



The use of hospital discharge data to compare outcomes of different surgical techniques: the example of cholecystectomy.

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5 **the example of cholecystectomy.**
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3 **The use of hospital discharge data to compare outcomes of different surgical techniques:**
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5 **the example of cholecystectomy.**
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8
9 **Abstract**
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11 **Objective**
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14 There is an increasing interest in using routinely collected health data to support large-scale
15 effectiveness evaluation of different treatment options. We evaluated short-term outcomes
16 after laparoscopic cholecystectomy (LC) or open cholecystectomy (OC) in gallstones using
17 hospital discharge data.
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22 **Design**
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24 Population-based cohort study.
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27 **Setting**
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29 Data were obtained from the Regional Hospital Discharge Registry Lazio Region in Central
30 Italy (around 5 million inhabitants) in 2007-2008.
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34 **Participants**
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36 All patients admitted to hospitals of Lazio with symptomatic gallstones (ICD9-CM = 574)
37 who underwent LC (ICD9-CM 51.23) or OC (ICD9-CM 51.22).
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41 **Outcome measures**
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43 1) “30-day surgical-related complications” defined as any complication of the biliary tract
44 (including bile duct injury, bile leak, postoperative bleeding, wound infection, cholecystis
45 injury); 2) “30-day systemic complications” defined as any complications of other organs
46 (including sepsis, infections from other organs, major cardiovascular events and selected
47 adverse events).
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53 **Results**
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3 13,651 patients were included; 86.1% had LC, 13.9% OC. 2.0% experienced surgical-related
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5 complications (SRC), 2.1% systemic complications (SC). The Odds Ratio (OR) of
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7 complications after LC versus OC was 0.60 ($p<0.001$) for SRC and 0.52 ($p<0.001$) for SC. As
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9 regards SRC, the advantage of LC was consistent across age categories, severity of gallstones
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11 and previous upper abdominal surgery, while there was no advantage among people with
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13 emergency admission (OR=0.94, $p = 0.764$). For SC, no significant advantage of LC was seen
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15 among very old people (OR=0.99, $p=0.975$) and among those with previous upper abdominal
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17 surgery (OR=0.86, $p=0.905$).
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20 21 **Conclusions**

22
23 This large observational study confirms that LC is more effective than OC with respect to
24
25 short-term complications. The advantage remains in sub-populations with higher preoperative
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27 risk, but it is different according to whether the complications affect the biliary tract or other
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29 organs or systems. Population-based linkage of administrative datasets can enlarge evidence
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31 of treatment benefits in clinical practice.
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39 **Key words:** administrative data, cholecystectomy, complications, effectiveness, outcomes
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Article summary

Article focus

-The advantage of laparoscopic cholecystectomy (LC) approach for the treatment of gallstone versus open surgery (OC) has been shown from RCTs but the evidence from observational studies is limited.

-The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments.

-We compared laparoscopic and open cholecystectomy in term of short-term outcomes using routinely collected databases in Lazio Region (Italy).

Key messages

-This population-based study contributes to enlarge the evidence on effectiveness of LC in a real-life setting.

-As regards surgical-related complications, the advantage of LC was consistent across age categories, severity of gallstones and previous upper abdominal surgery, while there was no advantage among people with emergency admission.

-For systemic complications, no significant advantage of LC was seen among very old people and among those with previous upper abdominal surgery.

Strengths and limitations

-Population-based design, large numbers and robustness of analytic procedures are the main strengths.

-It contributes to the debate on the complex methodology to estimated risk of adverse events after surgery using secondary databases to monitor quality of care.

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-The use of ICD-9-CM codes in the definition of severity of disease presentation and of complications is a major limit.

For peer review only

Introduction

Comparative effectiveness research (CER) is becoming central to monitor real-life impact of treatments and support public health decisions (1, 2). Although the basic concept of comparing therapies is not new, over the last few years many initiatives have been implemented in many countries to provide large-scale evidence on benefits and harms of different treatments (3-5). The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments (6,7). They include hospital in-patients records, birth and death registrations, outpatient care records, dispensed pharmacy drugs. Despite the advantages due to the large numbers and the population-level coverage, the analytic methods to reduce bias in CER studies are complex and new approaches are continuously developed (8,9).

In the Lazio Region (around 5.000.000 inhabitants) the P.Re.Val.E. Project (*Regional Program for Assessing the Outcomes of Health-care Interventions*) was launched in 2005. Its aims are: to measure the quality of health care provided in the Lazio Region, to describe variability of care provision across institutions and populations and to compare effectiveness of treatments for different medical and surgical conditions (10, 11). Over 60 outcomes indicators are calculated based on data obtained from record-linkage procedures of different health systems. The results are periodically updated and publicly disseminated with discussion on critical methodological points.

Cholecystectomy is one of the most common abdominal surgical procedures in developed countries. Since its introduction in the late '80s, laparoscopic cholecystectomy (LC) has replaced open cholecystectomy (OC) as the treatment of choice for symptomatic gallstones (12, 13). Although beneficial effects of LC have been widely demonstrated, there are

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3 relatively few studies showing the advantages from real-life settings using secondary
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5 databases (14-16). In the present study, we aimed at developing a methodology to measure
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7 short-term complications after LC or OC using large administrative databases on behalf of the
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9 P.Re.Val.E. Secondly, we tested the hypothesis that the advantages of LC versus OC could
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11 vary according to demographic and clinical patients' characteristics.
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20 **Methods**

21 Source of data

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23 Data was derived from the Lazio Hospital Information System (HIS), which provides
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25 information on patients' demographic data (gender, age, place of birth, place of residence),
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27 admission and discharge dates, discharge diagnoses (up to 6) and medical procedures or
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29 surgical interventions ((up to 6) according to the International Classification of disease, Ninth
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31 Revision, Clinical Modification (ICD-9-CM), status at discharge (alive, dead, transferred to
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33 another hospital), ward(s) of stay, date(s) of in-hospital transfer, and a regional code
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35 corresponding to the admitting facility for patients discharged from all public and private
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37 hospital of the Lazio Region (5.759.839 inhabitants).
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45 Study population

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47 All hospital admissions with a primary or secondary diagnosis of gallstones (International
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49 Classification of Diseases 9th Revision, Clinical Modification - ICD9-CM = 574) and a
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51 procedure code of cholecystectomy (ICD9-CM 51.22, 51.23), occurred in private and public
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53 hospitals of the Lazio Region between January 2007 and September 2008 were included, for a
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55 total of 16,432 cases (age 18+ years). Information was retrieved from the HIS. In order to
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3 increase the case specificity, several exclusion criteria were applied including long-term
4 hospitalizations, rehabilitations, day-hospitals, hospitalizations for delivery or trauma or
5 cancer, hospitalizations with abdominal surgical procedures other than cholecystectomy. The
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7 final population consisted of 13,651 subjects (**Figure 1**). See the online **Supplementary Data**
8
9 (Part 1) for details on the exclusion criteria and ICD9-CM codes.
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13 14 15 16 Patient-level risk factors

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18 The following characteristics were considered for each patient: Age (<70; 70-79; >=80 years
19 old); Gender; Severity of gallstones: it was classified as *low* (not-complicated), *moderate*
20 (presence of cholecystitis, cholangitis or biliary tract obstruction), and *high* (presence of both
21 inflammation and obstruction of the biliary tract); Previous upper abdominal surgery (based
22 on previous 2-year hospitalizations); Comorbidities (based on previous 2-year
23 hospitalizations) following validated algorithms (17-19); Type of admission: either *elective* or
24 *emergency*. See the online **Supplementary Data** (Part 2-4) for details on the ICD-9-CM
25 codes. The choice of *cut off* for age category was based on previous studies to distinguish
26 adult and old people (20-22).
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38 Outcomes

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40 We identified various complications within 30-days after the intervention and grouped them
41 in two categories: 1) “*30-day surgical-related complications*” defined as any complication of
42 the biliary tract (including bile duct injury, bile leak, postoperative bleeding, wound infection,
43 cholecystitis injury); 2) “*30-day systemic complications*” defined as any complications of other
44 organs (including sepsis, infections from other organs, major cardiovascular events and
45 selected adverse events). The complete list of complications with ICD-9-CM codes is
46 reported in the online **Supplementary Data** (Part 5). Among the various complications we
47 included some conditions reported in the list of Patient Safety Indicators recently developed
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3 by the Agency for Health Care Research and Quality (i.e. postoperative bleeding, wound
4 infection), while other items were specifically created on the basis of scientific literature on
5 digestive surgery (14-16,23,24). Depending on the type of complication, some ICD9-CM
6 codes were searched in both the index admission and the following ones in the 30-day period
7 after the surgery, others were searched only in later hospitalizations. For example, peritonitis
8 or acute pancreatitis was not counted as complications when reported in the index admission.
9 See the online **Supplementary Data** (Part 5) for details on the ICD9-CM codes. In the case
10 of a subsequent hospitalization occurred out of the study area (for example, in a region other
11 than Lazio), we obtained information through record linkage procedure between hospital
12 information systems. Because of the short follow up time, this happened in a minimal
13 proportion of cases (0.1%). The outcome variables were: “30-day surgical-related
14 complications” and “30-day systemic complications”; they were coded “1” if at least one of
15 the complications within the group was present and “0” if none was recorded.
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34 Type of cholecystectomy

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36 We defined the variable “*type of cholecystectomy*” (laparoscopic cholecystectomy, LC vs.
37 open cholecystectomy, OC). Since a specific ICD-9-code for a case converted from LC to OC
38 was not available, in the case of reported ICD-9-CM codes for both LC and OC (5%), the
39 patient was considered exposed to the open surgical procedure.
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47 Statistical analysis

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49 Multiple logistic regression models were fitted to estimate the relative risk of 30-day
50 complications (either “surgical-related” or “systemic”) after LC versus OC, adjusting for
51 demographical and clinical risk factors. The two outcome variables were analysed separately.
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56 Given the large amount of individual-level variables available, the risk factors were divided in
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3 two groups: 1) variables “a priori” chosen as confounders (age, gender, severity of gallstones,
4 previous upper abdominal surgery, and type of admission); 2) variables empirically tested
5 (comorbidities, which were selected using iterative stepwise statistical procedures) (9,25).
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10 Once the “best” predictive model was identified for each of the two outcome variables, the
11 treatment variable “*type of cholecystectomy*” was included, and the adjusted odds ratio (OR)
12 of LC versus open surgery was estimated, with corresponding 95% confidence interval (95%
13 CI) and p-value.
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21 In order to test the hypothesis of an effect modification by age, relative risk estimates for the
22 age groups were derived by adding an interaction term between the age group and the
23 treatment variable in the final multivariate logistic model. We obtained the OR of
24 laparoscopic vs. open surgery within each age stratum by adding the corresponding
25 interaction terms coefficients. Similarly, effect modification was tested with regard to
26 severity of cholelithiasis, previous upper abdominal surgery and type of admission. The
27 corresponding tests of heterogeneity of the stratum-specific risk estimates were computed but
28 not reported for ease of presentation.
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40 Sensitivity analyses were performed. First, in order to guarantee adequate control of
41 confounding factors we identified and adjusted for all the individual factors associated with
42 the treatment, within the propensity adjustment framework (26). This procedure is a two-step
43 technique: 1. it estimates the a priori probability of exposure for each subject, based on
44 clinical and demographic characteristics; 2. it standardizes for them in the association between
45 treatment and the study outcome. The individual factors related to the exposure in the present
46 study include age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of
47 admission, cardio-circulatory disease, cerebrovascular disease, COPD or respiratory failure,
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3 chronic nephropathy, chronic disease of the liver or pancreas. Second, to take into account the
4 potential heterogeneous experience in laparoscopic surgery across different hospitals because
5 of the patients' clustering within a single institution we perform a multilevel regression model
6 with random intercepts for hospitals (27).
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14 All the statistical analyses were performed using SAS Software version 8.0 (SAS Institute,
15 Inc. SAS/STAT software).
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23 **Results**

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25 A description of the study population, overall and by cholecystectomy procedure, is presented
26 in **Table 1**. Over 80% of the patients were younger than 70 years, and moderate to high
27 severity of the gallstones was diagnosed for 61.7%. As compared with patients undergoing
28 LC, those who underwent OC were more likely to be elderly, males, with a more severe
29 baseline disease and more chronic conditions. Furthermore, they were operated in emergency
30 in most of the cases (52.4%), whereas LC was performed in elective hospitalizations much
31 more frequently (73.9%).
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43 **Table 2** reports the relationship between demographic and clinical variables and the
44 occurrence of complications. The adjusted risk of systemic complications increased with age
45 and was much higher in patients with more severe baseline gallstones, whereas no clear age or
46 severity-related differences in risk emerged with regard to surgical-related 30-day
47 complications, once other co-factors were taken into account. Women were less likely to
48 experience both types of complications. Having had a previous intervention on the upper
49 digestive system seemed to enhance the risk of both surgical-related and systemic
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3 complications, though results are not statistically significant due to small power. Finally, the
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5 risk of both types of complications was more evident in emergency as opposed to scheduled
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7 interventions. Surgical-related complications were higher among subjects with obesity, blood
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9 disease, stroke or chronic nephropathy, whereas systemic complications were associated with
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11 blood diseases, ischemic heart disease, conduction disorders or dysrhythmias, COPD or
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13 respiratory failure, chronic nephropathy, and chronic diseases of the liver or pancreas.
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18 **Table 3** shows the relationship between type of cholecystectomy and outcomes, adjusted for
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20 the risk factors identified in Table 2. We report results of the advantage of LC vs. OC (OR,
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22 95% CI) in the cohort (first lines of the table) and in the each stratum of the variables tested in
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24 the models with interaction terms. The incidence of “30-day surgical-related complications”
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26 and “30-day systemic complications” was 2.0% and 2.1%, respectively. The incidence of “at
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28 least one 30-day complication” was 3%. The odds ratio of surgical related complications for
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30 patients who underwent LC as compared to patients with OC was 0.60 ($p < 0.001$). The
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32 corresponding figure for systemic complications was 0.52 ($p < 0.001$).
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36 As regards 30-day surgical-related complications, the protective effect of LC vs. OC was
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38 consistent across the age category, severity of cholelithiasis and previous upper abdominal
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40 surgery, while among people with emergency admission there was no advantage (OR=0.94 p
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42 = 0.764). Similarly, for systemic complications, the superiority of LC vs. OC was consistent
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44 regardless level of cholelithiasis severity, and elective/emergency admission, but for those
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46 80+ yrs aged people there was no advantage of LC vs. OC (OR 0.99, $p = 0.975$); also for
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48 patients with previous upper abdominal surgery there was a much weaker advantage
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50 (OR=0.86, $p=0.905$).
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3 When the association between type of cholecystectomy and short-term complications was
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5 adjusted with the propensity adjustment method, results were consistent with those obtained
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7 with the risk-adjustment procedure (LC vs. OC OR= 0.61 and OR=0.52 respectively for the
8
9 two outcomes). Finally, results were similar taking into account patients' clustering within
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11 different hospitals (*data not shown*).
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14 15 16 17 18 **Discussion** 19

20 From this large observational study based on linked administrative health records - taking
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22 into account the disomogeneous distribution of factors related to the probability to be offered
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24 open surgery - people who end up having a LC have a better short-term prognosis than those
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26 that get an OC for the treatment of gallstones. The superiority of laparoscopic approach in
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28 term of short-term outcomes is consistent in both genders, different severity in disease
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30 presentation and past history of upper abdominal surgery.
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36 This population-based study contributes to enlarge the evidence on effectiveness of LC in a
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38 real-life setting. It supports the usefulness of observational approaches. To our knowledge it is
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40 the first study in Italy to measure and compare outcomes of surgical treatments using data
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42 from secondary data sources. Despite RTCs are considered the optimal study design when
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44 comparing efficacy of treatments, observational studies provide a picture of treatment under
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46 usual circumstances of health-care practice and can answer to the question “*Does it work in*
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48 *practice?*” (6, 3). RTCs often have small sample size and may under represent vulnerable
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50 patient groups, including elderly patients with multiple comorbidities, children, and young
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52 women, and operate in a highly controlled environment that is far from routine clinical
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54 practice. Our study supports that LC is a reliable approach safer than OC not only in old age
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3 group - confirming previous findings (20, 28) - but also in presence of severe disease
4 presentation and in patients with past history of upper digestive system surgery. Beneficial
5 effect of LC as regards systemic complications tends to be lower in 80+ yrs aged in
6 comparison with younger ages, and in patients with emergency admission in comparison to
7 elective admissions as regards 30-day surgical-related complications. These data add to the
8 evidence on the complex relationship between age and outcomes after surgery (20-22, 28).
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18 A number of potential biases are present. First of all, people in the two groups of patients
19 analyzed are not homogenous with a higher frequency of elderly and more severe patients in
20 the open group than in the laparoscopic one. When comparing the effect of the two techniques
21 using two different populations, the so called “indication bias” may affect study validity (6,
22 29). To limit this problem we run the propensity adjustment analysis to take into account the
23 different distribution of factors strongly associated with the probability to receive open
24 surgery in the study population. This analytical approach confirmed the advantage of
25 laparoscopic vs. open surgery obtained in the main logistic regression analysis. Another
26 critical point is the potential different distribution of laparoscopic experience across surgeons;
27 however a sensitivity analysis which took into account this point led to similar results. The
28 use of ICD-9-CM codes in the definition of severity of disease presentation and of
29 complications is another major limit. Discharge abstract data have little insight into clinical
30 details and do not inform on the temporal relationship of the clinical conditions and processes,
31 then defining complications is a difficult task (30). In this respect, we tried to improve the
32 accuracy of our measures both 1) applying a specific coding algorithm with subsequent
33 hospital admissions used to retrieve adverse events and 2) excluding in the “count” of
34 complications specific items if reported in the index only (i.e. peritonitis) because of the
35 difficulty to determine if it was already present at admission. Moreover, we cannot exclude an
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3 under-notification of complications but it is unlikely that is influenced by the type of surgery.
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5 Another major problem is the potential misclassification of exposure since we were not able
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7 to measure the occurrence of conversion of LC to OC. The number of people that were
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9 switched from LC to OP is low in comparison to figures documented in other studies and it
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11 may represent a severe source of bias in our study (28,31).
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16 Beneficial effects of the laparoscopic approach versus traditional open surgery for the
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18 treatment of gallstones come from various randomized controlled trials (RCTs) (32). They
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20 found significant shorter hospital stay and quicker convalescence associated with LC but no
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22 differences in mortality, complications and operative time between the two procedures. A
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24 better trend with the laparoscopic approach, including morbidity and mortality, comes from
25
26 some observational studies. From a surveillance system in eight Swiss hospitals, surgical site
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28 infections were less common in laparoscopic approach in comparison to traditional open
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30 surgery (0.5% in LC vs. 1.8% in OC) (33). Significantly lower incidence of venous
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32 thromboembolism and surgical site-infections in laparoscopic cases versus open cases was
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34 recently observed in a large administrative dataset-based study in USA (14, 15). In-hospital
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36 mortality after cholecystectomy over a ten-years period was studied in USA: LC was
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38 associated with a low mortality rate (mean value in the period: 0.52%) while OC with a
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40 significantly higher rate (corresponding value: 4.9%) (16). In the era of evidence-based
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42 health care, population-based linkage of administrative health data have been increasingly
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44 used also in the field of surgery. However the methodology is not standardized and estimated
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46 risk of adverse events vary widely according to the type of interventions and to the type of
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48 complications and their operative definition. As a recent example in Europe, the incidence of
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50 conversion to OC after LC in all hospitals in England from 2005 to 2006 has been examined
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52 using Hospital Episode Statistics and resulted 4.6% for elective procedures and 9.4% for
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3 emergency procedures) (34). In USA, a set of indicators (Patient Safety Indicators (PSIs) has
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5 been introduced, validated and continuously under revision as algorithms based on the
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7 International Classification of Diseases, Ninth Revision, Clinical Modification (17). Our
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9 study contributes to the experience in using population-based linked health data and ICD-9-
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11 CM coding algorithms to compare treatment outcomes.
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16 Population-based linkage of routinely collected health data represents a precious tool to
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18 support large- scale and real-world practice evaluation by measuring specific outcomes and
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20 comparing them over time and across populations. Together with results from experimental
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22 research settings, the conclusions of research studies evaluating clinical outcomes through
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24 data linkage systems should be successfully incorporated into practice by clinicians/surgeons.
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AUTHOR'S CONTRIBUTION

All Authors participated in the study design, in defining the study protocol and methodology, in acquisition of data, in planning the analyses, in interpreting the results. M.S. performed the analyses. N.A and M.S. drafted the manuscript.

COMPETING INTERESTS STATEMENT

There is no competing interest.

DATA SHARING STATEMENT

We state that our work is an original research.

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Table 1. Study population, overall and by cholecystectomy procedure: distribution by age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of admission, comorbidities - Lazio Region, Italy, January 2007-September 2008

Patient characteristics	Laparoscopic cholecystectomy		Open cholecystectomy		Total		
	No.	%	No.	%	No.	%	
Total	11.752	86,1	1.899	13,9	13.651	100,0	
Age (years)							
	< 70	9.913	84,4	1.162	61,2	11.075	81,1
	70 - 79	1.543	13,1	485	25,5	2.028	14,9
	≥ 80	296	2,5	252	13,3	548	4,0
Gender							
	Men	4.349	37,0	979	51,6	5.328	39,0
	Women	7.403	63,0	920	48,4	8.323	61,0
Severity of cholelithiasis							
	Low	4.767	40,6	470	24,7	5.237	38,4
	Moderate	6.473	55,1	1.210	63,7	7.683	56,3
	High	512	4,4	219	11,5	731	5,4
Previous upper abdominal surgery							
	No	11.714	99,7	1.867	98,3	13.581	99,5
	Yes	38	0,3	32	1,7	70	0,5
Type of admission							
	Elective	8.690	73,9	903	47,6	9.593	70,3
	Emergency	3.062	26,1	996	52,4	4.058	29,7
Comorbidities (presence of the condition)							
	Cancer	232	2,0	75	3,9	307	2,2
	Diabetes	268	2,3	100	5,3	368	2,7
	Obesity	115	1,0	25	1,3	140	1,0
	Blood disease	146	1,2	62	3,3	208	1,5
	Hypertension	842	7,2	247	13,0	1.089	8,0
	Ischemic heart disease	246	2,1	107	5,6	353	2,6
	Past coronary revascularization	63	0,5	22	1,2	85	0,6
	Heart failure	47	0,4	41	2,2	88	0,6
	Other heart disease	158	1,3	76	4,0	234	1,7
	Conduction disorder or dysrhythmia	250	2,1	95	5,0	345	2,5
	Cerebrovascular disease	146	1,2	74	3,9	220	1,6
	Vascular disease	91	0,8	38	2,0	129	0,9
	COPD or respiratory failure	189	1,6	84	4,4	273	2,0
	Chronic nephropathy	68	0,6	46	2,4	114	0,8
	Chronic disease of the liver or pancreas	219	1,9	70	3,7	289	2,1

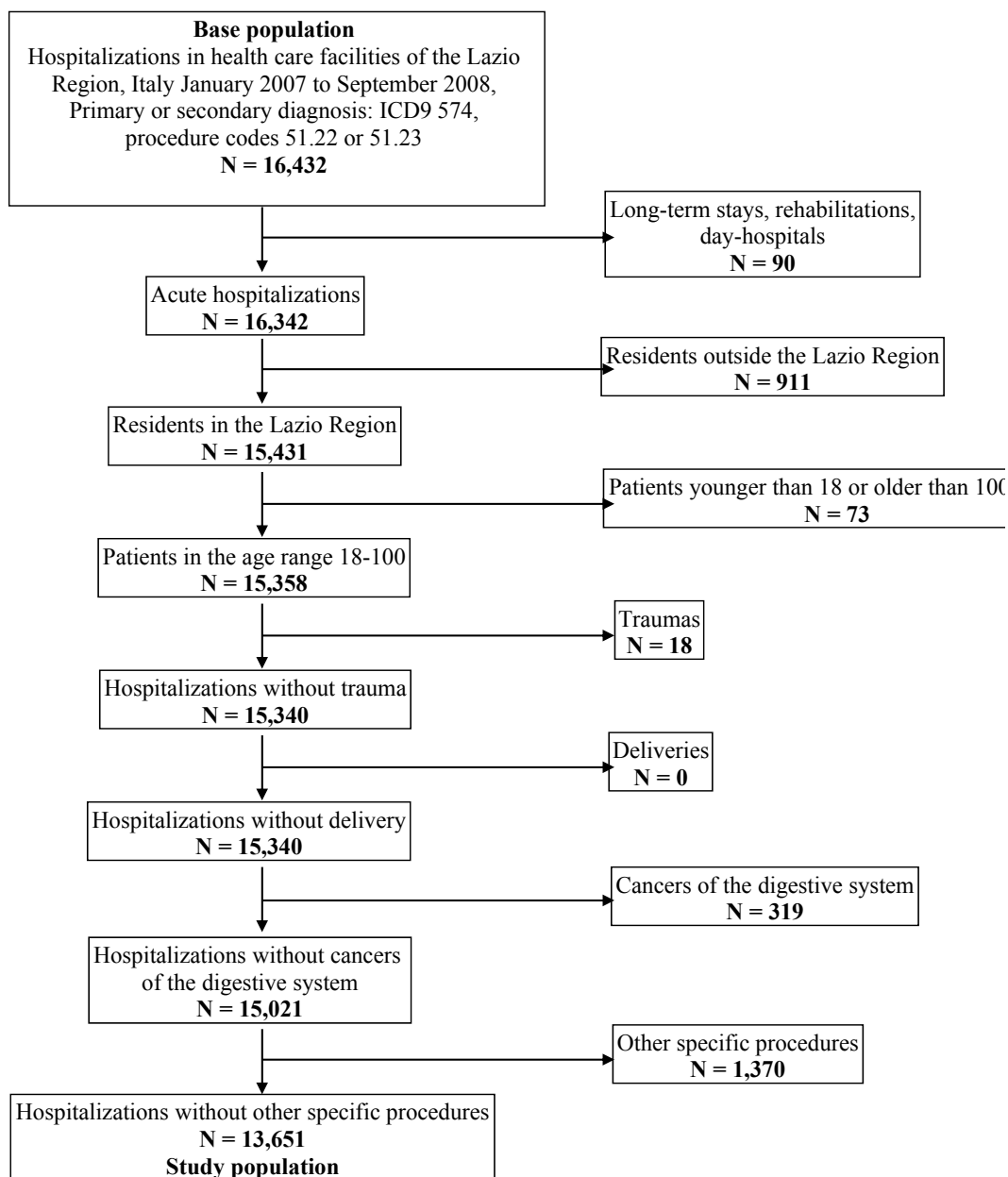
Table 2. Factors related to the incidence of 30-day complications after cholecystectomy. OR crude and adjusted, p-values - Lazio Region, Italy, January 2007-September 2008 (N = 13,651)

Patient characteristics	30-day surgical-related complications (N=278, 2.0%)					30-day systemic complications (N=280, 2.1%)					
	%	OR _{crude}	p	OR _{adj}	p	%	OR _{crude}	p	OR _{adj}	p	
Age (years)											
	< 70	1,8	1,00	-	1,00	-	1,5	1,00	-	1,00	-
	70 - 79	2,9	1,62	0,001	1,36	0,048	3,9	2,68	0,000	2,01	0,000
	≥ 80	3,3	1,84	0,015	1,21	0,475	7,1	5,13	0,000	2,79	0,000
Gender											
	Men	2,5	1,00	-	1,00	-	2,6	1,00	-	1,00	-
	Women	1,7	0,69	0,002	0,75	0,022	1,7	0,66	0,001	0,80	0,070
Severity of cholelithiasis											
	Low	1,9	1,00	-	1,00	-	1,2	1,00	-	1,00	-
	Moderate	2,0	1,08	0,538	0,96	0,733	2,2	1,84	0,000	1,55	0,004
	High	3,7	2,03	0,001	1,43	0,122	6,2	5,30	0,000	3,40	0,000
Previous upper abdominal surgery											
	No	2,0	1,00	-	1,00	-	2,0	1,00	-	1,00	-
	Yes	5,7	2,94	0,037	2,29	0,119	4,3	2,15	0,197	1,72	0,376
Type of admission											
	Elective	1,6	1,00	-	1,00	-	1,5	1,00	-	1,00	-
	Emergency	3,0	1,85	0,000	1,66	0,000	3,4	2,34	0,000	1,64	0,000
Comorbidities (presence of the condition)											
	Cancer	2,6	1,30	0,476	-	-	3,6	1,81	0,059	-	-
	Diabetes	3,3	1,65	0,095	-	-	4,4	2,24	0,002	-	-
	Obesity	5,0	2,57	0,016	2,35	0,034	4,3	2,16	0,067	-	-
	Blood disease	5,8	3,03	0,000	2,09	0,022	7,7	4,16	0,000	1,96	0,024
	Hypertension	2,9	1,46	0,050	-	-	4,0	2,20	0,000	-	-
	Ischemic heart disease	2,8	1,42	0,286	-	-	7,4	4,08	0,000	1,74	0,020
	Past coronary revascularization	2,4	1,16	0,836	-	-	9,4	5,08	0,000	-	-
	Heart failure	2,3	1,12	0,875	-	-	4,6	2,29	0,107	-	-
	Other heart disease	3,4	1,72	0,136	-	-	6,8	3,66	0,000	-	-
	Conduction disorder or dysrhythmia	4,1	2,09	0,008	-	-	7,0	3,81	0,000	1,73	0,025
	Cerebrovascular disease	5,9	3,12	0,000	1,98	0,025	7,7	4,19	0,000	-	-
	Vascular disease	0,8	0,37	0,328	-	-	8,5	4,59	0,000	-	-
	COPD or respiratory failure	2,6	1,27	0,534	-	-	7,7	4,22	0,000	2,02	0,006
	Chronic nephropathy	9,7	5,31	0,000	3,24	0,001	10,5	5,82	0,000	2,27	0,018
	Chronic disease of the liver or pancreas	3,5	1,75	0,087	-	-	4,8	2,51	0,001	1,97	0,020

Table 3. Association between type of cholecystectomy and 30-day complications: OR and p-values from crude model, risk-adjusted model, and models with interaction with age group, severity of cholelithiasis, previous upper abdominal surgery and type of admission - Lazio Region, Italy, January 2007 - September 2008

	30-day surgical-related complications (N=278, %=2.0)					30-day systemic complications (N=280, %=2.1)				
	%	OR _{crude}	p	OR _{adj}	p	%	OR _{crude}	p	OR _{adj}	p
Open cholecystectomy	3,9	1,00	-	1,00	-	5,2	1,00	-	1,00	-
Laparoscopic cholecystectomy	1,7	0,44	0,000	0,60	0,001	1,6	0,29	0,000	0,52	0,000
<i>Stratified results by each category</i>										
Age (years)										
< 70	1,8	0,49	0,000	0,62	0,012	1,5	0,34	0,000	0,47	0,000
70 - 79	2,9	0,45	0,003	0,57	0,043	3,9	0,35	0,000	0,47	0,002
≥ 80	3,3	0,41	0,082	0,51	0,184	7,1	0,71	0,309	0,99	0,975
Severity of cholelithiasis										
Low	1,9	0,37	0,000	0,46	0,003	1,2	0,29	0,000	0,43	0,005
Moderate	2,0	0,58	0,005	0,78	0,224	2,2	0,34	0,000	0,55	0,001
High	3,7	0,24	0,000	0,30	0,004	6,2	0,38	0,002	0,56	0,071
Previous upper abdominal surgery										
No	2,0	0,47	0,000	0,60	0,001	2,0	0,29	0,000	0,52	0,000
Yes	5,7	0,26	0,256	0,36	0,388	4,3	0,41	0,470	0,86	0,905
Type of admission										
Elective	1,6	0,31	0,000	0,37	0,000	1,5	0,33	0,000	0,48	0,000
Emergency	3,0	0,76	0,178	0,94	0,764	3,4	0,35	0,000	0,56	0,002

Figure 1. Selection of the study population



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For peer review only

SUPPLEMENTARY DATA

DETAILED METHODS

PART 1 - Cohort selection

Source of data: Hospital Information System (HIS)

Inclusion criteria

All hospital admissions with a primary or secondary contributing diagnosis of cholelithiasis (International Classification of Diseases 9th Revision, Clinical Modification - ICD9-CM = 574) and a procedure code of cholecystectomy (ICD9-CM 51.22, 51.23), occurred in private and public hospitals of the Lazio Region between January 2007 and September 2008 were included, for a total of 16,432 cases. The final population, after sequential exclusions, consisted of 13,651 subjects.

