Risk Factors Associated with Surgical Site Infection after Hepatectomy for Liver Disease

Masahiko Sakoda¹, Shinichi Ueno², Satoshi Iino¹, Kiyokazu Hiwatashi¹, Koji Minami¹, Hiroshi Kurahara¹, Yukou Mataki¹, Kousei Maemura¹, Hiroyuki Shinchi¹ and Shoji Natsugoe¹

¹. Department of Digestive Surgery, Breast and Thyroid Surgery, University of Kagoshima, Kagoshima 890-8520, Japan
². Department of Clinical Oncology, University of Kagoshima, Kagoshima 890-8520, Japan

Abstract: The incidence of postoperative SSI (surgical site infection) after hepatic resection has decreased gradually with the refinement of surgical techniques and perioperative management. However, postoperative SSI still develops in a few patients after hepatic resection, leading to increased medical costs, longer hospitalization and a reduced quality of life in the postoperative course. The purpose of this study was to analyze the risk factors of SSI and to assist in predicting the occurrence of SSI after hepatic resection. A retrospective analysis of 227 patients who underwent hepatic resection without biliary reconstruction for liver disease between January 2006 and December 2012 was performed. Patients were divided into two groups according the occurrence of SSI. The association between SSI and various clinical parameters was investigated. Nineteen patients developed SSI: 9 with superficial or deep SSI and 10 with organ/space SSI. In univariate analysis, preoperative platelets, aspartate aminotransferase and alanine aminotransferase concentrations, intraoperative blood loss, perioperative transfusion, procedure of skin closure, and postoperative bile leakage differed statistically between the two groups. Patients with SSI required significantly longer hospitalization than those without SSI. In multivariate analysis, conventional skin closure and postoperative bile leakage were the significant risk factors. It is important to prevent bile leakage to reduce postoperative SSI. Moreover, subcuticular suture for skin closure would be effective in preventing incisional SSI. Continuous efforts should be made to prevent SSI and further study is needed to develop additional new strategies for preventing SSI.

Key words: Hepatic resection, surgical site infection, subcuticular suture, bile leakage.

1. Introduction

As a result of recent advances in surgical techniques and perioperative management, hepatic resection has become a safe operation [1-3]. However, critical complications still develop in a few patients who undergo hepatic resection. SSI (surgical site infection) is one of the most important morbidities of surgery and leads to increased medical costs, longer hospitalization, and a reduced quality of life in the postoperative course [4, 5]. CDC (The Centers for Disease Control and Prevention) recommended various measures to prevent SSI in its 1999 guideline [6]. Since then, various measures have been taken by institutions and several reports of SSI have been published, mainly of cases of upper and lower gastrointestinal surgery or general surgery [7-12].

Recently, subcuticular suture with subcutaneous drainage or prophylactic antibiotics has been reported to be effective for preventing SSI after hepatic resection [13, 14]. However, it is well known that the incidence of SSI is greatly influenced by the patient’s underlying general status and perioperative factors [15], and the issue of risk factors and prevention measures for SSI after hepatic resection has not been clear. The aim of this study was to analyze the risk factors of SSI after hepatic resection with prevention measures according to the CDC guidelines and to assist in predicting the occurrence of SSI after hepatic resection for liver disease.
2. Materials and Methods

2.1 Patient Characteristics and Data Collection

Patients who underwent hepatic resection without biliary reconstruction for liver disease from January 2006 to December 2012 at our hospital were identified and reviewed retrospectively. Patients who underwent cholecystectomy along with hepatic resection were included in the study, but those who underwent simultaneous procedures, such as resection of organs other than the gallbladder or stoma closure, were excluded from the study. The Institutional Review Board approved this study. The demographics and clinical data for each patient were reviewed.

A history of the presenting illness was obtained for all patients and a complete physical examination was performed. A self-administered questionnaire was used to gain information on previous medical history, including diabetes mellitus. ASA (The American Society of Anesthesiologists) score was determined by an attending physician or anesthesiologist. Patient infectious status for HBV and HCV (hepatitis B and C viruses) was determined by testing for the presence of the hepatitis B surface antigen and hepatitis C antibodies.

Liver function was assessed by liver biochemistry test, child-pugh grade, indocyanine green retention test (ICGR15) and technetium-99m-galactosyl human serum albumin scintigraphy [16, 17]. The extent of hepatic resection was evaluated according to the disease progression, liver function and the general condition of the patients [18]. Tumor progression and resectability was assessed by imaging studies, such as contrast enhanced computed tomography scans, magnetic resonance imaging and ultrasonography.

