—**Original**—

Association of Respiratory Tract Infection after Gastroenterological Surgery with Postoperative Duration of Hospitalization and Medical Expenses: Subanalysis of Data from a Multicenter Study

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Background: Postoperative infections can be classified as surgical site infections and remote infections. Postoperative respiratory tract infections (PRTI) are a type of remote infection and may be associated with prolonged hospitalization and increased medical expenses. This study compared postoperative duration of hospitalization and medical expenses between patients with and without PRTI after gastrointestinal surgery.

Methods: We retrospectively analyzed data from a multicenter study of centers affiliated with the Japan Society for Surgical Infection and used 1-to-1 matching analysis to evaluate 86 patients who underwent gastrointestinal surgery during the period from March 1, 2014 through February 29, 2016.

Results: Duration of postoperative hospitalization was significantly longer for patients with PRTI (38.6 days) than for those without PRTI (16.1 days), and postoperative medical expenses were significantly higher for patients with PRTI (1388.2 USD) than for those without PRTI (629.4 USD).

Conclusions: Duration of hospitalization is longer and medical expenses are higher for patients that develop surgical site infections. This study found that this was also the case for patients with PRTI after gastrointestinal surgery. However, further studies are needed in order to confirm these results.

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Key words: Remote infection, medical expenses, postoperative respiratory infection, hospitalization period

Introduction

Postoperative infections can be classified as surgical site infections (SSI) or remote infections (RI), which occur in areas not directly exposed to operation procedures. RI include postoperative respiratory tract infections (PRTI), urinary tract infections, postoperative enteritis, and catheter-associated blood stream infections. The US Centers for Disease Control and Prevention (CDC) established the definitions of SSI in the "Guideline for Prevention of Surgical Site Infection" in 1999[1]. Since then, most studies of postoperative infections have focused on establishing prophylactic measures against SSI, and several reports have examined the correlation between SSI incidence and medical expenses[2–6].

Previous studies in Japan reported that the hospitalization period and medical expenses were significantly increased for patients with postoperative SSI [4-7]. In 2016, the World Health Organization published a global guideline for the prevention of SSI[8], and, in 2017, the CDC revised their 1999 guideline[9]. Adoption of these guidelines and establishment of preventive measures have helped decrease SSI incidence. Although many studies have inves-

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Table 1 Diagnostic criteria for postoperative respiratory tract infection

Definitions of PRTI	
Radiographic examination	Signs, symptoms, and tests
At least one of the following findings is observed in two or more consecutive sessions of chest X-ray photography	For any patient, at least one of the following
New/progressive and consistent infiltrative shadow	Other cryptogenic fever (≥38℃)
Calcification image	Leucopenia (<4,000/mm^3) or leukocytosis (≥12,000/mm^3)
Cavity formation	For patients aged ≥70, cryptogenic changes in the psychiatric state
	Additionally, at least two of the following
	New occurrence of purulent expectoration, changes in phlegm characteristics, increased airway secretion
	Increased need of aspiration
	Rale, bronchial breath sound
	Aggravated gas exchange [reduced oxygen saturation (≤240 PaO^2/FiO^2), increased oxygen demand, increased ventilation demand]

tigated SSI, few have examined RI to a similar extent[10].

Among RI types, postoperative respiratory infection is the most serious complication. Although the incidence of postoperative respiratory infection varies in relation to surgical modality and definition, the incidence rate ranges from 2% to 19%[11], and the mortality rate is 8% to 71%[12]. One of the few reports of respiratory complications after laparotomy, by Yang et al., reported an incidence rate of 5.8%[13], while a review of patients undergoing non-cardiac surgery reported an incidence rate of 6.8%[14]. However, no studies have examined the associations of incident postoperative respiratory infection with duration of hospitalization and medical expenses. We therefore performed a subanalysis of data from the 2015 Japan Postoperative Infectious Complications Survey conducted by the Clinical Research Support Committee of the Japan Society for Surgical Infection[15].

Methods

We retrospectively analyzed patient data from 18 teaching hospitals affiliated with the Japan Society for Surgical Infection. We included patients who had undergone elective gastrointestinal surgery during the period from March 1, 2014 through February 29, 2016. PRTI was defined as a condition in which a patient without SSI was suspected of having a respiratory infection, as seen on postoperative radiographs, and exhibited new, progressive, and consistent infiltrative shadows, calcification images, or cavity formation in 2 or more consecutive chest radiography sessions.

