCP (GallRiks) and are available via the corresponding author on request.

INTRODUCTION

National quality registry studies have been presented as a complement to Randomized controlled trials (RCTs). Registry based studies usually require less financial resources and enable data collection from large-scale patient cohorts without the unavoidable selection bias among those enrolled into clinical trials and always carry valid statistical power. Databases with long-term follow-up open up for conduct of studies focusing on rare events and effects occurring late in the clinical course. There are several instances where registry-based studies have improved the management of patients, for example in the treatment of non-ST-segment elevation acute coronary syndrome (NSTE-ACS), [1] the elimination of sub-standard orthopaedic prostheses from clinical use [2] and the effects of different surgical approaches and suture materials on the outcome of hernia surgery. [3 4] Accordingly registry studies can address clinical questions that due to statistical power issues, time and financial constraints would never have been studied under the design of a RCTs such as the value of intraoperative cholangiography in preventing bile duct injury in association with gallstone surgery [5 6] and the question whether and why women with inguinal herniorhapies have a significantly higher reoperation rate compared to males. [7] Furthermore, in a randomized clinical trial published in Lancet 2016 the outcome of closure of mesenteric defects in gastric bypass surgery was evaluated by analysing registry data from the Scandinavian Obesity Surgery Registry (SOREG). [8]

Thus, registry-based studies have a definite role in addressing many of the questions that arise in and have relevance for everyday clinical practice.

However, although population-based registry studies have high external validity, reflecting real-life data and the clinical routines as they are practised in the community at large, they are often hampered by the lack of uniform protocols and standardised routines for registering relevant data. This may skew the outcome since units, in which a limited awareness for

quality of care is prevailing, may well report data with incomplete accuracy, leading to a risk for lower coverage concerning the self-reported registrations on adverse events. Hence such a heterogeneity in the validity of data may seriously limit the options for correct interpretations in respective outcome analyses.

The aim of this study was therefore to analyse factors that may affect the validity of follow-up data in a national quality registry.

METHODS

The Swedish National Registry for Gallstone Surgery and Endoscopic retrograde cholangiopancreatography (ERCP) (www.gallriks.se)

The Swedish National Registry for Gallstone Surgery and ERCP (GallRiks) was established on 1 May 2005 as a registry for cholecystectomy and ERCP procedures. [9] The aim of the registry is to obtain a comprehensive database of individuals subjected to these interventions, including information on patient demographics and the indications and outcomes of interventions. All data entering are online. The initial procedures, including information on perioperative complications, are usually registered by operating clinicians. At a 30-day follow-up all medical records are reviewed for post-procedural adverse events and data are entered, usually by a local coordinator (nurse or a medical secretary). [9] GallRiks data are compared to patients´records on a regular basis by a dedicated independent validation team. A complete match between overall registry data and medical records has been reported in 98.2% of subjects with a 100% match for bile duct injury. [10]

Data extraction

Data on cholecystectomy and ERCP procedures performed between 1 January 2006 and 31 December 2014 and entered into the GallRiks registry were assessed. Non-index procedures

and procedures with incomplete data were excluded from the analysis. The complete 30-day follow-up frequency of cholecystectomy and ERCP procedures for individual units participating in the registry was calculated. We arbitrary chose the 90% limit for the 30-day complete follow-up in order to compare groups with sufficient number of procedures to reach enough statistical power to compare good follow-up (≥90%) with a less complete follow-up (<90%). Outcomes for peri- and postoperative complications were studied.

Definitions

For the purpose of this paper, and in accordance with the descriptions in the GallRiks database, adverse events are defined and described per consensus agreement.

Cholecystectomy: Surgical removal of the gallbladder in patients with an indication for removing the organ including symptomatic gallstone disease, neoplasms, and acalculous gallbladder conditions.

Endoscopic retrograde cholangiopancreatography (ERCP): An endoscopic technique for transpapillary access to the common bile duct and/or pancreatic duct including accessing the mentioned ducts through bilio- or pancreatico-digestive anastomoses, with diagnostic or therapeutic intent.

Index procedures: The first cholecystectomy and/or ERCP-procedure for each patient per in-hospital treatment period.

Intra-procedural adverse events for cholecystectomy: Bile duct injury, gut perforation, bleeding requiring intervention or other complications that adversely affected the operation.

Intra-procedural adverse events for ERCP: Bleeding, extravasation of contrast, perforation or any other reason for the ERCP being terminated prematurely.

Post-procedural adverse events: Complications during the 30-day follow-up period that require some form of medical or surgical intervention, including readmission and death.

Pancreatitis: Abdominal pain and an elevated amylase at least three times above normal at a time point more than 24 hours after terminating the procedure, as defined by Cotton. [11]

Statistical analysis

Statistical analyses were performed using JMP 12.2.0 (SAS, Cary, NC, USA). Comparisons of patient and procedure characteristics are presented in contingency tables, with pairwise differences analysed with Pearson Chi-square test. The influence of ≤90% follow-up on the risk of adverse events, pancreatitis and bleeding was analysed using multivariable logistic regression modelling. Each variable was tested in univariate and multivariate analyses for statistical significance, according to purposeful selection as described by Hosmer et al. [12] In the multivariate analysis the outcome was adjusted for sex, age (treated as a continuous variable in the models but presented dichotomized into < or ≥ than 60 years (median)), comorbidity dichotomized into ASA 1-2 and ASA 3-5, acute or elective procedure and indication. The models were tested for multicollinearity and effect modification and were finally assessed for goodness of fit. The effects of analysed variables are presented as odds ratios for adverse events with 95% confidence intervals.

RESULTS

Between January 1 2006 and December 31 2014, 162 212 cholecystectomies and ERCP procedures were registered in GallRiks. After the exclusion of 9328 non-index procedures and 57 procedures with incomplete data, 152 827 procedures remained for final analyses (95840 cholecystectomies and 56987 ERCPs) (figure 1). In total, 96.0% of the cholecystectomies and 95.4% of the ERCP procedures had a complete 30-day follow-up. The distribution of complete 30-day follow-up per hospital, for cholecystectomies and ERCP procedures are depicted in figure *2*. For the cholecystectomy group, 20% of the hospitals had a 30-day follow-up frequency of less than 90% compared to 17% for ERCPs (figure 2). The demographics, physical status assessment and urgency of intervention of included patients are given in table 1**.** Patients that were operated on with a cholecystectomy or underwent an ERCP in centres with incomplete follow-up were older and had a higher ASA-score compared to those with a more complete 30-day follow-up. The adverse event rates for cholecystectomy and ERCP (intraoperative and total postoperative, with pancreatitis and bleeding showed separately) are given in figure 3. The overall total postoperative adverse event rate for ERCP during the study period was 13.2% and the pancreatitis frequency 3.8%. The incidence of these post-intervention adverse event rates was rather stable over the study period, except for pancreatitis where a small but significant increase was noted (figure 3). The reported risk of post procedural complications as well as pancreatitis and bleeding per se after ERCP was significantly increased in those hospitals with a more frequent follow-up, both in absolute terms as well as when adjusted for confounders (table 3). The reported risk of postoperative adverse events, including post-ERCP pancreatitis, was twice as high compared to the group with less complete follow-up. The risk of bleeding within the 30-day follow-up period was 38% higher in the group with a better follow-up. On the contrary, the risk of intra-

operative adverse events was significantly reduced in the centres included in the ≥90% 30-day follow-up group (table 3).

The incidence of recorded adverse events for cholecystectomies during the corresponding period was 8.1% for postoperative adverse events, including 0.5% for pancreatitis. Although the absolute frequency of total postoperative adverse events after cholecystectomy was significantly higher in hospitals with a less complete 30-day follow-up, the risk of complications did not differ between the two groups when adjusted for confounders (table 2).

DISCUSSION

The results of this study, analysing data from the Swedish national registry for gallstone surgery and ERCP (GallRiks), emphasize the importance of considering a thorough follow-up as an important confounder when analysing the outcome of registry-based studies. Furthermore, differences in the follow-up frequency seemed to have a greater impact as a confounder in the more complicated interventional procedure ERCP than in the often technically less complicated procedure cholecystectomy.

Strengths and limitations of the study

The prospectively collected data in GallRiks from over 90% of the registered procedures in nearly all Swedish hospitals is a major strength of this study. The data registered in GallRiks have also been verified to have a high validity of over 98%. [10] Another strength is that this report includes data from University Hospitals, County Hospitals, District Hospitals and private units as well. The quality of data has been a concern already from the start of the registry and is guaranteed by continuous quality controls of the data-validity. However, due to financial and time constraints this prospective and integrated part of the registry has to be limited to approximately 30 randomly selected, cross-matches between patient records and GallRiks registrations at each hospital completed every third year.

Self-reported data always have the inherent risk of being subjected to certain bias. When analysing the results of quality registry data, factors like coverage of the relevant population by the registry data as well as the follow-up rate have to be taken into consideration. Another limitation of this study is that it presents data from a period of nine years (2006-2014) where the national coverage rate increased from 73% to 90%. There is, however, no systematic reason why the proportion of those with incomplete versus complete follow up shall depend

on the coverage rate as such. It must also be emphasized that, although we found significant differences between units with a high (≥90%) and units with <90% complete follow-up, the overall completeness must be considered excellent since only 4.0 % of the cholecystectomies and 4.6 % of the ERCPs have an incomplete follow-up. Nevertheless the absence of uniform study protocols makes it impossible to fully guarantee overall quality of data in population-based registers. Even if these data are considered to have high external validity the population-based registers may still produce some skewness of the data. The care for accuracy of reporting, and providing healthcare of high quality, may result in a positive correlation between self-reported adverse outcome and completeness of data. On the other hand centres, where the quality of care is poorer, may also have insufficient routines for scrutinising treatment outcome. The only way of avoiding this is a meticulous validation of all registered data, preferably with careful selective assessment of data from units with low coverage as well as to provide continuous education and support from the registry to the participating units with less complete follow-up routines.

Comparison with other studies

RCTs are considered one of the cornerstones of modern, evidence based medical science. It is regarded as the most accurate method to answer key clinical questions and to offer the highest levels of evidence that can be translated into the strongest treatment recommendations. [13] However, RCTs are also associated with definite drawbacks and logistic challenges[14 15] In addition, in the case of industry-funded research, and particularly so when study data are owned by the sponsoring body, study results that might have negative economic implications are sometimes withheld from publication, leading to publication bias. [16] Furthermore, the number of included patients necessary for creating sufficient power for testing of hypotheses in RCTs may preclude the completion of trials within reasonable time limits. [17] Moreover,

treatment methods that in RCTs originating from large academic institutions from which excellent results are reported, cannot always be repeated by and implemented in smaller and more resource-challenged facilities. It has also been shown that the outcome for patients excluded from randomisation often differs significantly from those enrolled in the randomised trial co-hort. [18] Thus, registry-based studies can and shall be looked upon as offering a complement to RCTs data, since they can more closely mirror the effect of a certain treatment-intervention in the entire population, given that good coverage is prevailing.

Several national quality registries have reported good coverage which is a prerequisite for a well-functioning quality registry, particularly so for cancer registries and in the paediatric population. [19 20] As for Sweden, there are 53 national quality registries that report their coverage to the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se/publikationer2015/2015-12-8). Of these 53 registries 19 cover specific interventional procedures, for example gynaecological operations, hip-replacement, hernia surgery, and cholecystectomy, to mention a few. The national coverage of these registries varies from 46% to 98%. In fact, some of these registries have a better coverage than the Swedish National Patient Registry (NPR) because many of the procedures are done by private hospitals that do not report to NPR as diligently as the government-funded hospitals.

