PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Thirty-day complications after laparoscopic or open cholecystectomy: a population-based cohort study in Italy.
AUTHORS	Agabiti, Nera; Stafoggia, Massimo; Davoli, Marina; Fusco, Danilo; Barone, Anna; Perucci, Carlo

VERSION 1 - REVIEW

REVIEWER	Dr. R. Vilallonga Univesitary Hospital Vall d'Hebron. endocrine, bariatric and metabolic Unit. General surgery Department. Barcelona. Spain.
REVIEW RETURNED	07-Sep-2012

THE STUDY	By using the example of the open or LPC cholecystectomy, we finally don't understand if the authors prefer to focus on the results or in the feasibility of a linked administrative health and Comparative effectiveness research (CER).
GENERAL COMMENTS	We have some concern on the data because it seems that patients with severe cholecystitis could have also bile duct obstruction. However the authors don't comment on the ERCP, intraoperative cholangiography intraoperative (open or lpc). could we clarify some more the data concerning the inclusionn criteria then. Did some patients had complication related to the whole management of the biliary disease?

REVIEWER	James P. Dolan, M.D., F.A.C.S Assistant Professor of Surgery Oregon Health and Science University Portland, Oregon Clinical Assistant Professor of Surgery, Uniformed Services University of the Health Sciences Bethesda, Maryland. I have no competing interests.
REVIEW RETURNED	06-Nov-2012

THE STUDY	Not a novel study. Complicated manuscript with sometimes confusing data that varifies what is already known. Strength is in linking admission through 30 day outcomes. This should be highlighted better. Good manuscript if revised for another journal. Not rising to the level of the BMJ.
GENERAL COMMENTS	In this manuscript, Agabiti and colleagues have sought to use

	hospitalization abstract data for a “fixed” population undergoing a specific procedure in order to explore the effectiveness of administrative datasets in defining treatment outcome. I thank the authors for the opportunity to review their contributions. I have a number of comments: Title: Please consider reframing your title. Overall: just a few syntax, spelling, sentence structure and grammar errors. My congratulations in this regard. Abstract: Rewrite “Objective.” There is ICD-9-CM for “partial cholecystectomy.” This should be included. What is “cholecystitis injury”? In addition, I cannot see any listing of the “bile duct injury” or “leak” in your Supplementary Data. Your Conclusions are vague and not supported by your results (“advantage remains in sub-populations with high preoperative risk…..”). Key words: you need more Article summary: -focus.. ”evidence from observational studies is limited.” Unfortunately not so, you should run a current literature review. Introduction: “ analytic methods to reduce bias in CER studies are complex…..continually developing.” There is now a considerable literature on this subject. “relatively few studies showing the advantages from real-life settings using secondary databases.” You should review the Swiss experience (?Geiger or U.S., Dolan 2005 or Flum…… Study population: ? partial cholecystectomy. Results: Study Population: partial cholecystectomy? 2007-2008 data already is 4 years old? Supplementary Data is overly extensive… Patient-level risk factors: define “severity of gallstones.” “Cholangitis” is not considered a moderate severity index. It is better classified as a “high” severity condition. It is life threatening. Cholangitis may be what you describe as “inflammation and obstruction..” which is appropriate for “high” Reference 18 is suspect. I would read it again and consider excluding it. Outcomes: Supplementary Data is overly extensive… Type of cholecystectomy: “ Since a specific ICD-9-code for a case converted from LC to OC was not available,” There is a ICD-9 code for this. Introduced in 1997 in U.S. systems. Statistical Analysis: “Multiple logistic regression models..” What specific type? (forward, reverse, stepwise, etc) “variables “a priori” chosen as confounders” What about diabetes, smoking, obesity? “ the treatment variable “type of cholecystectomy” was included..” Is this really valid? “In order to test the hypothesis of an effect modulation by age,” Hypothesis should be stated up front and not in the middle of a manuscript preparation. “..by adding the corresponding interaction terms coefficients.” I’m unsure how these were derived. “….corresponding tests of heterogeneity of the stratum specific……..computed but not reported…” How did they look? Computed value? I do agree with multilevel regression to see if there is a clustering effect…. RESULTS: Table 1. Similar findings have been reported previously. Does emergency admission influence outcomes?? Table 2: Confidence Intervals are not reported. These would make it