Exclusion criteria

- long-term hospitalizations, rehabilitations and day-hospitals
- patients residents outside the Lazio Region
- subjects younger than 18 or older than 100 years old
- hospitalizations for delivery (MDC 14)
- hospitalizations for any type of trauma (ICD-9-CM codes ICD-9-CM 800-897)
- hospitalizations with diagnoses of cancer of the digestive system (ICD-9-CM codes 150-159)
- hospitalizations with other abdominal surgical procedures, as follows:

ICD-9-CM code Description

Stomach

43.5 Partial gastrectomy with anastomosis to esophagus

43.6 Partial gastrectomy with anastomosis to duodenum

43.7 Partial gastrectomy with anastomosis to jejunum

43.8 Other partial gastrectomy

43.9 Total gastrectomy

44.31 High gastric bypass

44.39 Other gastroenterostomy

44.40 Suture of peptic ulcer, not otherwise specified

44.41 Suture of gastric ulcer site

44.42 Suture of duodenal ulcer site

44.5 Revision of gastric anastomosis

44.61 Suture of laceration of stomach

44.63 Closure of other gastric fistula

44.64 Gastropexy

44.65 Esophagogastroplasty

44.69 Other

Small intestine

45.31 Other local excision of lesion of duodenum

45.32 Other destruction of lesion of duodenum

45.33 Local excision of lesion or tissue of small intestine, except duodenum

45.34 Other destruction of lesion of small intestine, except duodenum

45.50 Isolation of intestinal segment, not otherwise specified

45.51 Isolation of segment of small intestine

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3 45.6 *Other excision of small intestine*
4 45.9 *Intestinal anastomosis*
5 45.91 *Small-to-small intestinal anastomosis*
6 45.92 *Anastomosis of small intestine to rectal stump*
7 45.93 *Other small-to-large intestinal anastomosis*
8 46.01 *Exteriorization of small intestine*
9 46.02 *Resection of exteriorized segment of small intestine*
10 46.60 *Fixation of intestine, not otherwise specified*
11 46.61 *Fixation of small intestine to abdominal wall*
12 46.62 *Other fixation of small intestine*
13 46.71 *Suture of laceration of duodenum*
14 46.72 *Closure of fistula of duodenum*
15 46.73 *Suture of laceration of small intestine, except duodenum*
16 46.74 *Closure of fistula of small intestine, except duodenum*
17 46.80 *Intra-abdominal manipulation of intestine, not otherwise specified*
18 46.81 *Intra-abdominal manipulation of small intestine*
19 46.93 *Revision of anastomosis of small intestine*
20 46.97 *Transplant of intestine*
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Liver

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24
25 50.2 *Local excision or destruction of liver tissue or lesion*
26 50.3 *Lobectomy of liver*
27 50.4 *Total hepatectomy*
28 50.5 *Liver transplant*
29 50.6 *Repair of liver*
30

Pancreas

31
32
33 52.22 *Other excision or destruction of lesion or tissue of pancreas or pancreatic duct*
34 52.3 *Marsupialization of pancreatic cyst*
35 52.4 *Internal drainage of pancreatic cyst*
36 52.5 *Partial pancreatectomy*
37 52.6 *Total pancreatectomy*
38 52.7 *Radical pancreaticoduodenectomy*
39 52.8 *Transplant of pancreas*
40 52.95 *Other repair of pancreas*
41 52.96 *Anastomosis of pancreas*
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Abdominal Hernia

44
45 53.4 *Repair of umbilical hernia*
46 53.5 *Repair of other hernia of anterior abdominal wall (without graft or prosthesis)*
47 53.6 *Repair of other hernia of anterior abdominal wall with graft or prosthesis*
48 53.7 *Repair of diaphragmatic hernia, abdominal approach*
49

Peritoneum

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51 54.4 *Excision or destruction of peritoneal tissue*
52 54.5 *Lysis of peritoneal adhesions*
53 54.6 *Suture of abdominal wall and peritoneum*
54 54.7 *Other repair of abdominal wall and peritoneum*
55
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Large intestine

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58 45.41 *Excision of lesion or tissue of large intestine*
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3 45.49 *Other destruction of lesion of large intestine*
4 45.7 *Open and other partial excision of large intestine*
5 45.8 *Total intra-abdominal colectomy*
6 45.94 *Large-to-large intestinal anastomosis*
7 46.03 *Exteriorization of large intestine*
8 46.04 *Resection of exteriorized segment of large intestine*
9 46.63 *Fixation of large intestine to abdominal wall*
10 46.64 *Other fixation of large intestine*
11 46.75 *Suture of laceration of large intestine*
12 46.76 *Closure of fistula of large intestine*
13 46.79 *Other repair of intestine*
14

15
16 **Other surgery**

17 55.4 *Partial nephrectomy*
18 55.5 *Complete nephrectomy*
19 56.2 *Ureterotomy*
20 56.4 *Ureterectomy*
21 57.1 *Cystotomy and cystostomy*
22 57.6 *Partial cystectomy*
23 57.7 *Total cystectomy*
24 65.3 *Unilateral oophorectomy*
25 65.4 *Unilateral salpingo-oophorectomy*
26 65.5 *Bilateral oophorectomy*
27 65.6 *Bilateral salpingo-oophorectomy*
28 66.4 *Total unilateral salpingectomy*
29 66.5 *Total bilateral salpingectomy*
30 68.3 *Subtotal abdominal hysterectomy*
31 68.4 *Total abdominal hysterectomy*
32 68.6 *Radical abdominal hysterectomy*
33 68.8 *Pelvic evisceration*
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40 **PART 2 - Codes to describe severity of cholelithiasis**

41 **1 - Cholelithiasis of the biliary tract without complications**

42
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44 574.20 *Calculus of gallbladder without mention of cholecystitis*
45 574.50 *Calculus of bile duct without mention of cholecystitis*
46 574.90 *Calculus of gallbladder and bile duct without cholecystitis*
47

48 **2. Cholelithiasis of the biliary tract with cholecystitis (without obstruction)**

49
50
51 574.10 *Calculus of gallbladder with other cholecystitis*
52 574.40 *Calculus of bile duct with other cholecystitis*
53 574.70 *Calculus of gallbladder and bile duct with other cholecystitis*
54

55 575.1 *Other cholecystitis AND*

56 574.20 *Calculus of gallbladder without mention of cholecystitis or*
57 574.50 *Calculus of bile duct without mention of cholecystitis or*
58 574.90 *Calculus of gallbladder and bile duct without cholecystitis*
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3 574.00 *Calculus of gallbladder with acute cholecystitis*
4 574.30 *Calculus of bile duct with acute cholecystitis*
5 574.60 *Calculus of gallbladder and bile duct with acute cholecystitis*
6 574.80 *Calculus of gallbladder and bile duct with acute and chronic cholecystitis*
7

8 575.0 *Acute cholecystitis AND*

9
10 574.20 *Calculus of gallbladder without mention of cholecystitis or*
11 574.50 *Calculus of bile duct without mention of cholecystitis or*
12 574.90 *Calculus of gallbladder and bile duct without cholecystitis*

13 576.1 *Cholangitis AND*

14 574.20 *Calculus of gallbladder without mention of cholecystitis or*
15 574.50 *Calculus of bile duct without mention of cholecystitis or*
16 574.90 *Calculus of gallbladder and bile duct without cholecystitis*
17

18 **3. Cholelithiasis of the biliary tract with obstruction (without cholecystitis)**

19 574.21 *Calculus of gallbladder without mention of cholecystitis*
20 574.51 *Calculus of bile duct without mention of cholecystitis*
21 574.91 *Calculus of gallbladder and bile duct without cholecystitis*
22

23 575.2 *Obstruction of gallbladder AND*

24 574.20 *Calculus of gallbladder without mention of cholecystitis or*
25 574.50 *Calculus of bile duct without mention of cholecystitis or*
26 574.90 *Calculus of gallbladder and bile duct without cholecystitis*
27

28 576.2 *Obstruction of bile duct AND*

29 574.20 *Calculus of gallbladder without mention of cholecystitis or*
30 574.50 *Calculus of bile duct without mention of cholecystitis or*
31 574.90 *Calculus of gallbladder and bile duct without cholecystitis*
32

33 575.3 *Hydrops of gallbladder*
34

35 **3. Cholelithiasis of the biliary tract with both obstruction and cholecystitis**

36
37
38 574.01 *Calculus of gallbladder with acute cholecystitis*
39 574.11 *Calculus of gallbladder with other cholecystitis*
40 574.31 *Calculus of bile duct with acute cholecystitis*
41 574.41 *Calculus of bile duct with other cholecystitis*
42 574.61 *Calculus of gallbladder and bile duct with acute cholecystitis*
43 574.71 *Calculus of gallbladder and bile duct with other cholecystitis*
44 574.81 *Calculus of gallbladder and bile duct with acute and chronic cholecystitis*
45
46

47 575.2 *Obstruction of gallbladder AND*

48 574.00 *Calculus of gallbladder with acute cholecystitis*
49 575.0 *Acute cholecystitis AND 574.20 Calculus of gallbladder without mention of*
50 *cholecystitis*
51 575.1 *Other cholecystitis AND 574.20 Calculus of gallbladder without mention of*
52 *cholecystitis*
53 574.30 *Calculus of bile duct with acute cholecystitis*
54 575.0 *Acute cholecystitis AND 574.50 Calculus of bile duct without mention of cholecystitis*
55 575.1 *Other cholecystitis AND 574.50 Calculus of bile duct without mention of cholecystitis*
56 574.60 *Calculus of gallbladder and bile duct with acute cholecystitis*
57 574.70 *Calculus of gallbladder and bile duct with other cholecystitis*
58
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3 574.80 *Calculus of gallbladder and bile duct with acute and chronic cholecystitis*
4
5

6 576.2 *Obstruction of bile duct AND*

7 574.00 *Calculus of gallbladder with acute cholecystitis*

8 575.0 *Acute cholecystitis AND 574.20 Calculus of gallbladder without mention of*
9 *cholecystitis*

10 575.1 *Other cholecystitis AND 574.20 Calculus of gallbladder without mention of*
11 *cholecystitis*

12 574.30 *Calculus of bile duct with acute cholecystitis*

13 575.0 *Acute cholecystitis AND 574.50 Calculus of bile duct without mention of cholecystitis*

14 575.1 *Other cholecystitis AND 574.50 Calculus of bile duct without mention of cholecystitis*

15 574.60 *Calculus of gallbladder and bile duct with acute cholecystitis*

16 574.70 *Calculus of gallbladder and bile duct with other cholecystitis*

17 574.80 *Calculus of gallbladder and bile duct with acute and chronic cholecystitis*
18
19
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21
22

23 **PART 3 - Codes to describe previous upper abdominal surgery**

24
25 Codes in the index admission – post procedural states

26 stomach V44.1, V45.75, V55.1

27 intestine V44.2, V44.4, V45.3, V45.72, V53.5, V55.2, V55.4, V42.84

28 liver V42.7

29 pancreas 42.83
30
31

32 Codes in the previous 2-year- hospitalizations

33
34 **Stomach**

35 43.5 *Partial gastrectomy with anastomosis to esophagus*

36 43.6 *Partial gastrectomy with anastomosis to duodenum*

37 43.7 *Partial gastrectomy with anastomosis to jejunum*

38 43.8 *Other partial gastrectomy*

39 43.9 *Total gastrectomy*

40 44.31 *High gastric bypass*

41 44.39 *Other gastroenterostomy*

42 44.40 *Suture of peptic ulcer, not otherwise specified*

43 44.41 *Suture of gastric ulcer site*

44 44.42 *Suture of duodenal ulcer site*

45 44.5 *Revision of gastric anastomosis*

46 44.61 *Suture of laceration of stomach*

47 44.63 *Closure of other gastric fistula*

48 44.64 *Gastropexy*

49 44.65 *Esophagogastroplasty*

50 44.69 *Other*
51
52
53

54 **Small intestine**

55 45.31 *Other local excision of lesion of duodenum*

56 45.32 *Other destruction of lesion of duodenum*

57 45.33 *Local excision of lesion or tissue of small intestine, except duodenum*

58 45.34 *Other destruction of lesion of small intestine, except duodenum*
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1
2
3 45.50 Isolation of intestinal segment, not otherwise specified
4 45.51 Isolation of segment of small intestine
5 45.6 Other excision of small intestine
6 45.9 Intestinal anastomosis
7 45.91 Small-to-small intestinal anastomosis
8 45.92 Anastomosis of small intestine to rectal stump
9 45.93 Other small-to-large intestinal anastomosis
10 46.01 Exteriorization of small intestine
11 46.02 Resection of exteriorized segment of small intestine
12 46.60 Fixation of intestine, not otherwise specified
13 46.61 Fixation of small intestine to abdominal wall
14 46.62 Other fixation of small intestine
15 46.71 Suture of laceration of duodenum
16 46.72 Closure of fistula of duodenum
17 46.73 Suture of laceration of small intestine, except duodenum
18 46.74 Closure of fistula of small intestine, except duodenum
19 46.80 Intra-abdominal manipulation of intestine, not otherwise specified
20 46.81 Intra-abdominal manipulation of small intestine
21 46.93 Revision of anastomosis of small intestine
22 46.97 Transplant of intestine
23
24
25

Liver

26
27 50.2 Local excision or destruction of liver tissue or lesion
28 50.3 Lobectomy of liver
29 50.4 Total hepatectomy
30 50.5 Liver transplant
31 50.6 Repair of liver
32
33

Pancreas

34
35 52.22 Other excision or destruction of lesion or tissue of pancreas or pancreatic duct
36 52.3 Marsupialization of pancreatic cyst
37 52.4 Internal drainage of pancreatic cyst
38 52.5 Partial pancreatectomy
39 52.6 Total pancreatectomy
40 52.7 Radical pancreaticoduodenectomy
41 52.8 Transplant of pancreas
42 52.95 Other repair of pancreas
43 52.96 Anastomosis of pancreas
44
45

Abdominal Hernia

46
47 53.4 Repair of umbilical hernia
48 53.5 Repair of other hernia of anterior abdominal wall (without graft or prosthesis)
49 53.6 Repair of other hernia of anterior abdominal wall with graft or prosthesis
50 53.7 Repair of diaphragmatic hernia, abdominal approach
51
52

Peritoneum

53
54 54.4 Excision or destruction of peritoneal tissue
55 54.5 Lysis of peritoneal adhesions
56 54.6 Suture of abdominal wall and peritoneum
57 54.7 Other repair of abdominal wall and peritoneum
58
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3 Large intestine

4 45.41 Excision of lesion or tissue of large intestine
5 45.49 Other destruction of lesion of large intestine
6 45.7 Open and other partial excision of large intestine
7 45.8 Total intra-abdominal colectomy
8 45.94 Large-to-large intestinal anastomosis
9 46.03 Exteriorization of large intestine
10 46.04 Resection of exteriorized segment of large intestine
11 46.63 Fixation of large intestine to abdominal wall
12 46.64 Other fixation of large intestine
13 46.75 Suture of laceration of large intestine
14 46.76 Closure of fistula of large intestine
15 46.79 Other repair of intestine
16
17

18 Other surgery

19 55.4 Partial nephrectomy
20 55.5 Complete nephrectomy
21 56.2 Ureterotomy
22 56.4 Ureterectomy
23 57.1 Cystotomy and cystostomy
24 57.6 Partial cystectomy
25 57.7 Total cystectomy
26 65.3 Unilateral oophorectomy
27 65.4 Unilateral salpingo-oophorectomy
28 65.5 Bilateral oophorectomy
29 65.6 Bilateral salpingo-oophorectomy
30 66.4 Total unilateral salpingectomy
31 66.5 Total bilateral salpingectomy
32 68.3 Subtotal abdominal hysterectomy
33 68.4 Total abdominal hysterectomy
34 68.6 Radical abdominal hysterectomy
35 68.8 Pelvic evisceration
36
37
38
39

40 **PART 4 - Codes to describe coexisting conditions**

41 On the basis of previous 2-year hospitalizations (following a validated coding algorithm – enhanced
42 Elixhauser AHRQ-Web-ICD-9-CM - see reference n. 17 cited in the text).
43
44

45 diabetes 250.xx; hypertension 401-405; obesity 280.0, ischemic disease 410-414, 429.7, previous
46 revascularization V45.81, V45.82, procedures 36.0, 36.1, heart failure 428, other cardiac disease
47 093.2, 391, 393-398, 420-425, 429, 745, 746.3-646.6, V15.1, V42.2, V43.2, V43.3, V45.0
48 arrhythmia / conduction disorders 426-427, cerebrovascular disease 430-438, vascular disease 440-
49 448, 557, hematologic disorders 280-285, 286, 287.1, 287.3-287.5, 288, 289, chronic respiratory
50 disease 490-496, 518.81, 518.82, chronic liver disease / pancreas 571, 572, 577.1, 577.9, chronic
51 renal disease 582-583, 585-588, V42.0, V45.1m V56, cancer 140-208.9
52
53
54
55

56 **PART 5 - Codes to describe outcomes**

57
58 **A) Surgical-related complications (within 30 day after the surgery)**
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60

in the index or in the subsequent hospitalizations (excluding hospitalizations for trauma ICD-9-CM 800-897) and delivery (MDC 14)

at least one of the following:

- 998.1 Hemorrhage or hematoma or seroma complicating a procedure
- 998.2 Accidental puncture or laceration during a procedure
- 998.3 Disruption of wound
- 998.4 Foreign body accidentally left during a procedure
- 998.5 Postoperative infection
- 998.6 Persistent postoperative fistula
- 998.7 Acute reaction to foreign substance accidentally left during a procedure
- 998.81 Emphysema (subcutaneous) (surgical) resulting from a procedure
- 998.83 Non-healing surgical wound
- 998.89 Other specified complications
- 997.4 Digestive system complications
- 998.9 Unspecified complication of procedure, not elsewhere classified

Only in the subsequent hospitalizations

at least one of the following:

- 567 Peritonitis and retroperitoneal infections
- 575.4 Perforation of gallbladder
- 575.5 Fistula of gallbladder
- 576.0 Postcholecystectomy syndrome
- 576.3 Perforation of bile duct
- 576.4 Fistula of bile duct
- 570 Acute and subacute necrosis of liver
- 789.0 Abdominal pain

B) Systemic complications (within 30 day after the surgery)

in the index or in the subsequent hospitalizations (excluding hospitalizations for trauma ICD-9-CM 800-897) and delivery (MDC 14)

at least one of the following:

- 997.0 Nervous system complications
- 997.1 Cardiac complications
- 997.3 Respiratory complications
- 998.0 Postoperative shock
- 410 Acute myocardial infarction
- 415.1 Pulmonary embolism and infarction
- 431 Intracerebral hemorrhage
- 433.x1 Occlusion and stenosis of precerebral arteries with infarction
- 434.x1 Occlusion of cerebral arteries with infarction
- 436 Acute, but ill-defined, cerebrovascular disease
- 480-486 Pneumonia
- 513.0 Abscess of lung
- 518.4 Acute edema of lung, unspecified
- 518.5 Pulmonary insufficiency following trauma and surgery
- 785.5 Shock without mention of trauma

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788.2 Retention of urine

Only in the subsequent hospitalizations
038 Septicemia

For peer review only



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

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4 **based cohort study in Italy.**
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51

52 <http://www.epidemiologia.lazio.it/prevale11/>
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3 **Thirty-day complications after laparoscopic or open cholecystectomy: a population-**
4 **based cohort study in Italy.**
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8
9 **Abstract**

10
11 **Objective**

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14 The objective of the study is to evaluate short-term complications after laparoscopic (LC) or
15 open cholecystectomy (OC) in patients with gallstones by using linked hospital discharge
16 data.
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21 **Design**

22
23 Population-based cohort study.
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26 **Setting**

27
28 Data were obtained from the Regional Hospital Discharge Registry Lazio Region in Central
29 Italy (around 5 million inhabitants) in 2007-2008.
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32 **Participants**

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34 All patients admitted to hospitals of Lazio with symptomatic gallstones (ICD9-CM = 574)
35 who underwent LC (ICD9-CM 51.23) or OC (ICD9-CM 51.22).
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39 **Outcome measures**

40
41 1)“30-day surgical-related complications” defined as any complication of the biliary tract
42 (including post-operative infection, hemorrhage or hematoma or seroma complicating a
43 procedure, persistent postoperative fistula, perforation of bile duct, disruption of wound); 2)
44
45
46 “30-day systemic complications” defined as any complications of other organs (including
47 sepsis, infections from other organs, major cardiovascular events and selected adverse
48 events).
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54 **Results**
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3 13,651 patients were included; 86.1% had LC, 13.9% OC. 2.0% experienced surgical-related
4 complications (SRC), 2.1% systemic complications (SC). The Odds Ratio (OR) of
5 complications after LC versus OC was 0.60 ($p<0.001$) for SRC and 0.52 ($p<0.001$) for SC. As
6
7 regards SRC, the advantage of LC was consistent across age categories, severity of gallstones
8 and previous upper abdominal surgery, while there was no advantage among people with
9 emergency admission (OR=0.94, $p = 0.764$). For SC, no significant advantage of LC was seen
10 among very old people (OR=0.99, $p=0.975$) and among those with previous upper abdominal
11 surgery (OR=0.86, $p=0.905$).
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20 **Conclusions**

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22 This large observational study confirms that LC is more effective than OC with respect to 30-
23 day complications. Population-based linkage of administrative datasets can enlarge evidence
24 of treatment benefits in clinical practice.
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34 **Key words:** administrative data, cohort study, effectiveness, gallstones, hospital discharge
35 data, laparoscopic cholecystectomy, open cholecystectomy, outcomes, population-based,
36 post-operative complications.
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Article summary

Article focus

-The advantage of laparoscopic cholecystectomy (LC) approach for the treatment of gallstone versus open surgery (OC) has been shown from RCTs and observational studies.

-The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments.

-We compared laparoscopic and open cholecystectomy in term of 30-day complications using routinely collected databases in Lazio Region (Italy).

Key messages

-This population-based study contributes to enlarge the evidence on effectiveness of LC in a real-life setting.

-As regards surgical-related complications, the advantage of LC was consistent across age categories, severity of gallstones and previous upper abdominal surgery, while there was no advantage among people with emergency admission.

-For systemic complications, no significant advantage of LC was seen among very old people and among those with previous upper abdominal surgery.

Strengths and limitations

-Population-based design, 30-day outcomes, large numbers and robustness of analytic procedures are the main strengths.

-It contributes to the debate on the complex methodology to estimated risk of adverse events after surgery using secondary databases to monitor quality of care.

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-The use of ICD-9-CM codes in the definition of severity of disease presentation and of complications is a major limit.

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Introduction

Comparative effectiveness research is becoming central to monitor real-life impact of treatments and support public health decisions (1, 2). Although the basic concept of comparing therapies is not new, over the last few years many initiatives have been implemented in several countries to provide large-scale evidence on benefits and harms of different treatments (3-5). The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments. They include hospital in-patients records, birth and death registrations, outpatient care records, dispensed pharmacy drugs (6-9).

In the Lazio Region (around 5.000.000 inhabitants) the P.Re.Val.E. Project (*Regional Program for Assessing the Outcomes of Health-care Interventions*) was launched in 2005. Its aims are: to measure the quality of health care provided in the Lazio Region, to describe variability of care provision across institutions and populations and to compare effectiveness of treatments for different medical and surgical conditions (10,11). Over 60 outcomes indicators are calculated based on data obtained from record-linkage procedures of different health systems. The results are periodically updated and publicly disseminated with discussion on critical methodological points.

