Abstract

Background: The influence of different hospital and surgeon volumes on short-term survival after hepatic resection is not clearly clarified. By taking the known prognostic factors into account, the purpose of this study is to assess the combined effects of hospital and surgeon volume on short-term survival after hepatic resection.

Methods: 13,159 patients who underwent hepatic resection between 2002 and 2006 were identified in the Taiwan National Health Insurance Research Database. Data were extracted from it and short-term survivals were confirmed through 2006. The Cox proportional hazards model was used to assess the relationship between survival and different hospital, surgeon volume and caseload combinations.

Results: High-volume surgeons in high-volume hospitals had the highest short-term survivals, following by high-volume surgeons in low-volume hospitals, low-volume surgeons in high-volume hospitals and low-volume surgeons in low-volume hospitals. Based on Cox proportional hazard models, although high-volume hospitals and surgeons both showed significant lower risks of short-term mortality at hospital and surgeon level analysis, after combining hospital and surgeon volume into account, high-volume surgeons in high-volume hospitals had significantly better outcomes; the hazard ratio of other three caseload combinations ranging from 1.66 to 2.08 (p<0.001) in 3-month mortality, and 1.28 to 1.58 (p<0.01) in 1-year mortality.

Conclusions: The combined effects of hospital and surgeon volume influenced the short-term survival after hepatic resection largely. After adjusting for the prognostic factors in the case mix, high-volume surgeons in high-volume hospitals had better short-term survivals. Centralization of hepatic resection to few surgeons and hospitals might improve patients’ prognosis.

Introduction

The discussion about the association between volume and mortality after the high-risk surgical procedures is ongoing. High-volume hospitals have better long-term survival rates for some operations [1,2]. Numerous studies have explored the association between surgeon volume and mortality for certain procedures [3,4,5,6], but few addressed on the relationship between surgeon volume for hepatic resection and short-term mortality [7,8,9]. Besides, most volume-outcome relationship studies explored the association between the two at hospital or surgeon level.

Hepatic surgery is not an unusual operation and is now performed at many hospitals worldwide [10]. In Asia, hepatocellular carcinoma (HCC) has a high prevalence [11]. Due to donor shortage remains a main problem in Asia, hepatic resection being considered the first line curative methods for some patients with HCC [12,13]. In addition, intra-hepatic cholangiocarcinoma, metastatic malignancies, and benign diseases, such as, trauma, intra-hepatic bile duct stone and benign tumors, also require hepatic resection [10].

However, a general limitation of most of the available studies, and those addressing survival after hepatic resection, is the lack of important prognostic factors, such as, indication for surgery, comorbidities, hepatitis/cirrhosis and cirrhosis-related complications and the combined effect of hospital and surgeon volume, which makes it difficult to take into account the relative effects of these correlated factors [7,8,9].

Therefore, by taking the known prognostic factors into consideration, the purpose of this study was to explore the combined effects of hospital and surgeon volume and the association between different surgeon volumes in high- and in low-volume hospitals in relation to short-term survival after hepatic resection.
Table 1. Baseline characteristics according to hospital volume and surgeon volume (n = 13159).