2.2 Operative Technique and Peri-operative Management

Hepatic resection was performed under intraoperative ultrasonography guidance with or without inflow occlusion (Pringle’s maneuver). Anatomic hepatic resection was performed whenever possible, whereas partial resection was performed in consideration of limited liver functional reserve, anatomic location of the tumor and benign disease. Parenchymal transection was performed using an ultrasonic dissector (CUSA) with bipolar electric cautery or saline-linked radiofrequency coagulator (Dissecting Sealer 3.0; TissueLink Medical, Dover, NH). All hepatic veins and Glissons more than 1 mm were ligated whenever possible with 2-0 or 3-0 braided silk or a vessel clip. Intraoperative bile leakage tests were routinely performed to detect bile leakage. With this procedure, we identified small bile leakage sites on the cut liver surface and could repair these sites by suturing using 4-0 or 5-0 PDSII (Johnson & Johnson Corp., Tokyo, Japan). One or two drains were inserted at the end of operation in the right subphrenic space or elsewhere close to the cut surface of the liver parenchyma.

Our clinical pathway for managing patients undergoing hepatic resection was changed according to the recommendations of the CDC guidelines as shown in Fig. 1. An intra-abdominal closed drainage system was used from May 2002. The timing of drain removal was also changed. Between 2000 and 2005, drains were removed on POD (postoperative day) 6 or 7 if the drainage fluid was clear and no bleeding or bile leakage was observed. From 2006, drains were removed within POD 5 under the same conditions. After closure of the fascia with interrupted sutures using 0 PDSII (Johnson & Johnson Corp., Tokyo, Japan), the surgical incisions in all patients were irrigated with 500 mL saline solution. Between January 2000 and February 2010, the skin was closed with conventional sutures using 2-0 monofilament nylon or skin staples. From March 2010, the skin was closed using an interrupted subcuticular suture [19] procedure with 4-0 PDSII suture material. From February 2006, for routine prophylactic antibiotics, administration of second-generation cepham antibiotics was initiated 30-60 min before skin
incision with another dose administered 3 h later. When the operation lasted more than 3 h, additional doses were given every 3 h thereafter during the operation. After the operation, additional prophylactic antibiotics were administered for 3 days. Between January 2000 and January 2006, antibiotics were administered for 5 to 7 days after the operation without preoperative prophylactic administration.

Postoperative bile leakage was defined as the drainage of macroscopic bile from the surgical drains for more than 7 days after the operation [20] and the definition of the International Study Group of Liver Surgery was used from May 2011 [21]. SSI was defined as a condition in which purulent discharge was observed from any incision or space that was manipulated during an operation, within 30 days of that operation and with or without microbiological evidence, according to the guideline issued by CDC [6].

### 2.3 Statistical Analysis

Differences between the two patient’s groups with or without postoperative SSI were analyzed using the Chi-square test for categorical variable and the unpaired t-test for continuous variables. Only significant variables in univariate analysis were included in the multivariate analysis using the logistic regression test. Data are presented as the mean ± standard deviation, and a P value of less than 0.05 was considered significant.

### 3. Results

During the period of study, 227 patients underwent hepatic resection without biliary reconstruction for liver disease and 19 of them (8%) developed SSI. Incisional SSIs, including superficial and deep SSIs, were observed in 9 patients and organ/space SSIs occurred in 10 patients. The transition of incidences of SSI according to period is shown in Fig. 1. Although the incidence of SSI has decreased by introduction of closed drainage system, the further incidence reduction by introduction of antibiotics administration before skin incision could not be found. The preoperative clinicopathological characteristics of the patients with or without postoperative SSI are shown in Table 1. No difference in these basic characteristics, except for preoperative platelets, AST (aspartate aminotransferase) and ALT (alanine aminotransferase) concentrations were observed between the two groups.

Peripheral platelet counts were significantly lower in
patients with SSI. AST and ALT concentrations were significantly higher in patients with SSI.