	easier for readers to consider confounders, modulators etc.. between crude and adjusted data. Table 3: Put your overall complication rate in the body of the table not in the heading. I had trouble locating it when you referred to it form the text. Would almost think type of cholecystectomy and 30 day complications should be switched on the table. Make complications the dependent variable. Not all the risk factors from Table 2 were used in adjusting in Table 3. Any influence of comorbidities? “The incidence of “at least one 30-day complication” was 3%. I could not locate this value.. Confidence Intervals are not reported. These would make it easier for readers to consider confounders, modulators etc.. between crude and adjusted data. In addition, OR are so low, comment please. Discussion: Overall your findings and discussion are hardly novel. This may be the first study in Italy but similar studies have been published using large datasets on the outcomes after LC vs. OC. Most of your discussion is devoted to proving that LC is superior to OC. This, however, is no longer a significant or novel issue since this has been proven in multiple studies, from differing perspectives, over the last decade. I believe your one strength in this study is to link 30-day outcomes to admissions and this is important. However, this has also been done in other countries. In addition, you should be cautious in reporting complications based on ICD-9 coding. Complications have been shown to be underreported when investigated using this means. References: A number of your references are Epub. Many of these should have journal citations at this point. See previous note for reference 18 Tables/Figures: Tables: Comments as above. Figure 1: ICD-9 procedure code for partial cholecystectomy? Deliveries, N=0. Please Comment Supplemental Data: Part 5: Where are the bile duct injury codes? Thank you for the opportunity to review this manuscript.

VERSION 1 – AUTHOR RESPONSE

Answers to Reviewer 1

1.By using the example of the open or LPC cholecystectomy, we finally don't understand if the authors prefer to focus on the results or in the feasibility of a linked administrative health and Comparative effectiveness research (CER).

We apologize for the confusion. Our main focus is on results. We are also interested in discussing the potentiality of population-based linked health data. Despite the increasing use of this source of data in the field of surgery, the estimated risks of adverse events vary widely according to the type of interventions and to the type of complications and their operative definition. We think that our example from a country in Southern Europe can provide a contribution to the topic.

2.We have some concern on the data because it seems that patients with severe cholecystitis could

have also bile duct obstruction. However the authors don't comment on the ERCP, intraoperative cholangiography intraoperative (open or lpc). could we clarify some more the data concerning the inclusionn criteria then. Did some patients had complication related to the whole management of the biliary disease?

Thank you for this suggestion. The main inclusion criteria is Cholelithiasis (ICD-9-CM code 576.4 any position) together with Colecystectomy (ICD-9-CM codes 51.22 and 51.23). We agree that in some patients complications could be related to the whole management of the biliary tract. The Regional Hospital Register includes up to six diagnostic/therapeutic procedures, but timing of procedures is not available. Then we do not know if a specific diagnostic procedure has been performed during o before the surgery. Following the reviewer's suggestion, we analysed the data and found that only few persons (n=3) had ICD-9-CM codes for ERCP. Given the small numbers, we think it had a limited impact on the overall results.

Answers to Reviewer 2

In this manuscript, Agabiti and colleagues have sought to use hospitalization abstract data for a "fixed" population undergoing a specific procedure in order to explore the effectiveness of administrative datasets in defining treatment outcome.
I thank the authors for the opportunity to review their contributions. I have a number of comments:

1.Title: Please consider reframing your title. Overall: just a few syntax, spelling, sentence structure and grammar errors. My congratulations in this regard.

New title: Thirty-day complications after laparoscopic or open cholecystectomy: a population-based cohort study in Italy

2.Abstract:
Rewrite "Objective." There is ICD-9-CM for "partial cholecystectomy." This should be included.
-We rewrote the objective.
-We a priori decided to exclude these codes to increase the specificity of our exposure definition. However, following the reviewer's suggestion, we checked the frequency of these codings in the cohort under study. We found 27 cases of "Other partial cholecystectomy" (ICD9=51.21) and 112 cases of "Partial laparoscopic cholecystectomy" (ICD9=51.24). Their inclusion would have increased the numbers of open and laparoscopic procedures to 2884 (+0.9%) and 13686 (+0.8%), respectively. Therefore we strongly doubt such inclusions would change results in a meaningful way.
We added a sentence in the Methods section – Study population (pg.7)

3.What is "cholecystitis injury"? In addition, I cannot see any listing of the "bile duct injury" or "leak" in your Supplementary Data.

