Reviewer A

Comment 1: Although a power measurement was performed to detect the minimum size of study patients the number of patients, especially the number of site infections is very small to identify and understand the bacterial profile.

Reply 1: I really appreciate you to review our manuscript. I definitively agree with you. We have calculated the required number of patients before study. The number was set to calculate the incidence of SSI. However, we need more cases to establish the bacterial profile. I am planning the next study of multiple institutions using a large number of patients.

Changes in the text: While the results of this study are encouraging, any conclusions should be tempered by the limitations of a single institution and small number of cases. Though the number of the patients to analyze the incidence of SSI was calculated, we need more cases to establish the bacterial profile of SSI at CDS. We are planning the next study of multiple institutions using a large number of patients.

Comment 2: Glycemic profile optimization is crucial and well known in surgical patients.

Reply 2: Thank you for your comment. I definitively agree with you. We reaffirmed the importance of glycemic profile optimization.

Changes in the text: As the comorbidity of diabetes has been widely regarded as a risk factor for delayed wound healing (14, 15), it is not easy to prevent SSI in patients with diabetes, even with preoperative glycemic control. We reaffirmed the importance of glycemic profile optimization.

Comment 3: English language editing recommended.

Reply 3: Thank you for your recommendation. I have already ordered English editing to Mr. Brian Quinn who is an English editor of Japanese Surgical Society. However, I have revised manuscript after the first English editing. So, I have reordered English editing again. Thank you.

Changes in the text: Please see the parts revised which is highlighted in the text.

Reviewer B

Comment 1: This topic is new and has never been evaluated and discussed before. However, in my opinion, the incidence of so called "SSI" at "CDS" in this article seems to be higher than I usually encounter. Isn't it a result of inappropriate management of drainage wound after the removal of the tube?

To clarify this suspicion, mode of their suturing or management after the tube removal in detail, the data of the postoperative condition of other surgical site than CDS, size of wound at CDS, type of SSI (the depth) should all be necessary.

Reply 1: I really appreciate you to review our manuscript. I definitively agree with you. We have added the data of SSI of main surgical site. In addition, we have added the description of management at CDS after tube removal and comments in methods. I really thank this comment to improve our manuscript.

Changes in the text: The other wounds except CDS were also observed. The SSI was not recognized and re-suturing or ointment treatment were not needed in the other wounds. The CDS was covered by the hydrocolloid dressing of Karayahesive ® (Alcare, Tokyo, Japan) and transparent waterproof sealant. The dressings were not exchanged in principle unless they were peeled off. The staples or sutures of CDS were removed at one to two weeks after tube removal (9).   (9: Teshima H, Kawano H, Kashikie H, et al. A new hydrocolloid dressing prevents surgical site infection of median sternotomy wounds. Surg Today. 2009;39(10):848-54.)

Comment 2: The definition of "delayed wound healing" is not clear. It seems to be that "delayed wound healing" was one of the characteristics of infectious sign?

Reply 2: Thank you for your comment. The description of definition of "delayed wound healing" was missing. We have added the description in the text. In addition, there were no patients with delayed wound healing in patients with SSI. Delayed wound healing could be considered one of the characteristics of SSI. But we defined SSI at the timing of removal of sutures and staples. This time we did not contain delayed wound healing in characteristics of SSI as delayed wound healing was diagnosed a week after suture/staple removal. We have added the comments in methods.

Changes in the text: After the staple/suture removal, we asked the patients and/or the family to observe the CDS and record the conditions even with or without SSI until CDS wound healing. In patients with SSI, a week after the staple/suture removal, next vit to the clinic was planned and we judged it delayed wound healing when the CDS wound did not healed. In patients without SSI, we got information of CDS wound

healing at the next visit.

Comment 3: Moreover, I speculate that the presented days that required for wound healing might have been greatly influenced by other factors such as the interval between "the dates of out-patient clinic" or "calendar holidays" as they get longer.
Reply 3: Thank you for your comment. We had this speculation before the beginning of the present study. So we asked all the patients and family to observe the CDS wound until healing after removal of suture/staple and records until the next visit to the clinic. We basically planned the next visit of SSI patients a week after SSI judgement. We could know the accurate date of wound healing. We have added the description of the date of the accurate date of wound healing.
Changes in the text: After the staple/suture removal, we asked the patients and/or the family to observe the CDS and record the conditions even with or without SSI until CDS wound healing. In patients with SSI, a week after the staple/suture removal, next vit to the clinic was planned and we judged it delayed wound healing when the CDS wound did not healed. In patients without SSI, we got information of CDS wound healing at the next visit.