Table 2 shows operative characteristics and postoperative morbidities. Laparoscopic hepatic resection was performed in 53 patients, only one of whom (2%) developed an incisional SSI. On the other hand, 18 patients (10%) developed postoperative SSI among 174 who underwent laparotomy. Incidence of remote site infection was 8 (3.5%) (pneumonia (n = 4), catheter infection (n = 2), pseudomembranous colitis (n = 1), unknown origin (n = 1). Other postoperative morbidities included hemorrhage (n = 5), bile leakage (n = 11), ileus (n = 9), pleural effusion (n = 5), duodenal ulcer (n = 3), cerebral infarction (n = 1), lymphorrhea (n = 2), upper gastrointestinal hypokinesis (n = 2), transient renal insufficiency (n = 1). There was no patient who underwent reoperation for postoperative bile leakage and one patient who underwent reoperation for postoperative hemorrhage. Another one patient died within 30 days of the operation because of postoperative liver failure. Among the 11 patients with postoperative bile leakage, 6 (55%) developed an organ/space SSI. In the univariate analysis, intraoperative blood loss, perioperative transfusion, procedure of skin closure and postoperative bile leakage differed statistically between the two groups. Patients with SSI required a significantly longer duration of hospital stay than patients without SSI.

The seven parameters shown by univariate analysis to vary significantly between patients with and without postoperative SSI were analyzed further by multivariate logistic regression (Table 3). Conventional skin closure and postoperative bile leakage were the significant risk factors for developing SSI after hepatic resection.
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### Table 2  Perioperative variables of patients with or without SSI.

<table>
<thead>
<tr>
<th>Variables</th>
<th>SSI (-) (n = 208)</th>
<th>SSI (+) (n = 19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative procedure laparotomy/laparoscopic</td>
<td>156/52</td>
<td>18/1</td>
<td>0.096</td>
</tr>
<tr>
<td>Anatomical/non-anatomical</td>
<td>155/53</td>
<td>15/4</td>
<td>0.88</td>
</tr>
<tr>
<td>Length of operation (min)</td>
<td>340 ± 114.</td>
<td>380 ± 76.</td>
<td>0.136</td>
</tr>
<tr>
<td>≥ 300/&lt; 300</td>
<td>136/69</td>
<td>17/2</td>
<td>0.07</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>1154 ± 1108</td>
<td>2700 ± 2099</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>≥ 1,000/&lt; 1,000</td>
<td>96/112</td>
<td>16/3</td>
<td>0.003</td>
</tr>
<tr>
<td>Perioperative transfusion (%)</td>
<td>47.1</td>
<td>73.7</td>
<td>0.048</td>
</tr>
<tr>
<td>Skin closure conventional/subcuticular suture</td>
<td>106/102</td>
<td>17/2</td>
<td>0.003</td>
</tr>
<tr>
<td>Postoperative morbidity hemorrhage (%)</td>
<td>1.4</td>
<td>10.5</td>
<td>0.077</td>
</tr>
<tr>
<td>Bile leakage (%)</td>
<td>2.4</td>
<td>31.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>1.4</td>
<td>5.3</td>
<td>0.76</td>
</tr>
<tr>
<td>Ileus (%)</td>
<td>4.3</td>
<td>0</td>
<td>0.754</td>
</tr>
<tr>
<td>Postoperative hospital stay (days)</td>
<td>15 ± 8</td>
<td>33 ± 20</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

### Table 3  Multivariate analysis of risk factors for SSI.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% confidence intervals</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt; 17 × 10^4/μL</td>
<td>1.79</td>
<td>0.53-6.038</td>
<td>0.349</td>
</tr>
<tr>
<td>AST ≥ 35 IU/L</td>
<td>2.25</td>
<td>0.485-10.417</td>
<td>0.301</td>
</tr>
<tr>
<td>ALT ≥ 35 IU/L</td>
<td>1.52</td>
<td>0.362-6.369</td>
<td>0.569</td>
</tr>
<tr>
<td>Blood loss ≥ 1,000 mL</td>
<td>2.72</td>
<td>0.54-13.699</td>
<td>0.225</td>
</tr>
<tr>
<td>Perioperative transfusion</td>
<td>1.81</td>
<td>0.414-7.937</td>
<td>0.431</td>
</tr>
<tr>
<td>Subcuticular suture</td>
<td>0.15</td>
<td>0.032-0.723</td>
<td>0.018</td>
</tr>
<tr>
<td>Bile leakage</td>
<td>9.84</td>
<td>1.911-50.702</td>
<td>0.006</td>
</tr>
</tbody>
</table>

SSI risk factors identified by univariate analysis were compared by multivariate analysis (logistic regression test).

### 4. Discussion

The incidence of SSI after hepatic resection was previously reported to be 20%–25% [22, 23]. In our clinical experience, the incidence of SSI was 8%, no higher than the rates of 5.8%-14.5% recently reported in other series [13, 24-27]. Thus, the incidence of postoperative SSI after hepatic resection has gradually and significantly decreased with the refinement of surgical techniques and perioperative management. However, postoperative SSI still develops in a few patients who undergo hepatic resection. Therefore, we herein analyzed the incidence of SSI following hepatic resection and clarified the risk factors for incisional and organ/space SSI.

