RESEARCH ARTICLE

Adverse outcomes after surgeries in patients with liver cirrhosis among Korean population: A population-based study

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Abstract

Background

Patients with liver cirrhosis have an increased risk of in-hospital mortality or postoperative complication after surgery. However, large-scale studies on the prognosis of these patients after surgery are lacking. The aim of the study was to investigate the adverse outcomes of patients with liver cirrhosis after surgery over five years.

Methods and findings

We used the Health Insurance Review and Assessment Service-National Inpatient Samples (HIRA-NIS) between 2012 and 2016. In-hospital mortality and hospital stay were analyzed using the data. Mortality rates according to the surgical department were also analyzed. Of the 1,662,887 patients who underwent surgery, 16,174 (1.0%) patients had cirrhosis. The in-hospital mortality (8.0% vs. 1.0%) and postoperative complications such as respiratory (6.0% vs. 5.3%) or infections (2.8% vs. 2.4%) was significantly higher in patients with cirrhosis than in those without cirrhosis. In addition, the total hospitalization period and use of the intensive care unit were significantly higher in patients with liver cirrhosis. In propensity score matching analysis, liver cirrhosis increased the risk of adverse outcome significantly [adjusted OR (aOR) 1.67, 95% CI 1.56–1.79, P<0.001], especially in-hospital mortality. In liver cirrhosis group, presence of decompensation or varices showed significantly increased postoperative complication or mortality. Adverse outcomes in patients with cirrhosis was the highest in patients who underwent otorhinolaryngology surgery (aOR 1.86), followed by neurosurgery (aOR 1.72), thoracic and cardiovascular surgery (aOR 1.56), and plastic surgery (aOR 1.36).
Conclusion

The adverse outcomes of patients with cirrhosis is significantly high after surgery, despite advances in cirrhosis treatment.

Introduction

The true prevalence of liver cirrhosis in the United States is difficult to determine since well-compensated, asymptomatic patients are easily undiagnosed. However, in 2015, Mellinger et al. suggested that at least 0.27% of the American adults with private health insurance had liver cirrhosis [1]. Moreover, the incidence of liver cirrhosis is increasing due to the increased prevalence of nonalcoholic fatty liver disease [2]. In recent years, effective antiviral agents and other treatment options for liver cirrhosis have contributed to increasing the life expectancy of these patients compared to any previous era [3,4]. Therefore, compared to the past, patients with liver cirrhosis are increasingly more likely to undergo surgery. The types of surgery for patients with cirrhosis are also becoming more diverse.

An accurate evaluation of liver function is necessary prior to surgical procedures with general anesthesia since the risk of surgery is affected by liver function [5]. It is well known that perioperative morbidity, mortality and morality in ICU in patients with cirrhosis is much higher than in a control group [6–8]. Therefore, the risk-benefit assessment should be scrutinized before the decision to operate to avoid unnecessary adverse events. Indeed, the most frequent reason hepatologists are consulted by other departments is related to preoperative evaluations. To date, the Mayo score has been widely used to assess the postoperative risk of patients with liver cirrhosis [9]. However, the Mayo score was based on a formula reported in 2007, and since then, there have been very few studies on the risk of liver cirrhosis surgery [9]. Most of these studies included small numbers, single-center experiences, and showed inconsistent results. In clinical practice, we often experience poor postoperative outcomes in patients classified as low risk by Mayo scores.

Therefore, the aim of this was i) to evaluate the in-hospital mortality of patients with liver cirrhosis after surgery, and ii) identify the risk factors using a nationwide population-based study over five years.

Materials and methods

Data source

The Republic of Korea has a universal health coverage system with mandatory social health insurance. National health insurance in Korea covers 98% of the total population, and the number of patients claiming health insurance per year is about 46 million, reaching 90% of the resident registered population. Claims data of the Health Insurance Review and Assessment Service (HIRA) are an important source of information for healthcare service research. Claims data are generated when healthcare service providers submit a claim to HIRA for review for reimbursement. To improve the accessibility to HIRA data for healthcare service researchers, HIRA extracted 13% of the data into a national inpatient sample data (HIRA-NIS) set using a stratified randomized sampling method. The HIRA-NIS data consists of five tables, a table of general information containing demographic information such as gender and age, indicators for inpatient and outpatient services, a table of diagnostic information, and a table of outpatient prescriptions.
Study sample

A flow chart of the study sample selection is shown in Fig 1. First, we obtained HIRA-NIS data for five years, from 2012 to 2016 (databases accessed: 1-May-2020). Among the subjects, 16,662,887 patients were classified as having undergone surgery during that period. The patients who underwent surgery were classified into two groups according to the diagnosis of cirrhosis before surgery, i) patients with liver cirrhosis and ii) patients without liver cirrhosis. The study protocol was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital (SCHBC 2020-04-021, date of registration 23-Apr-2020), and conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki. The requirement for informed consent from individual subjects was waived due to the retrospective nature of the study.