Besides having good coverage, it is of vital importance for quality registries to contain valid data. Dedicated validation processes should be in place for assessing and reporting the correctness of the included data at regular intervals. The issue of a complete follow-up is especially challenging in registries with focus on the management of benign diseases, since

these procedures do not have the same rigorous demands of a compulsory follow-up as those for malignant conditions (http://www.socialstyrelsen.se/publikationer2015/2015-12-8).

The impact of the level of completeness of the follow-up for the validity of reported outcomes in registries covering benign conditions, has not been previously probed and elucidated in the literature. A survey by Rystedt et al, based on the validation of GallRiks, showed a high completeness and correctness of entered data with an overall correctness of data of 98.2% and 100% for bile duct injuries. [10] However, in this publication the completeness of follow-up was not specifically addressed.

The compelling finding of this paper is that the reported incidence of postoperative adverse events after ERCP is significantly lower in hospitals with an incomplete 30-day follow-up frequency (<90%) as compared to those with a more complete follow-up (≥90%). Although these results could mirror true outcomes, it is more likely to be the result of failure to report some of the adverse events by the hospitals with a less stringent documentation system for follow-up. This assumption is supported by the finding that the reported incidence of intra-operative adverse event is significantly higher in the group with ≥90% 30-day follow-up, implying that hospitals with an immaculate and accurate information accrual system also follow up patients more diligently and report adverse events to a higher degree. This discrepancy, where a less frequent 30-day follow-up significantly affected the reported outcome in ERCP but not in cholecystectomy could imply that the effect of a complete 30-day follow-up is more pronounced in procedures with a higher complication profile, since ERCPs have a more congested post-operative complication profile compared to cholecystectomies.

Conclusions and implications

Our findings may have significant general implications on how we shall interpret outcome data from registry studies. Differences in the follow-up rate seemed to significantly affect the reported outcome. The findings suggest that the validation process has to include the completeness of follow-up. Differences in the follow-up frequency in registries affect the reported outcomes as exemplified by the complicated endoscopic ERCP procedures. The study emphasises the importance of complete follow-up, since this variable may well act as a quality indicator for the respective registry.

Future research

Future research should focus on how the degree of complete follow-up in quality registers can correlate to more objectively and not self-reported quality indicators.

Contributors

LE conceived the study, created the study design, participated in the statistical analysis, analysed the data, and drafted and revised the paper. He is guarantor. MB participated in the analysis and interpretation of data, and revised the paper. GS participated in the statistical analysis and interpretation of data, and drafted and revised the paper. EJ interpreted the data and revised the manuscript. BH conceived the study and reviewed the manuscript. LL interpreted data and reviewed the manuscript. JÖ conceived the study, created the study design, and drafted and revised the paper.

All authors have approved of the final draft submitted.

Ethical approval

The regional research ethics committee at Karolinska Institutet, Stockholm, Sweden, approved the study.

Transparency

The first author (LE) confirms that the manuscript is an honest, accurate, and transparent account of the study; that no important aspects of the study have been omitted.

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LEGEND TO FIGURES

Figure 1

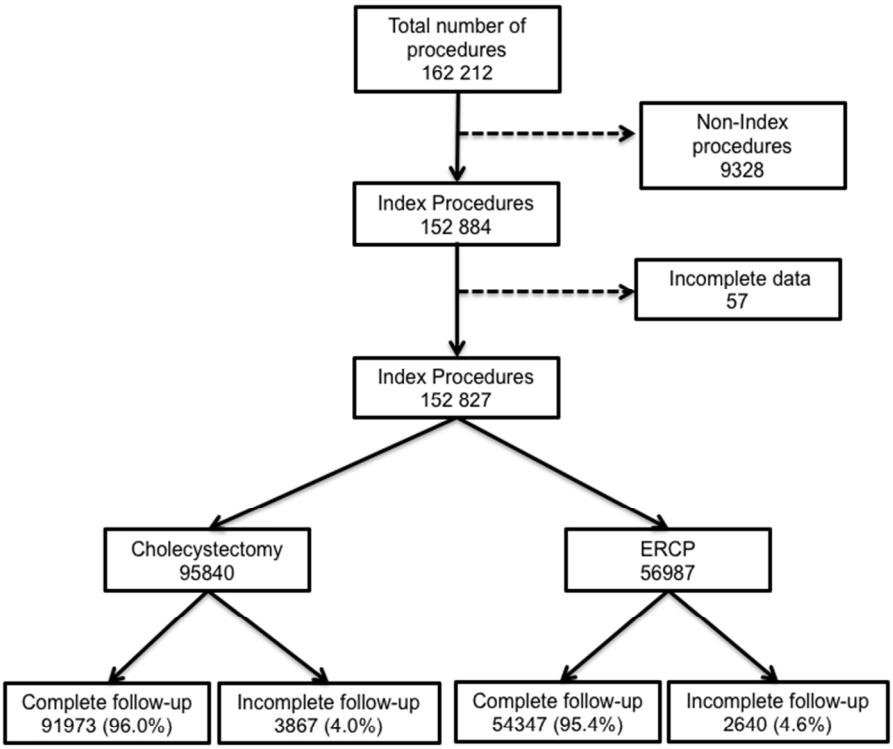
The procedures included in the analyses.

Figure 2

Complete 30-day follow-up frequencies following cholecystectomies and ERCP.

Figure 3

Adverse event rates after cholecystectomies and ERCP.



The procedures included in the analyses.

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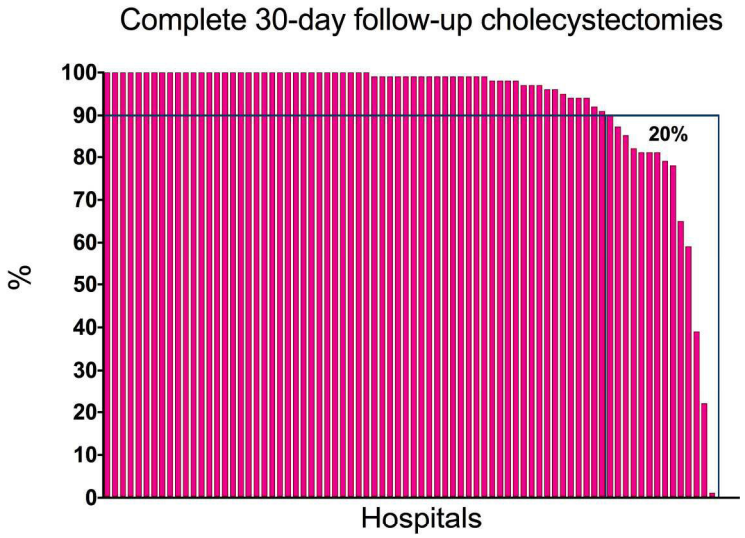

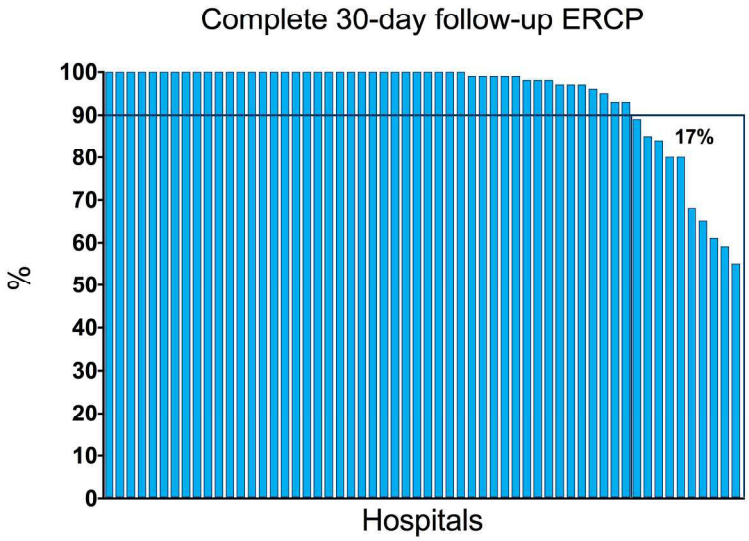

Complete 30-day follow-up frequencies following cholecystectomies and ERCP.

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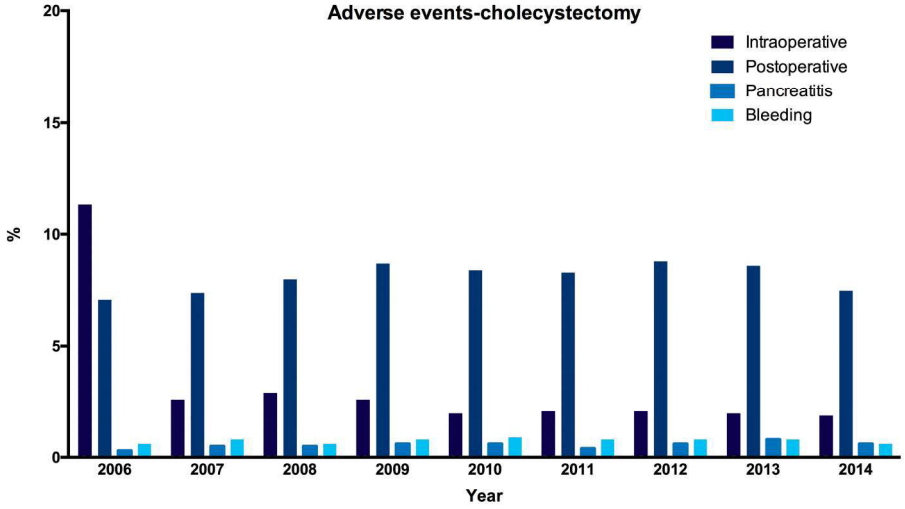

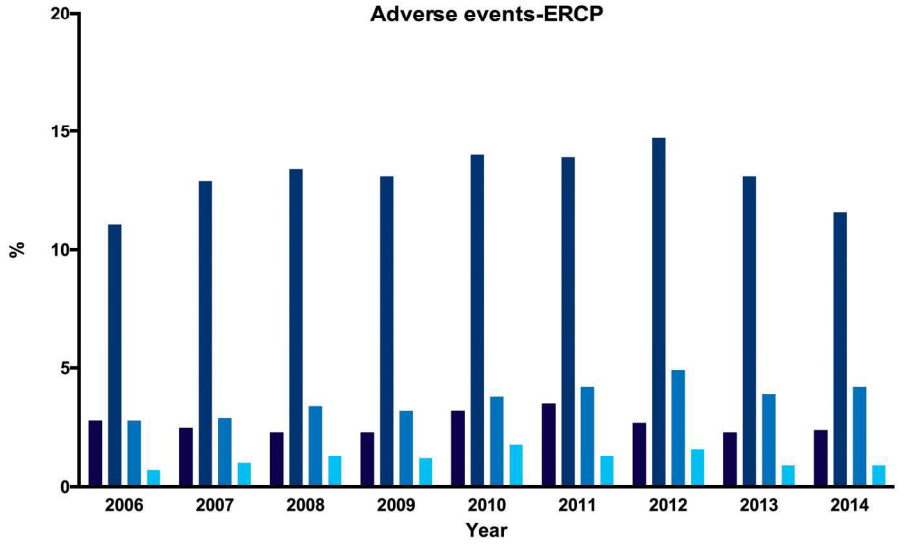

Adverse event rates after cholecystectomies and ERCP.