Comment 4: I would also point out that the postoperative management here with subscribing 5 days of oral antimicrobial agent to the patients is not appropriate according to the guidelines even though for patients with chest drainage tube in situ.
Reply 4: Thank you for your comment. We have traditionally continued oral antimicrobial agent at our institution, but we know it was not recommended in guidelines. In this study, we have revealed the bacterial profile. So, we planned to change the agent which cover the flora and continue oral taking.
Changes in the text: While the results of this study are encouraging, any conclusions should be tempered by the limitations of a single institution and small number of cases. Though the number of the patients to analyze the incidence of SSI was calculated, we need more cases to establish the bacterial profile of SSI at CDS. We are planning the next study of multiple institutions using a large number of patients. In addition, we have planned postoperative administration of oral antimicrobial agent for 5 days even it was not recommended in guidelines. It may influence the relatively high incidence of SSI or delayed wound healing.

Comment 5: The numbers and significance should be presented even if the difference was not significant.

Reply 5: Thank you for your comment. We have added the numbers and significances in all columns.
Changes in the text: Please see the table 3.

Comment 6: Were there any differences of risks according to Body mass index and the thickness of subcutaneous tissue at CDS?
Reply 6: Thank you for your comment. I definitively agree with you. I have added the numbers and significances of factors. I also added the data of BMI. It was not a significant factor. Unfortunately, we have no data of thickness of subcutaneous tissue. Thank you.
Changes in the text: Please see the table 3.

Reviewer C

Comment 1: In this paper, SSI is defined as existence of inflammatory findings at the timing of the removal of all sutures and staples and afterwards.
Where in the table is the number of SSI patients described initially?
Reply 1: I really appreciate you to review our manuscript. As you pointed out, we realized the need of them. I have added the description of SSI and numbers in table 1. In addition, the number of patients with pathogen at CDS at tube removal and delayed wound healing were added.
Changes in the text: Please see the table 1.

Comment 2: "Delayed wound healing" should be defined, concerning its duration etc..
Reply 2: Thank you for your comment. The description of definition of "delayed wound healing" was missing. We have added the description in the text. In addition, there were no patients with delayed wound healing in patients with SSI. Delayed wound healing could be considered one of the characteristics of SSI. But we defined SSI at the timing of removal of sutures and staples. This time we did not contain delayed wound healing in characteristics of SSI as delayed wound healing was diagnosed a week after suture/staple removal. We have added the comments in methods.
Changes in the text: After the staple/suture removal, we asked the patients and/or the family to observe the CDS and record the conditions even with or without SSI until CDS wound healing. In patients with SSI, a week after the staple/suture removal, next vit to the clinic was planned and we judged it delayed wound healing when the CDS wound did not healed. In patients without SSI, we got information of CDS wound

healing at the next visit.

Comment 3: In Figure 1, number of patients in each box should be described.
Reply 3: Thank you for your comment. I presume this comment was made about table 3. I have added the numbers in Figure 1.
Changes in the text: Please see Figure 1.

Comment 4: In Table 1, contents of pre- and post-operation should be described separately.
Reply 4: Thank you for your comment. As you pointed out, we realized the need of it. We have separated and described the factors.
Changes in the text: Please see table 1.

Comment 5: As a background, what are operative approaches, such as minimally invasive surgery or open?
Reply 5: Thank you for your comment. As you pointed out, we realized the need of them. We have added operative approach.
Changes in the text: Please see table 1.

Comment 6: Comorbidity is better described and analyzed using comorbidity index.
Reply 6: Thank you for comment. As you pointed out, we realized the need of it. We have added the Charlson comorbidity index as a factor and analyzed it.
Changes in the text: We have set the variables which were analyzed as possible risk factors for detection of pathogens at CDS, SSI and delayed wound healing as age, gender, body mass index (BMI), comorbidity, Charlson comorbidity index, smoking history, values of HbA1c, albumin, and choline esterase, approach of operation; thoracotomy, video-assisted thoracic surgery (VATS), or robot-assisted thoracic surgery (RATS), performed operation; lobectomy or segmentectomy, operation time, pathological diagnosis, pathological stage, and postoperative drainage period.