Definition of liver cirrhosis, severity and comorbidities

Liver cirrhosis was defined by at least one occurrence of the ICD-10 diagnosis codes K746 or K703 before surgery, regardless of the period. Decompensated cirrhosis was defined as the presence of any of the following procedures, medications, and diagnostic codes; procedure
(abdominal paracentesis, endoscopic treatment of esophageal or gastric varices, sclerotherapy),
medications (spironolactone, terlipressin, other systemic hemostatics, somatostatin, propranolol),
diagnostic code (hepatorenal syndrome, other peritonitis, hepatic failure unspecified,
oesophageal varices with bleeding in diseases classified elsewhere) [10].

We also investigated the presence of 11 comorbidities other than liver cirrhosis according
to ICD-10 codes: 1) hypertension (I10, I101, I109), 2) diabetes (E10-E14), 3) any type of malignancy
(all type of C code), 4) end-stage renal disease (N185-N186), 5) heart failure (I50), 6) chronic obstructive pulmonary disease (COPD) (J43-J44), 7) hyperlipidemia (E78), 8) mental
disorder (F00-F99), 9) ischemic heart disease (I20-I25), 10) Parkinson’s disease (G20), and 11) Systemic Lupus Erythematosus (M32). Also, the Charlson comorbidity index was calculated
[11].

Study outcome
In the case of NIRA-NIS, it is possible to know whether the patient died during hospitalization,
but the data does not provide information on whether death occurred during a follow-up
period. Therefore, the primary endpoint of this study was in-hospital mortality at the time of
hospitalization due to surgery. Secondary outcomes were postoperative complications. The
types of complications were classified as follows; respiratory, cardiac, infections, surgical
wound rupture, nervous system, bleeding or embolism [12]. The definition of postoperative
complication is described in S1 Table [12].

Statistical analysis
Frequencies and percentages are used for the descriptive statistics. Significant differences
between the groups were investigated using the \( \chi^2 \) test for categorical variables and Student’s
t-test for continuous variables. Logistic regression analysis was used to evaluate the relations-
ships between in-hospital mortality or complications and other factors. Regression analysis
was used to evaluate the relationship of medical cost and other factors. Propensity score
matching (PSM) analysis was performed to minimize the probability of selection bias by
pairing the liver cirrhosis (+) group and the liver cirrhosis (-) group based on propensity
scores. The PSM model included clinical variables with relevance to in-hospital mortality
(age, sex, medical insurance state, variable comorbidities, level of hospital, types of anesthe-
sia, and department of surgery). We used the nearest available matching (1: 1) method for
the estimated PSM. All statistical analyses were performed using R version 4.3.1 (The R
Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at
\( P < 0.05 \).

Results
Baseline characteristics
The characteristics of the participants classified by the presence of liver cirrhosis are described
in Table 1. The flow chart of the patients analyzed in the study is presented in Fig 1. During
this period, a total of 1,662,887 patients underwent surgery, of which 16,174 (0.97%) were
patients with liver cirrhosis. In the group with liver cirrhosis, the average age of the patients
was about 10 years older than the patients in the group without liver cirrhosis (\( P < 0.001 \)), and
the proportion of men was 71%, which was higher than in the group without liver cirrhosis
(\( P < 0.001 \)). In addition, the proportion of veterans or those with medical assistance, whose
economic level was not high, was 12.32%, which was significantly higher than that of the
group without liver cirrhosis at 4% (\( P < 0.001 \)). There was no difference in the proportion of
comorbidities between the groups with and without cirrhosis. The Charlson comorbidity index also showed no difference between the two groups (0.91 vs 0.93, $P = 0.238$). As a comorbid disease, hypertension was the highest (about 17% in both groups), followed by diabetes (10.4%).

Table 1. Baseline characteristics of the patients.