Previous studies reported that child-pugh grade and ICGR15 were not risk factor for SSI [24-26, 28], and our results were also verified. As for the reason, the liver function of operable cases was relatively well maintained and most patients had good child-pugh grade and ICGR15. Univariate analysis revealed that preoperative platelet counts, AST and ALT concentrations significantly influenced the risk of postoperative SSI complications after hepatic resection. It was reported that platelet count or mean platelet volume may give further information about liver fibrosis severity in hepatitis [29, 30]. Although not significant in multivariate analysis, it seems that preoperative platelet count, AST and ALT concentrations can be used as predictive factors of SSI after hepatic resection from our results.

Length of operation, intraoperative blood loss and perioperative transfusion have been reported to be risk factors of SSI in hepatic resection [24-26, 28]. Intraoperative blood loss and perioperative transfusion were associated with postoperative SSI in our study. If excessive intraoperative blood loss occurs, the effect of prophylactic antibiotics might become weak [6, 31, 32].
Excessive intraoperative blood loss and perioperative transfusion could induce immunosuppression in postoperative patients by reducing the natural killer cell and cytotoxic T-cell populations [33, 34]. In our operative protocol, the timing of intraoperative redosing with prophylactic antibiotics was every 3 h. In hepatic surgery with comparatively large amounts of blood loss, reducing these intervals or increasing the intraoperative dosage of additional prophylactic antibiotics will be required, in accordance with the recommendations of the CDC guideline [6].

In this study, we found a lower incidence of postoperative SSI in laparoscopic hepatic resection than in laparotomy. Laparoscopic hepatic resection is considered to be a minimally invasive operation with a low risk of postoperative SSI.

Among the various preventive measures against SSI, we found a significantly lower incidence of postoperative SSI in wounds closed by subcuticular absorbable suture than in those closed by conventional sutures using nylon or skin staples. Although the mechanism underlying the protective impact of subcuticular suture against SSI are not clear, previous studies have reported that there is a statistically higher blood flow in wounds sutured with subcuticular technique than in those with skin staples or mattress stitches, and buried suture strings beneath the surface of the skin prevent subcutaneous dead space and excessive tissue inflammation [35, 36]. In association with the skin closure, skin staples are often employed because of shorter operation time. Certainly, several studies have reported that staple closure is faster to perform than subcuticular suture, but staple closure is associated with significantly increased composite wound morbidity and duration of postoperative hospitalization compared to subcuticular suture [37-39].

During parenchymal resection in this study, vessels were ligated with braided silk or vessel clip. Harimoto et al. [25] reported that the incidence of SSI in the intra-abdominal absorbable sutures was lower than for silk sutures for both incisional SSI and organ/space SSI, however, there were no other significant differences. This is the only report of a prospective randomized clinical trial investigating the type of sutures used during hepatic resection to determine which is better in preventing SSI, absorbable sutures or non-absorbable sutures. They noted that SSI was observed in 11.3% of the absorbable sutures group, 8.0% were incisional SSI and 3.2% were organ/space SSI. In our study, incisional SSI was observed in 4.0% (9/227) and organ/space SSI was seen in 4.4% (10/227). Another study reported that using intra-abdominal absorbable sutures instead of silk sutures may reduce the risk of SSI, but only in colorectal surgery [40]. Therefore, it seems that intra-abdominal silk sutures are allowable considering the ease of handling, lower cost and the lack of evidence of a relationship between SSI and the type of suture material.

The incidence of postoperative bile leakage after hepatic resection was recently reported to be 2.2%-8.1% [13, 24-26, 28]. In our experience, the incidence of bile leakage was 4.8% (11/227), which is consistent with reports from other high volume centers. However, multivariate analysis revealed that postoperative bile leakage was the strongest risk factor of SSI. The presence of bile in the dead space after hepatic resection may constitute an ideal environment for bacterial growth and development organ/space SSI. Certainly, in this study the classification of SSI of all cases with bile leakage was organ/space SSI. It is most important to prevent bile leakage to reduce postoperative SSI.

In conclusion, according to our retrospective analysis, conventional skin closure and postoperative bile leakage were the significant risk factors of development of SSI after hepatic resection. Subcuticular suture for skin closure is effective in preventing postoperative incisional SSI and it is important to prevent bile leakage to reduce SSI. Continuous efforts should be made to prevent SSI and further study is needed to develop additional new
strategies to prevent SSI until this problem disappears.

References