| Variable                              | High-volume hospital | Low-volume hospital | P value |
|---------------------------------------|----------------------|---------------------|---------|
|                                       | High-volume surgeon (n = 3830) | Low-volume surgeon (n = 3035) | High-volume surgeon (n = 1010) | Low-volume surgeon (n = 5284) |
|                                       | n (%)                | n (%)               | n (%)   | n (%)   |
| Age, years (mean ± SD)                | 55.06 ± 13.95        | 56.56 ± 15.08       | 57.17 ± 12.96 | 58.00 ± 14.50 | <0.001   |
| Gender                                |                      |                     |         |         |
| Male                                  | 2561 (66.9)          | 1926 (63.5)         | 637 (63.1) | 3347 (63.3) | 0.002    |
| Female                                | 1269 (33.1)          | 1109 (36.5)         | 373 (36.9) | 1937 (36.7) |          |
| Indication for surgery                |                      |                     |         |         |
| Hepatocellular carcinoma              | 2667 (69.6)          | 1718 (56.6)         | 621 (61.5) | 3046 (57.6) | <0.001   |
| Cholangiocarcinoma                    | 166 (4.3)            | 143 (4.7)           | 51 (5.0)  | 276 (5.2)  |          |
| Metastatic malignancy                 | 159 (4.2)            | 441 (14.5)          | 74 (7.3)  | 486 (9.2)  |          |
| Benign disease                        | 838 (21.9)           | 733 (24.2)          | 264 (26.1) | 1476 (27.9) |          |
| Surgical procedure                    |                      |                     |         |         |
| Lobectomy or more                     | 983 (25.7)           | 732 (24.1)          | 232 (23.0) | 1423 (26.9) |          |
| < Lobectomy                           | 2847 (74.3)          | 2303 (75.9)         | 778 (77.0) | 3861 (73.1) |          |
| With hepatitis/cirrhosis              | 1629 (42.5)          | 1113 (36.7)         | 423 (41.9) | 1992 (37.7) | <0.001   |
| Pre-operative cirrhosis-related complication | 352 (9.2)         | 281 (9.3)           | 90 (8.9)  | 679 (12.9)  | <0.001   |
| Post-operative cirrhosis-related complication | 166 (4.3)         | 140 (4.6)           | 47 (4.7)  | 331 (6.3)   | <0.001   |
| Comorbidity                           |                      |                     |         |         |
| Hypertension                          | 440 (11.5)           | 433 (14.3)          | 135 (13.4) | 725 (13.7)  | 0.003    |
| Ischemic heart disease                | 38 (1.0)             | 52 (1.7)            | 12 (1.2)  | 95 (1.8)   | 0.009    |
| Arrhythmia                            | 33 (0.9)             | 34 (1.1)            | 5 (0.5)   | 68 (1.3)   | 0.066    |
| Heart failure                         | 5 (0.1)              | 18 (0.6)            | 3 (0.3)   | 24 (0.5)   | 0.012    |
| Cerebrovascular disease               | 14 (0.4)             | 23 (0.8)            | 6 (0.6)   | 58 (1.1)   | 0.011    |
| COPD and associated condition         | 30 (0.8)             | 31 (1.0)            | 8 (0.8)   | 69 (1.3)   | 0.085    |
| Renal disease                         | 43 (1.1)             | 83 (2.7)            | 18 (1.8)  | 147 (2.8)  | <0.001   |
| Diabetes                              | 364 (9.5)            | 384 (12.7)          | 125 (12.4) | 733 (13.9)  | <0.001   |
| Socioeconomic status                  |                      |                     |         |         |
| High                                  | 1051 (27.4)          | 651 (21.4)          | 220 (21.8) | 911 (17.2)  |          |
| Moderate                              | 1439 (37.6)          | 1163 (38.3)         | 433 (42.9) | 2308 (43.7) |          |
| Low                                   | 1340 (35.0)          | 1221 (40.2)         | 357 (35.3) | 2065 (39.1) |          |
| Geographic region                     |                      |                     |         |         |
| Northern                              | 1872 (48.9)          | 1393 (45.9)         | 413 (40.9) | 2311 (43.7) | <0.001   |
| Central                               | 730 (19.1)           | 591 (19.7)          | 185 (18.3) | 922 (17.4)  |          |
| Southern/Eastern                      | 1228 (32.1)          | 1045 (34.4)         | 412 (40.8) | 2051 (38.8) |          |
hepatic resection by using a population-based national database of Taiwan patients between 2002 and 2006.

**Materials and Methods**

**Ethics Statements**

This study was initiated after being approved by the Institutional Review Board of the Buddhist Dalin Tzu Chi General Hospital, Taiwan. Because the identification numbers and personal information of the individuals included in the study were not included in the secondary files, the review board stated that written consent from patients was not required.