| Variable                              | Total (N = 1,662,887) | Liver cirrhosis (-) (N = 1,646,713) | Liver cirrhosis (+) (N = 16,174) |
|---------------------------------------|-----------------------|-------------------------------------|----------------------------------|
| Age (year)                            | 50.06 ± 20.02         | 49.96 ± 20.06                       | 60.49 ± 11.65                   |
| Sex (n, %)                            |                       |                                     | <0.001                           |
| Male                                  | 758,536 (45.62)       | 746,996 (45.36)                     | 11,540 (71.35)                   |
| Female                                | 904,351 (54.38)       | 899,717 (54.64)                     | 4,634 (28.65)                    |
| Medical insurance state (n, %)        |                       |                                     | <0.001                           |
| Health insurance                     | 1,593,887 (95.85)     | 1,579,706 (95.93)                   | 14,181 (87.68)                   |
| Veterans or medical assistance        | 69,000 (4.15)         | 67,007 (4.06)                       | 1,993 (12.32)                    |
| Comorbidities (n, %)                  |                       |                                     |                                  |
| Charlson comorbidity index            | 0.91 ± 1.51           | 0.91 ± 1.51                         | 0.93 ± 1.54                     |
| Hypertension                          | 287,030 (17.26)       | 284,163 (17.25)                     | 2,867 (17.73)                    |
| Diabetes                              | 174,572 (10.50)       | 172,884 (10.49)                     | 1,688 (10.44)                    |
| Malignancy                            | 59,143 (3.56)         | 58,513 (3.55)                       | 630 (3.90)                      |
| End stage renal disease               | 2,729 (0.16)          | 2,696 (0.16)                        | 33 (0.20)                       |
| Chonic obstructive pulmonary disease  | 21,743 (1.31)         | 21,526 (1.30)                       | 217 (1.34)                      |
| Heart failure                         | 20,931 (1.26)         | 20,723 (1.25)                       | 208 (1.29)                      |
| Hyperlipidemia                        | 30,954 (1.86)         | 30,654 (1.82)                       | 299 (1.89)                      |
| Mental disorder                       | 253,143 (15.22)       | 250,661 (15.22)                     | 2,482 (15.35)                   |
| Ischemic heart disease                | 6927 (0.42)           | 6,860 (0.41)                        | 663 (4.1)                       |
| Parkinson’s disease                   | 5223 (0.32)           | 5,266 (0.32)                        | 570 (0.35)                      |
| Systemic Lupus Erythematous           | 2130 (0.13)           | 2,111 (0.13)                        | 19 (0.12)                       |
| Level of hospital (n, %)              |                       |                                     | <0.001                           |
| Primary clinic                        | 154,865 (93.3)        | 153,016 (93.32)                     | 147,03 (91.34)                  |
| Secondary hospital                    | 98,634 (5.96)         | 97,398 (5.94)                       | 1,236 (7.68)                    |
| Tertiary hospital                     | 12,248 (0.74)         | 12,090 (0.74)                       | 158 (0.98)                      |
| Missing                               | 7140                  |                                     |                                  |
| Types of anesthesia (n, %)            |                       |                                     | <0.001                           |
| Non-general anesthesia                | 112,799 (67.83)       | 111,909 (67.96)                     | 890 (55.06)                     |
| General anesthesia                    | 53,488 (32.17)        | 52,762 (32.04)                      | 7268 (44.94)                    |
| Department of surgery (n, %)          |                       |                                     |                                  |
| Orthopedic surgery                    | 397,700 (23.92)       | 394,803 (23.98)                     | 2,897 (17.91)                   |
| Ophthalmology                         | 246,197 (14.81)       | 244,118 (14.82)                     | 2,079 (12.85)                   |
| Plastic surgery                       | 150,611 (9.06)        | 146,113 (8.87)                      | 4,498 (27.81)                   |
| Dental surgery                        | 6,154 (0.37)          | 6,090 (0.36)                        | 64 (0.40)                       |
| Obstetrics and gynecology             | 191,168 (11.50)       | 190,092 (11.59)                     | 266 (1.64)                      |
| Otorhinolaryngology                   | 152,180 (9.15)        | 151,256 (9.18)                      | 924 (5.71)                      |
| Cardiothoracic surgery                | 51,794 (3.11)         | 50,947 (3.09)                       | 847 (5.24)                      |
| Neurosurgery                          | 148,244 (8.91)        | 146,784 (8.91)                      | 1,460 (9.03)                    |
| General surgery                       | 391,777 (23.56)       | 386,490 (23.47)                     | 5,287 (42.69)                   |
| Urology                               | 38,858 (2.34)         | 38,604 (2.34)                       | 254 (1.57)                      |
| NOTE. Data are presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. Abbreviations: N, number.

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comorbidities between the groups with and without cirrhosis. The Charlson comorbidity index also showed no difference between the two groups (0.91 vs 0.93, $P = 0.238$). As a comorbid disease, hypertension was the highest (about 17% in both groups), followed by diabetes (10.4%).
When classified at the hospital level, patients with cirrhosis had a higher rate of undergoing surgery in secondary or tertiary hospitals compared to the control group (8.66% vs. 6.68%, \(P < 0.001\)). In addition, liver cirrhosis patients had a significantly higher rate of general anesthesia than the control group (44.9% vs. 32.0%, \(P < 0.001\)).

There were differences in the type of surgery between the group with cirrhosis and the group without cirrhosis. In the group without cirrhosis, orthopedic surgery was the highest, followed by general surgery. In the group with cirrhosis of the liver, general surgery was the highest, followed by plastic surgery. Among the types of general surgery, cholecystectomy was common, and during plastic surgery, debridement and escharectomy due to pressure ulcers were common. The names of the top three surgeries by year, liver cirrhosis status, and surgical procedures are described in the supplementary material (S2 Table).

When cirrhotic patients were classified into compensated and decompensated according to liver function, the number of decompensated patients was 1102, corresponding to 6.8%.

**Postoperative outcomes according to the presence of liver cirrhosis**

The characteristics of the participants classified by the presence of liver cirrhosis are described in Table 1. The clinical outcomes after surgery are listed in Table 2. The average length of hospital stay was significantly longer in the liver cirrhosis (+) group (22.44 days vs 10.18 days, \(P < 0.001\)). Also, the medical cost of hospitalization was higher in the liver cirrhosis (+) group. In the liver cirrhosis group, the rate of admission to the intensive care unit after surgery was significantly higher than in the group without cirrhosis (24.3% vs. 4.8%, \(P < 0.001\)).