With respect to signs, symptoms, and tests, eligible patients had a cryptogenic fever, leucopenia (<4,000/mm^3), or leukocytosis (≧12,000/mm^3). For patients aged ≧70 years, the criteria include cryptogenic changes in a psychiatric state. Respiratory infection was also diagnosed when at least two of the following conditions were met: incident or worsening purulent expectoration, coughing, dyspnea, tachypnea, rales, symptoms with bronchial breath sounds, and aggravated gas exchange (reduced oxygen saturation: ≦240 PaO2/FiO2, increased oxygen demand, and increased ventilation demand) (**Table 1**).

The participating institutions were requested to register cases treated for respiratory infection as PRTI cases. The onset observation period of PRTI was 60 days after surgery. To compare postoperative hospitalization period and medical expenses between patients with and without PRTI, retrospective 1-to-1 variable-matching analysis was performed. For matching with the non-PRTI group, patients of the same sex and with the same surgical site and surgical procedure in the PRTI group were selected for variable-matching analysis. To evaluate the postoperative effects of PRTI, duration of hospitalization (in days) and medical expenses (in USD) were included as the primary evaluation items.

To exclude preoperative and intraoperative medical expenses incurred by patients, the number of days until discharge, transfer, or death was counted, with 1 day after surgery regarded as the initial date. Total medical expenses were estimated by using these data. Postoperative medical expenses, including the cost of medical products and materials during postoperative hospitalization, were calculated in relation to diagnostic category, based on the 2014 healthcare fee. Steroid use and American Society of Anesthesiologists score were also recorded. An exchange rate of 110 JPY = 1 USD was used for the calculations. This study was approved by the Institutional Review

Table 2 Patient characteristies

Backgrounds of patients providing data							
			PRTI (-)	(%)	PRTI (+)	(%)	Total
			n=43		N=43		
Sex		Male	33	71.7	33	71.7	66
		Female	10	23.3	10	23.3	20
Surgical site and surgical procedure	Esophagus	Endoscopic surgery	6	13	6	13	12
		Open surgery	6	7	6	7	12
	Stomach	Endoscopic surgery	1	2.2	1	2.2	2
		Open surgery	8	18.6	8	18.6	16
	Large intestine	Endoscopic surgery	8	18.6	8	18.6	16
		Open surgery	2	4.7	2	4.7	4
	Liver/pancreas	Endoscopic surgery	0	0	0	0	0
		Open surgery	8	18.6	8	18.6	16
	Gallbladder	Endoscopic surgery	2	1.7	2	4.7	4
		Open surgery	0	0	0	0	0
	Appendix	Endoscopic surgery	2	4.7	2	4.7	4
		Open surgery	0	0	0	0	0
ASA score		1	17	39.5	6	14	23
		2	26	60.5	37	86	63
Steroid administration		No	43	100	39	90.7	82
		Yes	0	0	4	9.3	4
Type of respiratory complications		Aspiration pneumonia	0	0	26	60.5	26
		VAP	0	0	3	6.9	3
		Others	0	0	14	32.6	14

ASA: American Society of Anesthesiologists
VAP: Ventilator-associated pneumonia

Board of Nippon Medical School Tamanagayama Hospital (approval no. 624).

For statistical analysis, the nonparametric Mann-Whitney U test was performed, and a P value of less than 0.05 considered to be statistically significant. Standard deviations and 95% confidence intervals are shown for means and medians. Bell Curve for Excel (Social Survey Research Information Co., Ltd.) was used for the analysis.

Results

The registered surgeries were procedures related to the esophagus, stomach, large intestine, liver/pancreas, gallbladder, and appendix; there were 86 cases (43 pairs). These 86 cases comprised 66 men (33 pairs) and 20 women (10 pairs). Mean age was 70.7 years in the PRTI group and 71.9 years in the non-PRTI group. When classified by condition, there were 12 pairs with esophageal disease, 9 pairs with gastric disease, 10 pairs with large-intestinal disease, 8 pairs with hepatic/pancreatic disease, 2 pairs with gallbladder disease, and 2 pairs with appendiceal disease.