**Patients and Study Design**

We used data between 2002 and 2006 from the National Health Insurance (NHI) Research Database, which covered medical benefit claims for over 23 million people in Taiwan (approximately 99 percent of Taiwan’s population) [14]. Taiwan’s NHI has the characteristics of universal insurance coverage, providing comprehensive services, and a single-payer system with the government as sole insurer. The database was monitored for completeness and accuracy by Taiwan’s Department of Health. Patients who underwent hepatic resection for cancer disease (HCC, cholangiocarcinoma, metastatic malignancy), and benign disease (e.g., trauma, intra-hepatic bile duct stone, benign tumors) between 2002 and 2006 were included. A total of 13,159 patients were identified. The mortality was identified from the National Register of Deaths Database. Hospitals and surgeons were sorted using similar methods as previous studies [15,16]. The method for defining high and low hospital and surgeon volume of hepatic resection was: (1) Hospitals were categorized by their total patient volume by using unique hospital identifiers in this database. The 13,159 patients were sorted into two approximately equal groups based on the cumulative hospital volume of hepatic resections performed [7,8]. The cumulative hospital volume of 245 and more cases was defined as high-volume hospital. By this definition, there were 13 high-volume centers for hepatic resection. (Table S1 in Appendix S1). (2) Surgeons were categorized by their total patient volume by using unique identifiers in this database. We initially divided patients into two approximately equal groups by cumulative surgeon volume, but many surgeons in Taiwan performed few hepatic resections annually, the volume cutoff was low. Surgeon volume cutoff was therefore chosen as roughly one-third of all patients undergoing hepatic resection by high-volume surgeons [9]. The cumulative surgeon volume of 25 and more cases was defined as high-volume surgeon. By this definition, there were 59 high-volume surgeons. (Table S2 in Appendix S1).

**Measurements**

The key dependent variable of interest was 30-day, 3-month and 1-year survival of these patients. Mortality was the outcome measure. Overall mortality included all causes of death occurring after the surgery. The key independent variables were the hospital volume, surgeon volume and the combination of surgeon and hospital volume, which were sorted into four groups based on volume (high-volume surgeons in high-volume hospitals, low-volume surgeons in high-volume hospitals, high-volume surgeons in low-volume hospitals, and low-volume surgeons in low-volume hospitals). Patient demographics included age, gender, indication for surgery, comorbidity, surgical procedure (major: lobectomy or more; minor: < lobectomy), and individual socioeconomic status (SES), geographic region, and urbanization level of residence. The comorbidities included hypertension, ischemic heart disease, arrhythmia, cerebrovascular disease, chronic obstructive pulmonary disease.
nary disease and associated conditions including chronic bronchi-
titis and asthma, renal disease, and diabetes. Patients' severity of
underlying liver disease was evaluated by presence or absence of
hepatitis/cirrhosis and cirrhosis-related complications. The cir-
rhosis-related complications included portal hypertension, esopha-
ageal/gastric varices bleeding, ascites, pleural effusion, encephalo-
pathy and hepatorenal syndrome. We identified the presence or
absence of these comorbidities and cirrhosis-related complications
for each patient by querying the Taiwan NHI database using the
International Classification of Diseases 9 codes (ICD-9). Any
cirrhosis-related complication existed before the admission for
surgery was defined as pre-operative cirrhosis-related complica-
tion. It was identified from the ICD-9 codes for inpatients within 6
months before surgery. Post-operative cirrhosis-related complica-
tion was identified from the ICD-9 codes for each discharge from
surgery in the cohort.

This study used income-related insurance payment amount as a
proxy measure of individual SES, which is an important
prognostic factor for survival [17,18]. The individuals were
classified into three groups: (1) low SES, lower than US$528 per
month (New Taiwan Dollars (NT) 0, $1 to $15,840), (2) moderate
SES, between US$528 to $833 per month (NT $15,841 to
$25,000), and (3) high SES, US$833 per month (NT $25,001) or
more [19]. We selected NT$15,840 as the low income level cutoff
point because this was the government-stipulated minimum wage
for full-time employees in Taiwan from 2002 to 2006.

Statistical Analysis
The SAS statistical package (version 9.2; SAS Institute, Inc.,
Cary, N.C.) and SPSS (version 15, SPSS Inc., Chicago, IL, USA)
were used to analyze the data. A p-value of \( P < 0.05 \) was used to
determine statistical significance. The cumulative 30-day, 3-
month, and 1-year survival rates and the survival curves were
constructed and compared using a log-rank test. Survival was
measured from the time after hepatic resection by using overall
death as censoring variables. The Cox proportional hazard
regression model was used to assess the hospital and the surgeon
volume and the combined effects of surgeon and hospital volume
on short-term survival after adjusting for patient demographic
variables.

Results
Of all hepatic resections between 2002 and 2006 in Taiwan,
61.2% was for HCC, 25.2% for benign disease, 8.8% for
metastatic malignancy and 4.8% for cholangiocarcinoma. Pa-
tients’ characteristics are summarized in Table 1. Among these
patients, 29.1% of them were operated by high-volume surgeons
in high-volume hospitals, 23.1% by low-volume surgeons in high-
volume hospitals, 7.7% by high-volume surgeons in low-volume
hospitals and 40.1% by low-volume surgeons in low-volume
hospitals.