When examining the incidence of postoperative complications, the incidence of complications of the respiratory system (6.0% vs. 5.4%, \(P = 0.001\)) and postoperative infection (2.9% vs. 2.4%, \(P < 0.001\)) was higher in the liver cirrhosis group than in the control group. However, the incidence of cardiac complication, surgical wound rupture, nervous system, bleeding, and embolism after surgery showed no difference between the two groups.

Lastly, postoperative in-hospital mortality was significantly higher in the cirrhosis group (8.0%) than in the group without cirrhosis (1.0%).

### Table 2. Clinical outcomes of the patients.

| Variables                   | Total (N = 1,662,887) | Liver cirrhosis (-) (N = 1,646,713) | Liver cirrhosis (+) (N = 16,174) |
|-----------------------------|-----------------------|-------------------------------------|----------------------------------|
| Average length of hospital stay (days) | 10.31 ± 26.68 | 10.18 ± 26.42 | 22.44 ± 43.11 | <0.001 |
| Average cost of hospitalization (won) | 4,041,522.51 ± 16,545,326.08 | 3,928,082 ± 15,618,768 | 14,674,804 ± 54,342,232 | <0.001 |
| Intensive care unit admission rate (n, %) | 83,930 (5.05) | 80,000 (4.86) | 39,30 (24.30) | <0.001 |
| Respiratory complication (n, %) | 89683 (5.39) | 88,713 (5.39) | 970 (6) | 0.001 |
| Cardiac | 43512 (2.62) | 43058 (2.61) | 454 (2.81) | 0.134 |
| Infections | 40573 (2.44) | 40107 (2.44) | 466 (2.88) | <0.001 |
| Surgical wound rupture | 176 (0.01) | 175 (0.01) | 1 (0.01) | 1.000 |
| Nervous system | 17,482 (1.05) | 17,325 (1.05) | 157 (0.97) | 0.331 |
| Bleeding | 449 (0.03) | 442 (0.03) | 7 (0.04) | 0.219 |
| Embolism | 1694 (0.1) | 1681 (0.1) | 13 (0.08) | 0.461 |
| In-hospital mortality (n, %) | 18,814 (1.13) | 17,520 (1.06) | 1,294 (8.00) | <0.001 |

NOTE. Data are presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. Abbreviations: N, number.

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Propensity score matching analysis

The group with cirrhosis had a poor postoperative clinical prognosis and higher in-hospital mortality than the group without cirrhosis. However, since the patients in the cirrhosis group were more than 10 years older than those in the non-cirrhosis group, it is difficult to determine whether these findings were due to age or liver cirrhosis. Therefore, PSM was performed to adjust for factors in addition to liver cirrhosis that may have affected the clinical outcomes or in-hospital mortality. Table 3 shows the PSM results matched for age, sex, medical insurance state, variable comorbidities, level of hospital, types of anesthesia, and department of surgery. In the matched set, there was no significant difference in the underlying characteristics between the two groups.

Impact of liver cirrhosis on the adverse outcomes (postoperative complications or mortality) and consumption of medical resources

Adverse outcomes were defined in-hospital mortality or postoperative complications. Multivariate analysis of the factors affecting adverse outcome was performed for the entire patient group and matched set (Table 4). After matching, liver cirrhosis significantly increased the risk of postoperative complications and mortality compared to the group without cirrhosis [adjusted odds ratio (OR) 1.67, 95% confidence interval (CI) 1.56–1.79, \(P<0.0001\)].

When the adverse outcomes were divided into in-hospital mortality and postoperative complication, especially in the liver cirrhosis group, in-hospital mortality was significantly increased by more than 3 times (adjusted OR 3.97, 95% CI 3.50–4.49, \(P<0.001\)) (S3 Table). On the other hand, the incidence of postoperative complication was not significant in the liver cirrhosis group than control group times (adjusted OR 1.08, 95% CI 1–1.16, \(P=0.052\)) (S4 Table).

Finally, the cost of hospitalization was significantly higher in cirrhosis compared to the control group (beta coefficient 7839090, \(P<0.001\)) (S5 Table).

Severity of liver cirrhosis on the adverse outcomes (postoperative complications or mortality)

Next, we investigated the impact of severity of liver disease on the mortality or postoperative complications in patients with liver cirrhosis. For the evaluation of liver disease severity, presence of decompensation, ascites, varices, chronic hepatitis B, chronic hepatitis C were used. In multivariate analysis, presence of decompensation (adjusted OR 1.26, 95% CI 1.06–1.50, \(P=0.009\)) or presence of varices (adjusted OR 1.41, 95% CI 1.19–1.66, \(P<0.0001\)) were related with mortality or post-operative complication in cirrhotic patients (Table 5).

In addition to these factors, older age (adjusted OR 1.01), male gender (adjusted OR 1.16), and multiple comorbidities such as diabetes, chronic obstructive pulmonary disease, heart disease were risk factors for adverse outcomes after surgery. In addition, among the types of surgery, otorhinolaryngology (adjusted OR 1.86), neurosurgery (adjusted OR 1.72), cardiothoracic surgery (adjusted OR 1.56), and plastic surgery (adjusted OR 1.36) showed higher postoperative mortality than other types of surgery (Table 5).