Cholecystectomy is one of the most common abdominal surgical procedures in developed countries. Since its introduction in the late '80s, laparoscopic cholecystectomy (LC) has replaced open cholecystectomy (OC) as the treatment of choice for symptomatic gallstones (12, 13). Beneficial effects of LC have been demonstrated in studies showing the advantages from real-life settings using secondary databases (9,14-19). In the present study we aimed at developing a methodology to measure short-term complications after LC or OC using large administrative databases on behalf of the P.Re.Val.E. Secondly, we tested the hypothesis that

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3 the advantages of LC versus OC could vary according to age and clinical patients'
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5 characteristics.
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11 12 13 14 **Methods**

15 16 Source of data

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18 Data was derived from the Lazio Hospital Information System (HIS), which provides
19
20 information on patients' demographic data (gender, age, place of birth, place of residence),
21
22 admission and discharge dates, discharge diagnoses (up to 6) and medical procedures or
23
24 surgical interventions ((up to 6) according to the International Classification of disease, Ninth
25
26 Revision, Clinical Modification (ICD-9-CM), status at discharge (alive, dead, transferred to
27
28 another hospital), ward(s) of stay, date(s) of in-hospital transfer, and a regional code
29
30 corresponding to the admitting facility for patients discharged from all public and private
31
32 hospital of the Lazio Region (5.759.839 inhabitants).
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39 Study population

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41 All hospital admissions with a primary or secondary diagnosis of gallstones (International
42
43 Classification of Diseases 9th Revision, Clinical Modification - ICD9-CM = 574) and a
44
45 procedure code of cholecystectomy (ICD9-CM 51.22, 51.23), occurred in private and public
46
47 hospitals of the Lazio Region between January 2007 and September 2008 were included, for a
48
49 total of 16,432 cases (age 18+ years). We a priori decided not to include codes for partial
50
51 cholecystectomy (ICD-9-CM 51.21 and 51.24) to increase the specificity of our exposure.
52
53 Information was retrieved from the HIS. In order to increase the case specificity, several
54
55 exclusion criteria were applied including long-term hospitalizations, rehabilitations, day-
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3 hospitals, hospitalizations for delivery or trauma or cancer, hospitalizations with abdominal
4
5 surgical procedures other than cholecystectomy. The final population consisted of 13,651
6
7 subjects (**Figure 1**). See the online **Supplementary Data** (Part 1) for details on the exclusion
8
9 criteria and ICD9-CM codes.
10

11 12 13 14 Patient-level risk factors

15
16 The following characteristics were considered for each patient: Age (<70; 70-79; >=80 years
17
18 old); Gender; Severity of gallstones: it was classified as *low* (not-complicated), *moderate*
19
20 (presence of cholecystitis or biliary tract obstruction), and *high* (presence of both
21
22 inflammation and obstruction of the biliary tract); Previous upper abdominal surgery (based
23
24 on previous 2-year hospitalizations); Comorbidities (based on previous 2-year
25
26 hospitalizations) following validated algorithms (20,21); Type of admission: either *elective* or
27
28 *emergency*. See the online **Supplementary Data** (Part 2-4) for details on the ICD-9-CM
29
30 codes. The choice of *cut off* for age category was based on previous studies to distinguish
31
32 adult and old people (22-24).
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36 Outcomes

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38 We identified various complications within 30-days after the intervention and grouped them
39
40 in two categories: 1) “*30-day surgical-related complications*” defined as any complication of
41
42 the biliary tract (including post-operative infection, hemorrhage or hematoma or seroma
43
44 complicating a procedure, persistent postoperative fistula, perforation of bile duct, disruption
45
46 of wound ()); 2) “*30-day systemic complications*” defined as any complications of other organs
47
48 (including sepsis, infections from other organs, major cardiovascular events and
49
50 selected adverse events). The complete list of complications with ICD-9-CM codes is
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52 reported in the online **Supplementary Data** (Part 5). Among the various complications we
53
54 included some conditions reported in the list of Patient Safety Indicators recently developed
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3 by the Agency for Health Care Research and Quality, while other items were specifically
4 created on the basis of scientific literature on digestive surgery (14-19,25,26). Depending on
5 the type of complication, some ICD9-CM codes were searched in both the index admission
6 and the following ones in the 30-day period after the surgery, others were searched only in
7 later hospitalizations. For example, peritonitis or acute pancreatitis was not counted as
8 complications when reported in the index admission. See the online **Supplementary Data**
9 (Part 5) for details on the ICD9-CM codes. In the case of a subsequent hospitalization
10 occurred out of the study area (for example, in a region other than Lazio), we obtained
11 information through record linkage procedure between hospital information systems. Because
12 of the short follow up time, this happened in a minimal proportion of cases (0.1%). The
13 outcome variables were: “30-day surgical-related complications” and “30-day systemic
14 complications”; they were coded “1” if at least one of the complications within the group was
15 present and “0” if none was recorded.
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34 Type of cholecystectomy

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36 As exposure variable we defined “*type of cholecystectomy*” (laparoscopic cholecystectomy,
37 LC vs. open cholecystectomy, OC). In the case of ICD-9-CM codes for both LC and OC
38 (5%), the patient was considered exposed to the open surgical procedure. We could not use
39 the specific ICD-9-code for a case converted from LC to OC (ICD-9-CM code V 64.41)
40 because it was highly under-reported in our Region in the study period.
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51 Statistical analysis

52 Multiple logistic regression models were fitted to estimate the relative risk of 30-day
53 complications (either “surgical-related” or “systemic”) after LC versus OC, adjusting for
54 demographical and clinical risk factors. The two outcome variables were analysed separately.
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3 The predictive model was made of two sets of predictors: 1) variables “a priori” chosen as
4 confounders (age, gender, severity of gallstones, previous upper abdominal surgery, and type
5 of admission); 2) variables empirically tested (comorbidities) which were selected using
6 iterative stepwise statistical procedures) (27). Once the “best” predictive model was identified
7 for each of the two outcome, the variable “*type of cholecystectomy*” was included, and the
8 adjusted odds ratio (OR) of LC versus open surgery was estimated, with corresponding 95%
9 confidence interval (95% CI) and p-value.
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21 In order to test the hypothesis of an effect modification by age, relative risk estimates for the
22 age groups were derived by adding an interaction term between the age group and the
23 treatment variable in the final multivariate logistic model. We obtained the OR of
24 laparoscopic vs. open surgery within each age stratum by adding the corresponding
25 interaction terms coefficients. This was accomplished by adding the coefficient from the
26 reference category and that from the age stratum of interest, and by computing the
27 corresponding standard error from the corresponding terms of the variance-covariance matrix.
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29 Similarly, effect modification was tested with regard to severity of cholelithiasis, previous
30 upper abdominal surgery and type of admission. The corresponding tests of heterogeneity of
31 the stratum-specific risk estimates were computed.
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45 Sensitivity analyses were performed. First, in order to guarantee adequate control of
46 confounding factors we identified and adjusted for all the individual factors associated with
47 the treatment, within the propensity adjustment framework (28). This procedure is a two-step
48 technique: 1. it estimates the a priori probability of exposure for each subject, based on
49 clinical and demographic characteristics; 2. it standardizes for them in the association between
50 treatment and the study outcome. The individual factors related to the exposure in the present
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3 study include age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of
4 admission, cardio-circulatory disease, cerebrovascular disease, COPD or respiratory failure,
5 chronic nephropathy, chronic disease of the liver or pancreas. Second, to take into account the
6 potential heterogeneous experience in laparoscopic surgery across different hospitals because
7 of the patients' clustering within a single institution we perform a multilevel regression model
8 with random intercepts for hospitals (29).
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18 All the statistical analyses were performed using SAS Software version 8.0 (SAS Institute,
19 Inc. SAS/STAT software).
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27 **Results**

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29 A description of the study population, overall and by cholecystectomy procedure, is presented
30 in **Table 1**. Over 80% of the patients were younger than 70 years, and moderate to high
31 severity of the gallstones was diagnosed for 61.7%. As compared with patients undergoing
32 LC, those who underwent OC were more likely to be elderly, males, with a more severe
33 baseline disease and more chronic conditions. Furthermore, they were operated in emergency
34 in most of the cases (52.4%), whereas LC was performed in elective hospitalizations much
35 more frequently (73.9%).
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47 **Table 2** reports the relationship between demographic and clinical variables and the
48 occurrence of complications. The adjusted risk of systemic complications increased with age
49 and was much higher in patients with more severe baseline gallstones, whereas no clear age or
50 severity-related differences in risk emerged with regard to surgical-related 30-day
51 complications, once other co-factors were taken into account. Women were less likely to
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3 experience both types of complications. Having had a previous intervention on the upper
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5 digestive system seemed to enhance the risk of both surgical-related and systemic
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7 complications, though results are not statistically significant due to small power. Finally, the
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9 risk of both types of complications was more evident in emergency as opposed to scheduled
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11 interventions. Surgical-related complications were higher among subjects with obesity, blood
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13 disease, stroke or chronic nephropathy, whereas systemic complications were associated with
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15 blood diseases, ischemic heart disease, conduction disorders or dysrhythmias, COPD or
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17 respiratory failure, chronic nephropathy, and chronic diseases of the liver or pancreas.
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22 **Table 3** shows the relationship between type of cholecystectomy and outcomes, adjusted for
23
24 the risk factors identified in Table 2. We report results of the advantage of LC vs. OC (OR,
25
26 95% CI) in the cohort and in the each stratum of the variables tested in the models with
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28 interaction terms. The incidence of “30-day surgical-related complications” and “30-day
29
30 systemic complications” was 2.0% and 2.1%, respectively. The odds ratio of surgical related
31
32 complications for patients who underwent LC as compared to patients with OC was 0.60
33
34 ($p < 0.001$). The corresponding figure for systemic complications was 0.52 ($p < 0.001$).
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38 As regards 30-day surgical-related complications, the protective effect of LC vs. OC was
39
40 consistent across the age category, severity of cholelithiasis and previous upper abdominal
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42 surgery, while among people with emergency admission there was no advantage (OR=0.94 p
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44 = 0.764). Similarly, for systemic complications, the superiority of LC vs. OC was consistent
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46 regardless level of cholelithiasis severity, and elective/emergency admission, but for those
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48 80+ yrs aged people there was no advantage of LC vs. OC (OR 0.99, $p = 0.975$); also for
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50 patients with previous upper abdominal surgery there was a much weaker advantage
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52 (OR=0.86, $p=0.905$).
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3 When the association between type of cholecystectomy and 30-day complications was
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5 adjusted with the propensity adjustment method, results were consistent with those obtained
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7 with the risk-adjustment procedure (LC vs. OC OR= 0.61 and OR=0.52 respectively for the
8
9 two outcomes). Finally, results were similar taking into account patients' clustering within
10
11 different hospitals (*data not shown*).
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14 15 16 17 18 **Discussion** 19

20 From this large observational study based on linked administrative health records - taking
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22 into account the disomogeneous distribution of factors related to the probability to be offered
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24 open surgery - people who end up having a LC have a better short-term prognosis than those
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26 that get an OC for the treatment of gallstones. The superiority of laparoscopic approach in
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28 term of 30-day complications is consistent in different age categories, different severity in
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30 disease presentation and past history of upper abdominal surgery.
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36 This population-based study contributes to enlarge the evidence on effectiveness of LC in a
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38 real-life setting by providing an example from the Southern Europe area. It supports the
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40 usefulness of observational approaches. The 30-day outcomes linked to admission represent
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42 one strength of this study. Despite RTCs are considered the optimal study design when
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44 comparing efficacy of treatments, observational studies provide a picture of treatment under
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46 usual circumstances of health-care practice and can answer to the question “*Does it work in*
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48 *practice?*” (3,8). RTCs often have small sample size and may under represent vulnerable
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50 patient groups, including elderly patients with multiple comorbidities, children, and young
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52 women, and operate in a highly controlled environment that is far from routine clinical
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54 practice. Our study supports that LC is a reliable approach safer than OC not only in old age
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3 group - confirming previous findings (22, 30) - but also in presence of severe disease
4 presentation and in patients with past history of upper digestive system surgery. Beneficial
5 effect of LC as regards systemic complications tends to be lower in 80+ yrs aged in
6 comparison with younger ages, and in patients with emergency admission in comparison to
7 elective admissions as regards 30-day surgical-related complications. These data add to the
8 evidence on the complex relationship between age and outcomes after surgery (22-24,30).
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18 A number of potential biases are present. First of all, people in the two groups of patients
19 analyzed are not homogenous with a higher frequency of elderly and more severe patients in
20 the open group than in the laparoscopic one. When comparing the effect of the two techniques
21 using two different populations, the so called “indication bias” may affect study validity
22 (8,31). To limit this problem we run the propensity adjustment analysis to take into account
23 the different distribution of factors strongly associated with the probability to receive open
24 surgery in the study population. This analytical approach confirmed the advantage of
25 laparoscopic vs. open surgery obtained in the main logistic regression analysis. Another
26 critical point is the potential different distribution of laparoscopic experience across surgeons;
27 however a sensitivity analysis which took into account this point led to similar results. The
28 use of ICD-9-CM codes in the definition of severity of disease presentation and of
29 complications is another major limit. Discharge abstract data have little insight into clinical
30 details and do not inform on the temporal relationship of the clinical conditions and processes,
31 then defining complications is a difficult task (32). In this respect, we tried to improve the
32 accuracy of our measures both 1) applying a specific coding algorithm with subsequent
33 hospital admissions used to retrieve adverse events and 2) excluding in the “count” of
34 complications specific items if reported in the index only (i.e. peritonitis) because of the
35 difficulty to determine if it was already present at admission. Moreover, we cannot exclude an
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3 under-notification of complications – a major limit of our source of data - but it is unlikely
4 that is influenced by the type of surgery. Another major problem is the potential
5 misclassification of exposure since we were not able to measure the occurrence of conversion
6 of LC to OC. The number of people that were switched from LC to OP is low in comparison
7 to figures documented in other studies and it may represent a severe source of bias in our
8 study (30,33).
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18 Beneficial effects of the laparoscopic approach versus traditional open surgery for the
19 treatment of gallstones come from various randomized controlled trials (RCTs) (34). They
20 found significant shorter hospital stay and quicker convalescence associated with LC but no
21 differences in mortality, complications and operative time between the two procedures. A
22 better trend with the laparoscopic approach, including morbidity and mortality, comes from
23 observational studies. From a surveillance system in eight Swiss hospitals, surgical site
24 infections were less common in laparoscopic approach in comparison to traditional open
25 surgery (0.5% in LC vs. 1.8% in OC) (35). Significantly lower incidence of venous
26 thromboembolism and surgical site-infections in laparoscopic cases versus open cases was
27 observed in a large administrative dataset-based study in USA (14, 15). National estimates
28 for LC in USA showed an increase in LC from 52% in 1991 to 75% in 2000 with a constantly
29 low mortality rate and a decrease in biliary reconstruction rate over time (16). On the basis of
30 the 1997-2006 trend analysis by the same authors LC was associated with a low mortality
31 rate (mean value in the period: 0.52%) while OC with a significantly higher rate
32 (corresponding value: 4.9%) (9). In a retrospective study using Medicare beneficiaries
33 common bile duct (CBD) injury during cholecystectomy was associated with a significant
34 higher risk of death in comparison to cholecystectomy without CBD injury over a 9.2 year
35 follow up period (17). From a Swiss 1995-2005 hospital database analysis the incidence rate
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3 of bile duct injury after LC was 0.3% and did not change over time (18). The incidence of
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5 conversion to OC after LC in all hospitals in England from 2005 to 2006 has been examined
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7 using Hospital Episode Statistics and resulted 4.6% for elective procedures and 9.4% for
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9 emergency procedures) (19).

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11 Population-based linkage of routinely collected health data represents a precious tool to
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13 support large- scale and real-world practice evaluation by measuring specific outcomes and
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15 comparing them over time and across populations. Together with results from experimental
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17 research settings, the conclusions of research studies evaluating clinical outcomes through
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19 data linkage systems should be successfully incorporated into practice by clinicians/surgeons.
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<http://www.epidemiologia.lazio.it/prevale11/>

AUTHOR'S CONTRIBUTION

All Authors participated in the study design, in defining the study protocol and methodology, in acquisition of data, in planning the analyses, in interpreting the results. M.S. performed the analyses. N.A and M.S. drafted the manuscript.

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Figure 1. Selection of the study population

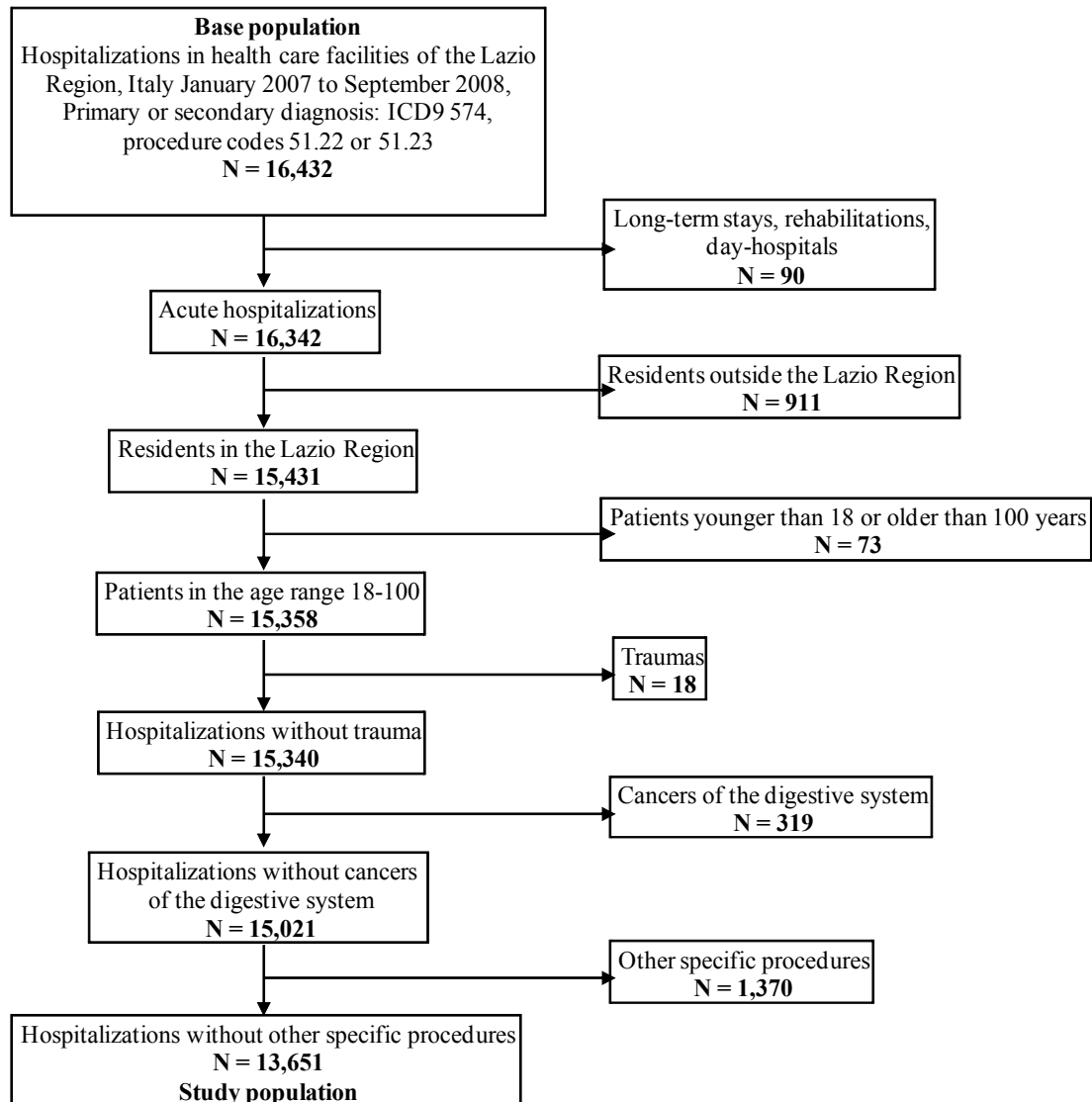


Table 1. Study population, overall and by cholecystectomy procedure: distribution by age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of admission, comorbidities - Lazio Region, Italy, January 2007-September 2008

Patient characteristics	Laparoscopic chole cystectomy		Open chole cystectomy		Total		
	N	%	N	%	N	%	
Total	11.752	86,1	1.899	13,9	13.651	100,0	
Age (years)							
	<70	9.913	84,4	1.162	61,2	11.075	81,1
	70-79	1.543	13,1	485	25,5	2.028	14,9
	≥ 80	296	2,5	252	13,3	548	4,0
		11.752					
Gender							
	Men	4.349	37,0	979	51,6	5.328	39,0
	Women	7.403	63,0	920	48,4	8.323	61,0
Severity of cholelithiasis							
	Low	4.767	40,6	470	24,7	5.237	38,4
	Moderate	6.456	54,9	1.200	63,2	7.656	56,1
	High	529	4,5	229	12,1	758	5,6
Previous upper abdominal surgery							
	No	11.714	99,7	1.867	98,3	13.581	99,5
	Yes	38	0,3	32	1,7	70	0,5
Type of admission							
	Elective	8.690	73,9	903	47,6	9.593	70,3
	Emergency	3.062	26,1	996	52,4	4.058	29,7
Comorbidities							
	Cancer	232	2,0	75	3,9	307	2,2
	Diabetes	268	2,3	100	5,3	368	2,7
	Obesity	115	1,0	25	1,3	140	1,0
	Blood disease	146	1,2	62	3,3	208	1,5
	Hypertension	842	7,2	247	13,0	1.089	8,0
	Ischemic heart disease	246	2,1	107	5,6	353	2,6
	Past coronary revascularization	63	0,5	22	1,2	85	0,6
	Heart failure	47	0,4	41	2,2	88	0,6
	Other heart disease	158	1,3	76	4,0	234	1,7
	Conduction disorders or dysrhythmia	250	2,1	95	5,0	345	2,5
	Cerebrovascular disease	146	1,2	74	3,9	220	1,6
	Vascular disease	91	0,8	38	2,0	129	0,9
	COPD* or respiratory failure	189	1,6	84	4,4	273	2,0
	Chronic nephropathy	68	0,6	46	2,4	114	0,8
	Chronic disease of the liver or pancreas	219	1,9	70	3,7	289	2,1

*Chronic Obstructive Pulmonary Disease

Table 2. Factors related to the incidence of 30-day complications after cholecystectomy. OR crude and adjusted, p-values - Lazio Region, Italy, January 2007-September 2008 (N = 13,651)

Patient characteristics	30-day surgical-related complications (N=278, 2.0%)						30-day systemic complications (N=280, 2.1%)												
	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p					
Age (years)																			
	< 70	1.8	1.00	-	-	-	1.00	-	-	-	-	1.5	1.00	-	-	-			
	70 - 79	2.9	1.62	1.21	2.18	0.001	1.36	1.00	1.83	0.048	3.9	2.68	2.04	3.52	0.000	2.01	1.51	2.67	0.000
	≥ 80	3.3	1.84	1.13	3.00	0.015	1.21	0.72	2.03	0.475	7.1	5.13	3.58	7.36	0.000	2.79	1.87	4.14	0.000
Gender																			
	Men	2.5	1.00	-	-	-	1.00	-	-	-	-	2.6	1.00	-	-	-	1.00	-	-
	Women	1.7	0.69	0.55	0.88	0.002	0.75	0.59	0.96	0.022	1.7	0.66	0.52	0.84	0.001	0.80	0.62	1.02	0.070
Severity of cholelithiasis																			
	Low	1.9	1.00	-	-	-	1.00	-	-	-	-	1.2	1.00	-	-	-	1.00	-	-
	Moderate	2.0	1.08	0.84	1.40	0.538	0.96	0.74	1.24	0.733	2.2	1.84	1.38	2.46	0.000	1.55	1.15	2.08	0.004
	High	3.7	2.03	1.32	3.14	0.001	1.43	0.91	2.24	0.122	6.2	5.30	3.59	7.83	0.000	3.40	2.26	5.11	0.000
Previous upper abdominal surgery																			
	No	2.0	1.00	-	-	-	1.00	-	-	-	-	2.0	1.00	-	-	-	1.00	-	-
	Yes	5.7	2.94	1.07	8.13	0.037	2.29	0.81	6.51	0.119	4.3	2.15	0.67	6.88	0.197	1.72	0.52	5.74	0.376
Type of admission																			
	Elective	1.6	1.00	-	-	-	1.00	-	-	-	-	1.5	1.00	-	-	-	1.00	-	-
	Emergency	3.0	1.85	1.45	2.35	0.000	1.66	1.29	2.13	0.000	3.4	2.34	1.85	2.97	0.000	1.64	1.27	2.11	0.000
Comorbidities (presence of the condition)																			
	Cancer	2.6	1.30	0.64	2.64	0.476	-	-	-	-	3.6	1.81	0.98	3.34	0.059	-	-	-	-
	Diabetes	3.3	1.65	0.92	2.97	0.095	-	-	-	-	4.4	2.24	1.34	3.75	0.002	-	-	-	-
	Obesity	5.0	2.57	1.19	5.55	0.016	2.35	1.29	2.13	0.034	4.3	2.16	0.95	4.94	0.067	-	-	-	-
	Blood disease	5.8	3.03	1.67	5.90	0.000	2.09	1.11	3.93	0.022	7.7	4.16	2.46	7.03	0.000	1.96	1.09	3.51	0.024
	Hypertension	2.9	1.46	1.00	2.13	0.050	-	-	-	-	4.0	2.20	1.58	3.05	0.000	-	-	-	-
	Ischemic heart disease	2.8	1.42	0.75	2.69	0.286	-	-	-	-	7.4	4.08	2.69	6.20	0.000	1.74	1.09	2.78	0.020
	Past coronary revascularization	2.4	1.16	0.28	4.74	0.836	-	-	-	-	9.4	5.08	2.43	10.62	0.000	-	-	-	-
	Heart failure	2.3	1.12	0.27	4.57	0.875	-	-	-	-	4.6	2.29	0.83	6.29	0.107	-	-	-	-
	Other heart disease	3.4	1.72	0.84	3.52	0.136	-	-	-	-	6.8	3.66	2.17	6.16	0.000	-	-	-	-
	Conduction disorder or dysrhythmia	4.1	2.09	1.21	3.62	0.008	-	-	-	-	7.0	3.81	2.47	5.88	0.000	1.73	1.07	2.79	0.025
	Cerebrovascular disease	5.9	3.12	1.76	5.54	0.000	1.98	1.09	3.60	0.025	7.7	4.19	2.52	6.98	0.000	-	-	-	-
	Vascular disease	0.8	0.37	0.05	2.68	0.328	-	-	-	-	8.5	4.59	2.45	8.62	0.000	-	-	-	-
	COPD or respiratory failure	2.6	1.27	0.60	2.72	0.534	-	-	-	-	7.7	4.22	2.66	6.70	0.000	2.02	1.23	3.31	0.006
	Chronic nephropathy	9.7	5.31	2.82	10.00	0.000	3.24	1.65	6.36	0.001	10.5	5.82	3.16	10.72	0.000	2.27	1.15	4.46	0.018
	Chronic disease of the liver or pancreas	3.5	1.75	0.92	3.33	0.087	-	-	-	-	4.8	2.51	1.45	4.35	0.001	1.97	1.11	3.48	0.020

Table 3. Association between type of cholecystectomy and 30-day complications: OR and p-values from crude model, risk-adjusted model, and models with interaction with age group, severity of cholelithiasis, previous upper abdominal surgery and type of admission; p value of heterogeneity of the strata-specific estimates - Lazio Region, Italy, January 2007 - September 2008

	%	OR _{crude}	95% CI		p	OR _{adj}	95% CI		p	P _{het}
<u>30-day surgical-related complications: N=278, %=2.0</u>										
Open cholecystectomy	3,9	1,00	-	-	-	1,00	-	-	-	-
Laparoscopic cholecystectomy	1,7	0,44	0,33	0,57	0,000	0,60	0,44	0,80	0,001	-
Age (years)										0,917
< 70	1,8	0,49	0,35	0,71	0,000	0,62	0,43	0,90	0,012	-
70 - 79	2,9	0,45	0,26	0,76	0,003	0,57	0,33	0,98	0,043	-
≥ 80	3,3	0,41	0,15	1,12	0,082	0,51	0,18	1,38	0,184	-
Severity of cholelithiasis										0,053
Low	1,9	0,37	0,22	0,61	0,000	0,46	0,28	0,77	0,003	-
Moderate	2,0	0,58	0,40	0,85	0,005	0,78	0,53	1,16	0,224	-
High	3,7	0,24	0,11	0,53	0,000	0,30	0,13	0,68	0,004	-
Previous upper abdominal surgery										0,654
No	2,0	0,45	0,34	0,59	0,000	0,60	0,44	0,81	0,001	-
Yes	5,7	0,26	0,03	2,64	0,256	0,36	0,03	3,69	0,388	-
Type of admission										0,001
Elective	1,6	0,32	0,22	0,46	0,000	0,37	0,25	0,55	0,000	-
Emergency	3,0	0,76	0,51	1,13	0,178	0,94	0,62	1,42	0,764	-
<u>30-day systemic complications: N=280, %=2.1</u>										
Open cholecystectomy	5,2	1,00	-	-	-	1,00	-	-	-	-
Laparoscopic cholecystectomy	1,6	0,29	0,23	0,37	0,000	0,52	0,40	0,69	0,000	-
Age (years)										0,136
< 70	1,5	0,34	0,24	0,49	0,000	0,47	0,32	0,68	0,000	-
70 - 79	3,9	0,35	0,22	0,55	0,000	0,47	0,29	0,75	0,002	-
≥ 80	7,1	0,71	0,37	1,37	0,309	0,99	0,50	1,94	0,975	-
Severity of cholelithiasis										0,755
Low	1,2	0,29	0,16	0,51	0,000	0,43	0,24	0,77	0,005	-
Moderate	2,2	0,34	0,25	0,47	0,000	0,55	0,39	0,77	0,001	-
High	6,2	0,38	0,21	0,70	0,002	0,56	0,30	1,05	0,071	-
Previous upper abdominal surgery										0,702
No	2,0	0,29	0,22	0,37	0,000	0,52	0,39	0,69	0,000	-
Yes	4,3	0,41	0,04	4,69	0,470	0,86	0,07	10,40	0,905	-
Type of admission										0,545
Elective	1,5	0,33	0,23	0,50	0,000	0,48	0,32	0,72	0,000	-
Emergency	3,4	0,35	0,25	0,49	0,000	0,56	0,39	0,81	0,002	-

^c There are no 30-day complications in patients with moderately high severity and undergoing laparotomic cholecystectomy

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8 ~~The use of hospital discharge data to compare outcomes of different surgical techniques:~~
9 ~~the example of cholecystectomy.~~

10 [Thirty-day complications after laparoscopic or open cholecystectomy: a population-](#)
11 [based cohort study in Italy.](#)

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44 **Short running head:** Effectiveness of cholecystectomy

45 **Word count for abstract:** ~~293~~264

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<http://www.epidemiologia.lazio.it/prevale11/>

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~~The use of hospital discharge data to compare outcomes of different surgical techniques: the example of cholecystectomy.~~

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

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Abstract

Objective

The objective of the study is to evaluate short-term complications after laparoscopic (LC) or open cholecystectomy (OC) in patients with gallstones by using linked hospital discharge data. There is an increasing interest in using routinely collected health data to support large-scale effectiveness evaluation of different treatment options. We evaluated short term outcomes after laparoscopic cholecystectomy (LC) or open cholecystectomy (OC) in gallstones using hospital discharge data.

Design

Population-based cohort study.

Setting

Data were obtained from the Regional Hospital Discharge Registry Lazio Region in Central Italy (around 5 million inhabitants) in 2007-2008.