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Table 1

Demographics, physical status assessment and urgency of intervention stratification of examinations for the 152 827 patients included in the study

		30-day follow-up of cholecystectomies					30-day follow-up of ERCP				
		≥90%		<90%			≥90%		<90%		
		n	**%**	**n**	**%**	***P***	**n**	**%**	**n**	**%**	***P***
Gender	Female	55908	67.3	8311	65.1	**<.0001**	25673	53.0	4460	52.0	0.0906
	Male	27159	32.7	4462	34.9		22743	47.0	4111	48.0	
Age (years)	≥60	26442	31.9	4462	35.0	**<.0001**	35532	73.6	6724	78.5	**<.0001**
	<60	56461	68.1	8290	65.0		12767	26.4	1843	21.5	
ASA	ASA 1-2	76478	92.1	11124	87.1	**<.0001**	33457	69.1	4748	55.4	**<.0001**
	ASA ≥3	6589	7.9	1649	12.9		14959	30.9	3823	44.6	
Acute/Scheduled	Acute	24237	29.2	4433	34.7	**<.0001**	30093	62.2	5055	59.0	**<.0001**
	Scheduled	58830	70.8	8340	65.3		18323	37.8	3516	41.0	

Table 2

Adverse event rates, Odds Ratios (OR) and 95% confidence intervals of hospitals with or without a 30-day follow-up frequency of cholecystectomies ≥ 90%

	Adverse events				
	≥90% n=83067		<90% n=12773		
	n	%	n	%	*P*
Intraoperative	2548	3.0	381	3.0	0.8826
Total postoperative	6681	8.0	1119	8.8	**0.0057**
Pancreatitis	455	0.6	66	0.5	0.6570
Bleeding	629	0.8	96	0.8	0.9454

	Adverse events				
	Pancreatic duct cannulation vs. no cannulation				
	Unadjusted		Adjusted*		
	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)	*P*
Intraoperative	0.99	(0.89-1.11)	0.93	(0.84-1.04)	0.2298
Total postoperative	0.91	(0.85-0.97)	0.98	(0.91-1.05)	0.5067
Pancreatitis	1.06	(0.83-1.39)	1.30	(0.99-1.75)	0.0606
Bleeding	1.01	(0.82-1.26)	0.97	(0.78-1.21)	0.7821

*Adjusted for sex, age, ASA class, acute interventions and indications.

Table 3

Adverse event rates, Odds Ratios (OR) and 95% confidence intervals of hospitals with or without a 30-day follow-up frequency of ERCPs ≥ 90%

	Adverse events				
	≥90% n=48416		<90% n=8571		
	n	%	n	%	*P*
Intraoperative	1267	2.6	252	2.9	0.0868
Total postoperative	6821	14.1	689	8.0	**<.0001**
Pancreatitis	1978	4.1	178	2.1	**<.0001**
Bleeding	591	1.2	76	0.9	**0.0081**

	Adverse events				
	≥90% vs <90% 30-day follow-up				
	Unadjusted		Adjusted*		
	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)	*P*
Intraoperative	0.89	(0.77-1.02)	0.76	(0.66-0.87)	**0.0002**
Total postoperative	1.88	(1.73-2.04)	1.92	(1.76-2.11)	**<.0001**
Pancreatitis	2.01	(1.73-2.35)	2.04	(1.72-2.43)	**<.0001**
Bleeding	1.38	(1.09-1.77)	1.38	(1.08-1.79)	**0.0100**

*Adjusted for sex, age, ASA class, acute interventions and indications.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2	Population-based register study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 4-5	
Objectives	3	State specific objectives, including any prespecified hypotheses	Abstract and page 5	
Methods				
Study design	4	Present key elements of study design early in the paper	Page 4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 5-6	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Pages 5-6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 6-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pages 5-7*	
Bias	9	Describe any efforts to address potential sources of bias	Pages 10-11	
Study size	10	Explain how the study size was arrived at	Pages 5-6	

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7	
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7	
		(*c*) Explain how missing data were addressed		Partly described on page 7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		The article is about this subject
		(*e*) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		Described in results.
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders		Table 1
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		That is what this article is all about
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		*Tables 2-3*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	In Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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Inversed relationship between completeness of follow-up and coverage of postoperative complications. A potential source of bias in patient registers.

Lars Enochsson[1], My Blohm[2,3], Gabriel Sandblom[2,4], Eduard Jonas[5], Bengt Hallerbäck[6], Lars Lundell[2], Johanna Österberg[2,3]

[1]Department of Surgical and Perioperative Sciences, Sunderby Research Unit, Umeå University, Sweden

[2]Division of Surgery, CLINTEC, Karolinska Institutet, Stockholm, Sweden

[3]Department of Surgery, Mora Hospital, Mora, Sweden

[4]Center for Digestive Diseases, Karolinska University Hospital, Huddinge, Stockholm, Sweden

[5]Surgical Gastroenterology Unit, Department of Surgery, Groote Schuur Hospital, University of Cape Town Health Sciences Faculty, Cape Town, South Africa

[6]Department of Surgery, Norra Älvsborg County Hospital, Trollhättan, Sweden

Correspondence to:

Lars Enochsson, MD, PhD
Department of Surgical and Perioperative Sciences, Umeå University, Umeå,
Sunderby Hospital
97180 Luleå,
Sweden
E-mail: lars.enochsson@umu.se
Phone: +46 920 28 31 05
Fax: +46 920 28 33 20

ABSTRACT

OBJECTIVE

To analyse factors that may affect the validity of follow-up data in a national quality registry.

DESIGN

Population-based register study.

SETTING

Data from the national Swedish Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (ERCP), GallRiks.

POPULATION

All cholecystectomies and ERCPs recorded in GallRiks between 1 Jan 2006 and 31 Dec 2014.

MAIN OUTCOME MEASURES

Outcomes for intra- as well as post-procedural adverse events between units with either a 30-day follow-up of ≥90% compared to those with a less frequent follow-up (<90%).

RESULTS

Between 2006 and 2014, 162 212 cholecystectomies and ERCP procedures were registered in GallRiks. After the exclusion of non-index procedures and those with incomplete data 152 827 procedures remained for final analyses. In patients having a cholecystectomy, there were no differences regarding the adverse event rates, irrespective of the follow-up frequency. However, in the more complicated endoscopic ERCP procedures, the postoperative adverse event rates were significantly higher in those with a more frequent and complete 30-day follow-up (OR 1.92; 95% CI 1.76-2.11).

CONCLUSIONS

Differences in the follow-up frequency in registries affect the reported outcomes as exemplified by the complicated endoscopic ERCP procedures. A high and complete follow-up rate shall serve as an additional quality indicator for surgical registries.

Strengths and limitations of this study

-The prospectively collected data from over 90% of the registered cholecystectomies and ERCP in nearly all Swedish hospitals is a major strength of this study.

-Data reported by the medical professional performing the procedure always have the inherent risk of being subjected to certain bias. However, the 30-day follow-up data are collected by coordinators that have not met the patients.

-Another limitation of this study is that it presents data from a period of nine years (2006-2014) where the national coverage rate increased from 73% to 90%.

Funding

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No competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement

There are no additional unpublished data from this study. The data in this study are extracted from the Swedish Registry for Gallstone Surgery and ERCP (GallRiks) and are available via the corresponding author on request.

INTRODUCTION

National quality registry studies have been presented as a complement to Randomized Controlled Trials (RCTs). Registry based studies usually require less financial resources and enable data collection from large-scale patient cohorts without the unavoidable selection bias among those enrolled into clinical trials and most often carry valid statistical power. Databases with long-term follow-up open up for conduct of studies focusing on rare events harms and effects occurring late in the clinical course. There are several instances where registry-based studies have improved the management of patients, for example in the treatment of non-ST-segment elevation acute coronary syndrome (NSTE-ACS), [1] the elimination of sub-standard orthopaedic prostheses from clinical use [2] and the effects of different surgical approaches and suture materials on the outcome of hernia surgery. [3 4] Accordingly registry studies can address clinical questions, that due to statistical power issues, time and financial constraints would never have been studied under the design of a RCTs such as the value of intraoperative cholangiography in preventing bile duct injury in association with gallstone surgery [5 6] with data from the Swedish Registry for Gallstone Surgery and ERCP (GallRiks) or the question whether and why women with inguinal herniorhapies have a significantly higher reoperation rate compared to males (data from the Swedish Hernia Registry). [7] Furthermore, in a randomized clinical trial published in Lancet 2016 the outcome of closure of mesenteric defects in gastric bypass surgery was evaluated by analysing registry data from the Scandinavian Obesity Surgery Registry (SOREG). [8]

Thus, registry-based studies have a definite role in addressing many of the questions that arise in and have relevance for everyday clinical practice.

However, although population-based registry studies have high external validity, reflecting real-life data and the clinical routines as they are practised in the community at large, they are often hampered by the lack of uniform protocols and standardised routines for registering

relevant data. This may skew the outcome since units, in which a limited awareness for quality of care is prevailing, may well report data with incomplete accuracy, leading to a risk for lower coverage concerning the registrations on adverse events by the participating units in the respective registers. Hence such a heterogeneity in the validity of data may seriously limit the options for correct interpretations in respective outcome analyses.

Aims

The aim of this study was to analyse the completeness in GallRiks of the follow-up frequency in relation to the intra-and postoperative outcome of reported complications.

METHODS

The Swedish National Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (ERCP) [9]

The national Swedish Registry for Gallstone Surgery and ERCP (GallRiks) was established on 1 May 2005 as a registry for cholecystectomy and ERCP procedures. [10] The aim of the registry is to obtain a comprehensive database of individuals subjected to these interventions, including information on patient demographics and the indications and outcomes of interventions. All data entering are online. The initial procedures, including information on perioperative complications, are usually registered by operating clinicians. At a 30-day follow-up all medical records are reviewed for post-procedural adverse events and data are entered, usually by a local coordinator (nurse or a medical secretary). [10] If a 30-day follow-up protocol of a cholecystectomy or ERCP is not complete or is missing it is noted by the system and these procedures can easily be assessed when analyzing the data. GallRiks data are compared to patients´ records on a regular basis by a dedicated independent validation team.

A complete match between overall registry data and medical records has been reported in 98.2% of subjects with a 100% match for bile duct injury. [11]

Data extraction

Data on cholecystectomy and ERCP procedures performed between 1 January 2006 and 31 December 2014 and entered into the GallRiks registry were assessed. Non-index procedures and procedures with incomplete data were excluded from the analysis. The complete 30-day follow-up frequency of cholecystectomy and ERCP procedures for individual units participating in the registry was calculated. We arbitrary chose the 90% limit for the 30-day complete follow-up in order to compare groups with sufficient number of procedures to reach enough statistical power to compare good follow-up (≥90%) with a less complete follow-up (<90%). Outcomes for peri- and postoperative complications were studied.

Definitions

For the purpose of this paper, and in accordance with the descriptions in the GallRiks database, adverse events are defined and described per consensus agreement.