Comment 7: Why were the three blood parameters selected?
Reply 7: Thank you for your comment. We set 3 factors which were recommended for analysis by infection control team (ICT).
Changes in the text: The values of HbA1c, albumin, and choline esterase were included by the recommendation of infection control team.

Comment 8: In Table 2, do "infectious sign positive patients" mean SSI?

Reply 8: Thank you for your comment. We described "infectious sign positive patients" as SSI positive. We changed the description to "SSI (+)"

Changes in the text: Please see table 2.

Comment 9: In Table 3, writing should be refined clearer and more accurate, especially the number of patients in each group.

Reply 9: Thank you for your comment. We have remade table 3.

Changes in the text: Please see table 2.

Comment 10: In Table 4-1, pathogen positive patients on drain removal count for 18. How many of them were eventually SSI?

Reply 10: Thank you for your comment. Only 5 patients eventually have resulted in SSI. It is shown in table 2.

Changes in the text: Please see table 2.

Comment 11: In Table 4-2, pathogen positive patients on removal of sutures count 16. Is this data reflected in Table 2?

Reply 11: Thank you for your comment.18 patients were diagnosed as SSI at the timing of suture/staple removal and they underwent second bacterial examination. In 16 of the 18 patients, pathogen was detected. So, it was not reflected in table 2.

Comment 12: Were the dressings after removal of chest tube closed or open?

Reply 12: Thank you for your comment. The wound was closed.

Changes in the text: The CDS was covered by the hydrocolloid dressing of Karayahesive ® (Alcare, Tokyo, Japan) and transparent waterproof sealant. The dressings were not exchanged in principle unless they were peeled off. The staples or sutures of CDS were removed at one to two weeks after tube removal (9).

Comment 13: Was the incidence of SSI average or high?

Reply 13: Thank you for your comment. There have been no data of incidence of SSI at CDS so far.

Comment 14: What is your hypothesis of bacterial flora alterations in case of SSI?

Reply 14: Thank you for your comment. In 5 of 18 cases with pathogens at tube removal were detected with SSI and pathogens at suture/staple removal. The pathogens

were same in 2 patients and in 3 patients the pathogens were different at both timings of tube removal and suture/staple removal. In 13 patients with SSI pathogens were not detected at tube removal and in 11of 13 patients, pathogens were newly detected at the timing of suture/staple removal. It is difficult to explain the alteration of pathogens in the 3 patients but pathogens were newly detected in the most patients (13/18). We speculated that pathogens of SSI appeared between tube removal and suture/staple removal in the most cases. If so, the timing of administration of antibiotics may be set after the chest tube has been removed

Changes in the text: In 5 of 18 cases with pathogens at tube removal were detected with SSI and pathogens at suture/staple removal. The pathogens were same in 2 patients and in 3 patients the pathogens were different at both timings of tube removal and suture/staple removal. In 13 patients with SSI pathogens were not detected at tube removal and in 11of 13 patients, pathogens were newly detected at the timing of suture/staple removal. It is difficult to explain the alteration of pathogens in the 3 patients but pathogens were newly detected in the most patients (13/18). We speculated that pathogens of SSI appeared between tube removal and suture/staple removal in the most cases. If so, the timing of administration of antibiotics may be set after the chest tube has been removed

Comment 15: What is your hypothesis of highly frequent SSIs in Squamous Cell Ca patients?

Reply 15: Thank you for your comment. We can only speculate it. The patients with squamous cell carcinoma are often with habits of smoking and drinking and with various comorbidities. These factors combine and may lead to SSI though individual factors are not significant.

Changes in the text: It is interesting that the pathological diagnosis of squamous cell carcinoma was suggested to be a risk factor for SSI and delayed wound healing. As a smoking history alone was not found to be a significant risk factor, the nutrition condition, drinking habit and other factors might combine and induce SSI and delayed wound healing.

Reviewer D

Comment 1: This statement is not clear: "Five of the 18 patients showed SSI of the CDS... at the timing of chest tube removal" (line 12-15)? When did the group of 5 and

the other of 13 patients showed SSI of CDS?

Reply 1: I really appreciate you to review our manuscript. This part was difficult to be understood. We have changed the description as shown below.