Participants

All patients admitted to hospitals of Lazio with symptomatic gallstones (ICD9-CM = 574) who underwent LC (ICD9-CM 51.23) or OC (ICD9-CM 51.22).

Outcome measures

1) "30-day surgical-related complications" defined as any complication of the biliary tract (including bile duct injury, bile leak, postoperative bleeding, wound infection, cholecystitis injury post-operative infection, hemorrhage or hematoma or seroma complicating a procedure, persistent postoperative fistula, perforation of bile duct, disruption of wound); 2) "30-day systemic complications" defined as any complications of other organs (including

sepsis, infections from other organs, major cardiovascular events and selected adverse events).

Results

13,651 patients were included; 86.1% had LC, 13.9% OC. 2.0% experienced surgical-related complications (SRC), 2.1% systemic complications (SC). The Odds Ratio (OR) of complications after LC versus OC was 0.60 ($p<0.001$) for SRC and 0.52 ($p<0.001$) for SC. As regards SRC, the advantage of LC was consistent across age categories, severity of gallstones and previous upper abdominal surgery, while there was no advantage among people with emergency admission (OR=0.94, $p = 0.764$). For SC, no significant advantage of LC was seen among very old people (OR=0.99, $p=0.975$) and among those with previous upper abdominal surgery (OR=0.86, $p=0.905$).

Conclusions

This large observational study confirms that LC is more effective than OC with respect to 30-day short term complications. ~~The advantage remains in sub-populations with higher preoperative risk, but it is different according to whether the complications affect the biliary tract or other organs or systems.~~ Population-based linkage of administrative datasets can enlarge evidence of treatment benefits in clinical practice.

Key words: ~~administrative data, cholecystectomy, complications, effectiveness, outcomes~~
administrative data, cohort study, effectiveness, gallstones, hospital discharge data, laparoscopic cholecystectomy, open cholecystectomy, outcomes, population-based, post-operative complications.

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Article summary

Article focus

-The advantage of laparoscopic cholecystectomy (LC) approach for the treatment of gallstone versus open surgery (OC) has been ~~shown from RCTs and observational studies, but the evidence from observational studies is limited.~~

-The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments.

-We compared laparoscopic and open cholecystectomy in term of ~~30-day complications short-term outcomes~~ using routinely collected databases in Lazio Region (Italy).

Key messages

-This population-based study contributes to enlarge the evidence on effectiveness of LC in a real-life setting.

-As regards surgical-related complications, the advantage of LC was consistent across age categories, severity of gallstones and previous upper abdominal surgery, while there was no advantage among people with emergency admission.

-For systemic complications, no significant advantage of LC was seen among very old people and among those with previous upper abdominal surgery.

Strengths and limitations

-Population-based design, 30-day outcomes, large numbers and robustness of analytic procedures are the main strengths.

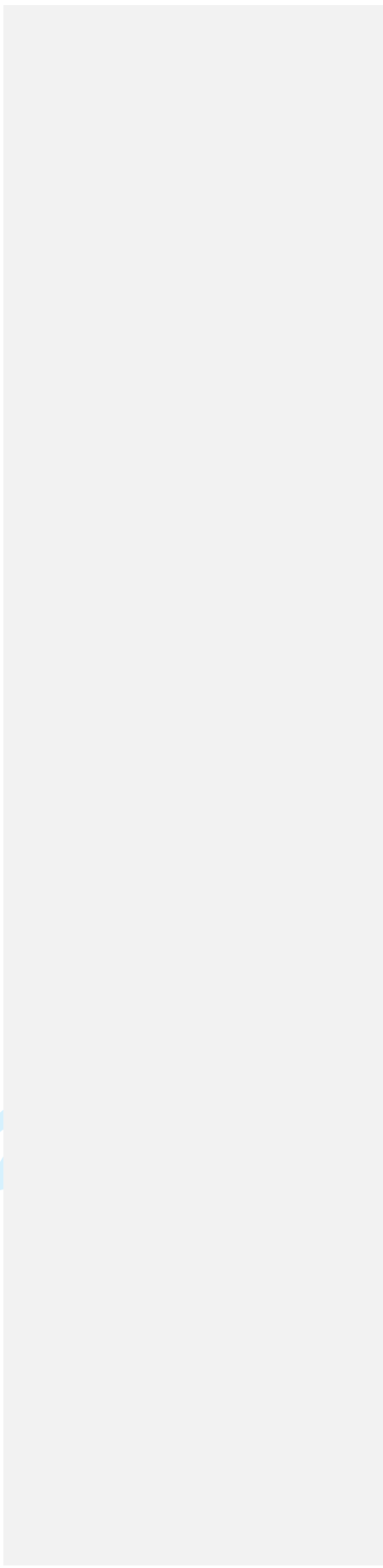
-It contributes to the debate on the complex methodology to estimated risk of adverse events after surgery using secondary databases to monitor quality of care.

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-The use of ICD-9-CM codes in the definition of severity of disease presentation and of complications is a major limit.

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Introduction

Comparative effectiveness research (CER) is becoming central to monitor real-life impact of treatments and support public health decisions (1, 2). Although the basic concept of comparing therapies is not new, over the last few years many initiatives have been implemented in ~~several~~many countries to provide large-scale evidence on benefits and harms of different treatments (3-5). The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments (6,7). They include hospital in-patients records, birth and death registrations, outpatient care records, dispensed pharmacy drugs (6-9). ~~Despite the advantages due to the large numbers and the population level coverage, the analytic methods to reduce bias in CER studies are complex and new approaches are continuously developed (8,9).~~

In the Lazio Region (around 5.000.000 inhabitants) the P.Re.Val.E. Project (*Regional Program for Assessing the Outcomes of Health-care Interventions*) was launched in 2005. Its aims are: to measure the quality of health care provided in the Lazio Region, to describe variability of care provision across institutions and populations and to compare effectiveness of treatments for different medical and surgical conditions (10,-11). Over 60 outcomes indicators are calculated based on data obtained from record-linkage procedures of different health systems. The results are periodically updated and publicly disseminated with discussion on critical methodological points.

Cholecystectomy is one of the most common abdominal surgical procedures in developed countries. Since its introduction in the late '80s, laparoscopic cholecystectomy (LC) has replaced open cholecystectomy (OC) as the treatment of choice for symptomatic gallstones (12, 13). ~~Although~~ Beneficial effects of LC have been widely demonstrated ~~in~~, there are

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7 relatively few studies showing the advantages from real-life settings using secondary
8 databases (9,14-19,14-16). In the present study, we aimed at developing a methodology to
9 measure short-term complications after LC or OC using large administrative databases on
10 behalf of the P.Re.Val.E. Secondly, we tested the hypothesis that the advantages of LC versus
11 OC could vary according to age demographic and clinical patients' characteristics.
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22 **Methods**

23 Source of data

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26 Data was derived from the Lazio Hospital Information System (HIS), which provides
27 information on patients' demographic data (gender, age, place of birth, place of residence),
28 admission and discharge dates, discharge diagnoses (up to 6) and medical procedures or
29 surgical interventions ((up to 6) according to the International Classification of disease, Ninth
30 Revision, Clinical Modification (ICD-9-CM), status at discharge (alive, dead, transferred to
31 another hospital), ward(s) of stay, date(s) of in-hospital transfer, and a regional code
32 corresponding to the admitting facility for patients discharged from all public and private
33 hospital of the Lazio Region (5.759.839 inhabitants).
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43 Study population

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45 All hospital admissions with a primary or secondary diagnosis of gallstones (International
46 Classification of Diseases 9th Revision, Clinical Modification - ICD9-CM = 574) and a
47 procedure code of cholecystectomy (ICD9-CM 51.22, 51.23), occurred in private and public
48 hospitals of the Lazio Region between January 2007 and September 2008 were included, for a
49 total of 16,432 cases (age 18+ years). [We a priori decided not to include codes for partial](#)
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[cholecystectomy \(ICD-9-CM 51.21 and 51.24\) to increase the specificity of our exposure.](#)

Information was retrieved from the HIS. In order to increase the case specificity, several exclusion criteria were applied including long-term hospitalizations, rehabilitations, day-hospitals, hospitalizations for delivery or trauma or cancer, hospitalizations with abdominal surgical procedures other than cholecystectomy. The final population consisted of 13,651 subjects (**Figure 1**). See the online **Supplementary Data** (Part 1) for details on the exclusion criteria and ICD9-CM codes.

Patient-level risk factors

The following characteristics were considered for each patient: Age (<70; 70-79; >=80 years old); Gender; Severity of gallstones: it was classified as *low* (not-complicated), *moderate* (presence of cholecystitis ~~or; cholangitis or~~ biliary tract obstruction), and *high* (presence of both inflammation and obstruction of the biliary tract); Previous upper abdominal surgery (based on previous 2-year hospitalizations); Comorbidities (based on previous 2-year hospitalizations) following validated algorithms ([20,21+7-19](#)); Type of admission: either *elective* or *emergency*. See the online **Supplementary Data** (Part 2-4) for details on the ICD-9-CM codes. The choice of *cut off* for age category was based on previous studies to distinguish adult and old people ([22-24+22](#)).

Outcomes

We identified various complications within 30-days after the intervention and grouped them in two categories: 1) “30-day surgical-related complications” defined as any complication of the biliary tract ([including post-operative infection, hemorrhage or hematoma or seroma complicating a procedure, persistent postoperative fistula, perforation of bile duct, disruption of wound](#) ~~(including bile duct injury, bile leak, postoperative bleeding, wound infection,~~

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7 [cholecystitis injury](#)); 2) “30-day systemic complications” defined as any complications of other
8 organs (including sepsis, infections from other organs, major cardiovascular events and
9 selected adverse events). The complete list of complications with ICD-9-CM codes is
10 reported in the online **Supplementary Data** (Part 5). Among the various complications we
11 included some conditions reported in the list of Patient Safety Indicators recently developed
12 by the Agency for Health Care Research and Quality (~~i.e. postoperative bleeding, wound~~
13 ~~infection~~), while other items were specifically created on the basis of scientific literature on
14 digestive surgery (14-196,25-263,24). Depending on the type of complication, some ICD9-
15 CM codes were searched in both the index admission and the following ones in the 30-day
16 period after the surgery, others were searched only in later hospitalizations. For example,
17 peritonitis or acute pancreatitis was not counted as complications when reported in the index
18 admission. See the online **Supplementary Data** (Part 5) for details on the ICD9-CM codes.
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20 In the case of a subsequent hospitalization occurred out of the study area (for example, in a
21 region other than Lazio), we obtained information through record linkage procedure between
22 hospital information systems. Because of the short follow up time, this happened in a minimal
23 proportion of cases (0.1%). The outcome variables were: “30-day surgical-related
24 complications” and “30-day systemic complications”; they were coded “1” if at least one of
25 the complications within the group was present and “0” if none was recorded.
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43 Type of cholecystectomy

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45 As exposure ~~We defined the~~ variable we defined “type of cholecystectomy” (laparoscopic
46 cholecystectomy, LC vs. open cholecystectomy, OC). In the case of ICD-9-CM codes for
47 both LC and OC (5%), the patient was considered exposed to the open surgical
48 procedure. ~~Since Unfortunately, the~~ We could not use the -specific ICD-9-code for a case
49 converted from LC to OC (ICD-9-CM code V 64.41) because it was ~~was~~ highly under-
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~~reported in our Region in the study period. no case in our study cohort, not available, in the case of reported ICD-9 CM codes for both LC and OC (5%), the patient was considered exposed to the open surgical procedure.~~

Statistical analysis

Multiple logistic regression models were fitted to estimate the relative risk of 30-day complications (either “surgical-related” or “systemic”) after LC versus OC, adjusting for demographical and clinical risk factors. The two outcome variables were analysed separately.

~~The predictive model was made of two sets of predictors: Given the large amount of individual level variables available, the risk factors were divided in two groups: 1) variables “a priori” chosen as confounders (age, gender, severity of gallstones, previous upper abdominal surgery, and type of admission); 2) variables empirically tested (comorbidities) which were selected using iterative stepwise statistical procedures (9,275). Once the “best” predictive model was identified for each of the two outcome variables, the treatment variable “type of cholecystectomy” was included, and the adjusted odds ratio (OR) of LC versus open surgery was estimated, with corresponding 95% confidence interval (95% CI) and p-value.~~

In order to test the hypothesis of an effect modification by age, relative risk estimates for the age groups were derived by adding an interaction term between the age group and the treatment variable in the final multivariate logistic model. We obtained the OR of laparoscopic vs. open surgery within each age stratum by adding the corresponding interaction terms coefficients. ~~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.~~

Similarly, effect modification was tested with regard to severity of cholelithiasis, previous

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7 upper abdominal surgery and type of admission. The corresponding tests of heterogeneity of
8 the stratum-specific risk estimates were computed, ~~but not reported for ease of presentation.~~
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12 Sensitivity analyses were performed. First, in order to guarantee adequate control of
13 confounding factors we identified and adjusted for all the individual factors associated with
14 the treatment, within the propensity adjustment framework (286). This procedure is a two-step
15 technique: 1. it estimates the a priori probability of exposure for each subject, based on
16 clinical and demographic characteristics; 2. it standardizes for them in the association between
17 treatment and the study outcome. The individual factors related to the exposure in the present
18 study include age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of
19 admission, cardio-circulatory disease, cerebrovascular disease, COPD or respiratory failure,
20 chronic nephropathy, chronic disease of the liver or pancreas. Second, to take into account the
21 potential heterogeneous experience in laparoscopic surgery across different hospitals because
22 of the patients' clustering within a single institution we perform a multilevel regression model
23 with random intercepts for hospitals (297).
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37 All the statistical analyses were performed using SAS Software version 8.0 (SAS Institute,
38 Inc. SAS/STAT software).
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45 Results

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47 A description of the study population, overall and by cholecystectomy procedure, is presented
48 in **Table 1**. Over 80% of the patients were younger than 70 years, and moderate to high
49 severity of the gallstones was diagnosed for 61.7%. As compared with patients undergoing
50 LC, those who underwent OC were more likely to be elderly, males, with a more sever
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7 baseline disease and more chronic conditions. Furthermore, they were operated in emergency
8 in most of the cases (52.4%), whereas LC was performed in elective hospitalizations much
9 more frequently (73.9%).
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14 **Table 2** reports the relationship between demographic and clinical variables and the
15 occurrence of complications. The adjusted risk of systemic complications increased with age
16 and was much higher in patients with more severe baseline gallstones, whereas no clear age or
17 severity-related differences in risk emerged with regard to surgical-related 30-day
18 complications, once other co-factors were taken into account. Women were less likely to
19 experience both types of complications. Having had a previous intervention on the upper
20 digestive system seemed to enhance the risk of both surgical-related and systemic
21 complications, though results are not statistically significant due to small power. Finally, the
22 risk of both types of complications was more evident in emergency as opposed to scheduled
23 interventions. Surgical-related complications were higher among subjects with obesity, blood
24 disease, stroke or chronic nephropathy, whereas systemic complications were associated with
25 blood diseases, ischemic heart disease, conduction disorders or dysrhythmias, COPD or
26 respiratory failure, chronic nephropathy, and chronic diseases of the liver or pancreas.
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41 **Table 3** shows the relationship between type of cholecystectomy and outcomes, adjusted for
42 the risk factors identified in Table 2. We report results of the advantage of LC vs. OC (OR,
43 95% CI) in the cohort (~~first lines of the table~~) and in the each stratum of the variables tested in
44 the models with interaction terms. The incidence of “30-day surgical-related complications”
45 and “30-day systemic complications” was 2.0% and 2.1%, respectively. ~~The incidence of “at
46 least one 30-day complication” was 3%.~~ The odds ratio of surgical related complications for
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patients who underwent LC as compared to patients with OC was 0.60 ($p<0.001$). The corresponding figure for systemic complications was 0.52 ($p<0.001$).

As regards 30-day surgical-related complications, the protective effect of LC vs. OC was consistent across the age category, severity of cholelithiasis and previous upper abdominal surgery, while among people with emergency admission there was no advantage (OR=0.94 $p = 0.764$). Similarly, for systemic complications, the superiority of LC vs. OC was consistent regardless level of cholelithiasis severity, and elective/emergency admission, but for those 80+ yrs aged people there was no advantage of LC vs. OC (OR 0.99, $p = 0.975$); also for patients with previous upper abdominal surgery there was a much weaker advantage (OR=0.86, $p=0.905$).

When the association between type of cholecystectomy and [30-day complications](#)~~short term complications~~ was adjusted with the propensity adjustment method, results were consistent with those obtained with the risk-adjustment procedure (LC vs. OC OR= 0.61 and OR=0.52 respectively for the two outcomes). Finally, results were similar taking into account patients' clustering within different hospitals (*data not shown*).

Discussion

From this large observational study based on linked administrative health records - taking into account the disomogeneous distribution of factors related to the probability to be offered open surgery - people who end up having a LC have a better short-term prognosis than those that get an OC for the treatment of gallstones. The superiority of laparoscopic approach in term of [30-day complications](#)~~short term outcomes~~ is consistent in [different age categories](#).

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7 ~~both genders~~, different severity in disease presentation and past history of upper abdominal
8 surgery.
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12 This population-based study contributes to enlarge the evidence on effectiveness of LC in a
13 real-life setting ~~by providing an example-contribution from the Southern Europe area.~~ It
14 supports the usefulness of observational approaches. ~~The 30-day outcomes linked to~~
15 ~~admission represents one strength of this study. - To our knowledge it is the first study in Italy~~
16 ~~to measure and compare outcomes of surgical treatments using data from secondary data~~
17 ~~sources.~~ Despite RTCs are considered the optimal study design when comparing efficacy of
18 treatments, observational studies provide a picture of treatment under usual circumstances of
19 health-care practice and can answer to the question “*Does it work in practice?*” (3,86,3).
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RTCs often have small sample size and may under represent vulnerable patient groups,
including elderly patients with multiple comorbidities, children, and young women, and
operate in a highly controlled environment that is far from routine clinical practice. Our study
supports that LC is a reliable approach safer than OC not only in old age group - confirming
previous findings (229, 3028) - but also in presence of severe disease presentation and in
patients with past history of upper digestive system surgery. Beneficial effect of LC as
regards systemic complications tends to be lower in 80+ yrs aged in comparison with younger
ages, and in patients with emergency admission in comparison to elective admissions as
regards 30-day surgical-related complications. These data add to the evidence on the complex
relationship between age and outcomes after surgery (22-24,300-22, 28).

A number of potential biases are present. First of all, people in the two groups of patients
analyzed are not homogenous with a higher frequency of elderly and more severe patients in
the open group than in the laparoscopic one. When comparing the effect of the two techniques

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7 using two different populations, the so called “indication bias” may affect study validity
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9 ([8,316,29](#)). To limit this problem we run the propensity adjustment analysis to take into
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11 account the different distribution of factors strongly associated with the probability to receive
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13 open surgery in the study population. This analytical approach confirmed the advantage of
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15 laparoscopic vs. open surgery obtained in the main logistic regression analysis. Another
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17 critical point is the potential different distribution of laparoscopic experience across surgeons;
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19 however a sensitivity analysis which took into account this point led to similar results. The
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21 use of ICD-9-CM codes in the definition of severity of disease presentation and of
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23 complications is another major limit. Discharge abstract data have little insight into clinical
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25 details and do not inform on the temporal relationship of the clinical conditions and processes,
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27 then defining complications is a difficult task ([320](#)). In this respect, we tried to improve the
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29 accuracy of our measures both 1) applying a specific coding algorithm with subsequent
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31 hospital admissions used to retrieve adverse events and 2) excluding in the “count” of
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33 complications specific items if reported in the index only (i.e. peritonitis) because of the
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35 difficulty to determine if it was already present at admission. Moreover, we cannot exclude an
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37 under-notification of complications – ~~another~~ [major limit of our source of data](#) - but it is
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39 unlikely that is influenced by the type of surgery. Another major problem is the potential
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41 misclassification of exposure since we were not able to measure the occurrence of conversion
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43 of LC to OC. The number of people that were switched from LC to OP is low in comparison
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45 to figures documented in other studies and it may represent a severe source of bias in our
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47 study ([30,3328,34](#)).

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49 Beneficial effects of the laparoscopic approach versus traditional open surgery for the
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51 treatment of gallstones come from various randomized controlled trials (RCTs) ([342](#)). They
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53 found significant shorter hospital stay and quicker convalescence associated with LC but no
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7 differences in mortality, complications and operative time between the two procedures. A
8 better trend with the laparoscopic approach, including morbidity and mortality, comes from
9 ~~some~~ observational studies. From a surveillance system in eight Swiss hospitals, surgical site
10 infections were less common in laparoscopic approach in comparison to traditional open
11 surgery (0.5% in LC vs. 1.8% in OC) (353). Significantly lower incidence of venous
12 thromboembolism and surgical site-infections in laparoscopic cases versus open cases was
13 ~~recently~~ observed in a large administrative dataset-based study in USA (14, 15). [National](#)
14 [estimates for LC in USA showed an increase in LC from 52% in 1991 to 75% in 2000 with a](#)
15 [constantly low mortality rate \(mean 0.45%\) and a decrease in biliary reconstruction rate over](#)
16 [time \(from 0.25% in 1992 to 0.09% in 1999\) \(16\). On the basis of the 1997-2006 trend](#)
17 [analysis by the same authors](#) ~~In hospital mortality after cholecystectomy over a ten years~~
18 ~~period was studied in USA:~~ LC was associated with a low mortality rate (mean value in the
19 period: 0.52%) while OC with a significantly higher rate (corresponding value: 4.9%) (946).
20 [In a retrospective study using Medicare beneficiaries common bile duct \(CBD\) injury during](#)
21 [cholecystectomy was associated with a significant higher risk of death in comparison to](#)
22 [cholecystectomy without CBD injury over a 9.2 year follow up period \(17\). From a -Swiss](#)
23 [1995-2005 hospital database analysis the incidence rate of bile duct injury after LC was 0.3%](#)
24 [and did not change over time \(18\). In the era of evidence based health care, population based](#)
25 [linkage of administrative health data have been increasingly used also in the field of surgery.](#)
26 ~~However the methodology is not standardized and estimated risk of adverse events vary~~
27 ~~widely according to the type of interventions and to the type of complications and their~~
28 ~~operative definition. As a recent example in Europe,~~ the incidence of conversion to OC after
29 LC in all hospitals in England from 2005 to 2006 has been examined using Hospital Episode
30 Statistics and resulted 4.6% for elective procedures and 9.4% for emergency procedures)
31 (1934). ~~In USA, a set of indicators (Patient Safety Indicators (PSIs) has been introduced,~~

~~validated and continuously under revision as algorithms based on the International Classification of Diseases, Ninth Revision, Clinical Modification (17). Our study contributes to the experience in using population based linked health data and ICD 9 CM coding algorithms to compare treatment outcomes.~~

Population-based linkage of routinely collected health data represents a precious tool to support large- scale and real-world practice evaluation by measuring specific outcomes and comparing them over time and across populations. Together with results from experimental research settings, the conclusions of research studies evaluating clinical outcomes through data linkage systems should be successfully incorporated into practice by clinicians/surgeons.

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AUTHOR'S CONTRIBUTION

All Authors participated in the study design, in defining the study protocol and methodology, in acquisition of data, in planning the analyses, in interpreting the results. M.S. performed the analyses. N.A and M.S. drafted the manuscript.

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Table 1. Study population, overall and by cholecystectomy procedure: distribution by age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of admission, comorbidities - Lazio Region, Italy, January 2007-September 2008

Patient characteristics	Laparoscopic cholecystectomy		Open cholecystectomy		Total	
	No.	%	No.	%	No.	%
Total	11.752	86,1	1.899	13,9	13.651	100,0
Age (years)						
< 70	9.913	84,4	1.162	61,2	11.075	81,1
70 - 79	1.543	13,1	485	25,5	2.028	14,9
≥ 80	296	2,5	252	13,3	548	4,0
Gender						
Men	4.349	37,0	979	51,6	5.328	39,0
Women	7.403	63,0	920	48,4	8.323	61,0
Severity of cholelithiasis						
Low	4.767	40,6	470	24,7	5.237	38,4
Moderate	6.473	55,1	1.210	63,7	7.683	56,3
High	512	4,4	219	11,5	731	5,4
Previous upper abdominal surgery						
No	11.714	99,7	1.867	98,3	13.581	99,5
Yes	38	0,3	32	1,7	70	0,5
Type of admission						
Elective	8.690	73,9	903	47,6	9.593	70,3
Emergency	3.062	26,1	996	52,4	4.058	29,7
Comorbidities (presence of the condition)						
Cancer	232	2,0	75	3,9	307	2,2
Diabetes	268	2,3	100	5,3	368	2,7
Obesity	115	1,0	25	1,3	140	1,0
Blood disease	146	1,2	62	3,3	208	1,5
Hypertension	842	7,2	247	13,0	1.089	8,0
Ischemic heart disease	246	2,1	107	5,6	353	2,6
Past coronary revascularization	63	0,5	22	1,2	85	0,6
Heart failure	47	0,4	41	2,2	88	0,6
Other heart disease	158	1,3	76	4,0	234	1,7
Conduction disorder or dysrhythmia	250	2,1	95	5,0	345	2,5
Cerebrovascular disease	146	1,2	74	3,9	220	1,6
Vascular disease	91	0,8	38	2,0	129	0,9
COPD or respiratory failure	189	1,6	84	4,4	273	2,0
Chronic nephropathy	68	0,6	46	2,4	114	0,8
Chronic disease of the liver or pancreas	219	1,9	70	3,7	289	2,1

Table 2. Factors related to the incidence of 30-day complications after cholecystectomy. OR crude and adjusted, p-values - Lazio Region, Italy, January 2007-September 2008 (N = 13,651)

Patient characteristics	30-day surgical-related complications (N=278, 2.0%)					30-day systemic complications (N=280, 2.1%)					
	%	OR _{crude}	p	OR _{adj}	p	%	OR _{crude}	p	OR _{adj}	p	
Age (years)											
	< 70	1,8	1,00	-	1,00	-	1,5	1,00	-	1,00	-
	70 - 79	2,9	1,62	0,001	1,36	0,048	3,9	2,68	0,000	2,01	0,000
	≥ 80	3,3	1,84	0,015	1,21	0,475	7,1	5,13	0,000	2,79	0,000
Gender											
	Men	2,5	1,00	-	1,00	-	2,6	1,00	-	1,00	-
	Women	1,7	0,69	0,002	0,75	0,022	1,7	0,66	0,001	0,80	0,070
Severity of cholelithiasis											
	Low	1,9	1,00	-	1,00	-	1,2	1,00	-	1,00	-
	Moderate	2,0	1,08	0,538	0,96	0,733	2,2	1,84	0,000	1,55	0,004
	High	3,7	2,03	0,001	1,43	0,122	6,2	5,30	0,000	3,40	0,000
Previous upper abdominal surgery											
	No	2,0	1,00	-	1,00	-	2,0	1,00	-	1,00	-
	Yes	5,7	2,94	0,037	2,29	0,119	4,3	2,15	0,197	1,72	0,376
Type of admission											
	Elective	1,6	1,00	-	1,00	-	1,5	1,00	-	1,00	-
	Emergency	3,0	1,85	0,000	1,66	0,000	3,4	2,34	0,000	1,64	0,000
Comorbidities (presence of the condition)											
	Cancer	2,6	1,30	0,476	-	-	3,6	1,81	0,059	-	-
	Diabetes	3,3	1,65	0,095	-	-	4,4	2,24	0,002	-	-
	Obesity	5,0	2,57	0,016	2,35	0,034	4,3	2,16	0,067	-	-
	Blood disease	5,8	3,03	0,000	2,09	0,022	7,7	4,16	0,000	1,96	0,024
	Hypertension	2,9	1,46	0,050	-	-	4,0	2,20	0,000	-	-
	Ischemic heart disease	2,8	1,42	0,286	-	-	7,4	4,08	0,000	1,74	0,020
	Past coronary revascularization	2,4	1,16	0,836	-	-	9,4	5,08	0,000	-	-
	Heart failure	2,3	1,12	0,875	-	-	4,6	2,29	0,107	-	-
	Other heart disease	3,4	1,72	0,136	-	-	6,8	3,66	0,000	-	-
	Conduction disorder or dysrhythmia	4,1	2,09	0,008	-	-	7,0	3,81	0,000	1,73	0,025
	Cerebrovascular disease	5,9	3,12	0,000	1,98	0,025	7,7	4,19	0,000	-	-
	Vascular disease	0,8	0,37	0,328	-	-	8,5	4,59	0,000	-	-
	COPD or respiratory failure	2,6	1,27	0,534	-	-	7,7	4,22	0,000	2,02	0,006
	Chronic nephropathy	9,7	5,31	0,000	3,24	0,001	10,5	5,82	0,000	2,27	0,018
	Chronic disease of the liver or pancreas	3,5	1,75	0,087	-	-	4,8	2,51	0,001	1,97	0,020

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Table 3. Association between type of cholecystectomy and 30-day complications: OR and p-values from crude model, risk-adjusted model, and models with interaction with age group, severity of cholelithiasis, previous upper abdominal surgery and type of admission - Lazio Region, Italy, January 2007 - September 2008