Cholecystectomy: Surgical removal of the gallbladder in patients with an indication for removing the organ including symptomatic gallstone disease, neoplasms, and acalculous gallbladder conditions.

Endoscopic retrograde cholangiopancreatography (ERCP): An endoscopic technique for transpapillary access to the common bile duct and/or pancreatic duct including accessing the mentioned ducts through bilio- or pancreatico-digestive anastomoses, with diagnostic or therapeutic intent.

Index procedures: The first cholecystectomy and/or ERCP-procedure for each patient per in-hospital treatment period.

Intra-procedural adverse events for cholecystectomy: Bile duct injury, gut perforation, bleeding requiring intervention or other complications that adversely affected the operation.

Intra-procedural adverse events for ERCP: Bleeding, extravasation of contrast, perforation or any other reason for the ERCP being terminated prematurely.

Post-procedural adverse events: Complications during the 30-day follow-up period that require some form of medical or surgical intervention, including readmission or death.

Pancreatitis: Abdominal pain and an elevated amylase at least three times above normal at a time point more than 24 hours after terminating the procedure, as defined by Cotton. [12]

Statistical analysis

Statistical analyses were performed using JMP 12.2.0 (SAS, Cary, NC, USA). Comparisons of patient and procedure characteristics are presented in contingency tables, with pairwise differences analysed with Pearson Chi-square test. The influence of ≤90% follow-up on the risk of adverse events, pancreatitis and bleeding was analysed using multivariable logistic regression modelling. Each variable was tested in univariate and multivariate analyses for statistical significance, according to purposeful selection as described by Hosmer et al. [13] In the multivariate analysis the outcome was adjusted for sex, age (treated as a continuous variable in the models but presented dichotomized into < or ≥ than 60 years (median)), comorbidity dichotomized into ASA 1-2 and ASA 3-5, acute or elective procedure and indication. The models were tested for multicollinearity and effect modification and were finally assessed for goodness of fit. The effects of analysed variables are presented as odds ratios for adverse events with 95% confidence intervals.

RESULTS

Between January 1 2006 and December 31 2014, 162 212 cholecystectomies and ERCP procedures were registered in GallRiks. After the exclusion of 9328 non-index procedures and 57 procedures with incomplete data, 152 827 procedures remained for final analyses (95840 cholecystectomies and 56987 ERCPs) (figure 1). In total, 96.0% of the cholecystectomies and 95.4% of the ERCP procedures had a complete 30-day follow-up. The distribution of complete 30-day follow-up per hospital, for cholecystectomies and ERCP procedures are depicted in figure 2. For the cholecystectomy group, 20% of the hospitals had a 30-day follow-up frequency of less than 90% compared to 17% for ERCPs (figure 2). The demographics, physical status assessment and urgency of intervention of included patients are given in table 1**.** Patients that were operated on with a cholecystectomy or underwent an ERCP in centres with incomplete follow-up were older and had a higher ASA-score compared to those with a more complete 30-day follow-up. The adverse event rates for cholecystectomy and ERCP (intraoperative and total postoperative, with pancreatitis and bleeding showed separately) are given in figure 3. The overall total postoperative adverse event rate for cholecystectomies was significantly higher for the hospitals with a less complete 30-day follow-up. However, these differences disappeared when adjustments were made for sex, age, ASA-class and whether the operations were acute or scheduled (table 2). The overall total postoperative adverse event rate for ERCP during the study period was 13.2% and the pancreatitis frequency 3.8%. The incidence of these post-intervention adverse event rates was rather stable over the study period, except for pancreatitis where a small but significant increase was noted (figure 3). The reported risk of post procedural complications as well as pancreatitis and bleeding per se after ERCP was significantly increased in those hospitals with a more frequent and complete follow-up, both in absolute terms as well as when adjusted for confounders (table 3). The reported risk of postoperative adverse events,

including post-ERCP pancreatitis, was nearly twice as high compared to the group with less complete follow-up. The risk of bleeding within the 30-day follow-up period was 38% higher in the group with a better follow-up. On the contrary, the risk of intra-operative adverse events was significantly reduced in the centres included in the ≥90% 30-day follow-up group (table 3).

DISCUSSION

The results of this study, analysing data from the nationwide Swedish Registry for Gallstone Surgery and ERCP (GallRiks), emphasize the importance of considering a thorough follow-up as an important confounder when analysing the outcome of registry-based studies. Furthermore, differences in the follow-up frequency seemed to have a greater impact as a confounder in the technically more complicated procedures like ERCP where complications like pancreatitis and cholangitis, usually are detected postoperatively in contrast to cholecystectomies where the adverse events and complications usually are detected intraoperatively. Thus, since the ERCP procedures to a higher extent are marred by postoperative complications, the demands for a thorough and logistically well designed follow-up organization with adequate resources are mandatory.

Strengths and limitations of the study

The prospectively collected data in GallRiks from over 90% of the registered procedures in nearly all Swedish hospitals is a major strength of this study. The data registered in GallRiks have also been verified to have a high validity of over 98%. [11] Another strength is that this report includes data from University Hospitals, County Hospitals, District Hospitals and private units as well. The quality of data has been a concern already from the start of the registry and is guaranteed by continuous quality controls of the data-validity. However, due to financial and time constraints this prospective and integrated part of the registry has to be limited to approximately 50 randomly selected, cross-matches between patient records and GallRiks registrations at each hospital completed every third year.

Data reported by the medical professionals performing the respective intervention or data assessment always have the inherent risk of being subjected to certain bias. When analysing

the results of quality registry data, factors like coverage of the relevant population by the registry data as well as the follow-up rate have to be taken into consideration. Another limitation of this study is that it presents data from a period of nine years (2006-2014) where the national coverage increased from 73% to 90%. However, there is no systematic reason why the proportion of those with incomplete versus complete follow up shall depend on the coverage rate as such. It must also be emphasized that, although we found significant differences between units with a high (≥90%) and units with <90% complete follow-up, the overall completeness must be considered excellent since only 4.0 % of the cholecystectomies and 4.6 % of the ERCPs have an incomplete follow-up. Nevertheless the absence of uniform study protocols makes it impossible to fully guarantee overall quality of data in population-based registers. Even if these data are considered to have high external validity the population-based registers may still produce some skewness of the data. The care for accuracy of reporting, and providing healthcare of high quality, may result in a positive correlation between self-reported adverse outcome and completeness of data. On the other hand centres, where the quality of care is poorer, may also have insufficient routines for scrutinising treatment outcome. The only way of avoiding this is a meticulous validation of all registered data, preferably with careful selective assessment of data from units with low coverage as well as to provide continuous education and support from the registry to the participating units with less complete follow-up routines.

Comparison with other studies

RCTs are considered one of the cornerstones of modern, evidence based medical science. It is regarded as the most accurate method to answer key clinical questions and to offer the highest levels of evidence that can be translated into the strongest treatment recommendations. [14] However, RCTs are also associated with definite drawbacks and logistic challenges. [15 16] In

addition, in the case of industry-funded research, and particularly so when study data are owned by the sponsoring body, study results that might have negative economic implications are sometimes withheld from publication, leading to publication bias. [17] Furthermore, the number of included patients necessary for creating sufficient power for testing of hypotheses in RCTs may preclude the completion of trials within reasonable time limits. [18] Moreover, treatment methods that in RCTs originating from large academic institutions from which excellent results are reported, cannot always be repeated by and implemented in smaller and more resource-challenged facilities. It has also been shown that the outcome for patients excluded from randomisation often differs significantly from those enrolled in the randomised trial co-hort. [19] Thus, registry-based studies can and shall be looked upon as offering a complement to RCTs data, since they can more closely mirror the effect of a certain treatment-intervention in the entire population, given that good coverage is prevailing.

Several national quality registries have reported good coverage which is a prerequisite for a well-functioning quality registry, particularly so for cancer registries and in the paediatric population. [20 21] As for Sweden, there are 53 national quality registries that report their coverage to the Swedish National Board of Health and Welfare [22]. Of these 53 registries 19 cover specific interventional procedures, for example gynaecological operations, hip-replacement, hernia surgery, and cholecystectomy, to mention a few. The national coverage of these registries varies from 46% to 98%. In fact, some of these registries have a better coverage than the Swedish National Patient Registry (NPR) because many of the procedures are done by private hospitals that do not report to NPR as diligently as the government-funded hospitals.

Besides having good coverage, it is of vital importance for quality registries to contain valid data. Dedicated validation processes should be in place for assessing and reporting the correctness of the included data at regular intervals. The issue of a complete follow-up is especially challenging in registries with focus on the management of benign diseases, since these procedures do not have the same rigorous demands of a compulsory follow-up as those for malignant conditions.

The impact of the level of completeness of the follow-up for the validity of reported outcomes in registries covering benign conditions, has not been previously probed and elucidated in the literature. A survey by Rystedt et al, based on the validation of GallRiks, showed a high completeness and correctness of entered data with an overall correctness of data of 98.2% and 100% for bile duct injuries. [11] However, in this publication the completeness of the 30-day follow-up was not specifically addressed.

The compelling finding of this paper is that the reported incidence of postoperative adverse events after ERCP is significantly lower in hospitals with an incomplete 30-day follow-up frequency (<90%) as compared to those with a more complete follow-up (≥90%). Although these results could mirror true outcomes, it is more likely to be the result of failure to report some of the adverse events by the hospitals with a less stringent documentation system for follow-up and/or a lack of coordinators. The coordinator has the liability, together with the GallRiks responsible surgeon, that the patient´s data are registered and monitored. A contract is signed with the head of the department that ≥90% follow-up in GallRiks should be done. The agreement is broken at the units that have <90% 30-day follow-up.

These assumptions of less stringent reporting are supported by the finding that the reported incidence of intra-operative adverse events is significantly higher in the group with ≥90% 30-day follow-up, implying that hospitals with an immaculate and accurate information accrual

system also follow up patients more diligently and report adverse events to a higher degree. This discrepancy, where a less frequent 30-day follow-up significantly affected the reported outcome in ERCP but not in cholecystectomy could imply that the effect of a complete 30-day follow-up is more pronounced in procedures with a higher complication profile, since ERCPs have a more congested post-operative complication profile compared to cholecystectomies.

Conclusions and implications

Our findings may have significant general implications on how we shall interpret outcome data from registry studies. Differences in the follow-up rate seemed to significantly affect the reported outcome. The findings suggest that the validation process has to include the completeness of follow-up. Differences in the follow-up frequency in registries affect the reported outcomes as exemplified by the complicated endoscopic ERCP procedures. The study emphasises the importance of complete follow-up, since this variable may well act as a quality indicator for the respective registry.

Future research

Future research should focus on how the degree of complete follow-up in quality registers can correlate to more objectively and not self-reported quality indicators.

Contributors

LE conceived the study, created the study design, participated in the statistical analysis, analysed the data, and drafted and revised the paper. He is guarantor. MB participated in the analysis and interpretation of data, and revised the paper. GS participated in the statistical analysis and interpretation of data, and drafted and revised the paper. EJ interpreted the data and revised the manuscript. BH conceived the study and reviewed the manuscript. LL interpreted data and reviewed the manuscript. JÖ conceived the study, created the study design, and drafted and revised the paper.

All authors have approved of the final draft submitted.

Ethical approval

The regional research ethics committee at Karolinska Institutet, Stockholm, Sweden, approved the study.