We apologize for the mistake. We changed the list of possible complications (in brackets) according to those items quoted in the Supplementary data. The new quoted items in the abstract and in the text (pg. 8, Outcomes) are: post-operative infection, hemorrhage or hematoma or seroma complicating a procedure, persistent postoperative fistula, perforation of bile duct, disruption of wound.

4.Your Conclusions are vague and not supported by your results ("advantage remains in sub-populations with high preoperative risk…..").
The sentence has been eliminated.

5.Key words: you need more
We added more key words: administrative data, cohort study, effectiveness, gallstones, hospital

discharge data, laparoscopic cholecystectomy, open cholecystectomy, outcomes, population-based, post-operative complications.

6.Article summary: -focus.. ”evidence from observational studies is limited.” Unfortunately not so, you should run a current literature review.

We deleted the sentence and run an updated literature review (see new references n.16-18 considered both in the introduction and discussion section).

6.Introduction: “ analytic methods to reduce bias in CER studies are complex…..continually developing.” There is now a considerable literature on this subject. “relatively few studies showing the advantages from real-life settings using secondary databases.” You should review the Swiss experience (?Geiger or U.S., Dolan 2005 or Flum……

We deleted the sentence “analytic methods….”. According to the reviewer we performed a literature review and added more references (see new references n.16-18 considered both in the introduction and discussion section).

7. Study population: ? partial cholecystectomy.
See comment to point 2.

8. Results:
Study Population: partial cholecystectomy? 2007-2008 data already is 4 years old? Supplementary Data is overly extensive…

For partial cholecystectomy see comments to point 2. Unfortunately the data is 4-years old and we are not able to update the analysis. Supplementary data have been shortened.

9.Patient-level risk factors: define “severity of gallstones.” “Cholangitis” is not considered a moderate severity index. It is better classified as a “high” severity condition. It is life threatening. Cholangitis may be what you describe as “inflammation and obstruction..” which is appropriate for “high”.

We agree with your comment. Cholangitis has been moved from the “moderate” to “high” severity category. Since codes for “cholangitis” were found only in 27 individuals (0.2%) (17 for LC and 10 in OC), results from multivariate models were substantially unchanged. In Table 1 numbers for the three categories of gallstone severity are minimally changed due to the switch of 27 individuals from moderate to high level category (17 in LC cohort and 10 in the OC cohort). We run again the analyses but the results remain substantially unchanged.

See Table 1 (lines for severity of cholelitiasis)

10. Reference 18 is suspect. I would read it again and consider excluding it.
We eliminated this reference.

11. Outcomes: Supplementary Data is overly extensive…
We shortened our Supplementary data (from 9 to 3 pages).

12.Type of cholecystectomy: “ Since a specific ICD-9-code for a case converted from LC to OC was not available,” There is a ICD-9 code for this. Introduced in 1997 in U.S. systems.

Thank you for this comment. The code for a case converted from LC to OC does exist in the ICD-9-CM (code V64.41 Laparoscopic surgical procedure converted to open procedure) classification but in

our Region (as in other regions of Italy) it is rarely used in practice. There is a well known high level of under-notification in our Region during the study period for this specific code. We found no 64.41 code in our study cohort. Only in 13 cases the more general code V64.4 “Closed surgical procedure converted to open procedure” was reported. We added at pg 9 of the methods section (“type of cholecystectomy”). The problem of under-notification and misclassification is commented in the manuscript in the discussion section.

13. Statistical Analysis:
- “Multiple logistic regression models..” What specific type? (forward, reverse, stepwise, etc)

As specified in the text, the predictive model was made of two sets of predictors: a priori and empirically tested. The latter set was evaluated via iterative stepwise procedures.

-“variables “a priori” chosen as confounders” What about diabetes, smoking, obesity?
Diabetes and obesity were included in the list of comorbidities empirically tested in the models (see previous answer). Unfortunately we do not have information on smoking. The association of diabetes and obesity with outcomes are shown in Table 2.

- “ the treatment variable “type of cholecystectomy” was included..” Is this really valid?
We eliminated the term “treatment”.

-“In order to test the hypothesis of an effect modulation by age,” Hypothesis should be stated up front and not in the middle of a manuscript preparation.
At the end of introduction we stated that “Secondly, we tested the hypothesis that the advantages of LC versus OC could vary according to demographic and clinical patients’ characteristics”. The new version of this sentence is “Secondly, we tested the hypothesis that the advantages of LC versus OC could vary according to age and clinical patients’ characteristics”.