Figure 1 shows the Kaplan-Meier survival probabilities after
hepatic resection in each volume group. The high-volume surgeon
in high-volume hospital had the highest survival and the low-volume surgeon in low-volume hospital had the lowest.

Table 2 shows the adjusted hazard ratios based on the Cox proportional hazards regression models after adjusting for patients’ age, gender, indication for surgery, surgical procedure, comorbidity, hepatitis/cirrhosis status, presence of pre-operative and post-operative cirrhosis-related complication, socioeconomic status, geographic region, and urbanization level of residence. In model 1, examining the relationships between hospital volume and short-term survival; after adjusting for other factors, low-volume hospitals had the hazard ratio of 1.50 (95% CI, 1.09–2.07) in 30-day mortality, 1.56 (95% CI, 1.30–1.86) in 3-month mortality, and 1.33 (95% CI, 1.21–1.46) in 1-year mortality compared to high-volume hospitals. In model 2, after adjusting for other factors, the relationships between surgeon volume and short-term survival showed that low-volume surgeons had the hazard ratio of 1.64 (95% CI, 1.12–2.41) in 30-day mortality, 1.62 (95% CI, 1.31–2.00) in 3-month mortality, and 1.41 (95% CI, 1.27–1.56) in 1-year mortality compared to high-volume surgeons. In model 3, examining the combined effects of hospital and surgeon volume, low-volume surgeons in high-volume hospitals demonstrated a significantly better outcome than high-volume surgeons. In model 3, examining the combined effects of hospital and surgeon volume, low-volume surgeons in high-volume hospitals had the hazard ratios ranging from 1.33–3.46 respectively compared to high-volume surgeons in high-volume hospitals. In 3-month mortality, patients not operated by high-volume surgeons in high-volume hospitals had the hazard ratios ranging from 1.66 to 2.08 (p<0.001). In 1-year mortality, patients not operated by high-volume surgeons in high-volume hospitals had the hazard ratios ranging from 1.28 to 1.58 (p<0.01).

Table 3 demonstrates other factors associated with short-term survival at three different time points after hepatic resection. Those had a negative influence on survival included increased age, undergoing major surgical procedure (lobectomy or more), presence of cirrhosis-related complication, ischemic heart disease, renal disease and with a low SES. Cholangiocarcinoma and metastatic malignancy had a poor outcome than HCC.

**Discussion**

The current study from a national database identifying 13,159 hepatic resections between 2002 and 2006 in Taiwan revealed that short-term survival after hepatic resection was largely influenced by the combined effects of hospital and surgeon volume. Surgeon volume had a significant impact on 30-day mortality, high-volume surgeons in high- and in low-volume hospitals demonstrated better outcomes than low-volume surgeons. When looking at 3-month and 1-year mortality, high-volume surgeons in high-volume hospitals demonstrated a significantly better outcome than other three.

The strength of this study are based on the fact that it was a nationwide population-based cross-sectional study, include almost all patients undergoing hepatic resection in Taiwan. At the end of 2006, the NHI covered 99.0% of Taiwan’s population [14], with nearly complete follow-up information of mortality among the whole study population, as well as the fact that the dataset was routinely monitored for diagnostic accuracy by the National Health Insurance Bureau of Taiwan. The current study not only took most of the known prognostic factors into account but also analyzed short-term survival at three time points after hepatic resection. Furthermore, hepatic resection had not been centralized in Taiwan to a significant degree during the study period, which allowed for investigation of the effect of volume.

Patient-related difference is important in the volume-outcome relationship study. Some studies revealed the minority, older, and low SES patients are more likely to be treated at low-volume hospitals [20,21]. And there is a negative association between SES and cancer survival rate [22,23,24]. A study from the United States also revealed that patients who underwent cancer operations for lung, esophagus, and pancreas tumors with more comorbidities were more likely to receive their cancer surgery at low-volume hospitals [25]. Although these trends were also seen in
In this current study, several of these variables were associated with increased short-term mortality and were entered into the multivariate analysis. After adjusting for case-mix in this fashion, there were no changes in the trends for mortality that low-volume providers had inferior outcomes.