Regarding outcomes, 3 patients (7.0%) died while hospitalized, including 1 patient who died of gastric disease and 2 who died of large-intestinal disease. Five patients were transferred to the hospital, and the remaining 78 patients were discharged from hospital. Steroid use was not associated with PRTI incidence. The most common PRTI type was aspiration pneumonia (n = 26; 60.5%). Other conditions were ventilator-associated pneumonia (n = 3; 7.0%) and other pulmonary complications in 14 cases (32.6%) (**Table 2**); 28 patients developed pulmonary complications within 7 days after surgery, and 15 developed pulmonary complications 8 or more days after surgery (**Figure 1**).

Duration of postoperative hospitalization—16.1 ± 10.2 days for the non-PRTI group and 38.6 ± 27.3 days for the PRTI group—was significantly longer for the PRTI group ($p < 0.001$; **Figure 2**). The rate of increase from the non-PRTI group to the PRTI group was 220%. When classified by diagnostic category, medical expenses were significantly higher in the PRTI group for prescriptions, injec-

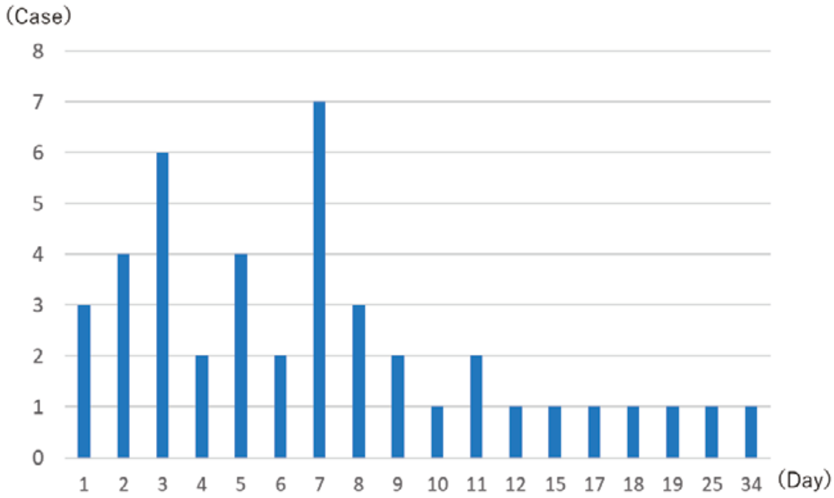

Fig 1. Onset day and number of cases of postoperative respiratory tract infection.