When the adverse outcomes were divided into postoperative complication (S6 Table) and in-hospital mortality (S7 Table), the presence of decompensation increased both morality and postoperative complication, but the presence of varices increased mortality, but was not related to postoperative complication.
In this nationwide population-based study, we found that the in-hospital mortality after surgery in patients with cirrhosis increased by about five times compared to the patients without cirrhosis.
Table 4. Multivariate logistic regression predicting adverse outcome (mortality or post-operative complication) of all patients.

| Variables                      | Unmatched set (N = 1,662,887) | Matched set (N = 32,194) |
|--------------------------------|---------------------------------|--------------------------|
|                                | Univariate                      | Multivariate             | Univariate | Multivariate |
|                                | OR (95% CI) p-value              | OR (95% CI) p-value       | OR (95% CI) p-value |
| Age (year)                     | 1.01 (1.01–1.01) <.0001          | 1.01 (1.01–1.01) <.0001   | 1.01 (1.01–1.02) 0.164 |
| Sex                            |                                 |                          |             |
| Female                         | 1 (Ref)                         |                           |             |
| Male                           | 1.06 (1.05–1.07) <.0001          | 1.07 (1.06–1.09) <.0001   | 1.04 (0.71–1.53) 0.843 |
| Medical insurance state        |                                 |                          |             |
| Health insurance               | 1 (Ref)                         |                           |             |
| Veterans or medical assistance | 1.28 (1.25–1.31) <.0001          | 1.21 (1.18–1.24) <.0001   | 0.84 (0.6–1.19) 0.3334 |
| Comorbidities (n, %)           |                                 |                          |             |
| Charlson comorbidity index     | 1.51 (1.5–1.51) <.0001           | 1.48 (1.47–1.49) <.0001   | 1.44 (1.37–1.5) <.0001 |
| Liver cirrhosis                | 1.77 (1.7–1.84) <.0001           | 1.68 (1.61–1.76) <.0001   | 1.61 (1.51–1.72) <.0001 |
| Hypertension                   | 3.44 (3.41–3.48) <.0001          | 0.75 (0.74–0.76) <.0001   | 2.4 (1.71–3.38) <.0001 |
| Diabetes                       | 3.12 (3.08–3.16) <.0001          | 1.78 (1.73–1.81) <.0001   | 1.39 (1.01–1.9) 0.0407 |
| Malignancy                     | 2.27 (2.22–2.32) <.0001          | 3.14 (3.05–3.23) <.0001   | 1.12 (0.77–1.63) 0.5639 |
| End stage renal disease        | 5.92 (5.49–6.39) <.0001          | 2.02 (1.84–2.23) <.0001   | 1.04 (0.6–1.19) 0.3334 |
| Chronic obstructive pulmonary disease | 7 (6.81–7.19) <.0001           | 2.27 (2.2–2.35) <.0001    | 3.24 (1.88–5.57) <.0001 |
| Heart failure                  | 14.99 (14.57–15.43) <.0001       | 0.38 (0.37–0.39) <.0001   | 4.56 (2.66–7.84) <.0001 |
| Hyperlipidemia                 | 3.11 (3.08–3.14) <.0001          | 1.09 (1.07–1.11) <.0001   | 1.86 (1.34–2.57) 0.0002 |
| Mental disorder                | 2.72 (2.69–2.75) <.0001          | 1.23 (1.21–1.25) <.0001   | 1.49 (1.09–2.04) 0.0125 |
| Ischemic heart disease         | 11.18 (11–11.36) <.0001          | 4.57 (4.48–4.66) <.0001   | 3.43 (2.29–5.16) <.0001 |
| Parkinson’s disease            | 4.42 (4.18–4.68) <.0001          | 1.26 (1.18–1.35) <.0001   | 2.08 (1.05–4.15) 0.0366 |
| Systemic Lupus Erythematosus   | 2.18 (1.97–2.42) <.0001          | 0.8 (0.71–0.9) 0.0002     | 0.8 (0.22–2.98) 0.7394 |
| Level of hospital              |                                 |                          |             |
| Primary hospital               | 1 (Ref)                         |                           |             |
| Secondary hospital             | 1.05 (1.03–1.07) <.0001          | 1.04 (1.02–1.06) 0.0004   | 0.63 (0.42–0.93) 0.0202 |
| Tertiary Hospital              | 1.09 (1.04–1.15) 0.0013          | 1.06 (1.13) 0.0512        | 0.58 (0.26–1.29) 0.1798 |
| Types of anesthesia            |                                 |                          |             |
| Non-General anesthesia         | 1 (Ref)                         |                           |             |
| General anesthesia             | 1.11 (1.1–1.13) <.0001           | 1.09 (1.08–1.11) <.0001   | 0.94 (0.67–1.32) 0.7297 |
| Department of surgery (n, %)   |                                 |                          |             |
| Orthopedic surgery             | 0.98 (0.97–0.99) <.0001          | 1.04 (1.02–1.05) <.0001   | 1.17 (0.79–1.72) 0.4332 |
| Ophthalmology                  | 0.97 (0.96–0.99) 0.0002          | 0.97 (0.96–0.99) 0.0343   | 0.82 (0.51–1.31) 0.4069 |
| Plastic surgery                | 1.23 (1.21–1.25) <.0001          | 1.23 (1.21–1.26) <.0001   | 1.15 (0.8–1.65) 0.4618 |
| Dental surgery                 | 1.11 (1.03–1.2) 0.0079          | 1.13 (1.04–1.23) 0.0031   | 0.5 (0.2–1.24) 0.1343 |
| Obstetrics and gynecology      | 0.88 (0.86–0.89) <.0001          | 1.11 (1.09–1.14) <.0001   | 0.77 (0.34–1.75) 0.5328 |
| Otorhinolaryngology            | 1.13 (1.11–1.15) <.0001          | 1.29 (1.27–1.32) <.0001   | 1.35 (0.88–2.07) 0.165 |
| Cardiothoracic surgery         | 1.4 (1.37–1.43) <.0001          | 1.46 (1.42–1.5) <.0001    | 0.86 (0.53–1.39) 0.5417 |
| Neurosurgery                   | 1.2 (1.18–1.22) <.0001          | 1.19 (1.17–1.22) <.0001   | 0.95 (0.61–1.49) 0.8186 |
| General surgery                | 1 (0.99–1.01) 0.5231            | 1.18 (0.84–1.64) 0.3478   |                |
| Urology                        | 0.97 (0.94–1) 0.0626            |                            | 0.56 (0.26–1.2) 0.1361 |