Transparency

The first author (LE) confirms that the manuscript is an honest, accurate, and transparent account of the study; that no important aspects of the study have been omitted.

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LEGEND TO FIGURES

Figure 1

The procedures included in the analyses.

Figure 2

Complete 30-day follow-up frequencies following cholecystectomies and ERCP.

Figure 3

Adverse event rates after cholecystectomies and ERCP.

Table 1

Demographics, physical status assessment and urgency of interventions for the 152 827 patients included in the study

		30-day follow-up of cholecystectomies				
		≥90%		<90%		
		n	**%**	**n**	**%**	***P***
Gender	Female	55908	67.3	8311	65.1	**<.0001**
	Male	27159	32.7	4462	34.9	
Age (years)	≥60	26442	31.9	4462	35.0	**<.0001**
	<60	56461	68.1	8290	65.0	
ASA	ASA 1-2	76478	92.1	11124	87.1	**<.0001**
	ASA ≥3	6589	7.9	1649	12.9	
Acute/ Scheduled	Acute	24237	29.2	4433	34.7	**<.0001**
	Scheduled	58830	70.8	8340	65.3	

		30-day follow-up of ERCP				
		≥90%		<90%		
		n	**%**	**n**	**%**	***P***
Gender	Female	25673	53.0	4460	52.0	0.0906
	Male	22743	47.0	4111	48.0	
Age (years)	≥60	35532	73.6	6724	78.5	**<.0001**
	<60	12767	26.4	1843	21.5	
ASA	ASA 1-2	33457	69.1	4748	55.4	**<.0001**
	ASA ≥3	14959	30.9	3823	44.6	
Acute/ Scheduled	Acute	30093	62.2	5055	59.0	**<.0001**
	Scheduled	18323	37.8	3516	41.0	

Table 2

Adverse event rates, Odds Ratios (OR) and 95% confidence intervals
of hospitals with or without a 30-day follow-up frequency of cholecystectomies ≥ 90%

	Adverse events				
	≥90% n=83067		<90% n=12773		
	n	%	n	%	*P*
Intraoperative	2548	3.0	381	3.0	0.8826
Total postoperative	6681	8.0	1119	8.8	**0.0057**
Pancreatitis	455	0.6	66	0.5	0.6570
Bleeding	629	0.8	96	0.8	0.9454

	Adverse events		
	≥90% vs <90% 30-day follow-up Adjusted*		
	Odds Ratio	(95% CI)	*P*
Intraoperative	0.93	(0.84-1.04)	0.2298
Total postoperative	0.98	(0.91-1.05)	0.5067
Pancreatitis	1.30	(0.99-1.75)	0.0606
Bleeding	0.97	(0.78-1.21)	0.7821

*Adjusted for sex, age, ASA class, acute interventions and indications.

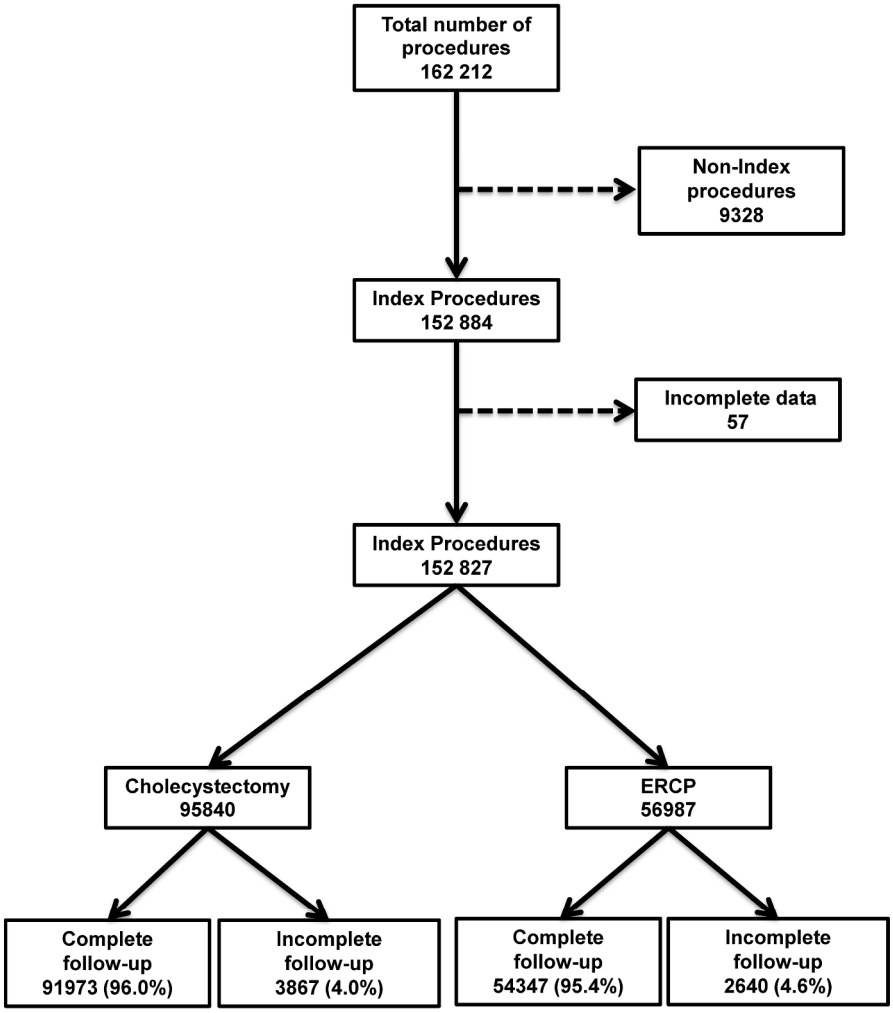
Table 3

Adverse event rates, Odds Ratios (OR) and 95% confidence intervals of hospitals with or without a 30-day follow-up frequency of ERCPs ≥ 90%

	Adverse events				
	≥90% n=48416		<90% n=8571		
	n	%	n	%	*P*
Intraoperative	1267	2.6	252	2.9	0.0868
Total postoperative	6821	14.1	689	8.0	**<.0001**
Pancreatitis	1978	4.1	178	2.1	**<.0001**
Bleeding	591	1.2	76	0.9	**0.0081**

	Adverse events		
	≥90% vs <90% 30-day follow-up Adjusted*		
	Odds Ratio	(95% CI)	*P*
Intraoperative	0.76	(0.66-0.87)	**0.0002**
Total postoperative	1.92	(1.76-2.11)	**<.0001**
Pancreatitis	2.04	(1.72-2.43)	**<.0001**
Bleeding	1.38	(1.08-1.79)	**0.0100**

*Adjusted for sex, age, ASA class, acute interventions and indications.



The procedures included in the analyses.

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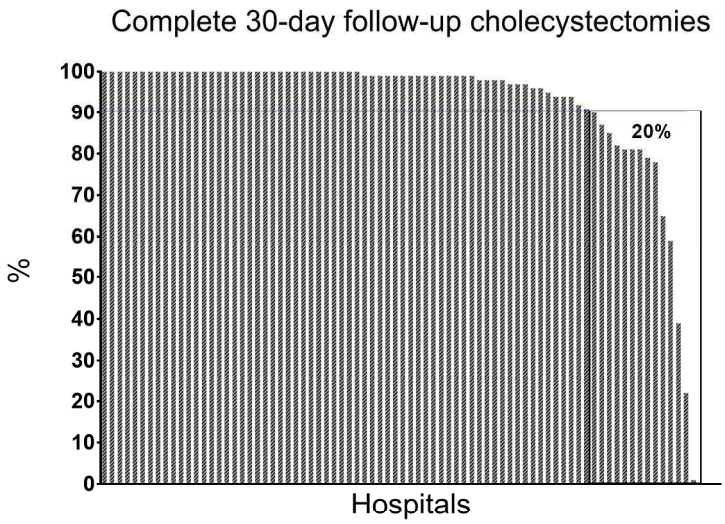
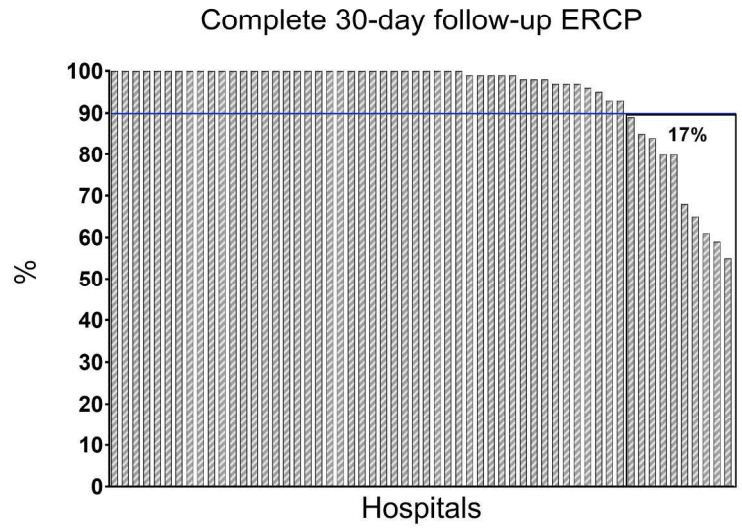
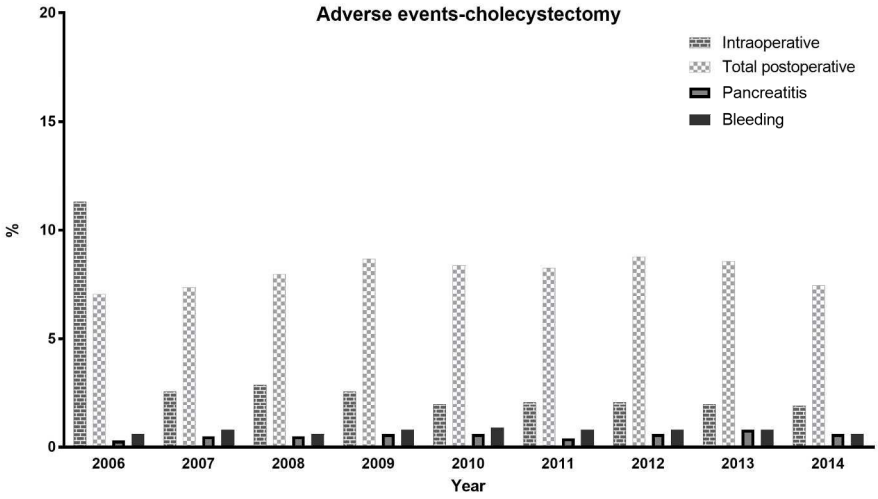
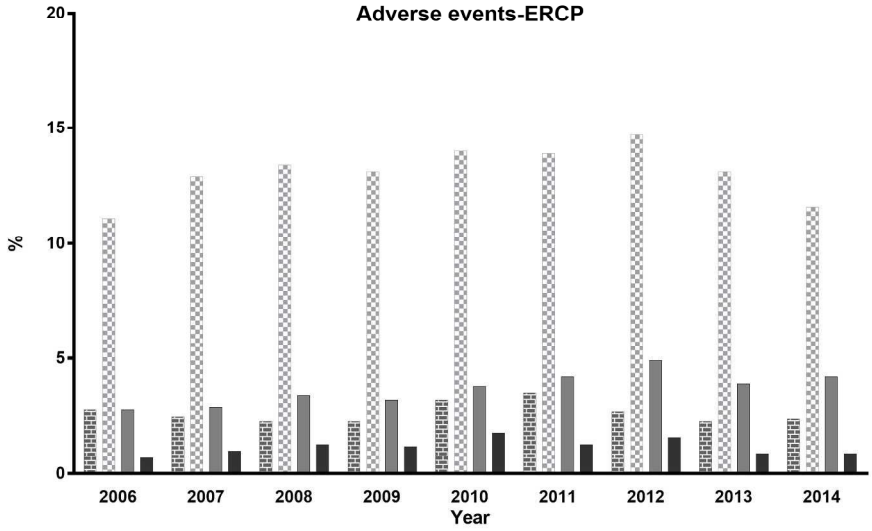




Complete 30-day follow-up frequencies following cholecystectomies and ERCP.