A great body of literature has addressed the relation between hospital volume for hepatic resection and mortality. Most previous studies reported a substantial inverse relation between hospital volume and mortality, but the roll of the surgeon volume was not fully established yet. A study from the United States reported that the surgeon volume for hepatic resection was not associated with in-hospital mortality [9], but the present study found contradictory results. In that study, it did not adjust for the known prognostic factors, eg, indication for surgery, hepatitis/cirrhosis, cirrhosis-related complications, socioeconomic status, and lacked an analysis for the combined effect of hospital and surgeon volume.

In agree with previous studies of volume-outcome relationship in some other procedures, surgeon volume was inversely associated with short-term mortality [3,4,6]. However, this association did not remain in 3-month and 1-year mortality after hepatic resection.

### Table 3. The adjusted hazard ratios of patient demographic variables.

| Variable                          | 30-day mortality risk | 3-month mortality risk | 1-year mortality risk |
|-----------------------------------|-----------------------|------------------------|-----------------------|
|                                   | HR 95% CI P value     | HR 95% CI P value      | HR 95% CI P value     |
| Age, year                         | 1.00 0.99–1.01 0.541  | 1.01 1.00–1.02 0.001   | 1.008 1.004–1.01 <0.001 |
| Gender                            |                       |                        |                       |
| Male                              | 1                     | 1                      | 1                     |
| Female                            | 0.94 0.67–1.32 0.728  | 1.04 0.86–1.26 0.640   | 1.05 0.95–1.16 0.306  |
| Indication for surgery            |                       |                        |                       |
| Hepatocellular carcinoma          | 1                     | 1                      | 1                     |
| Cholangiocarcinoma                | 0.89 0.45–1.76 0.743  | 1.52 1.13–2.06 0.005   | 2.06 1.78–2.40 <0.001 |
| Metastatic malignancy             | 1.20 0.65–2.19 0.556  | 1.34 0.98–1.82 0.060   | 1.34 1.14–1.56 <0.001 |
| Benign disease                    | 0.88 0.56–1.38 0.599  | 0.49 0.36–0.66 <0.001  | 0.27 0.22–0.32 <0.001 |
| Surgical treatment                |                       |                        |                       |
| Lobectomy or more                 | 1                     | 1                      | 1                     |
| < Lobectomy                       | 0.66 0.47–0.93 0.019  | 0.71 0.59–0.86 0.001   | 0.64 0.58–0.71 <0.001 |
| With hepatitis/cirrhosis          | 1.29 0.90–1.84 0.160  | 1.01 0.83–1.23 0.876   | 0.92 0.83–1.02 0.156  |
| Pre-operative cirrhosis-related complication | 0.44 0.16–1.20 0.110  | 3.11 2.43–3.98 <0.001  | 5.93 5.29–6.64 <0.001 |
| Post-operative cirrhosis-related complication | 7.22 2.53–20.61 <0.001 | 1.32 0.98–1.79 0.065   | 0.44 0.37–5.33 <0.001 |
| Comorbidity                       |                       |                        |                       |
| Hypertension                      | 0.85 0.51–1.41 0.536  | 0.63 0.47–0.85 0.003   | 0.71 0.61–0.83 <0.001 |
| Ischemic heart disease            | 3.87 1.99–7.52 <0.001 | 2.73 1.76–4.22 <0.001  | 1.67 1.24–2.26 0.001  |
| Arrhythmia                        | 1.87 0.68–5.16 0.224  | 0.92 0.43–1.96 0.842   | 0.76 0.49–1.18 0.226  |
| Heart failure                     | 1.59 0.48–5.21 0.440  | 1.95 0.98–3.88 0.055   | 1.83 1.05–3.19 0.031  |
| Cerebrovascular disease           | 1.57 0.38–6.41 0.527  | 2.77 1.51–5.07 0.001   | 1.43 0.91–2.27 0.118  |
| COPD and associated condition     | 2.67 0.97–7.32 0.056  | 1.02 0.48–2.16 0.956   | 1.24 0.85–1.81 0.258  |
| Renal disease                     | 8.96 5.95–13.47 <0.001 | 5.11 3.89–6.70 <0.001  | 2.62 2.14–3.21 <0.001 |
| Diabetes                          | 0.91 0.56–1.45 0.694  | 1.05 0.82–1.35 0.684   | 0.92 0.80–1.06 0.306  |
| Socioeconomic status              |                       |                        |                       |
| Low                               | 1                     | 1                      | 1                     |
| Moderate                          | 0.78 0.55–1.11 0.183  | 1.05 0.87–1.29 0.569   | 1.14 1.02–1.27 0.014  |
| High                              | 0.40 0.22–0.73 0.003  | 0.42 0.30–0.59 <0.001  | 0.77 0.67–0.89 0.001  |
| Geographic region                 |                       |                        |                       |
| Northern                          | 1                     | 1                      | 1                     |
| Central                           | 1.65 1.08–2.51 0.019  | 1.18 0.92–1.50 0.174   | 1.05 0.93–1.20 0.389  |
| Southern/Eastern                  | 0.91 0.61–1.35 0.647  | 0.85 0.68–1.05 0.137   | 0.89 0.80–1.01 0.060  |
| Urbanization level of residence   |                       |                        |                       |
| Urban                             | 1                     | 1                      | 1                     |
| Suburban                          | 1.11 0.72–1.71 0.633  | 0.89 0.71–1.12 0.337   | 0.96 0.85–1.09 0.586  |
| Rural                             | 1.49 0.93–2.37 0.091  | 0.99 0.77–1.28 0.987   | 1.04 0.91–1.19 0.500  |