*Matching variable: Age, Sex, Medical insurance state, Hypertension, Diabetes, Malignancy, End stage renal disease, Chronic obstructive pulmonary disease, Heart failure, Hyperlipidemia, Mental disorder, Ischemic heart disease, Parkinson’s disease, Systemic Lupus Erythematosus, Level of hospital, Types of anesthesia, Department of surgery.

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Table 5. Multivariate logistic regression predicting adverse outcome (mortality or post-operative complication) in patients with liver cirrhosis.

Patients with liver cirrhosis (N = 16,174)

| Variables                      | Univariate          | Multivariate        |
|--------------------------------|---------------------|---------------------|
|                                | OR (95% CI)         | p-value             | OR (95% CI)         | p-value             |
| **Age (year)**                 | 1.01 (1.01–1.01)    | <.0001              | 1.01 (1.01–1.02)    | <.0001              |
| **Sex**                        |                     |                     |                     |                     |
| Female                         | 1 (Ref)             |                     |                     |                     |
| Male                           | 1.12 (1.02–1.22)    | 0.0144              | 1.16 (1.05–1.27)    | 0.0032              |
| **Medical insurance state**    |                     |                     |                     |                     |
| Health insurance               | 1 (Ref)             |                     |                     |                     |
| Veterans or medical assistance | 1.09 (0.97–1.23)    | 0.1419              |                     |                     |
| **Comorbidities (n, %)**       | 1.34 (1.31–1.38)    | <.0001              | 1.36 (1.3–1.41)     | <.0001              |
| Charlson comorbidity index     |                     |                     |                     |                     |
| Hypertension                   | 2.34 (2.13–2.56)    | <.0001              |                     |                     |
| Diabetes                       | 2.19 (1.95–2.44)    | <.0001              | 1.13 (1.1–1.28)     | 0.0556              |
| Malignancy                     | 1.54 (1.28–1.85)    | <.0001              | 0.63 (0.53–0.74)    | <.0001              |
| End stage renal disease        | 2.55 (1.25–5.18)    | 0.01                | 0.42 (0.18–0.99)    | 0.046               |
| Chronic obstructive pulmonary disease | 4.45 (3.4–5.82) | <.0001              |                     |                     |
| Heart failure                  | 10.45 (7.76–14.07)  | <.0001              | 2.41 (1.71–3.39)    | <.0001              |
| Hyperlipidemia                 | 2.19 (2–2.4)        | <.0001              | 1.07 (0.94–1.21)    | 0.3074              |
| Mental disorder                | 1.87 (1.69–2.06)    | <.0001              | 1.09 (0.97–1.22)    | 0.1625              |
| Ischemic heart disease         | 7.6 (6.47–8.93)     | <.0001              | 3.94 (3.26–4.75)    | <.0001              |
| Parkinson’s disease            | 4.03 (2.39–6.78)    | <.0001              | 1.33 (0.72–2.45)    | 0.3585              |
| Systemic Lupus Erythematosus   | 2.6 (1.02–6.6)      | 0.0452              | 1.4 (0.5–3.89)      | 0.5213              |
| **Level of hospital**          |                     |                     |                     |                     |
| Primary hospital (= Clinic)    | 1 (Ref)             |                     |                     |                     |
| Secondary hospital (= Hospital, General hospital) | 0.93 (0.8–1.09) | 0.3815              |                     |                     |
| Tertiary Hospital              | 1.31 (0.9–1.9)      | 0.1583              |                     |                     |
| **Types of anesthesia**        |                     |                     |                     |                     |
| Non-General anesthesia         |                     |                     |                     |                     |
| General anesthesia             | 0.98 (0.9–1.06)     | 0.6099              |                     |                     |
| **Severity of liver cirrhosis**|                     |                     |                     |                     |
| Decompensated liver cirrhosis | 1.69 (1.47–1.95)    | <.0001              | 1.26 (1.06–1.5)     | 0.009               |
| Chronic hepatitis B            | 1.16 (0.84–1.60)    | 0.3797              |                     |                     |
| Chronic hepatitis C            | 2.06 (1.34–5.03)    | 0.0046              | 1.3 (0.6–2.83)      | 0.5087              |
| Ascites                        | 1.52 (1.15–1.99)    | 0.0028              | 0.95 (0.68–1.33)    | 0.7771              |
| Varices                        | 1.42 (1.22–1.66)    | <.0001              | 1.41 (1.19–1.66)    | <.0001              |
| Hepatic encephalopathy         | 1.37 (0.45–4.20)    | 0.5842              |                     |                     |
| **Department of surgery (n, %)**|                     |                     |                     |                     |
| Orthopedic surgery             | 0.99 (0.89–1.09)    | 0.7785              |                     |                     |
| Ophthalmology                  | 0.76 (0.67–0.86)    | <.0001              | 0.85 (0.73–0.98)    | 0.0267              |
| Plastic surgery                | 1.28 (1.18–1.4)     | <.0001              | 1.36 (1.23–1.51)    | <.0001              |
| Dental surgery                 | 0.64 (0.3–1.33)     | 0.2292              |                     |                     |
| Obstetrics and gynecology      | 0.74 (0.52–1.04)    | 0.0839              |                     |                     |
| Otorhinolaryngology            | 1.67 (1.43–1.94)    | <.0001              | 1.86 (1.58–2.2)     | <.0001              |
| Cardiothoracic surgery         | 1.32 (1.12–1.56)    | 0.0009              | 1.56 (1.31–1.86)    | <.0001              |
| Neurosurgery                   | 1.57 (1.38–1.78)    | <.0001              | 1.72 (1.49–1.99)    | <.0001              |
| General surgery                | 0.83 (0.76–0.91)    | <.0001              | 1.01 (0.91–1.12)    | 0.8661              |