167x256mm (300 x 300 DPI)





Adverse event rates after cholecystectomies and ERCP.

198x247mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2	Population-based register study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 4-5	
Objectives	3	State specific objectives, including any prespecified hypotheses	Abstract and page 5	
Methods				
Study design	4	Present key elements of study design early in the paper	Page 4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 5-6	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Pages 5-6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 6-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pages 5-7*	
Bias	9	Describe any efforts to address potential sources of bias	Pages 10-11	
Study size	10	Explain how the study size was arrived at	Pages 5-6	

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7	
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7	
		(*c*) Explain how missing data were addressed		Partly described on page 7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		The article is about this subject
		(*e*) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		Described in results.
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders		Table 1
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		That is what this article is all about
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		*Tables 2-3*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	In Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Inversed relationship between completeness of follow-up and coverage of postoperative complications in gallstone surgery and ERCP. A potential source of bias in patient registers.

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Inversed relationship between completeness of follow-up and coverage of postoperative complications in gallstone surgery and ERCP. A potential source of bias in patient registers.

Lars Enochsson[1],My Blohm[2,3], Gabriel Sandblom[2,4], Eduard Jonas[5], Bengt Hallerbäck[6],Lars Lundell[2],Johanna Österberg[2,3]

[1]Department of Surgical and Perioperative Sciences, Sunderby Research Unit, Umeå University, Sweden

[2]Division of Surgery, CLINTEC, KarolinskaInstitutet, Stockholm, Sweden

[3]Department of Surgery, Mora Hospital, Mora, Sweden

[4]Center for Digestive Diseases, Karolinska University Hospital, Huddinge, Stockholm, Sweden

[5]Surgical Gastroenterology Unit, Department of Surgery, Groote Schuur Hospital, University of Cape Town Health Sciences Faculty, Cape Town, South Africa

[6]Department of Surgery, NorraÄlvsborg County Hospital, Trollhättan, Sweden

Correspondence to:

Lars Enochsson, MD, PhD
Department of Surgical and Perioperative Sciences, Umeå University, Umeå,
Sunderby Hospital
97180 Luleå,
Sweden
E-mail: lars.enochsson@umu.se
Phone: +46 920 28 31 05
Fax: +46 920 28 33 20

ABSTRACT

OBJECTIVE

To analyse the completeness in GallRiks of the follow-up frequency in relation to the intra- and postoperative outcome.

DESIGN

Population-based register study.

SETTING

Data from the national Swedish Registry forGallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (ERCP), GallRiks.

POPULATION

All cholecystectomies and ERCPs recorded in GallRiks between 1 Jan 2006 and 31 Dec 2014.

MAIN OUTCOMEMEASURES

Outcomes for intra- as well as post-procedural adverse events between units with either a 30-day follow-up of ≥90% compared to those with a less frequent follow-up (<90%).

RESULTS

Between 2006 and 2014, 162 212 cholecystectomies and ERCP procedures were registered in GallRiks. After the exclusion of non-index procedures and those with incomplete data 152 827 procedures remained for final analyses. In patients having a cholecystectomy, there were no differences regarding the adverse event rates, irrespective of the follow-up frequency. However, in the more complicated endoscopic ERCP procedures, the postoperative adverse event rates were significantly higher in those with a more frequent and complete 30-day follow-up (OR 1.92; 95% CI 1.76-2.11).

CONCLUSIONS

Differences in the follow-up frequency in registries affect the reported outcomes as exemplified by the complicated endoscopic ERCP procedures.A high and completefollow-up rate shall serve as an additional quality indicator for surgical registries.

Strengths and limitations of this study

-The prospectively collected data from over 90% of the registered cholecystectomies and ERCP in nearly all Swedish hospitals is a major strength of this study.

-Data reported by the medical professional performing the procedure always have the inherent risk of being subjected to certain bias. However, the 30-day follow-up data are collected by coordinators that have not met the patients.

-Another limitation of this study is that it presents data from a period of nine years (2006-2014) where the national coverage rate increased from 73% to 90%.

Funding

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No competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing statement

There are no additional unpublished data from this study. The data in this study are extractedfrom the Swedish Registry forGallstone Surgery and ERCP (GallRiks) and are available via the corresponding author on request.

INTRODUCTION

National quality registry studies have been presented as a complement to Randomized Controlled Trials (RCTs). Registry based studies usually require less financial resources and enable data collection fromlarge-scale patient cohorts without the unavoidable selection bias among those enrolled into clinical trialsand most often carry valid statistical power. Databases with long-term follow-up open upfor conduct of studies focusingon rare events harms and effects occurring late in the clinical course. There are several instances where registry-based studies have improved the management of patients, for examplein the treatment of non-ST-segment elevation acute coronary syndrome (NSTE-ACS),[1]the elimination ofsub-standard orthopaedic prostheses from clinical use [2]and the effects of different surgical approaches and suture materials on the outcome of hernia surgery.[3 4]Accordingly registry studies canaddress clinical questions, that due to statistical power issues, time and financial constraints would never have been studied under the design of aRCTs such asthe value of intraoperative cholangiography in preventing bile duct injury inassociation with gallstone surgery[5 6]with data from the Swedish Registry for Gallstone Surgery and ERCP (GallRiks) or the question whether and why women with inguinal herniorhapies have a significantly higher reoperation rate compared to males(data from the Swedish Hernia Registry).[7]Furthermore, in a randomized clinical trial published in Lancet 2016 the outcome of closure of mesenteric defects in gastric bypass surgery was evaluated by analysing registry data from the Scandinavian Obesity Surgery Registry (SOREG).[8]

Thus, registry-based studies have a definite role in addressing many of the questions that arise in and have relevance for everyday clinical practice.

However, although population-based registry studies have high external validity, reflecting real-life data and the clinical routines as they are practised in the community at large, they are often hampered by the lack of uniform protocols and standardised routines for registering

relevant data. This may skew the outcomesince units,in which a limited awareness for quality of care is prevailing,may well report data with incomplete accuracy, leading to a risk forlower coverage concerning theregistrations on adverse events by the participating units in the respective registers.Hence such a heterogeneity in the validity of data may seriously limit the options for correct interpretations in respective outcome analyses.

Aims

To analyse the completeness in GallRiks of the follow-up frequency in relation to the intra- and postoperative outcome.

METHODS

The Swedish National Registry for Gallstone Surgery and Endoscopic Retrograde Cholangiopancreatography (ERCP)[9]

Thenational Swedish Registry for Gallstone Surgery andERCP (GallRiks)was established on 1 May 2005 as a registry for cholecystectomy and ERCP procedures.[10] The aim of the registry is to obtain a comprehensive database of individuals subjected to these interventions, including information on patient demographics and the indications and outcomes of interventions.All data entering are online. Theinitial procedures, including information on perioperative complications, are usuallyregistered by operatingclinicians. At a 30-day follow-up all medical records are reviewed forpost-procedural adverse events and dataare entered, usually by alocal coordinator (nurse or a medical secretary).[10]If a 30-day follow-up protocol of a cholecystectomy or ERCP is not complete or is missing it is noted by the system and these procedures can easily be assessed when analyzing the data. GallRiks data are compared to patients´ records on a regular basis by a dedicated independent validation team.A complete

match between overall registry data and medical records has been reported in 98.2% of subjects with a 100% matchfor bile duct injury.[11]

Data extraction

Data on cholecystectomy and ERCP procedures performed between1 January 2006 and 31 December 2014 and entered into the GallRiks registry were assessed. Non-index proceduresand procedures with incomplete data were excluded from the analysis. The complete 30-day follow-up frequency of cholecystectomy and ERCP procedures for individual units participating in the registry was calculated. We arbitrary chose the 90% limit for the 30-day complete follow-up in order to compare groups with sufficient number of procedures to reach enough statistical power to compare good follow-up (≥90%) with a less complete follow-up (<90%). Outcomes forperi- and postoperative complicationswere studied.

Definitions

For the purpose of this paper, and in accordance with the descriptions in the GallRiks database, adverse events are defined and described per consensus agreement.

Cholecystectomy: Surgical removal of the gallbladder in patients with an indication for removing the organ including symptomatic gallstone disease, neoplasms, and acalculous gallbladder conditions.

*Endoscopic retrograde cholangiopancreatography (ERCP):*An endoscopic technique for transpapillary access to the common bile duct and/or pancreatic ductincluding accessingthementioned ducts through bilio- or pancreatico-digestive anastomoses, with diagnostic or therapeutic intent.

*Index procedures:*The first cholecystectomy and/or ERCP-procedure for each patientper in-hospital treatment period.

*Intra-procedural adverse events for cholecystectomy:*Bile duct injury, gut perforation, bleeding requiring intervention or other complications that adversely affected the operation.

*Intra-procedural adverse events for ERCP:*Bleeding, extravasation of contrast, perforation or any other reason for the ERCP being terminated prematurely.

*Post-procedural adverse events:*Complications during the 30-day follow-up period that require some form of medical or surgical intervention, including readmission or death.

*Pancreatitis:*Abdominal pain and an elevated amylase at leastthree times above normal at a time point more than 24 hours after terminating the procedure, as defined by Cotton.[12]

Statistical analysis

Statistical analyses were performed using JMP 12.2.0 (SAS, Cary, NC, USA). Comparisons of patient and procedure characteristics are presented in contingency tables, with pairwise differences analysed with Pearson Chi-square test. The influence of ≤90% follow-up on the risk of adverse events, pancreatitis and bleeding was analysed using multivariable logistic regression modelling. Each variable was testedin univariate and multivariateanalyses for statistical significance, according to purposeful selection as described by Hosmer et al.[13]In the multivariate analysis the outcome was adjusted for sex, age (treated as a continuous variable in the models but presented dichotomized into < or ≥than 60 years(median)), comorbidity dichotomized into ASA 1-2 and ASA 3-5, acute or elective procedure and indication. The models were tested for multicollinearity and effect modification and were finally assessed for goodness of fit. The effects of analysed variables are presented as odds ratios for adverse events with 95% confidence intervals.