Abbreviation: HR, hazard ratio; 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease.

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for high-volume surgeons in low-volume hospitals after taking hospital volume into account. This finding indicates that hospital-volume factors, eg, more specialties for perioperative care of liver diseases, skilled nursing staff and developed intensive care units, account for the effect of surgeon volume on short-term mortality, might influence the risk of mortality after hepatic resection.

In line with previous studies, high-volume hospital or high-volume surgeon was a predictor of survival [7,8,9]. In the present study, it provides an additional insight on the volume-outcome relationship based on the combination of surgeon and hospital volume that high-volume surgeons in high-volume hospitals was a predictor of short-term survival after hepatic resection; high-volume surgeons in low-volume hospitals as well as low-volume surgeons in high-volume hospitals were not. Nevertheless, the positive association remained in high-volume surgeons when comparing with low-volume surgeons. These results indicated the effect of surgeon volume on patients' short-term survival after hepatic resection. Surgeons should maintain a higher volume of hepatic resections and increase experience for a better outcome.

It also has been suggested that the referral of patients to high-volume hospitals will provide a better application of recommended processes of care [2,26]. In the present study, patients who underwent hepatic resection by low-volume surgeons in high-volume hospitals had an increased risk of mortality compared to those who underwent hepatic resection by high-volume surgeons in high-volume hospitals. Our finding suggests that in addition to referring patients to a high-volume hospital, referring patients to a high-volume surgeon in high-volume hospital may be another important consideration.

There are some limitations to this study. First, diagnosis and any comorbidity were completely dependent on ICD codes, any coding errors in patients' underlying diseases could lead to disparities in comorbidity and cirrhosis-related complication. Nonetheless, the National Health Insurance Bureau of Taiwan randomly reviews the charts and interviews patients in order to verify diagnostic accuracy [27]. Second, instead of surgical mortality, the all-cause mortality was used. But the short-term surgical and all-cause mortality differ only to a small degree and it is unlikely that the differences would be systematically different for high- and low-volume providers. Third, the cutoff used for assessing surgeon volume can be considered a little low; however, they are comparable to those of previous large studies that addressed hospital and surgeon volume from the United States [7,9,20].

In summary, our findings provide supports for the combined effects of hospital and surgeon volume with regard to short-term survival after hepatic resection. This population-based study revealed that short-term survival after hepatic resection was largely influenced by the combined effects of hospital and surgeon volume. There was a clear association between high-volume surgeons in high-volume hospitals and better short-term survival. Centralization of hepatic resection to few surgeons and hospitals might improve patients' prognosis.

Supporting Information

Appendix S1 The process of defining the hospital and the surgeon volume. Table S1, defining the category of hospital volume. Table S2, defining the category of surgeon volume.

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Author Contributions

Conceived and designed the experiments: CMC CCL. Performed the experiments: CMC WYY CKW CCL. Analyzed the data: CMC WYY CKW CHL CCL. Contributed reagents/materials/analysis tools: CMC WYY CKW CHL CCL. Wrote the paper: CMC CCL.

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