-“..by adding the corresponding interaction terms coefficients.” I’m unsure how these were derived.
“….corresponding tests of heterogeneity of the stratum specific……..computed but not reported…”
How did they look? Computed value? I do agree with multilevel regression to see if there is a clustering effect….

As added in the text, this was accomplished by adding the coefficient from the reference category and that from the age stratum of interest, and by computing the corresponding standard error from the corresponding terms of the variance-covariance matrix.
See Methods – Statistical analysis pg. 10-11

14. RESULTS:
-Table 1. Similar findings have been reported previously. Does emergency admission influence outcomes??
Emergency admission is strongly associated with both treatment (Table 1) and the outcomes (Table 2).

-Table 2: Confidence Intervals are not reported. These would make it easier for readers to consider confounders, modulators etc.. between crude and adjusted data.
Added in Table 2 and 3.

-Table 3:
Put your overall complication rate in the body of the table not in the heading. I had trouble locating it when you referred to it form the text.
Would almost think type of cholecystectomy and 30 day complications should be switched on the

table. Make complications the dependent variable.

Since results of effect modifications are outcome-specific, it is not clear how the table should be switched. Anyway, we added the figures of the outcomes in the body of the table and we also added the p-values of heterogeneity across strata-specific estimates and confidence intervals, as requested.

-Not all the risk factors from Table 2 were used in adjusting in Table 3. Any influence of comorbidities?

Since comorbidities were chosen via multivariate stepwise procedures, only those associated with the outcome were retained. Therefore we exclude any influence due to omitted comorbidities.

-"The incidence of "at least one 30-day complication" was 3%. I could not locate this value..onfidence Intervals are not reported. These would make it easier for readers to consider confounders, modulators etc.. between crude and adjusted data. In addition, OR are so low, comment please.

We apologize for the confusion. We decided to eliminate this sentence from the text.

15. Discussion:
Overall your findings and discussion are hardly novel. This may be the first study in Italy but similar studies have been published using large datasets on the outcomes after LC vs. OC. Most of your discussion is devoted to proving that LC is superior to OC. This, however, is no longer a significant or novel issue since this has been proven in multiple studies, from differing perspectives, over the last decade. I believe your one strength in this study is to link 30-day outcomes to admissions and this is important. However, this has also been done in other countries. In addition, you should be cautious in reporting complications based on ICD-9 coding. Complications have been shown to be underreported when investigated using this means.

Thank you for this comment. We reduced the emphasis on the novelty of this study and highlighted the well known limitation of administrative (see third paragraph of the Discussion). We strengthened the advantage on linked population dataset to measure 30-day outcomes (see second paragraph of the Discussion).

16. References:
A number of your references are Epub. Many of these should have journal citations at this point.
See previous note for reference 18
-All references were checked.

17. Tables/Figures:
Tables: Comments as above.
Tables: answers as above.
18. Figure 1: ICD-9 procedure code for partial cholecystectomy? Deliveries, N=0. Please Comment
For partial cholecystectomy see answer to comment 2. For delivery: we refers to the exclusion of MDC 14 (delivery) when we started the selection of our study population from the regional hospital discharge dataset, as we automatically do for all other surgical cohorts in our Regional Outcome Program (PREVALE). Of course in this study there is no delivery. We agree that this information is redundant and we eliminated the box from the figure 1.
19. Supplemental Data:
Part 5: Where are the bile duct injury codes?
576.3 Perforation of bile duct and 576.4 Fistula of bile duct (they are reported in Supplementary data)

VERSION 2 – REVIEW

REVIEWER	Dr. Ramon VILALLONGA Universitary Hospital Vall d'Hebron. Barcelona. Spain
REVIEW RETURNED	22-Dec-2012

RESULTS & CONCLUSIONS	The results however are already known but they are seated in a southern country such as Italy. The authors should try to explain why the groups are not homogenous when comparing them in terms of comorbidities.... Was it related to the anesthesia risk (ASA), the risk of laparoscopy?

VERSION 2 – AUTHOR RESPONSE

Reviewer: Dr. Ramon VILALLONGA
Universitary Hospital Vall d'Hebron. Barcelona. Spain
The results however are already known but they are seated in a southern country such as Italy.
The authors should try to explain why the groups are not homogenous when comparing them in terms of comorbidities.... Was it related to the anesthesia risk (ASA), the risk of laparoscopy?

Thank you for this comment. We agree that the high frequency of comorbidities in OC group in comparison to LC group is related to the anestehesia risk. We modified the text at pg 14 second paragraph.