RESULTS

Between January 1 2006 and December 31 2014, 162 212 cholecystectomies and ERCP procedures were registered in GallRiks. After the exclusion of 9328 non-index procedures and 57 procedures with incomplete data,152 827 procedures remainedfor final analyses (95840 cholecystectomies and 56987 ERCPs) (figure1). In total, 96.0% of the cholecystectomies and 95.4% of the ERCP procedures had a complete 30-day follow-up. The distribution of complete 30-day follow-up per hospital, for cholecystectomies and ERCP procedures are depictedin figure2. For the cholecystectomy group, 20% of the hospitals had a 30-day follow-up frequency of less than 90% compared to 17% for ERCPs (figure 2). The demographics, physical status assessment and urgency of interventionofincluded patients are given in table 1**.** Patients that were operated on with a cholecystectomy or underwent an ERCP in centres with incompletefollow-up were older and had a higher ASA-score compared to those with a more complete30-day follow-up. The adverse event rates for cholecystectomy and ERCP (intraoperative and total postoperative, with pancreatitis and bleedingshowed separately) are given in figure 3. The overall total postoperative adverse event rate for cholecystectomies was significantly higher for the hospitals with a less complete 30-day follow-up. However, these differences disappeared when adjustments were made for sex, age, ASA-class and whether the operations were acute or scheduled (table 2).

The overall total postoperative adverse event rate for ERCP during the study period was 13.2% and the pancreatitis frequency 3.8%. The incidence of these post-interventionadverse event rateswas rather stable over the study period,except forpancreatitiswhere a small but significant increase was noted (figure 3). The reported risk of post procedural complications as well as pancreatitis and bleeding per se after ERCP was significantly increased in those hospitals with a more frequent and complete follow-up, both in absolute terms as well as when adjusted for confounders (table 3). The reported risk of postoperative adverse events,

including post-ERCP pancreatitis, was nearly twice as high compared to the group with less complete follow-up. The risk of bleeding within the 30-day follow-up period was 38% higher in the group with a better follow-up. On the contrary, the risk of intra-operative adverse events was significantly reduced in the centres included in the ≥90% 30-day follow-up group (table 3). The overall 30-day mortality of cholecystectomies and ERCP in this study was 2.3%. However, since mortality figures are automatically transferred to the register from the Swedish Central Death Register they are not affected by the local routines and management of the reporting hospitals.

DISCUSSION

The results of this study, analysing data from thenationwide Swedish Registry for Gallstone Surgery and ERCP (GallRiks), emphasize the importance of consideringa thorough follow-up as an important confounder when analysing the outcome of registry-based studies. Furthermore, differences in the follow-up frequency seemed to have a greater impact as a confounder in the technically more complicated procedures like ERCP where complications like pancreatitis and cholangitis, usually are detected postoperatively in contrast to cholecystectomies where the adverse events and complications usually are detected intraoperatively.Thus, since the ERCP procedures to a higher extent are marred by postoperative complications, the demands for a thorough and logistically well designed follow-up organization with adequate resources are mandatory.

Strengths and limitations of the study

The prospectively collected data in GallRiks from over 90% of the registered procedures in nearly all Swedish hospitals is a major strength of this study. The data registered in GallRiks have also been verified to have a high validity of over 98%.[11] Another strength is that this report includes data from University Hospitals, County Hospitals, District Hospitals and private units as well. The quality of data has been a concern already from the start of the registry and is guaranteed by continuous quality controls of the data-validity. However, due to financial and time constraints this prospective and integrated part of the registry has to be limited to approximately 50 randomly selected, cross-matches between patient records and GallRiks registrations at each hospital completed every third year.

Data reported by the medical professionals performing the respective intervention or data assessment always have the inherent risk of being subjected tocertain bias. When analysing

the results of quality registry data, factors like coverage of the relevant population by the registry data as well as the follow-up rate have to be taken into consideration. Another limitation of this study is that it presents data from a period of nine years (2006-2014) where the national coverageincreased from 73% to 90%.However, there is no systematic reason why the proportion of those with incomplete versus complete follow up shall depend on the coverage rate as such. It must also be emphasized that, although we found significant differences between units with a high (≥90%) and units with <90%complete follow-up, the overall completeness must be considered excellent since only 4.0 % of the cholecystectomies and 4.6% of the ERCPs have an incomplete follow-up. Nevertheless the absence of uniform study protocols makes it impossible to fully guarantee overall quality of data in population-based registers. Even if these data are considered to have high external validitythe population-based registers may still produce some skewness of the data. The care for accuracy of reporting, and providing healthcare of high quality, may result in a positive correlation between self-reported adverse outcome and completeness of data. On the other hand centres, where the quality of care is poorer, may also have insufficient routines for scrutinising treatment outcome. The only way of avoiding this is a meticulous validation of all registered data, preferably with careful selective assessment of data from units with low coverage as well as to provide continuous education and support from the registry to the participating units with less complete follow-up routines.

Comparison with other studies

RCTs are considered one of the cornerstones of modern,evidence based medical science. It is regarded as the most accurate method to answer key clinical questions andto offer the highest levels of evidence that can be translated into the strongest treatment recommendations.[14] However, RCTs are also associated with definite drawbacks and logistic challenges. [15 16] In

addition, in the case of industry-funded research, and particularly so when study data are owned by the sponsoring body, study results that might have negative economic implicationsare sometimes withheld from publication, leading to publication bias.[17] Furthermore, the number of included patients necessary for creating sufficient power for testing of hypotheses in RCTs may preclude the completion of trials within reasonable time limits.[18]Moreover, treatment methods that in RCTs originating from large academic institutions from which excellent resultsare reported, cannot always be repeated by and implemented insmaller and more resource-challenged facilities. It has also been shown that the outcome for patients excluded from randomisation often differs significantly from those enrolled in the randomised trial co-hort.[19] Thus, registry-based studies can and shall be looked upon as offeringa complement to RCTs data, since they can more closely mirror the effect of a certain treatment-interventionin the entire population, given that good coverage is prevailing.

Severalnational quality registries have reported good coverage which is a prerequisite for a well-functioning quality registry, particularly so for cancer registries and in the paediatric population.[20 21]As for Sweden, there are 53 national quality registriesthat report their coverage to the Swedish National Board of Health and Welfare[22]. Of these 53 registries 19 cover specific interventional procedures,for examplegynaecologicaloperations, hip-replacement, herniasurgery, and cholecystectomy, to mention a few. The national coverage of these registries varies from 46% to 98%. In fact, some of these registries have a better coverage than the Swedish National Patient Registry (NPR) because many of the procedures are done by private hospitals that do not report to NPR as diligently as the government-funded hospitals.

Besides having good coverage, it is of vitalimportance for quality registries to containvalid data. Dedicated validation processes should be in place for assessing and reporting the correctness of the included data at regular intervals. The issue of a complete follow-up is especially challenging in registrieswith focus on the management of benign diseases, since these procedures do not have the same rigorous demands of a compulsory follow-up asthose for malignant conditions.

The impact of the level of completeness of thefollow-up for the validity of reported outcomes in registries covering benign conditions,has not been previously probed and elucidated in the literature. A survey by Rystedt et al, based on the validation of GallRiks, showed a high completeness and correctness of entered data with an overall correctness of data of 98.2% and 100%for bile duct injuries.[11] However, in this publication the completeness of the 30-day follow-up was not specifically addressed. There may also be a relative preponderance of smaller units among those with low completeness. It is often more difficult to organise standardised routines when the volumes are low. This could explain the relatively high completeness on the national level despite the very low completeness at a few hospitals.

The compelling finding of this paper is that the reported incidence of postoperative adverse events after ERCPis significantly lower in hospitals with an incomplete 30-day follow-up frequency (<90%) as compared to those with a morecomplete follow-up (≥90%). Although these results could mirror true outcomes, it is more likely to be the result of failure to reportsome of the adverse events by the hospitals with a less stringentdocumentation system for follow-up and/or a lack of coordinators. The coordinator has the liability, together with the GallRiks responsible surgeon, that the patient´s data are registered and monitored. A contract is signed with the head of the department that ≥90% follow-up in GallRiks should be done. The agreement is broken at the units that have <90% 30-day follow-up.

These assumptionsof less stringent reporting aresupported by the finding that the reported incidence of intra-operative adverse events is significantly higher in the group with ≥90% 30-day follow-up, implying that hospitals with an immaculate and accurate information accrualsystem also followup patients more diligentlyand report adverse events to a higher degree. This discrepancy, where a less frequent 30-day follow-up significantly affected the reported outcome in ERCP but not in cholecystectomy could imply that the effect of a complete 30-day follow-up is more pronounced in procedures with a higher complication profile, since ERCPs have a more congested post-operative complication profile compared to cholecystectomies.

Conclusions and implications

Our findings may have significant general implications on how we shallinterpret outcome data from registry studies.Differences in the follow-up rate seemed tosignificantly affect the reported outcome.The findings suggest that thevalidationprocess has to include the completenessof follow-up. Differences in the follow-up frequency in registries affect the reported outcomes as exemplified by the complicated endoscopic ERCP procedures. The study emphasises the importance of complete follow-up, since this variable may well act as a quality indicator for the respective registry.

Future research

Future research should focus on how the degree of complete follow-up in quality registers can correlate to more objectively and not self-reported quality indicators.

Contributors

LE conceived the study, created the study design, participated in the statistical analysis, analysed the data, and drafted and revised the paper. He is guarantor. MB participated in the analysis and interpretation of data, and revised the paper. GS participated in the statistical analysis and interpretation of data, and drafted and revised the paper. EJ interpreted the data and revised the manuscript. BH conceived the study and reviewed the manuscript. LL interpreted data and reviewed the manuscript. JÖ conceived the study, created the study design, and drafted and revised the paper.

All authors have approved of the final draft submitted.

Ethical approval

The regional research ethics committee at KarolinskaInstitutet, Stockholm, Sweden, approved the study.

Transparency

The first author (LE) confirms that the manuscript is an honest, accurate, and transparent account of the study; that no important aspects of the study have been omitted.

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LEGEND TO FIGURES

Figure 1

The procedures included in the analyses.

Figure 2

Complete 30-day follow-up frequencies following cholecystectomies and ERCP. The hospitals are ordered on the x-axis by level of completeness.

Figure 3

Adverse event rates after cholecystectomies and ERCP.

Table 1

Demographics, physical status assessment and urgency of interventions for the 152 827 patients included in the study

		30-day follow-up of cholecystectomies				
		≥90%		<90%		
		n	**%**	**n**	**%**	***P***
Gender	Female	55908	67.3	8311	65.1	**<.0001**
	Male	27159	32.7	4462	34.9	
Age (years)	≥60	26442	31.9	4462	35.0	**<.0001**
	<60	56461	68.1	8290	65.0	
ASA	ASA 1-2	76478	92.1	11124	87.1	**<.0001**
	ASA ≥3	6589	7.9	1649	12.9	
Acute/ Scheduled	Acute	24237	29.2	4433	34.7	**<.0001**
	Scheduled	58830	70.8	8340	65.3	

		30-day follow-up of ERCP				
		≥90%		<90%		
		n	**%**	**n**	**%**	***P***
Gender	Female	25673	53.0	4460	52.0	0.0906
	Male	22743	47.0	4111	48.0	
Age (years)	≥60	35532	73.6	6724	78.5	**<.0001**
	<60	12767	26.4	1843	21.5	
ASA	ASA 1-2	33457	69.1	4748	55.4	**<.0001**
	ASA ≥3	14959	30.9	3823	44.6	
Acute/ Scheduled	Acute	30093	62.2	5055	59.0	**<.0001**
	Scheduled	18323	37.8	3516	41.0	

Table 2

Adverse event rates, Odds Ratios (OR) and 95% confidence intervals
of hospitals with or without a 30-day follow-up frequency of cholecystectomies ≥ 90%

	Adverse events				
	≥90% n=83067		<90% n=12773		
	n	%	n	%	*P*
Intraoperative	2548	3.0	381	3.0	0.8826
Total postoperative	6681	8.0	1119	8.8	**0.0057**
Pancreatitis	455	0.6	66	0.5	0.6570
Bleeding	629	0.8	96	0.8	0.9454

	Adverse events		
	≥90% vs <90% 30-day follow-up Adjusted*		
	Odds Ratio	(95% CI)	*P*
Intraoperative	0.93	(0.84-1.04)	0.2298
Total postoperative	0.98	(0.91-1.05)	0.5067
Pancreatitis	1.30	(0.99-1.75)	0.0606
Bleeding	0.97	(0.78-1.21)	0.7821

*Adjusted for sex, age, ASA class, acute interventions and indications.