	30-day surgical-related complications (N=278, %=2.0)					30-day systemic complications (N=280, %=2.1)				
	%	OR _{crude}	p	OR _{adj}	p	%	OR _{crude}	p	OR _{adj}	p
Open cholecystectomy	3,9	1,00	-	1,00	-	5,2	1,00	-	1,00	-
Laparoscopic cholecystectomy	1,7	0,44	0,000	0,60	0,001	1,6	0,29	0,000	0,52	0,000
<i>Stratified results by each category</i>										
<i>Age (years)</i>										
< 70	1,8	0,49	0,000	0,62	0,012	1,5	0,34	0,000	0,47	0,000
70 - 79	2,9	0,45	0,003	0,57	0,043	3,9	0,35	0,000	0,47	0,002
≥ 80	3,3	0,41	0,082	0,51	0,184	7,1	0,71	0,309	0,99	0,975
<i>Severity of cholelithiasis</i>										
Low	1,9	0,37	0,000	0,46	0,003	1,2	0,29	0,000	0,43	0,005
Moderate	2,0	0,58	0,005	0,78	0,224	2,2	0,34	0,000	0,55	0,001
High	3,7	0,24	0,000	0,30	0,004	6,2	0,38	0,002	0,56	0,071
<i>Previous upper abdominal surgery</i>										
No	2,0	0,47	0,000	0,60	0,001	2,0	0,29	0,000	0,52	0,000
Yes	5,7	0,26	0,256	0,36	0,388	4,3	0,41	0,470	0,86	0,905
<i>Type of admission</i>										
Elective	1,6	0,31	0,000	0,37	0,000	1,5	0,33	0,000	0,48	0,000
Emergency	3,0	0,76	0,178	0,94	0,764	3,4	0,35	0,000	0,56	0,002

Table 1. Study population, overall and by cholecystectomy procedure: distribution by age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of admission, comorbidities - Lazio Region, Italy, January 2007-September 2008

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	N	%	N	%	N	%
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Age (years)						
<70	9.913	84,4	1.162	61,2	11.075	81,1
70-79	1.543	13,1	485	25,5	2.028	14,9
≥ 80	296	2,5	252	13,3	548	4,0
	11.752					
Gender						
Men	4.349	37,0	979	51,6	5.328	39,0
Women	7.403	63,0	920	48,4	8.323	61,0
Severity of cholelithiasis						
Low	4.767	40,6	470	24,7	5.237	38,4
Moderate	6.456	54,9	1.200	63,2	7.656	56,1
High	529	4,5	229	12,1	758	5,6
Previous upper abdominal surgery						
No	11.714	99,7	1.867	98,3	13.581	99,5
Yes	38	0,3	32	1,7	70	0,5
Type of admission						
Elective	8.690	73,9	903	47,6	9.593	70,3
Emergency	3.062	26,1	996	52,4	4.058	29,7
Comorbidities						
Cancer	232	2,0	75	3,9	307	2,2
Diabetes	268	2,3	100	5,3	368	2,7
Obesity	115	1,0	25	1,3	140	1,0
Blood disease	146	1,2	62	3,3	208	1,5
Hypertension	842	7,2	247	13,0	1.089	8,0
Ischemic heart disease	246	2,1	107	5,6	353	2,6
Past coronary revascularization	63	0,5	22	1,2	85	0,6
Heart failure	47	0,4	41	2,2	88	0,6
Other heart disease	158	1,3	76	4,0	234	1,7
Conduction disorders or dysrhythmia	250	2,1	95	5,0	345	2,5
Cerebrovascular disease	146	1,2	74	3,9	220	1,6
Vascular disease	91	0,8	38	2,0	129	0,9
COPD* or respiratory failure	189	1,6	84	4,4	273	2,0
Chronic nephropathy	68	0,6	46	2,4	114	0,8
Chronic disease of the liver or pancreas	219	1,9	70	3,7	289	2,1

*Chronic Obstructive Pulmonary Disease

Table 2. Factors related to the incidence of 30-day complications after cholecystectomy. OR crude and adjusted, p-values - Lazio Region, Italy, January 2007-September 2008 (N = 13,651)

Patient characteristics	30-day surgical-related complications (N=278, 2.0%)						30-day systemic complications (N=280, 2.1%)												
	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p					
Age (years)																			
	< 70	1.8	1.00	-	-	1.00	-	1.5	1.00	-	-	1.00	-	-					
	70 - 79	2.9	1.62	1.21	2.18	0.001	1.36	1.00	1.83	0.048	3.9	2.68	2.04	3.52	0.000	2.01	1.51	2.67	0.000
	≥ 80	3.3	1.84	1.13	3.00	0.015	1.21	0.72	2.03	0.475	7.1	5.13	3.58	7.36	0.000	2.79	1.87	4.14	0.000
Gender																			
	Men	2.5	1.00	-	-	1.00	-	2.6	1.00	-	-	1.00	-	-					
	Women	1.7	0.69	0.55	0.88	0.002	0.75	0.59	0.96	0.022	1.7	0.66	0.52	0.84	0.001	0.80	0.62	1.02	0.070
Severity of cholelithiasis																			
	Low	1.9	1.00	-	-	1.00	-	1.2	1.00	-	-	1.00	-	-					
	Moderate	2.0	1.08	0.84	1.40	0.538	0.96	0.74	1.24	0.733	2.2	1.84	1.38	2.46	0.000	1.55	1.15	2.08	0.004
	High	3.7	2.03	1.32	3.14	0.001	1.43	0.91	2.24	0.122	6.2	5.30	3.59	7.83	0.000	3.40	2.26	5.11	0.000
Previous upper abdominal surgery																			
	No	2.0	1.00	-	-	1.00	-	2.0	1.00	-	-	1.00	-	-					
	Yes	5.7	2.94	1.07	8.13	0.037	2.29	0.81	6.51	0.119	4.3	2.15	0.67	6.88	0.197	1.72	0.52	5.74	0.376
Type of admission																			
	Elective	1.6	1.00	-	-	1.00	-	1.5	1.00	-	-	1.00	-	-					
	Emergency	3.0	1.85	1.45	2.35	0.000	1.66	1.29	2.13	0.000	3.4	2.34	1.85	2.97	0.000	1.64	1.27	2.11	0.000
Comorbidities (presence of the condition)																			
	Cancer	2.6	1.30	0.64	2.64	0.476	-	3.6	1.81	0.98	3.34	0.059	-	-	-	-	-	-	-
	Diabetes	3.3	1.65	0.92	2.97	0.065	-	4.4	2.24	1.34	3.75	0.002	-	-	-	-	-	-	-
	Obesity	5.0	2.57	1.19	5.55	0.016	2.35	1.29	2.13	0.034	4.3	2.16	0.95	4.94	0.067	-	-	-	-
	Blood disease	5.8	3.03	1.67	5.50	0.000	2.09	1.11	3.93	0.022	7.7	4.16	2.46	7.03	0.000	1.96	1.09	3.51	0.024
	Hypertension	2.9	1.48	1.00	2.13	0.050	-	4.0	2.20	1.58	3.05	0.000	-	-	-	-	-	-	-
	Ischemic heart disease	2.8	1.42	0.75	2.69	0.286	-	7.4	4.08	2.69	6.20	0.000	1.74	1.09	2.78	0.020	-	-	-
	Past coronary revascularization	2.4	1.16	0.28	4.74	0.836	-	9.4	5.08	2.43	10.62	0.000	-	-	-	-	-	-	-
	Heart failure	2.3	1.12	0.27	4.57	0.875	-	4.6	2.29	0.83	6.29	0.107	-	-	-	-	-	-	-
	Other heart disease	3.4	1.72	0.84	3.52	0.136	-	6.8	3.66	2.17	6.16	0.000	-	-	-	-	-	-	-
	Conduction disorder or dysrhythmia	4.1	2.09	1.21	3.62	0.008	-	7.0	3.81	2.47	5.88	0.000	1.73	1.07	2.79	0.025	-	-	-
	Cerebrovascular disease	5.9	3.12	1.78	5.54	0.000	1.98	1.09	3.60	0.025	7.7	4.19	2.52	6.98	0.000	-	-	-	-
	Vascular disease	0.8	0.37	0.05	2.68	0.328	-	8.5	4.59	2.45	8.62	0.000	-	-	-	-	-	-	-
	COPD or respiratory failure	2.6	1.27	0.60	2.72	0.534	-	7.7	4.22	2.66	6.70	0.000	2.02	1.23	3.31	0.006	-	-	-
	Chronic nephropathy	9.7	5.31	2.82	10.00	0.000	3.24	1.65	6.36	0.001	10.5	5.82	3.16	10.72	0.000	2.27	1.15	4.46	0.018
	Chronic disease of the liver or pancreas	3.5	1.75	0.92	3.33	0.087	-	4.8	2.51	1.45	4.35	0.001	1.97	1.11	3.48	0.020	-	-	-

Table 3. Association between type of cholecystectomy and 30-day complications: OR and p-values from crude model, risk-adjusted model, and models with interaction with age group, severity of cholelithiasis, previous upper abdominal surgery and type of admission; p value of heterogeneity of the strata-specific estimates - Lazio Region, Italy, January 2007 - September 2008

	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p	P _{het}	
<u>30-day surgical-related complications: N=278, %=2.0</u>									
Open cholecystectomy	3,9	1,00	-	-	1,00	-	-	-	-
Laparoscopic cholecystectomy	1,7	0,44	0,33	0,57	0,000	0,60	0,44	0,80	0,001
Age (years)									0,917
< 70	1,8	0,49	0,35	0,71	0,000	0,62	0,43	0,90	0,012
70 - 79	2,9	0,45	0,26	0,76	0,003	0,57	0,33	0,98	0,043
≥ 80	3,3	0,41	0,15	1,12	0,082	0,51	0,18	1,38	0,184
Severity of cholelithiasis									0,053
Low	1,9	0,37	0,22	0,61	0,000	0,46	0,28	0,77	0,003
Moderate	2,0	0,58	0,40	0,85	0,005	0,78	0,53	1,16	0,224
High	3,7	0,24	0,11	0,53	0,000	0,30	0,13	0,68	0,004
Previous upper abdominal surgery									0,654
No	2,0	0,45	0,34	0,59	0,000	0,60	0,44	0,81	0,001
Yes	5,7	0,26	0,03	2,64	0,256	0,36	0,03	3,69	0,388
Type of admission									0,001
Elective	1,6	0,32	0,22	0,46	0,000	0,37	0,25	0,55	0,000
Emergency	3,0	0,76	0,51	1,13	0,178	0,94	0,62	1,42	0,764
<u>30-day systemic complications: N=280, %=2.1</u>									
Open cholecystectomy	5,2	1,00	-	-	1,00	-	-	-	-
Laparoscopic cholecystectomy	1,6	0,29	0,23	0,37	0,000	0,52	0,40	0,69	0,000
Age (years)									0,136
< 70	1,5	0,34	0,24	0,49	0,000	0,47	0,32	0,68	0,000
70 - 79	3,9	0,35	0,22	0,55	0,000	0,47	0,29	0,75	0,002
≥ 80	7,1	0,71	0,37	1,37	0,309	0,99	0,50	1,94	0,975
Severity of cholelithiasis									0,755
Low	1,2	0,29	0,16	0,51	0,000	0,43	0,24	0,77	0,005
Moderate	2,2	0,34	0,25	0,47	0,000	0,55	0,39	0,77	0,001
High	6,2	0,38	0,21	0,70	0,002	0,56	0,30	1,05	0,071
Previous upper abdominal surgery									0,702
No	2,0	0,29	0,22	0,37	0,000	0,52	0,39	0,69	0,000
Yes	4,3	0,41	0,04	4,69	0,470	0,86	0,07	10,40	0,905
Type of admission									0,545
Elective	1,5	0,33	0,23	0,50	0,000	0,48	0,32	0,72	0,000
Emergency	3,4	0,35	0,25	0,49	0,000	0,56	0,39	0,81	0,002

^c There are no 30-day complications in patients with moderately high severity and undergoing laparotomic cholecystectomy

SUPPLEMENTARY DATA

DETAILED METHODS

PART 1 - Cohort selection

Source of data: Hospital Information System (HIS)

Inclusion criteria

All hospital admissions with a primary or secondary contributing diagnosis of *cholelithiasis* (International Classification of Diseases 9th Revision, Clinical Modification - ICD9-CM = 574) and a procedure code of *cholecystectomy* (ICD9-CM 51.22, 51.23), occurred in private and public hospitals of the Lazio Region between January 2007 and September 2008 were included, for a total of 16,432 cases. The final population, after sequential exclusions, consisted of 13,651 subjects.

Exclusion criteria

- long-term hospitalizations, rehabilitations and day-hospitals
- patients residents outside the Lazio Region
- subjects younger than 18 or older than 100 years old
- hospitalizations for delivery (MDC 14)
- hospitalizations for any type of trauma (ICD-9-CM codes ICD-9-CM 800-897)
- hospitalizations with diagnoses of cancer of the digestive system (ICD-9-CM codes 150-159)
- hospitalizations with other abdominal surgical procedures (selected ICD-9-CM codes)

PART 2 - Codes to describe severity of cholelithiasis

1 - Cholelithiasis of the biliary tract without complications

574.20; 574.50; 574.90

2. Cholelithiasis of the biliary tract with cholecystitis (without obstruction)

574.10; 574.40; 574.70; 575.1 AND 574.20 or 574.50 or 574.90; 574.00; 574.30; 574.60; 574.80; 575.0 AND 574.20 or 574.50 or 574.90

3. Cholelithiasis of the biliary tract with obstruction (without cholecystitis)

574.21; 574.51; 574.01; 574.91; 575.2 AND 574.20 or 574.50 or 574.90; 576.2 AND 574.20 or 574.50 or 574.90; 575.3

4. Cholelithiasis of the biliary tract with both obstruction and cholecystitis

574.01; 574.11; 574.31; 574.41; 574.61; 574.71; 574.81; 575.2 AND 574.00; 575.0 AND 574.20 575.1 AND 574.20 574.30; 575.0 AND 574.50; 575.1 AND 574.50; 574.60; 574.70; 574.80; 576.1; 576.2 AND 574.00; 575.0 AND 574.20; 575.1 AND 574.20; 574.30; 575.0 AND 574.50; 575.1 AND 574.50; 574.60; 574.70; 574.80

PART 3 - Codes to describe previous upper abdominal surgery

Codes in the index admission – post procedural states

stomach V44.1, V45.75, V55.1; *intestine* V44.2, V44.4, V45.3, V45.72, V53.5, V55.2, V55.4, V42.84; *liver* V42.7; *pancreas* 42.83

Codes in the previous 2-year- hospitalizations

Stomach

43.5,43.6,43.7,,43.8,43.9,44.31,44.39,44.40,44.41,44.42,44.5,44.61,44.63,44.64,44.65,44.69

Small intestine

45.31,45.32,45.33,45.34,45.50,45.51,45.6,45.9,45.91,45.92,45.93,46.01,46.02,46.60,46.61,
46.62,46.71,46.72,46.73,46.74,46.80,46.81,46.93,46.97

Liver

50.2,50.3, 50.4,50.5,50.6

Pancreas

52.22,52.3,52.4,52.5,52.6,52.7,52.8,52.95,52.96

Abdominal Hernia

53.4,53.5,53.6,53.7

Peritoneum

54.4,54.5,54.6,54.7

Large intestine

45.41,45.49,45.7,45.8,45.94,46.03,46.04,46.63,46.64,46.75,46.76,46.79

Other surgery

55.4,55.5,56.2,56.4,57.1,57.6,57.7,65.3,65.4,65.5,65.6,66.4,66.5,68.3,68.4,68.6,68.8

PART 4 - Codes to describe coexisting conditions

On the basis of previous 2-year hospitalizations (following a validated coding algorithm – enhanced Elixhauser AHRQ-Web-ICD-9-CM - see reference n. 17 cited in the text).

diabetes 250.xx; hypertension 401-405; obesity 280.0, ischemic disease 410-414, 429.7, previous revascularization V45.81, V45.82, procedures 36.0, 36.1, heart failure 428, other cardiac disease 093.2, 391, 393-398, 420-425, 429, 745, 746.3-646.6, V15.1, V42.2, V43.2, V43.3, V45.0 arrhythmia / conduction disorders 426-427, cerebrovascular disease 430-438, vascular disease 440-448, 557, hematologic disorders 280-285, 286, 287.1, 287.3-287.5, 288, 289, chronic respiratory disease 490-496, 518.81, 518.82, chronic liver disease / pancreas 571, 572, 577.1, 577.9, chronic renal disease 582-583, 585-588, V42.0, V45.1m V56, cancer 140-208.9

PART 5 - Codes to describe outcomes

A) Surgical-related complications (within 30 day after the surgery)

in the index or in the subsequent hospitalizations (excluding hospitalizations for trauma ICD-9-CM 800-897) and delivery (MDC 14)

at least one of the following:

998.1 Hemorrhage or hematoma or seroma complicating a procedure; 998.2 Accidental puncture or laceration during a procedure; 998.3 Disruption of wound; 998.4 Foreign body accidentally left during a procedure; 998.5 Postoperative infection; 998.6 Persistent postoperative fistula; 998.7 Acute reaction to foreign substance accidentally left during a procedure; 998.81 Emphysema (subcutaneous) (surgical) resulting from a procedure; 998.83 Non-healing surgical wound; 998.89 Other specified complications; 997.4 Digestive system complications; 998.9 Unspecified complication of procedure, not elsewhere classified

1
2
3 Only in the subsequent hospitalizations

4
5 at least one of the following:

6 *567 Peritonitis and retroperitoneal infections; 575.4 Perforation of gallbladder; 575.5 Fistula*
7 *of gallbladder; 576.0 Postcholecystectomy syndrome; 576.3 Perforation of bile duct; 576.4*
8 *Fistula of bile duct; 570 Acute and subacute necrosis of liver; 789.0 Abdominal pain*

9
10
11 **B) Systemic complications (within 30 day after the surgery)**

12 in the index or in the subsequent hospitalizations (excluding hospitalizations for trauma ICD-9-CM
13 800-897) and delivery (MDC 14)

14
15
16 at least one of the following:

17 *997.0 Nervous system complications; 997.1 Cardiac complications; 997.3 Respiratory*
18 *complications; 998.0 Postoperative shock; 410 Acute myocardial infarction; 415.1 Pulmonary*
19 *embolism and infarction; 431 Intracerebral haemorrhage; 433.x1 Occlusion and stenosis of*
20 *precerebral arteries with infarction; 434.x1 Occlusion of cerebral arteries with infarction; 436*
21 *Acute, but ill-defined, cerebrovascular disease; 480-486 Pneumonia; 513.0 Abscess of lung*
22 *518.4 Acute edema of lung, unspecified; 518.5 Pulmonary insufficiency following trauma and*
23 *surgery; 785.5 Shock without mention of trauma; 788.2 Retention of urine*

24
25
26 Only in the subsequent hospitalizations

27 *038 Septicemia*
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SUPPLEMENTARY DATA

DETAILED METHODS

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- hospitalizations for any type of trauma (ICD-9-CM codes ICD-9-CM 800-897)
- hospitalizations with diagnoses of cancer of the digestive system (ICD-9-CM codes 150-159)
- hospitalizations with other abdominal surgical procedures (selected ICD-9-CM codes, as

follows:

~~ICD-9-CM code Description~~

~~Stomach~~

- ~~43.5 Partial gastrectomy with anastomosis to esophagus~~
- ~~43.6 Partial gastrectomy with anastomosis to duodenum~~
- ~~43.7 Partial gastrectomy with anastomosis to jejunum~~
- ~~43.8 Other partial gastrectomy~~
- ~~43.9 Total gastrectomy~~
- ~~44.31 High gastric bypass~~
- ~~44.39 Other gastroenterostomy~~
- ~~44.40 Suture of peptic ulcer, not otherwise specified~~
- ~~44.41 Suture of gastric ulcer site~~
- ~~44.42 Suture of duodenal ulcer site~~
- ~~44.5 Revision of gastric anastomosis~~
- ~~44.61 Suture of laceration of stomach~~
- ~~44.63 Closure of other gastric fistula~~
- ~~44.64 Gastropexy~~
- ~~44.65 Esophagogastroplasty~~
- ~~44.69 Other~~

~~Small intestine~~

- ~~45.31 Other local excision of lesion of duodenum~~
- ~~45.32 Other destruction of lesion of duodenum~~
- ~~45.33 Local excision of lesion or tissue of small intestine, except duodenum~~
- ~~45.34 Other destruction of lesion of small intestine, except duodenum~~
- ~~45.50 Isolation of intestinal segment, not otherwise specified~~

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7	<i>45.51 Isolation of segment of small intestine</i> _____
8	<i>45.6 Other excision of small intestine</i> _____
9	<i>45.9 Intestinal anastomosis</i> _____
10	<i>45.91 Small-to-small intestinal anastomosis</i> _____
11	<i>45.92 Anastomosis of small intestine to rectal stump</i> _____
12	<i>45.93 Other small to large intestinal anastomosis</i> _____
13	<i>46.01 Exteriorization of small intestine</i> _____
14	<i>46.02 Resection of exteriorized segment of small intestine</i> _____
15	<i>46.60 Fixation of intestine, not otherwise specified</i> _____
16	<i>46.61 Fixation of small intestine to abdominal wall</i> _____
17	<i>46.62 Other fixation of small intestine</i> _____
18	<i>46.71 Suture of laceration of duodenum</i> _____
19	<i>46.72 Closure of fistula of duodenum</i> _____
20	<i>46.73 Suture of laceration of small intestine, except duodenum</i> _____
21	<i>46.74 Closure of fistula of small intestine, except duodenum</i> _____
22	<i>46.80 Intra-abdominal manipulation of intestine, not otherwise specified</i> _____
23	<i>46.81 Intra-abdominal manipulation of small intestine</i> _____
24	<i>46.93 Revision of anastomosis of small intestine</i> _____
25	<i>46.97 Transplant of intestine</i> _____
26	Liver _____
27	<i>50.2 Local excision or destruction of liver tissue or lesion</i> _____
28	<i>50.3 Lobectomy of liver</i> _____
29	<i>50.4 Total hepatectomy</i> _____
30	<i>50.5 Liver transplant</i> _____
31	<i>50.6 Repair of liver</i> _____
32	_____
33	Pancreas _____
34	<i>52.22 Other excision or destruction of lesion or tissue of pancreas or pancreatic duct</i> _____
35	<i>52.3 Marsupialization of pancreatic cyst</i> _____
36	<i>52.4 Internal drainage of pancreatic cyst</i> _____
37	<i>52.5 Partial pancreatectomy</i> _____
38	<i>52.6 Total pancreatectomy</i> _____
39	<i>52.7 Radical pancreaticoduodenectomy</i> _____
40	<i>52.8 Transplant of pancreas</i> _____
41	<i>52.95 Other repair of pancreas</i> _____
42	<i>52.96 Anastomosis of pancreas</i> _____
43	_____
44	Abdominal Hernia _____
45	<i>53.4 Repair of umbilical hernia</i> _____
46	<i>53.5 Repair of other hernia of anterior abdominal wall (without graft or prosthesis)</i> _____
47	<i>53.6 Repair of other hernia of anterior abdominal wall with graft or prosthesis</i> _____
48	<i>53.7 Repair of diaphragmatic hernia, abdominal approach</i> _____
49	_____
50	Peritoneum _____
51	<i>54.4 Excision or destruction of peritoneal tissue</i> _____
52	<i>54.5 Lysis of peritoneal adhesions</i> _____
53	<i>54.6 Suture of abdominal wall and peritoneum</i> _____
54	<i>54.7 Other repair of abdominal wall and peritoneum</i> _____
55	_____
56	Large intestine _____
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~~45.41 Excision of lesion or tissue of large intestine~~
~~45.49 Other destruction of lesion of large intestine~~
~~45.7 Open and other partial excision of large intestine~~
~~45.8 Total intra-abdominal colectomy~~
~~45.94 Large to large intestinal anastomosis~~
~~46.03 Exteriorization of large intestine~~
~~46.04 Resection of exteriorized segment of large intestine~~
~~46.63 Fixation of large intestine to abdominal wall~~
~~46.64 Other fixation of large intestine~~
~~46.75 Suture of laceration of large intestine~~
~~46.76 Closure of fistula of large intestine~~
~~46.79 Other repair of intestine~~

Other surgery

~~55.4 Partial nephrectomy~~
~~55.5 Complete nephrectomy~~
~~56.2 Ureterotomy~~
~~56.4 Ureterectomy~~
~~57.1 Cystotomy and cystostomy~~
~~57.6 Partial cystectomy~~
~~57.7 Total cystectomy~~
~~65.3 Unilateral oophorectomy~~
~~65.4 Unilateral salpingo-oophorectomy~~
~~65.5 Bilateral oophorectomy~~
~~65.6 Bilateral salpingo-oophorectomy~~
~~66.4 Total unilateral salpingectomy~~
~~66.5 Total bilateral salpingectomy~~
~~68.3 Subtotal abdominal hysterectomy~~
~~68.4 Total abdominal hysterectomy~~
~~68.6 Radical abdominal hysterectomy~~
~~68.8 Pelvic evisceration~~

PART 2 - Codes to describe severity of cholelithiasis

1 - Cholelithiasis of the biliary tract without complications

~~574.20 Calculus of gallbladder without mention of cholecystitis~~
~~574.50 Calculus of bile duct without mention of cholecystitis~~
~~574.90 Calculus of gallbladder and bile duct without cholecystitis~~

2. Cholelithiasis of the biliary tract with cholecystitis (without obstruction)

~~574.10 Calculus of gallbladder with other cholecystitis~~
~~574.40 Calculus of bile duct with other cholecystitis~~
~~574.70 Calculus of gallbladder and bile duct with other cholecystitis~~

575.1 Other cholecystitis AND
574.20 Calculus of gallbladder without mention of cholecystitis or or
574.50 Calculus of bile duct without mention of cholecystitis or or

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7 574.90 ~~Calculus of gallbladder and bile duct without cholecystitis~~
8 574.00 ~~Calculus of gallbladder with acute cholecystitis~~
9 574.30 ~~Calculus of bile duct with acute cholecystitis~~
10 574.60 ~~Calculus of gallbladder and bile duct with acute cholecystitis~~
11 574.80 ~~Calculus of gallbladder and bile duct with acute and chronic cholecystitis~~

12
13 575.0 ~~Acute cholecystitis-AND~~

14 574.20 ~~Calculus of gallbladder without mention of cholecystitis or~~

15 574.50 ~~Calculus of bile duct without mention of cholecystitis or~~

16 574.90 ~~Calculus of gallbladder and bile duct without cholecystitis~~

17 ~~576.1 Cholangitis AND~~

18 ~~574.20 Calculus of gallbladder without mention of cholecystitis or~~

19 ~~574.50 Calculus of bile duct without mention of cholecystitis or~~

20 ~~574.90 Calculus of gallbladder and bile duct without cholecystitis~~

21 **3. Cholelithiasis of the biliary tract with obstruction (without cholecystitis)**

22 574.21 ~~Calculus of gallbladder without mention of cholecystitis~~

23 574.51 ~~Calculus of bile duct without mention of cholecystitis~~

24 574.91 ~~Calculus of gallbladder and bile duct without cholecystitis~~

25
26 575.2 ~~Obstruction of gallbladder-AND~~

27 574.20 ~~Calculus of gallbladder without mention of cholecystitis or~~

28 574.50 ~~Calculus of bile duct without mention of cholecystitis or~~

29 574.90 ~~Calculus of gallbladder and bile duct without cholecystitis~~

30
31 576.2 ~~Obstruction of bile duct-AND~~

32 574.20 ~~Calculus of gallbladder without mention of cholecystitis or~~

33 574.50 ~~Calculus of bile duct without mention of cholecystitis or~~

34 574.90 ~~Calculus of gallbladder and bile duct without cholecystitis~~

35 575.3 ~~Hydrops of gallbladder~~

36
37 **4. Cholelithiasis of the biliary tract with both obstruction and cholecystitis**

38 574.01 ~~Calculus of gallbladder with acute cholecystitis~~

39 574.11 ~~Calculus of gallbladder with other cholecystitis~~

40 574.31 ~~Calculus of bile duct with acute cholecystitis~~

41 574.41 ~~Calculus of bile duct with other cholecystitis~~

42 574.61 ~~Calculus of gallbladder and bile duct with acute cholecystitis~~

43 574.71 ~~Calculus of gallbladder and bile duct with other cholecystitis~~

44 574.81 ~~Calculus of gallbladder and bile duct with acute and chronic cholecystitis~~

45
46 575.2 ~~Obstruction of gallbladder-AND~~

47 574.00 ~~Calculus of gallbladder with acute cholecystitis~~

48 575.0 ~~Acute cholecystitis-AND~~ 574.20 ~~Calculus of gallbladder without mention of~~
49 ~~cholecystitis~~

50 575.1 ~~Other cholecystitis-AND~~ 574.20 ~~Calculus of gallbladder without mention of~~
51 ~~cholecystitis~~

52 574.30 ~~Calculus of bile duct with acute cholecystitis~~

53 575.0 ~~Acute cholecystitis-AND~~ 574.50 ~~Calculus of bile duct without mention of cholecystitis~~

54 575.1 ~~Other cholecystitis-AND~~ 574.50 ~~Calculus of bile duct without mention of cholecystitis~~