(Continued)
cirrhosis, and additionally found that the risk varied according to age, sex, and the type of surgery.

Previous studies showed that the burden of liver cirrhosis is growing regardless of the region [13]. In particular, with the recent use of effective therapeutic agents for hepatitis B and hepatitis C, the likelihood of liver cirrhosis patients surviving to old age is higher than previously. Therefore, patients with cirrhosis have a greater chance of undergoing a variety of surgeries, just like patients without cirrhosis. In fact, the most frequent reason hepatologists at tertiary hospitals are consulted by other departments is related to the risk of surgery in patients with cirrhosis. However, the interest of hepatologists on the topic of surgical risk in patients with cirrhosis is relatively low, so the number of related studies is insufficient compared to other topics.

The results of published studies indicated that the postoperative mortality rate for general patients without cirrhosis is 1.1%, whereas the mortality rate for patients with cirrhosis is 8.3–25% [14,15]. The factors influencing the risk of surgery in patients with cirrhosis are liver function and the type of surgery [16,17]. In particular, it is known that the Child-Pugh and MELD scores are related to postoperative patient prognosis [18–20]. Since the paper published by Swee et al. in 2007, the Mayo score is now widely used in clinical practice [9]. However, the Mayo score is a scoring system for digestive, orthopedic, and cardiovascular surgery only, and is difficult to apply to other types of surgery. In addition, a study reported that this scoring system model tended to overestimate mortality, especially one year after surgery [21]. This is probably because of improvements in the overall care of critically ill patients since the mid-2000s [19]. Recent studies are difficult to generalize because of the relatively small numbers, single-center studies, and analyses of limited types of surgery. Our study was the first to identify the risk of surgery in patients with cirrhosis using large-scale data from a nationwide population.

In our study, the in-hospital mortality of the patients with cirrhosis was 8%. Compared to the general population, it was more than seven times higher, and even after age-sex correction, it was more than five times higher. In addition, the rate of admission to the intensive care unit, the duration of hospitalization, and hospitalization costs were all significantly higher. Considering that previous studies reported that the in-hospital mortality rate of liver cirrhosis patients was 8.3–25%, the postoperative outcomes seem to have improved compared to the previous reports. This can be explained by two factors. The first is that the recent intraoperative and postoperative treatment for patients with cirrhosis of the liver has advanced, and the second is that most of the patients who have already undergone surgery are likely to have compensated cirrhosis and thus, relatively good liver function.