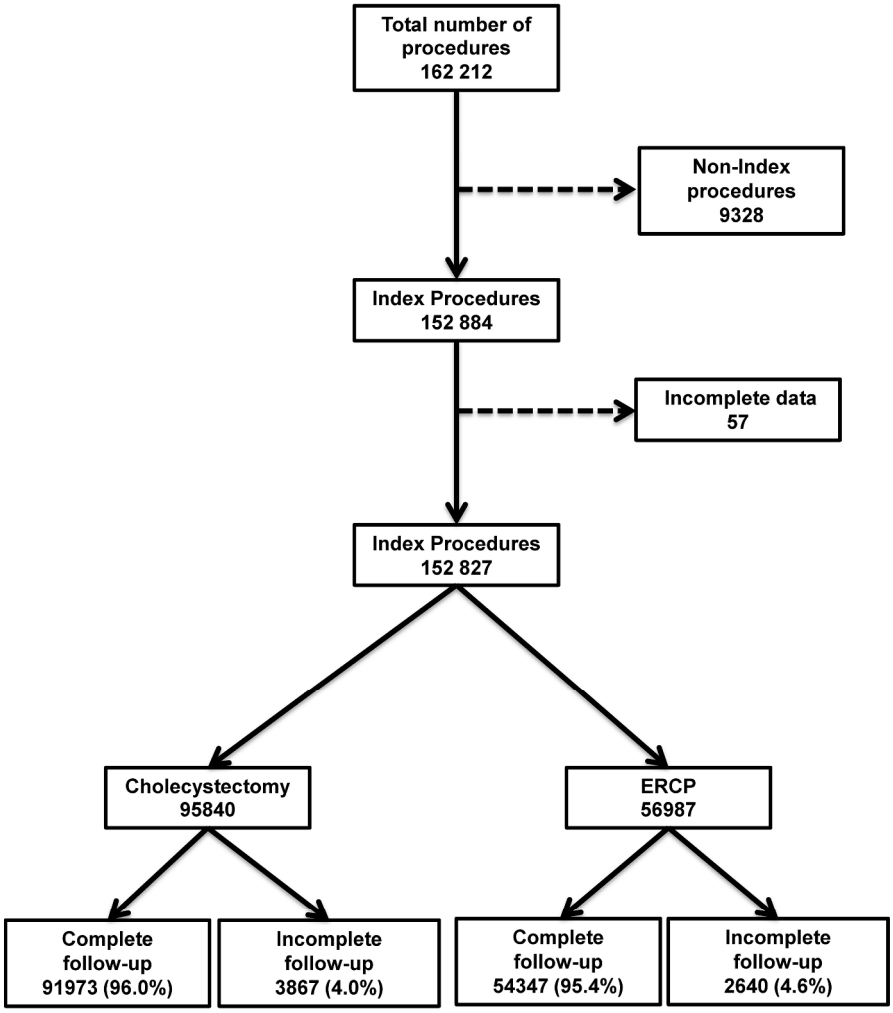
Table 3

Adverse event rates, Odds Ratios (OR) and 95% confidence intervals of hospitals with or without a 30-day follow-up frequency of ERCPs ≥ 90%

	Adverse events				
	≥90% n=48416		<90% n=8571		
	n	%	n	%	*P*
Intraoperative	1267	2.6	252	2.9	0.0868
Total postoperative	6821	14.1	689	8.0	**<.0001**
Pancreatitis	1978	4.1	178	2.1	**<.0001**
Bleeding	591	1.2	76	0.9	**0.0081**

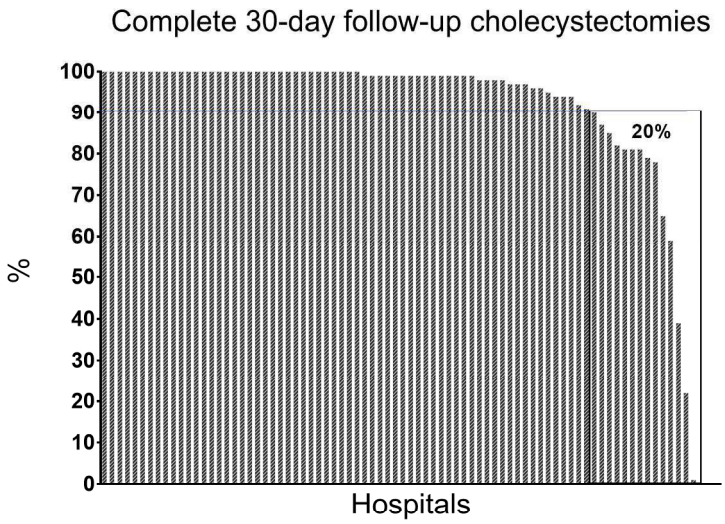
	Adverse events		
	≥90% vs <90% 30-day follow-up Adjusted*		
	Odds Ratio	(95% CI)	*P*
Intraoperative	0.76	(0.66-0.87)	**0.0002**
Total postoperative	1.92	(1.76-2.11)	**<.0001**
Pancreatitis	2.04	(1.72-2.43)	**<.0001**
Bleeding	1.38	(1.08-1.79)	**0.0100**

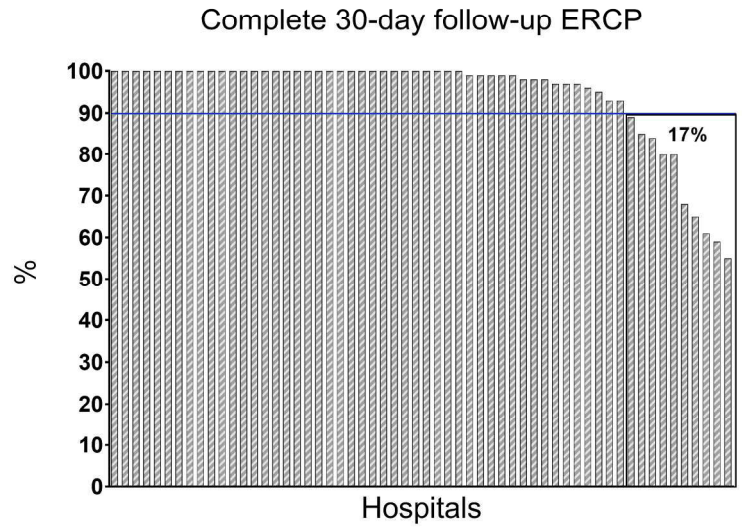
*Adjusted for sex, age, ASA class, acute interventions and indications.



The procedures included in the analyses.

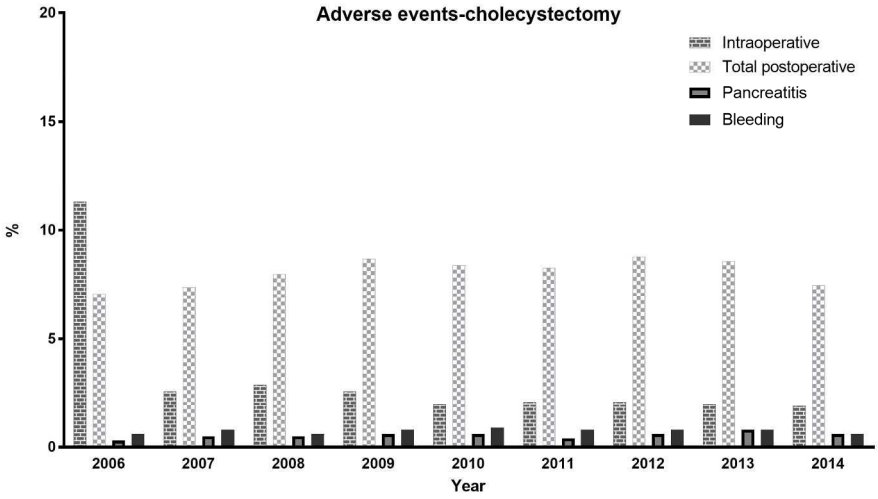
254x338mm (300 x 300 DPI)

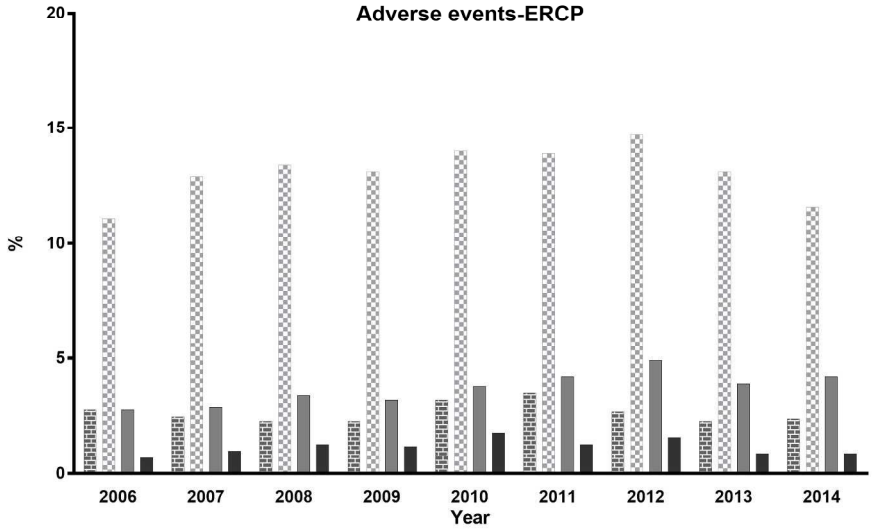




Complete 30-day follow-up frequencies following cholecystectomies and ERCP. The hospitals are ordered on the x-axis by level of completeness.

167x256mm (300 x 300 DPI)





Adverse event rates after cholecystectomies and ERCP.

198x247mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2	Population-based register study
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 4-5	
Objectives	3	State specific objectives, including any prespecified hypotheses	Abstract and page 5	
Methods				
Study design	4	Present key elements of study design early in the paper	Page 4	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pages 5-6	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Pages 5-6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pages 6-7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Pages 5-7*	
Bias	9	Describe any efforts to address potential sources of bias	Pages 10-11	
Study size	10	Explain how the study size was arrived at	Pages 5-6	

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 7	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 7	
		(*b*) Describe any methods used to examine subgroups and interactions	Page 7	
		(*c*) Explain how missing data were addressed		Partly described on page 7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		The article is about this subject
		(*e*) Describe any sensitivity analyses		
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed		Described in results.
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders		Table 1
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		That is what this article is all about
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		*Tables 2-3*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		Tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized		
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	In Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 3

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.