55 574.60 ~~Calculus of gallbladder and bile duct with acute cholecystitis~~

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- 574.70 ~~Calculus of gallbladder and bile duct with other cholecystitis~~
 574.80 ~~Calculus of gallbladder and bile duct with acute and chronic cholecystitis~~

576.1 cholangitis

576.2 ~~Obstruction of bile duct~~ AND

- 574.00 ~~Calculus of gallbladder with acute cholecystitis~~
 575.0 ~~Acute cholecystitis~~ AND 574.20 ~~Calculus of gallbladder without mention of cholecystitis~~
 575.1 ~~Other cholecystitis~~ AND 574.20 ~~Calculus of gallbladder without mention of cholecystitis~~
 574.30 ~~Calculus of bile duct with acute cholecystitis~~
 575.0 ~~Acute cholecystitis~~ AND 574.50 ~~Calculus of bile duct without mention of cholecystitis~~
 575.1 ~~Other cholecystitis~~ AND 574.50 ~~Calculus of bile duct without mention of cholecystitis~~
 574.60 ~~Calculus of gallbladder and bile duct with acute cholecystitis~~
 574.70 ~~Calculus of gallbladder and bile duct with other cholecystitis~~
 574.80 ~~Calculus of gallbladder and bile duct with acute and chronic cholecystitis~~

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PART 3 - Codes to describe previous upper abdominal surgery

Codes in the index admission – post procedural states

- stomach V44.1, V45.75, V55.1;
 intestine V44.2, V44.4, V45.3, V45.72, V53.5, V55.2, V55.4, V42.84;
 liver V42.7;
 pancreas 42.83

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Codes in the previous 2-year- hospitalizations

Stomach

- 43.5 ~~Partial gastrectomy with anastomosis to esophagus~~
 43.6 ~~Partial gastrectomy with anastomosis to duodenum~~
 43.7 ~~Partial gastrectomy with anastomosis to jejunum~~
 43.8 ~~Other partial gastrectomy~~
 43.9 ~~Total gastrectomy~~
 44.31 ~~High gastric bypass~~
 44.39 ~~Other gastroenterostomy~~
 44.40 ~~Suture of peptic ulcer, not otherwise specified~~
 44.41 ~~Suture of gastric ulcer site~~
 44.42 ~~Suture of duodenal ulcer site~~
 44.5 ~~Revision of gastric anastomosis~~
 44.61 ~~Suture of laceration of stomach~~
 44.63 ~~Closure of other gastric fistula~~
 44.64 ~~Gastropexy~~
 44.65 ~~Esophagogastroplasty~~
 44.69 ~~Other~~

Small intestine

- 45.31 ~~Other local excision of lesion of duodenum~~

~~45.32-Other destruction of lesion of duodenum~~
~~45.33-Local excision of lesion or tissue of small intestine, except duodenum~~
~~45.34-Other destruction of lesion of small intestine, except duodenum~~
~~45.50-Isolation of intestinal segment, not otherwise specified~~
~~45.51-Isolation of segment of small intestine~~
~~45.6-Other excision of small intestine~~
~~45.9-Intestinal anastomosis~~
~~45.91-Small to small intestinal anastomosis~~
~~45.92-Anastomosis of small intestine to rectal stump~~
~~45.93-Other small to large intestinal anastomosis~~
~~46.01-Exteriorization of small intestine~~
~~46.02-Resection of exteriorized segment of small intestine~~
~~46.60-Fixation of intestine, not otherwise specified~~
~~46.61-Fixation of small intestine to abdominal wall~~
~~46.62-Other fixation of small intestine~~
~~46.71-Suture of laceration of duodenum~~
~~46.72-Closure of fistula of duodenum~~
~~46.73-Suture of laceration of small intestine, except duodenum~~
~~46.74-Closure of fistula of small intestine, except duodenum~~
~~46.80-Intra-abdominal manipulation of intestine, not otherwise specified~~
~~46.81-Intra-abdominal manipulation of small intestine~~
~~46.93-Revision of anastomosis of small intestine~~
~~46.97-Transplant of intestine~~

Liver

~~50.2-Local excision or destruction of liver tissue or lesion~~
~~50.3-Lobectomy of liver~~
~~50.4-Total hepatectomy~~
~~50.5-Liver transplant~~
~~50.6-Repair of liver~~

Pancreas

~~52.22-Other excision or destruction of lesion or tissue of pancreas or pancreatic duct~~
~~52.3-Marsupialization of pancreatic cyst~~
~~52.4-Internal drainage of pancreatic cyst~~
~~52.5-Partial pancreatectomy~~
~~52.6-Total pancreatectomy~~
~~52.7-Radical pancreaticoduodenectomy~~
~~52.8-Transplant of pancreas~~
~~52.95-Other repair of pancreas~~
~~52.96-Anastomosis of pancreas~~

Abdominal Hernia

~~53.4-Repair of umbilical hernia~~
~~53.5-Repair of other hernia of anterior abdominal wall (without graft or prosthesis)~~
~~53.6-Repair of other hernia of anterior abdominal wall with graft or prosthesis~~
~~53.7-Repair of diaphragmatic hernia, abdominal approach~~

Peritoneum

~~54.4-Excision or destruction of peritoneal tissue~~
~~54.5-Lysis of peritoneal adhesions~~

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7 54.6 ~~Suture of abdominal wall and peritoneum~~
8 54.7 ~~Other repair of abdominal wall and peritoneum~~
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10 Large intestine

- 11 45.41 ~~Excision of lesion or tissue of large intestine~~
12 45.49 ~~Other destruction of lesion of large intestine~~
13 45.7 ~~Open and other partial excision of large intestine~~
14 45.8 ~~Total intra-abdominal colectomy~~
15 45.94 ~~Large-to-large intestinal anastomosis~~
16 46.03 ~~Exteriorization of large intestine~~
17 46.04 ~~Resection of exteriorized segment of large intestine~~
18 46.63 ~~Fixation of large intestine to abdominal wall~~
19 46.64 ~~Other fixation of large intestine~~
20 46.75 ~~Suture of laceration of large intestine~~
21 46.76 ~~Closure of fistula of large intestine~~
22 46.79 ~~Other repair of intestine~~

23 Other surgery

- 24 55.4 ~~Partial nephrectomy~~
25 55.5 ~~Complete nephrectomy~~
26 56.2 ~~Ureterotomy~~
27 56.4 ~~Ureterectomy~~
28 57.1 ~~Cystotomy and cystostomy~~
29 57.6 ~~Partial cystectomy~~
30 57.7 ~~Total cystectomy~~
31 65.3 ~~Unilateral oophorectomy~~
32 65.4 ~~Unilateral salpingo-oophorectomy~~
33 65.5 ~~Bilateral oophorectomy~~
34 65.6 ~~Bilateral salpingo-oophorectomy~~
35 66.4 ~~Total unilateral salpingectomy~~
36 66.5 ~~Total bilateral salpingectomy~~
37 68.3 ~~Subtotal abdominal hysterectomy~~
38 68.4 ~~Total abdominal hysterectomy~~
39 68.6 ~~Radical abdominal hysterectomy~~
40 68.8 ~~Pelvic evisceration~~
41

42 **PART 4 - Codes to describe coexisting conditions**

43 On the basis of previous 2-year hospitalizations (following a validated coding algorithm – enhanced
44 Elixhauser AHRQ-Web-ICD-9-CM - see reference n. 17 cited in the text).

45
46 diabetes 250.xx; hypertension 401-405; obesity 280.0, ischemic disease 410-414, 429.7, previous
47 revascularization V45.81, V45.82, procedures 36.0, 36.1, heart failure 428, other cardiac disease
48 093.2, 391, 393-398, 420-425, 429, 745, 746.3-646.6, V15.1, V42.2, V43.2, V43.3, V45.0
49 arrhythmia / conduction disorders 426-427, cerebrovascular disease 430-438, vascular disease 440-
50 448, 557, hematologic disorders 280-285, 286, 287.1, 287.3-287.5, 288, 289, chronic respiratory
51 disease 490-496, 518.81, 518.82, chronic liver disease / pancreas 571, 572, 577.1, 577.9, chronic
52 renal disease 582-583, 585-588, V42.0, V45.1m V56, cancer 140-208.9
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7 **PART 5 - Codes to describe outcomes**
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9 **A) Surgical-related complications (within 30 day after the surgery)**
10 in the index or in the subsequent hospitalizations (excluding hospitalizations for trauma ICD-9-
11 CM 800-897) and delivery (MDC 14)

12 at least one of the following:

- 13 998.1 Hemorrhage or hematoma or seroma complicating a procedure
14 998.2 Accidental puncture or laceration during a procedure
15 998.3 Disruption of wound
16 998.4 Foreign body accidentally left during a procedure
17 998.5 Postoperative infection
18 998.6 Persistent postoperative fistula
19 998.7 Acute reaction to foreign substance accidentally left during a procedure
20 998.81 Emphysema (subcutaneous) (surgical) resulting from a procedure
21 998.83 Non-healing surgical wound
22 998.89 Other specified complications
23 997.4 Digestive system complications
24 998.9 Unspecified complication of procedure, not elsewhere classified

25
26 Only in the subsequent hospitalizations

27 at least one of the following:

- 28 567 Peritonitis and retroperitoneal infections
29 575.4 Perforation of gallbladder
30 575.5 Fistula of gallbladder
31 576.0 Postcholecystectomy syndrome
32 576.3 Perforation of bile duct
33 576.4 Fistula of bile duct
34 570 Acute and subacute necrosis of liver
35 789.0 Abdominal pain
36

37
38 **B) Systemic complications (within 30 day after the surgery)**
39

40 in the index or in the subsequent hospitalizations (excluding hospitalizations for trauma ICD-9-CM
41 800-897) and delivery (MDC 14)

42 at least one of the following:

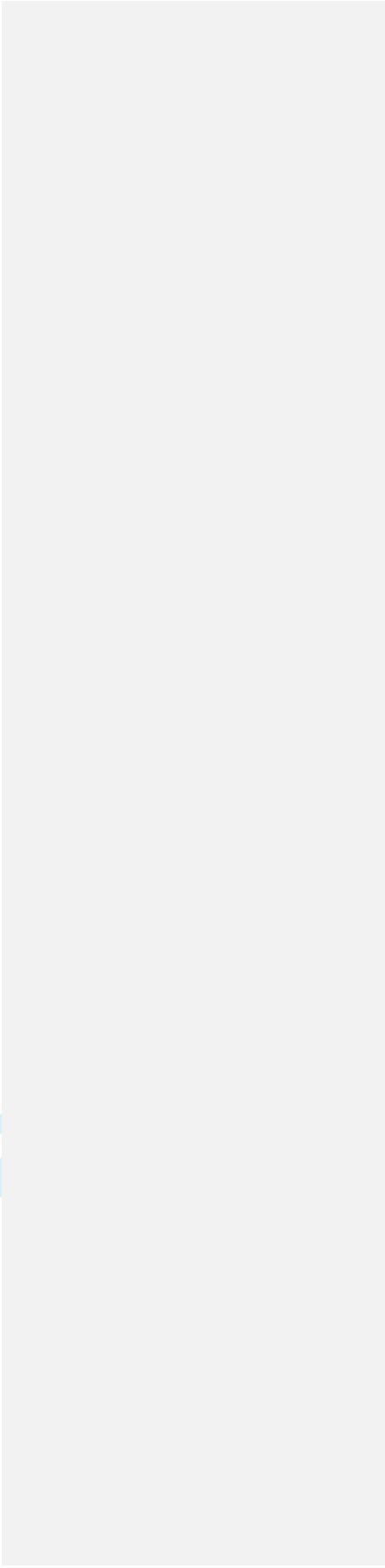
- 43 997.0 Nervous system complications
44 997.1 Cardiac complications
45 997.3 Respiratory complications
46 998.0 Postoperative shock
47 410 Acute myocardial infarction
48 415.1 Pulmonary embolism and infarction
49 431 Intracerebral hemorrhage
50 433.x1 Occlusion and stenosis of precerebral arteries with infarction
51 434.x1 Occlusion of cerebral arteries with infarction
52 436 Acute, but ill-defined, cerebrovascular disease
53 480-486 Pneumonia
54 513.0 Abscess of lung
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518.4 Acute edema of lung, unspecified
518.5 Pulmonary insufficiency following trauma and surgery
785.5 Shock without mention of trauma
788.2 Retention of urine

Only in the subsequent hospitalizations
038 Septicemia

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

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3 **Thirty-day complications after laparoscopic or open cholecystectomy: a population-**
4 **based cohort study in Italy.**
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3 **Thirty-day complications after laparoscopic or open cholecystectomy: a population-**
4 **based cohort study in Italy.**
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8
9 **Abstract**

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11 **Objective**

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14 The objective of the study is to evaluate short-term complications after laparoscopic (LC) or
15 open cholecystectomy (OC) in patients with gallstones by using linked hospital discharge
16 data.
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21 **Design**

22 Population-based cohort study.
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24

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26 **Setting**

27 Data were obtained from the Regional Hospital Discharge Registry Lazio Region in Central
28 Italy (around 5 million inhabitants) in 2007-2008.
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32 **Participants**

33 All patients admitted to hospitals of Lazio with symptomatic gallstones (ICD9-CM = 574)
34 who underwent LC (ICD9-CM 51.23) or OC (ICD9-CM 51.22).
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39 **Outcome measures**

40 1)“30-day surgical-related complications” defined as any complication of the biliary tract
41 (including post-operative infection, hemorrhage or hematoma or seroma complicating a
42 procedure, persistent postoperative fistula, perforation of bile duct, disruption of wound); 2)
43 “30-day systemic complications” defined as any complications of other organs (including
44 sepsis, infections from other organs, major cardiovascular events and selected adverse
45 events).
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54 **Results**
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3 13,651 patients were included; 86.1% had LC, 13.9% OC. 2.0% experienced surgical-related
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5 complications (SRC), 2.1% systemic complications (SC). The Odds Ratio (OR) of
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7 complications after LC versus OC was 0.60 ($p<0.001$) for SRC and 0.52 ($p<0.001$) for SC. As
8
9 regards SRC, the advantage of LC was consistent across age categories, severity of gallstones
10
11 and previous upper abdominal surgery, while there was no advantage among people with
12
13 emergency admission (OR=0.94, $p = 0.764$). For SC, no significant advantage of LC was seen
14
15 among very old people (OR=0.99, $p=0.975$) and among those with previous upper abdominal
16
17 surgery (OR=0.86, $p=0.905$).
18
19

20 21 **Conclusions**

22
23 This large observational study confirms that LC is more effective than OC with respect to 30-
24
25 day complications. Population-based linkage of administrative datasets can enlarge evidence
26
27 of treatment benefits in clinical practice.
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34 **Key words:** administrative data, cohort study, effectiveness, gallstones, hospital discharge
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36 data, laparoscopic cholecystectomy, open cholecystectomy, outcomes, population-based,
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38 post-operative complications.
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Article summary

Article focus

-The advantage of laparoscopic cholecystectomy (LC) approach for the treatment of gallstone versus open surgery (OC) has been shown from RCTs and observational studies.

-The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments.

-We compared laparoscopic and open cholecystectomy in term of 30-day complications using routinely collected databases in Lazio Region (Italy).

Key messages

-This population-based study contributes to enlarge the evidence on effectiveness of LC in a real-life setting.

-As regards surgical-related complications, the advantage of LC was consistent across age categories, severity of gallstones and previous upper abdominal surgery, while there was no advantage among people with emergency admission.

-For systemic complications, no significant advantage of LC was seen among very old people and among those with previous upper abdominal surgery.

Strengths and limitations

-Population-based design, 30-day outcomes, large numbers and robustness of analytic procedures are the main strengths.

-It contributes to the debate on the complex methodology to estimated risk of adverse events after surgery using secondary databases to monitor quality of care.

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-The use of ICD-9-CM codes in the definition of severity of disease presentation and of complications is a major limit.

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Introduction

Comparative effectiveness research is becoming central to monitor real-life impact of treatments and support public health decisions (1, 2). Although the basic concept of comparing therapies is not new, over the last few years many initiatives have been implemented in several countries to provide large-scale evidence on benefits and harms of different treatments (3-5). The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments. They include hospital in-patients records, birth and death registrations, outpatient care records, dispensed pharmacy drugs (6-9).

In the Lazio Region (around 5.000.000 inhabitants) the P.Re.Val.E. Project (*Regional Program for Assessing the Outcomes of Health-care Interventions*) was launched in 2005. Its aims are: to measure the quality of health care provided in the Lazio Region, to describe variability of care provision across institutions and populations and to compare effectiveness of treatments for different medical and surgical conditions (10,11). Over 60 outcomes indicators are calculated based on data obtained from record-linkage procedures of different health systems. The results are periodically updated and publicly disseminated with discussion on critical methodological points.

Cholecystectomy is one of the most common abdominal surgical procedures in developed countries. Since its introduction in the late '80s, laparoscopic cholecystectomy (LC) has replaced open cholecystectomy (OC) as the treatment of choice for symptomatic gallstones (12, 13). Beneficial effects of LC have been demonstrated in studies showing the advantages from real-life settings using secondary databases (9,14-19). In the present study we aimed at developing a methodology to measure short-term complications after LC or OC using large administrative databases on behalf of the P.Re.Val.E. Secondly, we tested the hypothesis that

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3 the advantages of LC versus OC could vary according to age and clinical patients'
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5 characteristics.
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11 12 13 14 **Methods**

15 16 Source of data

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18 Data was derived from the Lazio Hospital Information System (HIS), which provides
19
20 information on patients' demographic data (gender, age, place of birth, place of residence),
21
22 admission and discharge dates, discharge diagnoses (up to 6) and medical procedures or
23
24 surgical interventions ((up to 6) according to the International Classification of disease, Ninth
25
26 Revision, Clinical Modification (ICD-9-CM), status at discharge (alive, dead, transferred to
27
28 another hospital), ward(s) of stay, date(s) of in-hospital transfer, and a regional code
29
30 corresponding to the admitting facility for patients discharged from all public and private
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32 hospital of the Lazio Region (5.759.839 inhabitants).
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39 Study population

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41 All hospital admissions with a primary or secondary diagnosis of gallstones (International
42
43 Classification of Diseases 9th Revision, Clinical Modification - ICD9-CM = 574) and a
44
45 procedure code of cholecystectomy (ICD9-CM 51.22, 51.23), occurred in private and public
46
47 hospitals of the Lazio Region between January 2007 and September 2008 were included, for a
48
49 total of 16,432 cases (age 18+ years). We a priori decided not to include codes for partial
50
51 cholecystectomy (ICD-9-CM 51.21 and 51.24) to increase the specificity of our exposure.
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53 Information was retrieved from the HIS. In order to increase the case specificity, several
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55 exclusion criteria were applied including long-term hospitalizations, rehabilitations, day-
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3 hospitals, hospitalizations for delivery or trauma or cancer, hospitalizations with abdominal
4 surgical procedures other than cholecystectomy. The final population consisted of 13,651
5 subjects (**Figure 1**). See the online **Supplementary Data** (Part 1) for details on the exclusion
6 criteria and ICD9-CM codes. According to the Regional Law, the present study, which was
7 based on anonymous computer records from health information systems, did not require for
8 ethical approval.
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16 17 18 Patient-level risk factors 19

20 The following characteristics were considered for each patient: Age (<70; 70-79; >=80 years
21 old); Gender; Severity of gallstones: it was classified as *low* (not-complicated), *moderate*
22 (presence of cholecystitis or biliary tract obstruction), and *high* (presence of both
23 inflammation and obstruction of the biliary tract); Previous upper abdominal surgery (based
24 on previous 2-year hospitalizations); Comorbidities (based on previous 2-year
25 hospitalizations) following validated algorithms (20,21); Type of admission: either *elective* or
26 *emergency*. See the online **Supplementary Data** (Part 2-4) for details on the ICD-9-CM
27 codes. The choice of *cut off* for age category was based on previous studies to distinguish
28 adult and old people (22-24).
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40 Outcomes 41

42 We identified various complications within 30-days after the intervention and grouped them
43 in two categories: 1) “*30-day surgical-related complications*” defined as any complication of
44 the biliary tract (including post-operative infection, hemorrhage or hematoma or seroma
45 complicating a procedure, persistent postoperative fistula, perforation of bile duct, disruption
46 of wound ()); 2) “*30-day systemic complications*” defined as any complications of other organs
47 (including sepsis, infections from other organs, major cardiovascular events and
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3 selected adverse events). The complete list of complications with ICD-9-CM codes is
4 reported in the online **Supplementary Data** (Part 5). Among the various complications we
5 included some conditions reported in the list of Patient Safety Indicators recently developed
6 by the Agency for Health Care Research and Quality, while other items were specifically
7 created on the basis of scientific literature on digestive surgery (14-19,25,26). Depending on
8 the type of complication, some ICD9-CM codes were searched in both the index admission
9 and the following ones in the 30-day period after the surgery, others were searched only in
10 later hospitalizations. For example, peritonitis or acute pancreatitis was not counted as
11 complications when reported in the index admission. See the online **Supplementary Data**
12 (Part 5) for details on the ICD9-CM codes. In the case of a subsequent hospitalization
13 occurred out of the study area (for example, in a region other than Lazio), we obtained
14 information through record linkage procedure between hospital information systems. Because
15 of the short follow up time, this happened in a minimal proportion of cases (0.1%). The
16 outcome variables were: “*30-day surgical-related complications*” and “*30-day systemic*
17 *complications*”; they were coded “1” if at least one of the complications within the group was
18 present and “0” if none was recorded.
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40 Type of cholecystectomy

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42 As exposure variable we defined “*type of cholecystectomy*” (laparoscopic cholecystectomy,
43 LC vs. open cholecystectomy, OC). In the case of ICD-9-CM codes for both LC and OC
44 (5%), the patient was considered exposed to the open surgical procedure. We could not use
45 the specific ICD-9-code for a case converted from LC to OC (ICD-9-CM code V 64.41)
46 because it was highly under-reported in our Region in the study period.
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55 Statistical analysis

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3 Multiple logistic regression models were fitted to estimate the relative risk of 30-day
4 complications (either “surgical-related” or “systemic”) after LC versus OC, adjusting for
5 demographical and clinical risk factors. The two outcome variables were analysed separately.
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7 The predictive model was made of two sets of predictors: 1) variables “a priori” chosen as
8 confounders (age, gender, severity of gallstones, previous upper abdominal surgery, and type
9 of admission); 2) variables empirically tested (comorbidities) which were selected using
10 iterative stepwise statistical procedures) (27). Once the “best” predictive model was identified
11 for each of the two outcome, the variable “*type of cholecystectomy*” was included, and the
12 adjusted odds ratio (OR) of LC versus open surgery was estimated, with corresponding 95%
13 confidence interval (95% CI) and p-value.
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27 In order to test the hypothesis of an effect modification by age, relative risk estimates for the
28 age groups were derived by adding an interaction term between the age group and the
29 treatment variable in the final multivariate logistic model. We obtained the OR of
30 laparoscopic vs. open surgery within each age stratum by adding the corresponding
31 interaction terms coefficients. This was accomplished by adding the coefficient from the
32 reference category and that from the age stratum of interest, and by computing the
33 corresponding standard error from the corresponding terms of the variance-covariance matrix.
34 Similarly, effect modification was tested with regard to severity of cholelithiasis, previous
35 upper abdominal surgery and type of admission. The corresponding tests of heterogeneity of
36 the stratum-specific risk estimates were computed.
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51 Sensitivity analyses were performed. First, in order to guarantee adequate control of
52 confounding factors we identified and adjusted for all the individual factors associated with
53 the treatment, within the propensity adjustment framework (28). This procedure is a two-step
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3 technique: 1. it estimates the a priori probability of exposure for each subject, based on
4 clinical and demographic characteristics; 2. it standardizes for them in the association between
5 treatment and the study outcome. The individual factors related to the exposure in the present
6 study include age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of
7 admission, cardio-circulatory disease, cerebrovascular disease, COPD or respiratory failure,
8 chronic nephropathy, chronic disease of the liver or pancreas. Second, to take into account the
9 potential heterogeneous experience in laparoscopic surgery across different hospitals because
10 of the patients' clustering within a single institution we perform a multilevel regression model
11 with random intercepts for hospitals (29).
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25 All the statistical analyses were performed using SAS Software version 8.0 (SAS Institute,
26 Inc. SAS/STAT software).
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34 **Results**

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36 A description of the study population, overall and by cholecystectomy procedure, is presented
37 in **Table 1**. Over 80% of the patients were younger than 70 years, and moderate to high
38 severity of the gallstones was diagnosed for 61.7%. As compared with patients undergoing
39 LC, those who underwent OC were more likely to be elderly, males, with a more severe
40 baseline disease and more chronic conditions. Furthermore, they were operated in emergency
41 in most of the cases (52.4%), whereas LC was performed in elective hospitalizations much
42 more frequently (73.9%).
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54 **Table 2** reports the relationship between demographic and clinical variables and the
55 occurrence of complications. The adjusted risk of systemic complications increased with age
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3 and was much higher in patients with more severe baseline gallstones, whereas no clear age or
4 severity-related differences in risk emerged with regard to surgical-related 30-day
5 complications, once other co-factors were taken into account. Women were less likely to
6 experience both types of complications. Having had a previous intervention on the upper
7 digestive system seemed to enhance the risk of both surgical-related and systemic
8 complications, though results are not statistically significant due to small power. Finally, the
9 risk of both types of complications was more evident in emergency as opposed to scheduled
10 interventions. Surgical-related complications were higher among subjects with obesity, blood
11 disease, stroke or chronic nephropathy, whereas systemic complications were associated with
12 blood diseases, ischemic heart disease, conduction disorders or dysrhythmias, COPD or
13 respiratory failure, chronic nephropathy, and chronic diseases of the liver or pancreas.
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29 **Table 3** shows the relationship between type of cholecystectomy and outcomes, adjusted for
30 the risk factors identified in Table 2. We report results of the advantage of LC vs. OC (OR,
31 95% CI) in the cohort and in the each stratum of the variables tested in the models with
32 interaction terms. The incidence of “30-day surgical-related complications” and “30-day
33 systemic complications” was 2.0% and 2.1%, respectively. The odds ratio of surgical related
34 complications for patients who underwent LC as compared to patients with OC was 0.60
35 (p<0.001). The corresponding figure for systemic complications was 0.52 (p<0.001).
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45 As regards 30-day surgical-related complications, the protective effect of LC vs. OC was
46 consistent across the age category, severity of cholelithiasis and previous upper abdominal
47 surgery, while among people with emergency admission there was no advantage (OR=0.94 p
48 = 0.764). Similarly, for systemic complications, the superiority of LC vs. OC was consistent
49 regardless level of cholelithiasis severity, and elective/emergency admission, but for those
50 80+ yrs aged people there was no advantage of LC vs. OC (OR 0.99, p = 0.975); also for
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3 patients with previous upper abdominal surgery there was a much weaker advantage
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5 (OR=0.86, p=0.905).
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10 When the association between type of cholecystectomy and 30-day complications was
11
12 adjusted with the propensity adjustment method, results were consistent with those obtained
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14 with the risk-adjustment procedure (LC vs. OC OR= 0.61 and OR=0.52 respectively for the
15
16 two outcomes). Finally, results were similar taking into account patients' clustering within
17
18 different hospitals (*data not shown*).
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21 22 23 24 25 **Discussion**

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27 From this large observational study based on linked administrative health records - taking
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29 into account the disomogeneous distribution of factors related to the probability to be offered
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31 open surgery - people who end up having a LC have a better short-term prognosis than those
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33 that get an OC for the treatment of gallstones. The superiority of laparoscopic approach in
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35 term of 30-day complications is consistent in different age categories, different severity in
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37 disease presentation and past history of upper abdominal surgery.
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42 This population-based study contributes to enlarge the evidence on effectiveness of LC in a
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44 real-life setting by providing an example from the Southern Europe area. It supports the
45
46 usefulness of observational approaches. The 30-day outcomes linked to admission represent
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48 one strength of this study. Despite RTCs are considered the optimal study design when
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50 comparing efficacy of treatments, observational studies provide a picture of treatment under
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52 usual circumstances of health-care practice and can answer to the question “*Does it work in*
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54 *practice?*” (3,8). RTCs often have small sample size and may under represent vulnerable
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3 patient groups, including elderly patients with multiple comorbidities, children, and young
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5 women, and operate in a highly controlled environment that is far from routine clinical
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7 practice. Our study supports that LC is a reliable approach safer than OC not only in old age
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9 group - confirming previous findings (22, 30) - but also in presence of severe disease
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11 presentation and in patients with past history of upper digestive system surgery. Beneficial
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13 effect of LC as regards systemic complications tends to be lower in 80+ yrs aged in
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15 comparison with younger ages, and in patients with emergency admission in comparison to
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17 elective admissions as regards 30-day surgical-related complications. These data add to the
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19 evidence on the complex relationship between age and outcomes after surgery (22-24,30).
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25 A number of potential biases are present. First of all, people in the two groups of patients
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27 analyzed are not homogenous in term of anesthesia risk due to higher frequency of elderly
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29 and more comorbidities in the open group than in the laparoscopic one. When comparing the
30
31 effect of the two techniques using two different populations, the so called “indication bias”
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33 may affect study validity (8,31). To limit this problem we run the propensity adjustment
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35 analysis to take into account the different distribution of factors strongly associated with the
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37 probability to receive open surgery in the study population. This analytical approach
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39 confirmed the advantage of laparoscopic vs. open surgery obtained in the main logistic
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41 regression analysis. Another critical point is the potential different distribution of laparoscopic
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43 experience across surgeons; however a sensitivity analysis which took into account this point
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45 led to similar results. The use of ICD-9-CM codes in the definition of severity of disease
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47 presentation and of complications is another major limit. Discharge abstract data have little
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49 insight into clinical details and do not inform on the temporal relationship of the clinical
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51 conditions and processes, then defining complications is a difficult task (32). In this respect,
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53 we tried to improve the accuracy of our measures both 1) applying a specific coding
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3 algorithm with subsequent hospital admissions used to retrieve adverse events and 2)
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5 excluding in the “count” of complications specific items if reported in the index only (i.e.
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7 peritonitis) because of the difficulty to determine if it was already present at admission.
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9 Moreover, we cannot exclude an under-notification of complications – a major limit of our
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11 source of data - but it is unlikely that is influenced by the type of surgery. Another major
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13 problem is the potential misclassification of exposure since we were not able to measure the
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15 occurrence of conversion of LC to OC. The number of people that were switched from LC to
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17 OP is low in comparison to figures documented in other studies and it may represent a severe
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19 source of bias in our study (30,33).
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25 Beneficial effects of the laparoscopic approach versus traditional open surgery for the
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27 treatment of gallstones come from various randomized controlled trials (RCTs) (34). They
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29 found significant shorter hospital stay and quicker convalescence associated with LC but no
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31 differences in mortality, complications and operative time between the two procedures. A
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33 better trend with the laparoscopic approach, including morbidity and mortality, comes from
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35 observational studies. From a surveillance system in eight Swiss hospitals, surgical site
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37 infections were less common in laparoscopic approach in comparison to traditional open
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39 surgery (0.5% in LC vs. 1.8% in OC) (35). Significantly lower incidence of venous
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41 thromboembolism and surgical site-infections in laparoscopic cases versus open cases was
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43 observed in a large administrative dataset-based study in USA (14, 15). National estimates
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45 for LC in USA showed an increase in LC from 52% in 1991 to 75% in 2000 with a constantly
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47 low mortality rate and a decrease in biliary reconstruction rate over time (16). On the basis of
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49 the 1997-2006 trend analysis by the same authors LC was associated with a low mortality
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51 rate (mean value in the period: 0.52%) while OC with a significantly higher rate
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53 (corresponding value: 4.9%) (9). In a retrospective study using Medicare beneficiaries
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3 common bile duct (CBD) injury during cholecystectomy was associated with a significant
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5 higher risk of death in comparison to cholecystectomy without CBD injury over a 9.2 year
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7 follow up period (17). From a Swiss 1995-2005 hospital database analysis the incidence rate
8
9 of bile duct injury after LC was 0.3% and did not change over time (18). The incidence of
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11 conversion to OC after LC in all hospitals in England from 2005 to 2006 has been examined
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13 using Hospital Episode Statistics and resulted 4.6% for elective procedures and 9.4% for
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15 emergency procedures) (19).