In our study, the risk factors for postoperative in-hospital mortality in patients with cirrhosis were older age, male gender, low SES, and certain types of surgery. Old age is a risk factor already identified by other studies, and the other risk factors were newly identified in this study [9]. Low SES status can result in malnutrition. Indeed, malnutrition or hypoalbuminemia has already been reported as risk factors in previous studies [22].
Regarding the type of surgery, the risk of otorhinolaryngology, neurosurgery, and cardiothoracic surgery was high in our study. First, in relation to otorhinolaryngology surgery, several small-scale head and neck cancer cohort results have been reported. In the previous study, the mortality rate of the group with liver disease was reported to be about 6 times higher than that of the control group, which is considerably higher than that of our study 3.8 times [23]. In our study, the proportion of tracheotomies was the highest among the otorhinolaryngology surgery. Second, in the case of neurosurgery, the results of brain surgery in patients with cirrhosis have been reported. Overall, the risk of brain surgery in cirrhotic patients was very high, and mortality was reported at 24% and morbidity at 52.1% [24]. Even in child A, the complication rate was 38.7%, and the risk increased as the child-Pugh score increased [24]. In our study, the mortality increased by more than about twice, and this is the same conclusion as the previous study. Third, cardiovascular surgery, which was the highest risk in our study, was reported as the same high risk in other studies. Generally, thoracic surgery was classified as a high-risk surgery, attributed to the hemodynamic alterations in patients with cirrhosis [25–27]. Recently, cardiovascular disease has increased in patients with liver cirrhosis caused by fatty liver. But studies are limited about intraoperative and postoperative issues. Overall, mortality and morbidity were high, but varying from study to study, and reported up to 4–70% [5].

On the other hand, in the case of general surgery or orthopedics, there was no significant difference in in-hospital mortality. The general surgery classified in this study include various types of surgery, and the risk is reported differently depending on the type of surgery. It has been reported that there is no difference in mortality in cholecystectomy or hernia operation compared to the control group, and it is performed commonly in clinical practice [5,28]. Meanwhile, other abdominal surgery including pancreatic surgery was classified as high risk [9,29,30]. In our study, the risk of in-hospital mortality in the patients undergoing general surgery, who mainly received intraperitoneal surgery, was rather low compared to patients undergoing surgery in other surgical departments. In this study, it is likely that the rate of general surgery belonging to the low-risk group was high.

Meanwhile, the high risk of plastic surgery was newly found in our study. Among plastic surgery, debridement, and escharectomy due to pressure ulcers were most frequently performed, and the risk of mortality after surgery was probably increased by patient factors rather than the type of surgery.

The items used in the Mayo score are age, American Society of Anesthesiologists score, and scoring system related to liver function evaluation. The results of our study indicate that sex, socioeconomic status, and the type of surgery should be reflected in the surgical risk assessment. If these items are added to the existing Mayo score, it will be possible to more accurately predict the surgical risk of patients with cirrhosis.

Our study had several limitations. First of all, there is an inevitable selection bias arising from the retrospective design. Since this study defined liver cirrhosis based on the diagnosis code, it is possible that cirrhosis that was not diagnosed before surgery was not included. In addition, patients with advanced liver cirrhosis are often unable to perform surgery, and sicker patients might excluded from the beginning. Therefore, only patients with relatively well-preserved liver function are selectively included, and there is a possibility of risk underestimation. And out-patient surgery was not included in this study.

Second, there is no information on the Child-Pugh or MELD scores. It was difficult to calculate accurate liver function because we could not get the information of blood test, ascites or hepatic encephalopathy. Instead, we tried to overcome this problem by using the definition of decompensated cirrhosis, which has been commonly verified in previous studies [10]. In this study, mortality was reported to be significantly higher in the decompensation group, and if MELD or child-Pugh data can be obtained similar results are expected.
Third, since we classified patients into departments that performed surgery rather than the type of surgery, it was difficult to find out the risk for each type of surgery. In addition, in this study, it was difficult to distinguish from emergency surgery and elective surgery, so the effect of emergency surgery, which is known as a common risk factor in previous studies, on the mortality rate was not calculated [31–33]. Finally, there are various risk factors that influence the mortality rate after surgery other than liver cirrhosis. This study attempted to overcome this through propensity score matching, but it is possible that factors other than matching items influenced mortality. In addition, a significant correlation between liver cirrhosis and postoperative mortality could be proven, but it was difficult to see the cause-effect relation between these two factors. Overall, it may be difficult to generalize our study results to all patients with cirrhosis due to the limitations mentioned above.

In conclusion, the in-hospital mortality of patients with cirrhosis is significantly high, despite the advances in cirrhosis treatment. For precise surgical risk assessment of these patients, not only liver function, but also age, sex, and the type of surgery should be considered. In the future, an accurate formula for predicting postoperative mortality in patients with cirrhosis should be developed.

Supporting information
S1 Table. Definition of post-operative complication.
(DOCX)
S2 Table. Top 3 surgical indications by year, department, and liver cirrhosis.
(DOCX)
S3 Table. Multivariate logistic regression predicting in-hospital mortality of all patients.
(DOCX)
S4 Table. Multivariate logistic regression predicting post-operative complication of all patients.
(DOCX)
S5 Table. Multivariate linear regression analysis predicting medical cost of all patients.
(DOCX)
S6 Table. Multivariate logistic regression predicting post-operative complication in patients with liver cirrhosis.
(DOCX)
S7 Table. Multivariate logistic regression predicting in-hospital mortality in patients with liver cirrhosis.
(DOCX)

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