Changes in the text: Five of the 18 patients with detection of pathogens at chest tube removal showed SSI of the CDS at the timing of suture and/or staple removal.

Comment 2: Specify which variables were analyzed as possible risk factors for SSI in materials and methods and define these variables (i.e. in Table 3 what do you mean with pathological diagnoses 2?).

Reply 2: Thank you for your comment. We have added the statement of variables and possible risk factors in methods.

Changes in the text: We have set the variables which were analyzed as possible risk factors for detection of pathogens at CDS, SSI and delayed wound healing as age, gender, body mass index (BMI), comorbidity, Charlson comorbidity index, smoking history, values of HbA1c, albumin, and choline esterase, approach of operation (thoracotomy, VATS, or RATS), performed operation (lobectomy or segmentectomy), operation time, pathological diagnosis, pathological stage, and postoperative drainage period.

Comment 3: To define a variable as a possible risk factor, univariable and multivariable analyses should be performed. Please add this analysis.

Reply 3: Thank you for your comment. Multivariate analysis was added.

Changes in the text: However, both factors, diagnosis of squamous cell carcinoma and higher HbA1c level, were not significant (p=0.072 and 0.11, respectively) in multivariate analysis.

Comment 4: Which surgical approach did you use? Thoracotomy? VATS? others?

Reply 4: Thank you for your comment. As you pointed out, we realized the need of them. We have added operative approach.

Changes in the text:

1. We have set the variables which were analyzed as possible risk factors for detection of pathogens at CDS, SSI and delayed wound healing as age, gender, body mass index (BMI), comorbidity, Charlson comorbidity index, smoking history, values of HbA1c, albumin, and choline esterase, approach of operation; thoracotomy, video-assisted thoracic surgery (VATS), or robot-assisted thoracic surgery (RATS), performed operation; lobectomy or segmentectomy, operation time, pathological diagnosis,

pathological stage, and postoperative drainage period.

2. The approach of lobectomy or segmentectomy was selected with thoracotomy (n=13), VATS (n=72), or RATS (n=14).

3. Please see in table s1 and 3.

Comment 5: How did you treat patients with SSI? Only with local medication? Did you add any i.v. antibiotic therapy?

Reply 5: Thank you for your comment. It was stated in results.

Changes in the text:

1. If necessary, the wound was treated using oral antibiotics or ointment.

2. One patient required re-suturing due to wound dehiscence following staple and suture removal.

Comment 6: Antibiotic prophylaxis does not include the routine use of antibiotics during the postoperative period in asymptomatic patients, as you did in your study. Please discuss this point as a limitation.

Short-term antibiotic prophylaxis is actually recommended in oncologic thoracic surgery.

Reply 6. Thank you for your comment. We have traditionally continued oral antimicrobial agent at our institution, but we know it was not recommended in guidelines. In this study, we have revealed the bacterial profile. So we planned to change the agent which cover the flora and continue oral taking. As a limitation, we have added comments in discussion.

Changes in the text: Though the number of the patients to analyze the incidence of SSI was calculated, we need more cases to establish the bacterial profile of SSI at CDS. We are planning the next study of multiple institutions using a large number of patients. In addition, we have planned postoperative administration of oral antimicrobial agent for 5 days even it was not recommended in guidelines. It may influence the relatively high incidence of SSI or delayed wound healing.

Comment 7: I would suggest to integrate reference; please take into consideration at least J Thorac Dis. 2017 Sep;9(9):3255-3264. doi: 10.21037/jtd.2017.08.165.

Reply 7. Thank you for your comment. We have added references.

Changes in the text: The postoperative management of chest tubes for patients undergoing lobectomy may influence the postoperative conditions of patients, hospital length of stay, and healthcare costs. Guidelines for management of chest tube have been

proposed (10, 11).

(10)Gao S, Zhang Z, Aragón J, et al. The Society for Translational Medicine: clinical practice guidelines for the postoperative management of chest tube for patients undergoing lobectomy. J Thorac Dis. 2017;9:3255-3264.

(11)Brunelli A, Beretta E, Cassivi SD, et al. Consensus definitions to promote an evidence-based approach to management of the pleural space. A collaborative proposal by ESTS, AATS, STS, and GTSC. Eur J Cardiothorac Surg. 2011;40:291-7.