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18 Population-based linkage of routinely collected health data represents a precious tool to
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20 support large- scale and real-world practice evaluation by measuring specific outcomes and
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22 comparing them over time and across populations. Together with results from experimental
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24 research settings, the conclusions of research studies evaluating clinical outcomes through
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26 data linkage systems should be successfully incorporated into practice by clinicians/surgeons.
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AUTHOR'S CONTRIBUTION

All Authors participated in the study design, in defining the study protocol and methodology, in acquisition of data, in planning the analyses, in interpreting the results. M.S. performed the analyses. N.A and M.S. drafted the manuscript.

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Figure 1. Selection of the study population

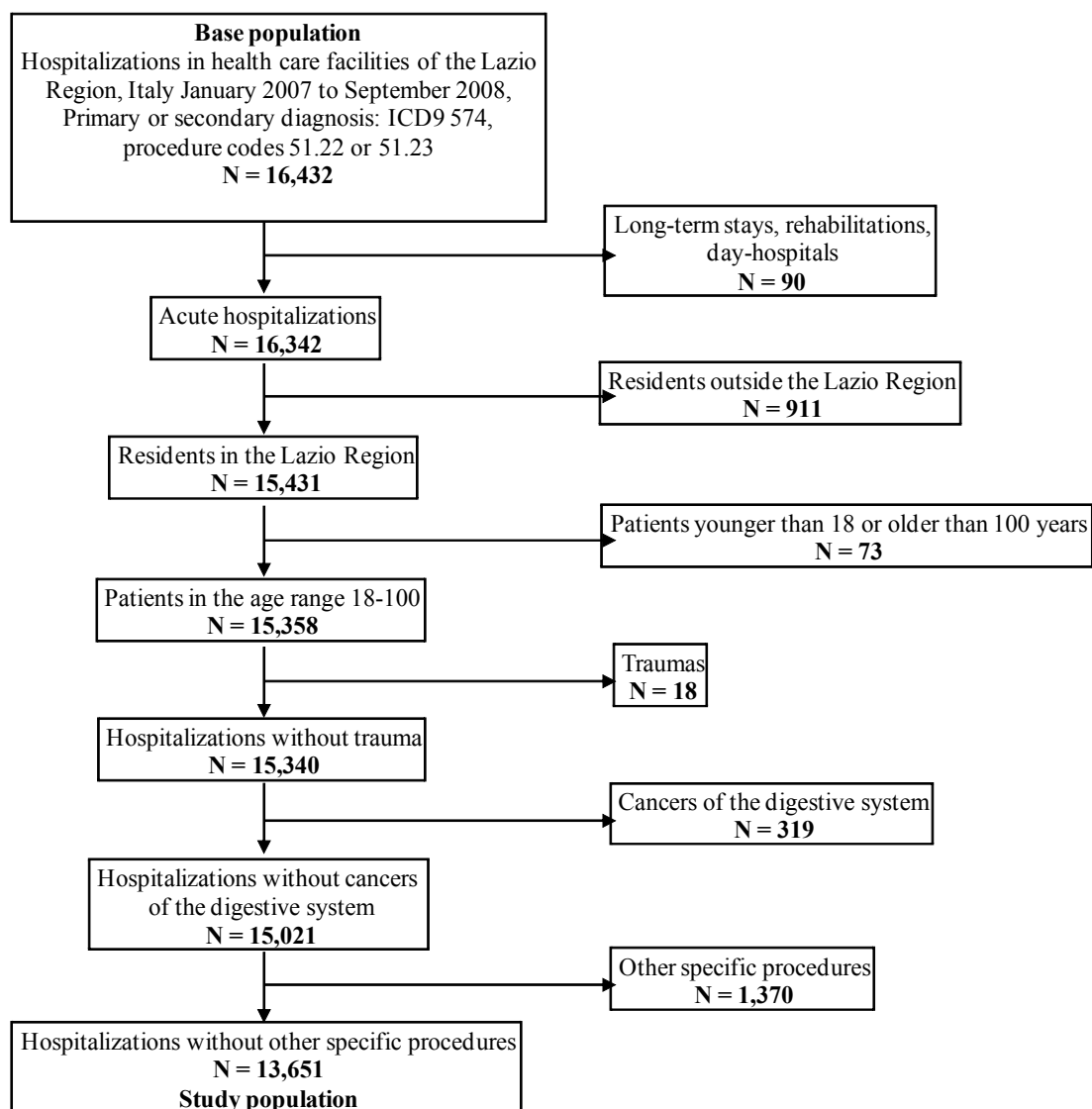


Table 1. Study population, overall and by cholecystectomy procedure: distribution by age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of admission, comorbidities - Lazio Region, Italy, January 2007-September 2008

Patient characteristics	Laparoscopic chole cystectomy		Open chole cystectomy		Total		
	N	%	N	%	N	%	
Total	11.752	86,1	1.899	13,9	13.651	100,0	
Age (years)							
	<70	9.913	84,4	1.162	61,2	11.075	81,1
	70-79	1.543	13,1	485	25,5	2.028	14,9
	≥ 80	296	2,5	252	13,3	548	4,0
		11.752					
Gender							
	Men	4.349	37,0	979	51,6	5.328	39,0
	Women	7.403	63,0	920	48,4	8.323	61,0
Severity of cholelithiasis							
	Low	4.767	40,6	470	24,7	5.237	38,4
	Moderate	6.456	54,9	1.200	63,2	7.656	56,1
	High	529	4,5	229	12,1	758	5,6
Previous upper abdominal surgery							
	No	11.714	99,7	1.867	98,3	13.581	99,5
	Yes	38	0,3	32	1,7	70	0,5
Type of admission							
	Elective	8.690	73,9	903	47,6	9.593	70,3
	Emergency	3.062	26,1	996	52,4	4.058	29,7
Comorbidities							
	Cancer	232	2,0	75	3,9	307	2,2
	Diabetes	268	2,3	100	5,3	368	2,7
	Obesity	115	1,0	25	1,3	140	1,0
	Blood disease	146	1,2	62	3,3	208	1,5
	Hypertension	842	7,2	247	13,0	1.089	8,0
	Ischemic heart disease	246	2,1	107	5,6	353	2,6
	Past coronary revascularization	63	0,5	22	1,2	85	0,6
	Heart failure	47	0,4	41	2,2	88	0,6
	Other heart disease	158	1,3	76	4,0	234	1,7
	Conduction disorders or dysrhythmia	250	2,1	95	5,0	345	2,5
	Cerebrovascular disease	146	1,2	74	3,9	220	1,6
	Vascular disease	91	0,8	38	2,0	129	0,9
	COPD* or respiratory failure	189	1,6	84	4,4	273	2,0
	Chronic nephropathy	68	0,6	46	2,4	114	0,8
	Chronic disease of the liver or pancreas	219	1,9	70	3,7	289	2,1

*Chronic Obstructive Pulmonary Disease

Table 2. Factors related to the incidence of 30-day complications after cholecystectomy. OR crude and adjusted, p-values - Lazio Region, Italy, January 2007-September 2008 (N = 13,651)

Patient characteristics	30-day surgical-related complications (N=278, 2.0%)						30-day systemic complications (N=280, 2.1%)									
	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p		
Age (years)																
	< 70	1.8	1.00	-	-	-	1.00	-	-	-	-	1.5	1.00	-	-	
	70 - 79	2.9	1.62	1.21	2.18	0.001	1.36	1.00	1.83	0.048	3.9	2.68	2.04	3.52	0.000	
	≥ 80	3.3	1.84	1.13	3.00	0.015	1.21	0.72	2.03	0.475	7.1	5.13	3.58	7.36	0.000	
Gender																
	Men	2.5	1.00	-	-	-	1.00	-	-	-	-	2.6	1.00	-	-	
	Women	1.7	0.69	0.55	0.88	0.002	0.75	0.59	0.96	0.022	1.7	0.66	0.52	0.84	0.001	
Severity of cholelithiasis																
	Low	1.9	1.00	-	-	-	1.00	-	-	-	-	1.2	1.00	-	-	
	Moderate	2.0	1.08	0.84	1.40	0.538	0.96	0.74	1.24	0.733	2.2	1.84	1.38	2.46	0.000	
	High	3.7	2.03	1.32	3.14	0.001	1.43	0.91	2.24	0.122	6.2	5.30	3.59	7.83	0.000	
Previous upper abdominal surgery																
	No	2.0	1.00	-	-	-	1.00	-	-	-	-	2.0	1.00	-	-	
	Yes	5.7	2.94	1.07	8.13	0.037	2.29	0.81	6.51	0.119	4.3	2.15	0.67	6.88	0.197	
Type of admission																
	Elective	1.6	1.00	-	-	-	1.00	-	-	-	-	1.5	1.00	-	-	
	Emergency	3.0	1.85	1.45	2.35	0.000	1.66	1.29	2.13	0.000	3.4	2.34	1.85	2.97	0.000	
Comorbidities (presence of the condition)																
	Cancer	2.6	1.30	0.64	2.64	0.476	-	-	-	-	-	3.6	1.81	0.98	3.34	0.059
	Diabetes	3.3	1.65	0.92	2.97	0.095	-	-	-	-	-	4.4	2.24	1.34	3.75	0.002
	Obesity	5.0	2.57	1.19	5.55	0.016	2.35	1.29	2.13	0.034	4.3	2.16	0.95	4.94	0.067	
	Blood disease	5.8	3.03	1.67	5.90	0.000	2.09	1.11	3.93	0.022	7.7	4.16	2.46	7.03	0.000	
	Hypertension	2.9	1.46	1.00	2.13	0.050	-	-	-	-	-	4.0	2.20	1.58	3.05	0.000
	Ischemic heart disease	2.8	1.42	0.75	2.69	0.286	-	-	-	-	-	7.4	4.08	2.69	6.20	0.000
	Past coronary revascularization	2.4	1.16	0.28	4.74	0.836	-	-	-	-	-	9.4	5.08	2.43	10.62	0.000
	Heart failure	2.3	1.12	0.27	4.57	0.875	-	-	-	-	-	4.6	2.29	0.83	6.29	0.107
	Other heart disease	3.4	1.72	0.84	3.52	0.136	-	-	-	-	-	6.8	3.66	2.17	6.16	0.000
	Conduction disorder or dysrhythmia	4.1	2.09	1.21	3.62	0.008	-	-	-	-	-	7.0	3.81	2.47	5.88	0.000
	Cerebrovascular disease	5.9	3.12	1.76	5.54	0.000	1.98	1.09	3.60	0.025	7.7	4.19	2.52	6.98	0.000	
	Vascular disease	0.8	0.37	0.05	2.68	0.328	-	-	-	-	-	8.5	4.59	2.45	8.62	0.000
	COPD or respiratory failure	2.6	1.27	0.60	2.72	0.534	-	-	-	-	-	7.7	4.22	2.66	6.70	0.000
	Chronic nephropathy	9.7	5.31	2.82	10.00	0.000	3.24	1.65	6.36	0.001	10.5	5.82	3.16	10.72	0.000	
	Chronic disease of the liver or pancreas	3.5	1.75	0.92	3.33	0.087	-	-	-	-	-	4.8	2.51	1.45	4.35	0.001

Table 3. Association between type of cholecystectomy and 30-day complications: OR and p-values from crude model, risk-adjusted model, and models with interaction with age group, severity of cholelithiasis, previous upper abdominal surgery and type of admission; p value of heterogeneity of the strata-specific estimates - Lazio Region, Italy, January 2007 - September 2008

	%	OR _{crude}	95% CI		p	OR _{adj}	95% CI		p	P _{het}
<u>30-day surgical-related complications: N=278, %=2.0</u>										
Open cholecystectomy	3,9	1,00	-	-	-	1,00	-	-	-	-
Laparoscopic cholecystectomy	1,7	0,44	0,33	0,57	0,000	0,60	0,44	0,80	0,001	-
Age (years)										0,917
< 70	1,8	0,49	0,35	0,71	0,000	0,62	0,43	0,90	0,012	-
70 - 79	2,9	0,45	0,26	0,76	0,003	0,57	0,33	0,98	0,043	-
≥ 80	3,3	0,41	0,15	1,12	0,082	0,51	0,18	1,38	0,184	-
Severity of cholelithiasis										0,053
Low	1,9	0,37	0,22	0,61	0,000	0,46	0,28	0,77	0,003	-
Moderate	2,0	0,58	0,40	0,85	0,005	0,78	0,53	1,16	0,224	-
High	3,7	0,24	0,11	0,53	0,000	0,30	0,13	0,68	0,004	-
Previous upper abdominal surgery										0,654
No	2,0	0,45	0,34	0,59	0,000	0,60	0,44	0,81	0,001	-
Yes	5,7	0,26	0,03	2,64	0,256	0,36	0,03	3,69	0,388	-
Type of admission										0,001
Elective	1,6	0,32	0,22	0,46	0,000	0,37	0,25	0,55	0,000	-
Emergency	3,0	0,76	0,51	1,13	0,178	0,94	0,62	1,42	0,764	-
<u>30-day systemic complications: N=280, %=2.1</u>										
Open cholecystectomy	5,2	1,00	-	-	-	1,00	-	-	-	-
Laparoscopic cholecystectomy	1,6	0,29	0,23	0,37	0,000	0,52	0,40	0,69	0,000	-
Age (years)										0,136
< 70	1,5	0,34	0,24	0,49	0,000	0,47	0,32	0,68	0,000	-
70 - 79	3,9	0,35	0,22	0,55	0,000	0,47	0,29	0,75	0,002	-
≥ 80	7,1	0,71	0,37	1,37	0,309	0,99	0,50	1,94	0,975	-
Severity of cholelithiasis										0,755
Low	1,2	0,29	0,16	0,51	0,000	0,43	0,24	0,77	0,005	-
Moderate	2,2	0,34	0,25	0,47	0,000	0,55	0,39	0,77	0,001	-
High	6,2	0,38	0,21	0,70	0,002	0,56	0,30	1,05	0,071	-
Previous upper abdominal surgery										0,702
No	2,0	0,29	0,22	0,37	0,000	0,52	0,39	0,69	0,000	-
Yes	4,3	0,41	0,04	4,69	0,470	0,86	0,07	10,40	0,905	-
Type of admission										0,545
Elective	1,5	0,33	0,23	0,50	0,000	0,48	0,32	0,72	0,000	-
Emergency	3,4	0,35	0,25	0,49	0,000	0,56	0,39	0,81	0,002	-

^c There are no 30-day complications in patients with moderately high severity and undergoing laparotomic cholecystectomy

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7 **Thirty-day complications after laparoscopic or open cholecystectomy: a population-**
8 **based cohort study in Italy.**
9

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51 <http://www.epidemiologia.lazio.it/prevale11/>
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7 **Thirty-day complications after laparoscopic or open cholecystectomy: a population-**
8 **based cohort study in Italy.**
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11
12 **Abstract**

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14 **Objective**

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16 The objective of the study is to evaluate short-term complications after laparoscopic (LC) or
17 open cholecystectomy (OC) in patients with gallstones by using linked hospital discharge
18 data.
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22 **Design**

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24 Population-based cohort study.

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26 **Setting**

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28 Data were obtained from the Regional Hospital Discharge Registry Lazio Region in Central
29 Italy (around 5 million inhabitants) in 2007-2008.
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32 **Participants**

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34 All patients admitted to hospitals of Lazio with symptomatic gallstones (ICD9-CM = 574)
35 who underwent LC (ICD9-CM 51.23) or OC (ICD9-CM 51.22).
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38 **Outcome measures**

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40 1)“30-day surgical-related complications” defined as any complication of the biliary tract
41 (including post-operative infection, hemorrhage or hematoma or seroma complicating a
42 procedure, persistent postoperative fistula, perforation of bile duct, disruption of wound); 2)
43 “30-day systemic complications” defined as any complications of other organs (including
44 sepsis, infections from other organs, major cardiovascular events and selected adverse
45 events).
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51 **Results**
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13,651 patients were included; 86.1% had LC, 13.9% OC. 2.0% experienced surgical-related complications (SRC), 2.1% systemic complications (SC). The Odds Ratio (OR) of complications after LC versus OC was 0.60 ($p < 0.001$) for SRC and 0.52 ($p < 0.001$) for SC. As regards SRC, the advantage of LC was consistent across age categories, severity of gallstones and previous upper abdominal surgery, while there was no advantage among people with emergency admission (OR=0.94, $p = 0.764$). For SC, no significant advantage of LC was seen among very old people (OR=0.99, $p=0.975$) and among those with previous upper abdominal surgery (OR=0.86, $p=0.905$).

Conclusions

This large observational study confirms that LC is more effective than OC with respect to 30-day complications. Population-based linkage of administrative datasets can enlarge evidence of treatment benefits in clinical practice.

Key words: administrative data, cohort study, effectiveness, gallstones, hospital discharge data, laparoscopic cholecystectomy, open cholecystectomy, outcomes, population-based, post-operative complications.

Article summary

Article focus

-The advantage of laparoscopic cholecystectomy (LC) approach for the treatment of gallstone versus open surgery (OC) has been shown from RCTs and observational studies.

-The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments.

-We compared laparoscopic and open cholecystectomy in term of 30-day complications using routinely collected databases in Lazio Region (Italy).

Key messages

-This population-based study contributes to enlarge the evidence on effectiveness of LC in a real-life setting.

-As regards surgical-related complications, the advantage of LC was consistent across age categories, severity of gallstones and previous upper abdominal surgery, while there was no advantage among people with emergency admission.

-For systemic complications, no significant advantage of LC was seen among very old people and among those with previous upper abdominal surgery.

Strengths and limitations

-Population-based design, 30-day outcomes, large numbers and robustness of analytic procedures are the main strengths.

-It contributes to the debate on the complex methodology to estimated risk of adverse events after surgery using secondary databases to monitor quality of care.

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-The use of ICD-9-CM codes in the definition of severity of disease presentation and of complications is a major limit.

For peer review only

Introduction

Comparative effectiveness research is becoming central to monitor real-life impact of treatments and support public health decisions (1, 2). Although the basic concept of comparing therapies is not new, over the last few years many initiatives have been implemented in several countries to provide large-scale evidence on benefits and harms of different treatments (3-5). The use of linked administrative health records has become one of the most powerful tools in observational studies aimed at comparing treatments. They include hospital in-patients records, birth and death registrations, outpatient care records, dispensed pharmacy drugs (6-9).

In the Lazio Region (around 5.000.000 inhabitants) the P.Re.Val.E. Project (*Regional Program for Assessing the Outcomes of Health-care Interventions*) was launched in 2005. Its aims are: to measure the quality of health care provided in the Lazio Region, to describe variability of care provision across institutions and populations and to compare effectiveness of treatments for different medical and surgical conditions (10,11). Over 60 outcomes indicators are calculated based on data obtained from record-linkage procedures of different health systems. The results are periodically updated and publicly disseminated with discussion on critical methodological points.

Cholecystectomy is one of the most common abdominal surgical procedures in developed countries. Since its introduction in the late '80s, laparoscopic cholecystectomy (LC) has replaced open cholecystectomy (OC) as the treatment of choice for symptomatic gallstones (12, 13). Beneficial effects of LC have been demonstrated in studies showing the advantages from real-life settings using secondary databases (9,14-19). In the present study we aimed at developing a methodology to measure short-term complications after LC or OC using large administrative databases on behalf of the P.Re.Val.E. Secondly, we tested the hypothesis that

the advantages of LC versus OC could vary according to age and clinical patients' characteristics.

Methods

Source of data

Data was derived from the Lazio Hospital Information System (HIS), which provides information on patients' demographic data (gender, age, place of birth, place of residence), admission and discharge dates, discharge diagnoses (up to 6) and medical procedures or surgical interventions ((up to 6) according to the International Classification of disease, Ninth Revision, Clinical Modification (ICD-9-CM), status at discharge (alive, dead, transferred to another hospital), ward(s) of stay, date(s) of in-hospital transfer, and a regional code corresponding to the admitting facility for patients discharged from all public and private hospital of the Lazio Region (5.759.839 inhabitants).

Study population

All hospital admissions with a primary or secondary diagnosis of gallstones (International Classification of Diseases 9th Revision, Clinical Modification - ICD9-CM = 574) and a procedure code of cholecystectomy (ICD9-CM 51.22, 51.23), occurred in private and public hospitals of the Lazio Region between January 2007 and September 2008 were included, for a total of 16,432 cases (age 18+ years). We a priori decided not to include codes for partial cholecystectomy (ICD-9-CM 51.21 and 51.24) to increase the specificity of our exposure. Information was retrieved from the HIS. In order to increase the case specificity, several exclusion criteria were applied including long-term hospitalizations, rehabilitations, day-

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7 hospitals, hospitalizations for delivery or trauma or cancer, hospitalizations with abdominal
8 surgical procedures other than cholecystectomy. The final population consisted of 13,651
9 subjects (**Figure 1**). See the online **Supplementary Data** (Part 1) for details on the exclusion
10 criteria and ICD9-CM codes. [According to the Regional Law, the present study, which was](#)
11 [based on anonymous computer records from health information systems, did not require for](#)
12 [ethical approval.](#)
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20 Patient-level risk factors

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22 The following characteristics were considered for each patient: Age (<70; 70-79; >=80 years
23 old); Gender; Severity of gallstones: it was classified as *low* (not-complicated), *moderate*
24 (presence of cholecystitis or biliary tract obstruction), and *high* (presence of both
25 inflammation and obstruction of the biliary tract); Previous upper abdominal surgery (based
26 on previous 2-year hospitalizations); Comorbidities (based on previous 2-year
27 hospitalizations) following validated algorithms (20,21); Type of admission: either *elective* or
28 *emergency*. See the online **Supplementary Data** (Part 2-4) for details on the ICD-9-CM
29 codes. The choice of *cut off* for age category was based on previous studies to distinguish
30 adult and old people (22-24).
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39 Outcomes

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41 We identified various complications within 30-days after the intervention and grouped them
42 in two categories: 1) “*30-day surgical-related complications*” defined as any complication of
43 the biliary tract (including post-operative infection, hemorrhage or hematoma or seroma
44 complicating a procedure, persistent postoperative fistula, perforation of bile duct, disruption
45 of wound ()); 2) “*30-day systemic complications*” defined as any complications of other organs
46 (including sepsis, infections from other organs, major cardiovascular events and
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selected adverse events). The complete list of complications with ICD-9-CM codes is reported in the online **Supplementary Data** (Part 5). Among the various complications we included some conditions reported in the list of Patient Safety Indicators recently developed by the Agency for Health Care Research and Quality, while other items were specifically created on the basis of scientific literature on digestive surgery (14-19,25,26). Depending on the type of complication, some ICD9-CM codes were searched in both the index admission and the following ones in the 30-day period after the surgery, others were searched only in later hospitalizations. For example, peritonitis or acute pancreatitis was not counted as complications when reported in the index admission. See the online **Supplementary Data** (Part 5) for details on the ICD9-CM codes. In the case of a subsequent hospitalization occurred out of the study area (for example, in a region other than Lazio), we obtained information through record linkage procedure between hospital information systems. Because of the short follow up time, this happened in a minimal proportion of cases (0.1%). The outcome variables were: “30-day surgical-related complications” and “30-day systemic complications”; they were coded “1” if at least one of the complications within the group was present and “0” if none was recorded.

Type of cholecystectomy

As exposure variable we defined “*type of cholecystectomy*” (laparoscopic cholecystectomy, LC vs. open cholecystectomy, OC). In the case of ICD-9-CM codes for both LC and OC (5%), the patient was considered exposed to the open surgical procedure. We could not use the specific ICD-9-code for a case converted from LC to OC (ICD-9-CM code V 64.41) because it was highly under-reported in our Region in the study period.

Statistical analysis

Multiple logistic regression models were fitted to estimate the relative risk of 30-day complications (either “surgical-related” or “systemic”) after LC versus OC, adjusting for demographical and clinical risk factors. The two outcome variables were analysed separately. The predictive model was made of two sets of predictors: 1) variables “a priori” chosen as confounders (age, gender, severity of gallstones, previous upper abdominal surgery, and type of admission); 2) variables empirically tested (comorbidities) which were selected using iterative stepwise statistical procedures (27). Once the “best” predictive model was identified for each of the two outcome, the variable “*type of cholecystectomy*” was included, and the adjusted odds ratio (OR) of LC versus open surgery was estimated, with corresponding 95% confidence interval (95% CI) and p-value.

In order to test the hypothesis of an effect modification by age, relative risk estimates for the age groups were derived by adding an interaction term between the age group and the treatment variable in the final multivariate logistic model. We obtained the OR of laparoscopic vs. open surgery within each age stratum by adding the corresponding interaction terms coefficients. 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. Similarly, effect modification was tested with regard to severity of cholelithiasis, previous upper abdominal surgery and type of admission. The corresponding tests of heterogeneity of the stratum-specific risk estimates were computed.

Sensitivity analyses were performed. First, in order to guarantee adequate control of confounding factors we identified and adjusted for all the individual factors associated with the treatment, within the propensity adjustment framework (28). This procedure is a two-step

technique: 1. it estimates the a priori probability of exposure for each subject, based on clinical and demographic characteristics; 2. it standardizes for them in the association between treatment and the study outcome. The individual factors related to the exposure in the present study include age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of admission, cardio-circulatory disease, cerebrovascular disease, COPD or respiratory failure, chronic nephropathy, chronic disease of the liver or pancreas. Second, to take into account the potential heterogeneous experience in laparoscopic surgery across different hospitals because of the patients' clustering within a single institution we perform a multilevel regression model with random intercepts for hospitals (29).

All the statistical analyses were performed using SAS Software version 8.0 (SAS Institute, Inc. SAS/STAT software).

Results

A description of the study population, overall and by cholecystectomy procedure, is presented in **Table 1**. Over 80% of the patients were younger than 70 years, and moderate to high severity of the gallstones was diagnosed for 61.7%. As compared with patients undergoing LC, those who underwent OC were more likely to be elderly, males, with a more severe baseline disease and more chronic conditions. Furthermore, they were operated in emergency in most of the cases (52.4%), whereas LC was performed in elective hospitalizations much more frequently (73.9%).

Table 2 reports the relationship between demographic and clinical variables and the occurrence of complications. The adjusted risk of systemic complications increased with age

and was much higher in patients with more severe baseline gallstones, whereas no clear age or severity-related differences in risk emerged with regard to surgical-related 30-day complications, once other co-factors were taken into account. Women were less likely to experience both types of complications. Having had a previous intervention on the upper digestive system seemed to enhance the risk of both surgical-related and systemic complications, though results are not statistically significant due to small power. Finally, the risk of both types of complications was more evident in emergency as opposed to scheduled interventions. Surgical-related complications were higher among subjects with obesity, blood disease, stroke or chronic nephropathy, whereas systemic complications were associated with blood diseases, ischemic heart disease, conduction disorders or dysrhythmias, COPD or respiratory failure, chronic nephropathy, and chronic diseases of the liver or pancreas.

Table 3 shows the relationship between type of cholecystectomy and outcomes, adjusted for the risk factors identified in Table 2. We report results of the advantage of LC vs. OC (OR, 95% CI) in the cohort and in the each stratum of the variables tested in the models with interaction terms. The incidence of “30-day surgical-related complications” and “30-day systemic complications” was 2.0% and 2.1%, respectively. The odds ratio of surgical related complications for patients who underwent LC as compared to patients with OC was 0.60 ($p < 0.001$). The corresponding figure for systemic complications was 0.52 ($p < 0.001$).

As regards 30-day surgical-related complications, the protective effect of LC vs. OC was consistent across the age category, severity of cholelithiasis and previous upper abdominal surgery, while among people with emergency admission there was no advantage (OR=0.94 $p = 0.764$). Similarly, for systemic complications, the superiority of LC vs. OC was consistent regardless level of cholelithiasis severity, and elective/emergency admission, but for those 80+ yrs aged people there was no advantage of LC vs. OC (OR 0.99, $p = 0.975$); also for

patients with previous upper abdominal surgery there was a much weaker advantage (OR=0.86, p=0.905).

When the association between type of cholecystectomy and 30-day complications was adjusted with the propensity adjustment method, results were consistent with those obtained with the risk-adjustment procedure (LC vs. OC OR= 0.61 and OR=0.52 respectively for the two outcomes). Finally, results were similar taking into account patients' clustering within different hospitals (*data not shown*).

Discussion

From this large observational study based on linked administrative health records - taking into account the disomogeneous distribution of factors related to the probability to be offered open surgery - people who end up having a LC have a better short-term prognosis than those that get an OC for the treatment of gallstones. The superiority of laparoscopic approach in term of 30-day complications is consistent in different age categories, different severity in disease presentation and past history of upper abdominal surgery.

This population-based study contributes to enlarge the evidence on effectiveness of LC in a real-life setting by providing an example from the Southern Europe area. It supports the usefulness of observational approaches. The 30-day outcomes linked to admission represent one strength of this study. Despite RTCs are considered the optimal study design when comparing efficacy of treatments, observational studies provide a picture of treatment under usual circumstances of health-care practice and can answer to the question “*Does it work in practice?*” (3,8). RTCs often have small sample size and may under represent vulnerable

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7 patient groups, including elderly patients with multiple comorbidities, children, and young
8 women, and operate in a highly controlled environment that is far from routine clinical
9 practice. Our study supports that LC is a reliable approach safer than OC not only in old age
10 group - confirming previous findings (22, 30) - but also in presence of severe disease
11 presentation and in patients with past history of upper digestive system surgery. Beneficial
12 effect of LC as regards systemic complications tends to be lower in 80+ yrs aged in
13 comparison with younger ages, and in patients with emergency admission in comparison to
14 elective admissions as regards 30-day surgical-related complications. These data add to the
15 evidence on the complex relationship between age and outcomes after surgery (22-24,30).
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26 A number of potential biases are present. First of all, people in the two groups of patients
27 analyzed are not homogenous in term of with a higher anesthesia risk due to higher frequency
28 of elderly and more comorbidities severe patients in the open group in the open group than
29 in the laparoscopic one. When comparing the effect of the two techniques using two different
30 populations, the so called “indication bias” may affect study validity (8,31). To limit this
31 problem we run the propensity adjustment analysis to take into account the different
32 distribution of factors strongly associated with the probability to receive open surgery in the
33 study population. This analytical approach confirmed the advantage of laparoscopic vs. open
34 surgery obtained in the main logistic regression analysis. Another critical point is the potential
35 different distribution of laparoscopic experience across surgeons; however a sensitivity
36 analysis which took into account this point led to similar results. The use of ICD-9-CM codes
37 in the definition of severity of disease presentation and of complications is another major
38 limit. Discharge abstract data have little insight into clinical details and do not inform on the
39 temporal relationship of the clinical conditions and processes, then defining complications is a
40 difficult task (32). In this respect, we tried to improve the accuracy of our measures both 1)
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7 applying a specific coding algorithm with subsequent hospital admissions used to retrieve
8 adverse events and 2) excluding in the “count” of complications specific items if reported in
9 the index only (i.e. peritonitis) because of the difficulty to determine if it was already present
10 at admission. Moreover, we cannot exclude an under-notification of complications – a major
11 limit of our source of data - but it is unlikely that is influenced by the type of surgery. Another
12 major problem is the potential misclassification of exposure since we were not able to
13 measure the occurrence of conversion of LC to OC. The number of people that were switched
14 from LC to OP is low in comparison to figures documented in other studies and it may
15 represent a severe source of bias in our study (30,33).
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26 Beneficial effects of the laparoscopic approach versus traditional open surgery for the
27 treatment of gallstones come from various randomized controlled trials (RCTs) (34). They
28 found significant shorter hospital stay and quicker convalescence associated with LC but no
29 differences in mortality, complications and operative time between the two procedures. A
30 better trend with the laparoscopic approach, including morbidity and mortality, comes from
31 observational studies. From a surveillance system in eight Swiss hospitals, surgical site
32 infections were less common in laparoscopic approach in comparison to traditional open
33 surgery (0.5% in LC vs. 1.8% in OC) (35). Significantly lower incidence of venous
34 thromboembolism and surgical site-infections in laparoscopic cases versus open cases was
35 observed in a large administrative dataset-based study in USA (14, 15). National estimates
36 for LC in USA showed an increase in LC from 52% in 1991 to 75% in 2000 with a constantly
37 low mortality rate and a decrease in biliary reconstruction rate over time (16). On the basis of
38 the 1997-2006 trend analysis by the same authors LC was associated with a low mortality
39 rate (mean value in the period: 0.52%) while OC with a significantly higher rate
40 (corresponding value: 4.9%) (9). In a retrospective study using Medicare beneficiaries
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common bile duct (CBD) injury during cholecystectomy was associated with a significant higher risk of death in comparison to cholecystectomy without CBD injury over a 9.2 year follow up period (17). From a Swiss 1995-2005 hospital database analysis the incidence rate of bile duct injury after LC was 0.3% and did not change over time (18). The incidence of conversion to OC after LC in all hospitals in England from 2005 to 2006 has been examined using Hospital Episode Statistics and resulted 4.6% for elective procedures and 9.4% for emergency procedures) (19).

Population-based linkage of routinely collected health data represents a precious tool to support large- scale and real-world practice evaluation by measuring specific outcomes and comparing them over time and across populations. Together with results from experimental research settings, the conclusions of research studies evaluating clinical outcomes through data linkage systems should be successfully incorporated into practice by clinicians/surgeons.

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[A-vailable at http://www.epidemiologia.lazio.it/prevale11/](http://www.epidemiologia.lazio.it/prevale11/)

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AUTHOR'S CONTRIBUTION

All Authors participated in the study design, in defining the study protocol and methodology, in acquisition of data, in planning the analyses, in interpreting the results. M.S. performed the analyses. N.A and M.S. drafted the manuscript.

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Figure 1. Selection of the study population

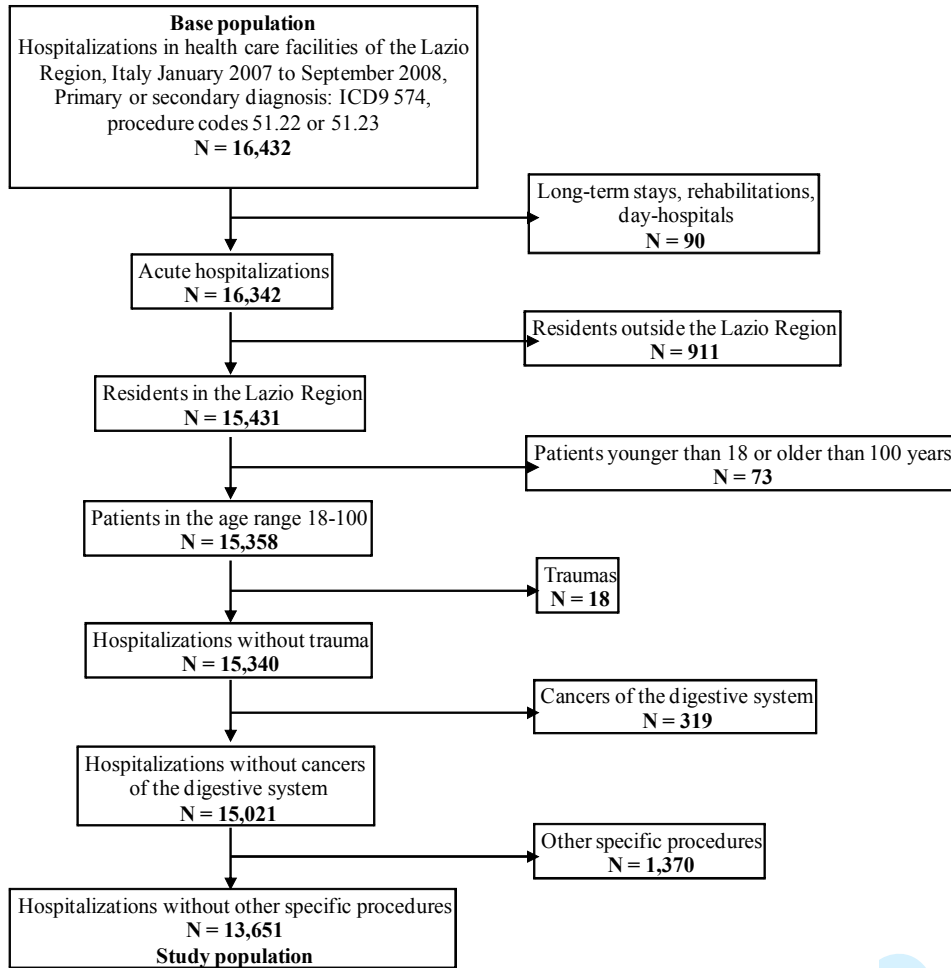


Table 1. Study population, overall and by cholecystectomy procedure: distribution by age, gender, severity of cholelithiasis, previous upper abdominal surgery, type of admission, comorbidities - Lazio Region, Italy, January 2007-September 2008

Patient characteristics	Laparoscopic cholecystectomy		Open cholecystectomy		Total		
	N	%	N	%	N	%	
Total	11.752	86,1	1.899	13,9	13.651	100,0	
Age (years)							
	<70	9.913	84,4	1.162	61,2	11.075	81,1
	70-79	1.543	13,1	485	25,5	2.028	14,9
	≥ 80	296	2,5	252	13,3	548	4,0
		11.752					
Gender							
	Men	4.349	37,0	979	51,6	5.328	39,0
	Women	7.403	63,0	920	48,4	8.323	61,0
Severity of cholelithiasis							
	Low	4.767	40,6	470	24,7	5.237	38,4
	Moderate	6.456	54,9	1.200	63,2	7.656	56,1
	High	529	4,5	229	12,1	758	5,6
Previous upper abdominal surgery							
	No	11.714	99,7	1.867	98,3	13.581	99,5
	Yes	38	0,3	32	1,7	70	0,5
Type of admission							
	Elective	8.690	73,9	903	47,6	9.593	70,3
	Emergency	3.062	26,1	996	52,4	4.058	29,7
Comorbidities							
	Cancer	232	2,0	75	3,9	307	2,2
	Diabetes	268	2,3	100	5,3	368	2,7
	Obesity	115	1,0	25	1,3	140	1,0
	Blood disease	146	1,2	62	3,3	208	1,5
	Hypertension	842	7,2	247	13,0	1.089	8,0
	Ischemic heart disease	246	2,1	107	5,6	353	2,6
	Past coronary revascularization	63	0,5	22	1,2	85	0,6
	Heart failure	47	0,4	41	2,2	88	0,6
	Other heart disease	158	1,3	76	4,0	234	1,7
	Conduction disorders or dysrhythmia	250	2,1	95	5,0	345	2,5
	Cerebrovascular disease	146	1,2	74	3,9	220	1,6
	Vascular disease	91	0,8	38	2,0	129	0,9
	COPD* or respiratory failure	189	1,6	84	4,4	273	2,0
	Chronic nephropathy	68	0,6	46	2,4	114	0,8
	Chronic disease of the liver or pancreas	219	1,9	70	3,7	289	2,1

*Chronic Obstructive Pulmonary Disease

Table 2. Factors related to the incidence of 30-day complications after cholecystectomy. OR crude and adjusted, p-values - Lazio Region, Italy, January 2007-September 2008 (N = 13,651)

Patient characteristics	30-day surgical-related complications (N=278, 2.0%)						30-day systemic complications (N=280, 2.1%)												
	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p					
Age (years)																			
	< 70	1.8	1.00	-	-	1.00	-	-	1.5	1.00	-	-	1.00	-					
	70 - 79	2.9	1.62	1.21	2.18	0.001	1.36	1.00	1.83	0.048	3.9	2.68	2.04	3.52	0.000	2.01	1.51	2.67	0.000
	≥ 80	3.3	1.84	1.13	3.00	0.015	1.21	0.72	2.03	0.475	7.1	5.13	3.58	7.36	0.000	2.79	1.87	4.14	0.000
Gender																			
	Men	2.5	1.00	-	-	1.00	-	-	2.6	1.00	-	-	1.00	-					
	Women	1.7	0.69	0.55	0.88	0.002	0.75	0.59	0.96	0.022	1.7	0.66	0.52	0.84	0.001	0.80	0.62	1.02	0.070
Severity of cholelithiasis																			
	Low	1.9	1.00	-	-	1.00	-	-	1.2	1.00	-	-	1.00	-					
	Moderate	2.0	1.08	0.84	1.40	0.538	0.96	0.74	1.24	0.733	2.2	1.84	1.38	2.46	0.000	1.55	1.15	2.08	0.004
	High	3.7	2.03	1.32	3.14	0.001	1.43	0.91	2.24	0.122	6.2	5.30	3.59	7.83	0.000	3.40	2.26	5.11	0.000
Previous upper abdominal surgery																			
	No	2.0	1.00	-	-	1.00	-	-	2.0	1.00	-	-	1.00	-					
	Yes	5.7	2.94	1.07	8.13	0.037	2.29	0.81	6.51	0.119	4.3	2.15	0.67	6.88	0.197	1.72	0.52	5.74	0.376
Type of admission																			
	Elective	1.6	1.00	-	-	1.00	-	-	1.5	1.00	-	-	1.00	-					
	Emergency	3.0	1.85	1.45	2.35	0.000	1.66	1.29	2.13	0.000	3.4	2.34	1.85	2.97	0.000	1.64	1.27	2.11	0.000
Comorbidities (presence of the condition)																			
	Cancer	2.6	1.30	0.64	2.64	0.476	-	-	3.6	1.81	0.98	3.34	0.059	-	-	-	-	-	-
	Diabetes	3.3	1.65	0.92	2.97	0.065	-	-	4.4	2.24	1.34	3.75	0.002	-	-	-	-	-	-
	Obesity	5.0	2.57	1.19	5.55	0.016	2.35	1.29	2.13	0.034	4.3	2.16	0.95	4.94	0.067	-	-	-	-
	Blood disease	5.8	3.03	1.67	5.50	0.000	2.09	1.11	3.93	0.022	7.7	4.16	2.46	7.03	0.000	1.96	1.09	3.51	0.024
	Hypertension	2.9	1.48	1.00	2.13	0.050	-	-	4.0	2.20	1.58	3.05	0.000	-	-	-	-	-	-
	Ischemic heart disease	2.8	1.42	0.75	2.69	0.286	-	-	7.4	4.08	2.69	6.20	0.000	1.74	1.09	2.78	0.020	-	-
	Past coronary revascularization	2.4	1.16	0.28	4.74	0.836	-	-	9.4	5.08	2.43	10.62	0.000	-	-	-	-	-	-
	Heart failure	2.3	1.12	0.27	4.57	0.875	-	-	4.6	2.29	0.83	6.29	0.107	-	-	-	-	-	-
	Other heart disease	3.4	1.72	0.84	3.52	0.136	-	-	6.8	3.66	2.17	6.16	0.000	-	-	-	-	-	-
	Conduction disorder or dysrhythmia	4.1	2.09	1.21	3.62	0.008	-	-	7.0	3.81	2.47	5.88	0.000	1.73	1.07	2.79	0.025	-	-
	Cerebrovascular disease	5.9	3.12	1.78	5.54	0.000	1.98	1.09	3.60	0.025	7.7	4.19	2.52	6.98	0.000	-	-	-	-
	Vascular disease	0.8	0.37	0.05	2.68	0.328	-	-	8.5	4.59	2.45	8.62	0.000	-	-	-	-	-	-
	COPD or respiratory failure	2.6	1.27	0.60	2.72	0.534	-	-	7.7	4.22	2.66	6.70	0.000	2.02	1.23	3.31	0.006	-	-
	Chronic nephropathy	9.7	5.31	2.82	10.00	0.000	3.24	1.65	6.36	0.001	10.5	5.82	3.16	10.72	0.000	2.27	1.15	4.46	0.018
	Chronic disease of the liver or pancreas	3.5	1.75	0.92	3.33	0.087	-	-	4.8	2.51	1.45	4.35	0.001	1.97	1.11	3.48	0.020	-	-

Table 3. Association between type of cholecystectomy and 30-day complications: OR and p-values from crude model, risk-adjusted model, and models with interaction with age group, severity of cholelithiasis, previous upper abdominal surgery and type of admission; p value of heterogeneity of the strata-specific estimates - Lazio Region, Italy, January 2007 - September 2008

	%	OR _{crude}	95% CI	p	OR _{adj}	95% CI	p	P _{het}	
<u>30-day surgical-related complications: N=278, %=2.0</u>									
Open cholecystectomy	3,9	1,00	-	-	1,00	-	-	-	-
Laparoscopic cholecystectomy	1,7	0,44	0,33	0,57	0,000	0,60	0,44	0,80	0,001
Age (years)									0,917
< 70	1,8	0,49	0,35	0,71	0,000	0,62	0,43	0,90	0,012
70 - 79	2,9	0,45	0,26	0,76	0,003	0,57	0,33	0,98	0,043
≥ 80	3,3	0,41	0,15	1,12	0,082	0,51	0,18	1,38	0,184
Severity of cholelithiasis									0,053
Low	1,9	0,37	0,22	0,61	0,000	0,46	0,28	0,77	0,003
Moderate	2,0	0,58	0,40	0,85	0,005	0,78	0,53	1,16	0,224
High	3,7	0,24	0,11	0,53	0,000	0,30	0,13	0,68	0,004
Previous upper abdominal surgery									0,654
No	2,0	0,45	0,34	0,59	0,000	0,60	0,44	0,81	0,001
Yes	5,7	0,26	0,03	2,64	0,256	0,36	0,03	3,69	0,388
Type of admission									0,001
Elective	1,6	0,32	0,22	0,46	0,000	0,37	0,25	0,55	0,000
Emergency	3,0	0,76	0,51	1,13	0,178	0,94	0,62	1,42	0,764
<u>30-day systemic complications: N=280, %=2.1</u>									
Open cholecystectomy	5,2	1,00	-	-	1,00	-	-	-	-
Laparoscopic cholecystectomy	1,6	0,29	0,23	0,37	0,000	0,52	0,40	0,69	0,000
Age (years)									0,136
< 70	1,5	0,34	0,24	0,49	0,000	0,47	0,32	0,68	0,000
70 - 79	3,9	0,35	0,22	0,55	0,000	0,47	0,29	0,75	0,002
≥ 80	7,1	0,71	0,37	1,37	0,309	0,99	0,50	1,94	0,975
Severity of cholelithiasis									0,755
Low	1,2	0,29	0,16	0,51	0,000	0,43	0,24	0,77	0,005
Moderate	2,2	0,34	0,25	0,47	0,000	0,55	0,39	0,77	0,001
High	6,2	0,38	0,21	0,70	0,002	0,56	0,30	1,05	0,071
Previous upper abdominal surgery									0,702
No	2,0	0,29	0,22	0,37	0,000	0,52	0,39	0,69	0,000
Yes	4,3	0,41	0,04	4,69	0,470	0,86	0,07	10,40	0,905
Type of admission									0,545
Elective	1,5	0,33	0,23	0,50	0,000	0,48	0,32	0,72	0,000
Emergency	3,4	0,35	0,25	0,49	0,000	0,56	0,39	0,81	0,002

^c There are no 30-day complications in patients with moderately high severity and undergoing laparotomic cholecystectomy

SUPPLEMENTARY DATA

DETAILED METHODS

PART 1 - Cohort selection

Source of data: Hospital Information System (HIS)

Inclusion criteria

All hospital admissions with a primary or secondary contributing diagnosis of *cholelithiasis* (International Classification of Diseases 9th Revision, Clinical Modification - ICD9-CM = 574) and a procedure code of *cholecystectomy* (ICD9-CM 51.22, 51.23), occurred in private and public hospitals of the Lazio Region between January 2007 and September 2008 were included, for a total of 16,432 cases. The final population, after sequential exclusions, consisted of 13,651 subjects.

Exclusion criteria

- long-term hospitalizations, rehabilitations and day-hospitals
- patients residents outside the Lazio Region
- subjects younger than 18 or older than 100 years old
- hospitalizations for delivery (MDC 14)
- hospitalizations for any type of trauma (ICD-9-CM codes ICD-9-CM 800-897)
- hospitalizations with diagnoses of cancer of the digestive system (ICD-9-CM codes 150-159)
- hospitalizations with other abdominal surgical procedures (selected ICD-9-CM codes)

PART 2 - Codes to describe severity of cholelithiasis

1 - Cholelithiasis of the biliary tract without complications

574.20; 574.50; 574.90

2. Cholelithiasis of the biliary tract with cholecystitis (without obstruction)

574.10; 574.40; 574.70; 575.1 AND 574.20 or 574.50 or 574.90; 574.00; 574.30; 574.60; 574.80; 575.0 AND 574.20 or 574.50 or 574.90

3. Cholelithiasis of the biliary tract with obstruction (without cholecystitis)

574.21; 574.51; 574.01; 574.91; 575.2 AND 574.20 or 574.50 or 574.90; 576.2 AND 574.20 or 574.50 or 574.90; 575.3

4. Cholelithiasis of the biliary tract with both obstruction and cholecystitis

574.01; 574.11; 574.31; 574.41; 574.61; 574.71; 574.81; 575.2 AND 574.00; 575.0 AND 574.20 575.1 AND 574.20 574.30; 575.0 AND 574.50; 575.1 AND 574.50; 574.60; 574.70; 574.80; 576.1; 576.2 AND 574.00; 575.0 AND 574.20; 575.1 AND 574.20; 574.30; 575.0 AND 574.50; 575.1 AND 574.50; 574.60; 574.70; 574.80

PART 3 - Codes to describe previous upper abdominal surgery

Codes in the index admission – post procedural states

stomach V44.1, V45.75, V55.1; intestine V44.2, V44.4, V45.3, V45.72, V53.5, V55.2, V55.4, V42.84; liver V42.7; pancreas 42.83

Codes in the previous 2-year- hospitalizations

Stomach

43.5,43.6,43.7,,43.8,43.9,44.31,44.39,44.40,44.41,44.42,44.5,44.61,44.63,44.64,44.65,44.69

Small intestine

45.31,45.32,45.33,45.34,45.50,45.51,45.6,45.9,45.91,45.92,45.93,46.01,46.02,46.60,46.61,
46.62,46.71,46.72,46.73,46.74,46.80,46.81,46.93,46.97

Liver

50.2,50.3, 50.4,50.5,50.6

Pancreas

52.22,52.3,52.4,52.5,52.6,52.7,52.8,52.95,52.96

Abdominal Hernia

53.4,53.5,53.6,53.7

Peritoneum

54.4,54.5,54.6,54.7

Large intestine

45.41,45.49,45.7,45.8,45.94,46.03,46.04,46.63,46.64,46.75,46.76,46.79

Other surgery

55.4,55.5,56.2,56.4,57.1,57.6,57.7,65.3,65.4,65.5,65.6,66.4,66.5,68.3,68.4,68.6,68.8

PART 4 - Codes to describe coexisting conditions

On the basis of previous 2-year hospitalizations (following a validated coding algorithm – enhanced Elixhauser AHRQ-Web-ICD-9-CM - see reference n. 17 cited in the text).

diabetes 250.xx; hypertension 401-405; obesity 280.0, ischemic disease 410-414, 429.7, previous revascularization V45.81, V45.82, procedures 36.0, 36.1, heart failure 428, other cardiac disease 093.2, 391, 393-398, 420-425, 429, 745, 746.3-646.6, V15.1, V42.2, V43.2, V43.3, V45.0 arrhythmia / conduction disorders 426-427, cerebrovascular disease 430-438, vascular disease 440-448, 557, hematologic disorders 280-285, 286, 287.1, 287.3-287.5, 288, 289, chronic respiratory disease 490-496, 518.81, 518.82, chronic liver disease / pancreas 571, 572, 577.1, 577.9, chronic renal disease 582-583, 585-588, V42.0, V45.1m V56, cancer 140-208.9

PART 5 - Codes to describe outcomes

A) Surgical-related complications (within 30 day after the surgery)

in the index or in the subsequent hospitalizations (excluding hospitalizations for trauma ICD-9-CM 800-897) and delivery (MDC 14)

at least one of the following:

998.1 Hemorrhage or hematoma or seroma complicating a procedure; 998.2 Accidental puncture or laceration during a procedure; 998.3 Disruption of wound; 998.4 Foreign body accidentally left during a procedure; 998.5 Postoperative infection; 998.6 Persistent postoperative fistula; 998.7 Acute reaction to foreign substance accidentally left during a procedure; 998.81 Emphysema (subcutaneous) (surgical) resulting from a procedure; 998.83 Non-healing surgical wound; 998.89 Other specified complications; 997.4 Digestive system complications; 998.9 Unspecified complication of procedure, not elsewhere classified

1
2
3 Only in the subsequent hospitalizations
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5 at least one of the following:

6 *567 Peritonitis and retroperitoneal infections; 575.4 Perforation of gallbladder; 575.5 Fistula*
7 *of gallbladder; 576.0 Postcholecystectomy syndrome; 576.3 Perforation of bile duct; 576.4*
8 *Fistula of bile duct; 570 Acute and subacute necrosis of liver; 789.0 Abdominal pain*
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13 ***B) Systemic complications (within 30 day after the surgery)***
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15 in the index or in the subsequent hospitalizations (excluding hospitalizations for trauma ICD-9-CM
16 800-897) and delivery (MDC 14)
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18 at least one of the following:

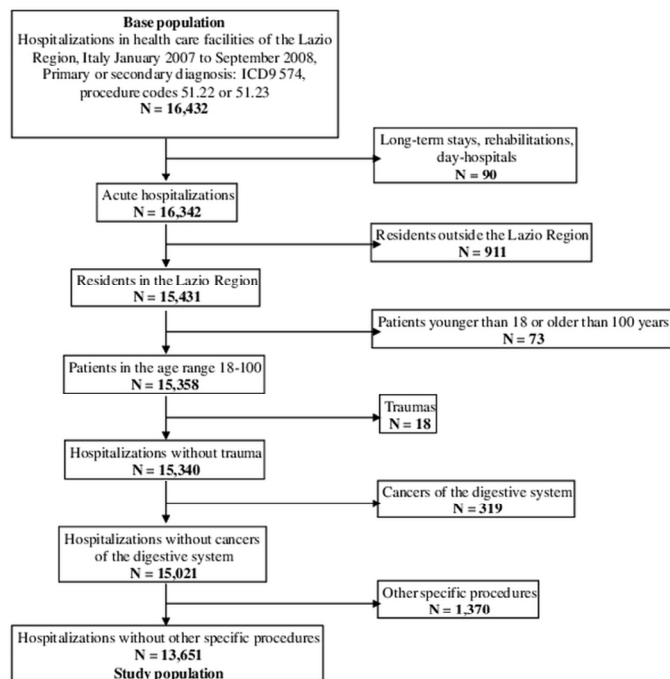
19 *997.0 Nervous system complications; 997.1 Cardiac complications; 997.3 Respiratory*
20 *complications; 998.0 Postoperative shock; 410 Acute myocardial infarction; 415.1 Pulmonary*
21 *embolism and infarction; 431 Intracerebral haemorrhage; 433.x1 Occlusion and stenosis of*
22 *precerebral arteries with infarction; 434.x1 Occlusion of cerebral arteries with infarction; 436*
23 *Acute, but ill-defined, cerebrovascular disease; 480-486 Pneumonia; 513.0 Abscess of lung*
24 *518.4 Acute edema of lung, unspecified; 518.5 Pulmonary insufficiency following trauma and*
25 *surgery; 785.5 Shock without mention of trauma; 788.2 Retention of urine*
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29 Only in the subsequent hospitalizations

30 *038 Septicemia*
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Figure 1. Selection of the study population



90x116mm (300 x 300 DPI)