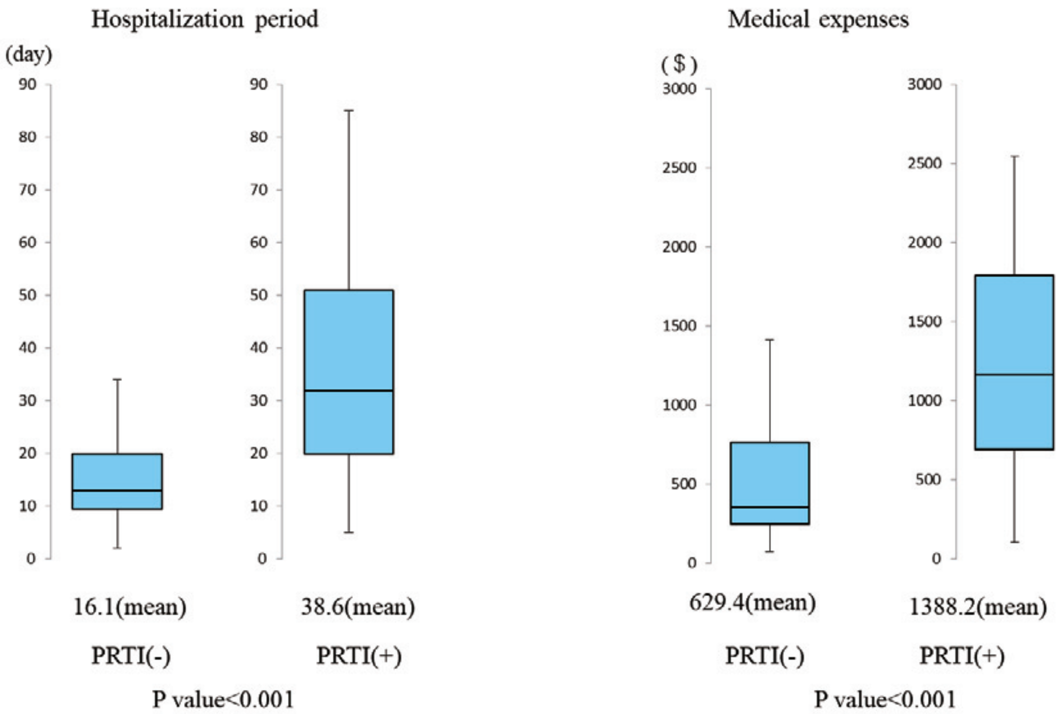

Fig 2. Duration of hospitalization and medical expenses in the PRTI and non-PRTI groups.

tions, treatments, examinations, image diagnoses, and other categories. Although surgery/anesthesia expenses were slightly higher in the PRTI group, the difference was not significant (**Table 3**). When duration of hospitalization and medical expenses attributable to PRTI onset were analyzed in relation to surgical approach (endoscopic surgery vs open surgery), both approaches were associated with significantly longer duration of hospitalization and higher medical expenses (**Table 4**). However, in a comparison of the rates of increase in duration of hospitalization and medical expenses attributable to PRTI onset, both rates were higher for endoscopic surgery than for open surgery (**Figure 3**).

Discussion

Among RI, PRTI are associated with more-serious complications and poorer prognosis. No clear definition of PRTI has been established, and studies of PRTI incidence and prognosis are greatly outnumbered by studies of SSI. However, the significance of postoperative pulmonary complications is now better understood. In systematic reviews of surgical operations for non-cardiorespiratory

Table 3 Medical expenses, by diagnostic category

Medical expenses based on diagnostic category									
	PRTI (-)			PRTI (+)			95% confidence interval for difference	*P* value	In-creased ratio %
	Mean	SD	Median	Mean	SD	Mediun			
Prescription	14.8	17.3	7.2	33.4	44.3	19.9	[3.9 ~ 33.2]	0.014	227
Injection	58	70.7	29.4	222.0	260.0	132.4	[80.0 ~ 248.0]	<0.001	383
Treatment	13.3	19.9	3.2	52.4	65.7	18.1	[18.9 ~ 59.5]	<0.001	394
Surgery/anesthesia	113.5	382.6	7.4	194.2	501.1	11.1	[-38.5 ~ 200.0]	0.179	171
Examination	37.2	33.1	23.0	85.0	1,901.3	71.7	[25.85 ~ 69.8]	<0.001	228
Image diagnosis	26.4	27.7	15.3	73.0	54.7	54.9	[29.01 ~ 64.2]	<0.001	276
Others	14.9	35.2	0	44.3	82.5	9.8	[2.54 ~ 56.2]	0.032	297
Hospitalization	351.4	274.8	246.1	683.9	438.3	595.3	[170.22 ~ 494.8]	<0.001	195

Table 4 Duration of hospitalization and medical expenses after endoscopic surgery and open surgery

Endoscopic surgery (19 pairs)									
	PRTI (−)			PRTI (+)			95% confidence interval for difference	*P* value	In-creased ratio %
	Mean	SD	Median	Mean	SD	Median			
Hospitalization period (day)	12.5	6.3	12	46.8	36.1	43	[16.8 ~ 52]	<0.001	376
Medical expenses ($)	395.3	263.1	327.6	1,491.9	1,153.3	1,240.8	[521 ~ 1,672.2]	<0.001	377
Open surgery (24 pairs)									
	PRTI (−)			PRTI (+)			95% confidence interval for difference	*P* value	In-creased ratio %
	Mean	SD	Median	Mean	SD	Median			
Hospitalization period (day)	19	11.8	14	32.1	15.7	28.5	[5 ~ 21.1]	0.003	169
Medical expenses ($)	814.7	849.9	355.4	1,306.1	1,040.5	1,094.1	[23.8 ~ 958.9]	0.040	160

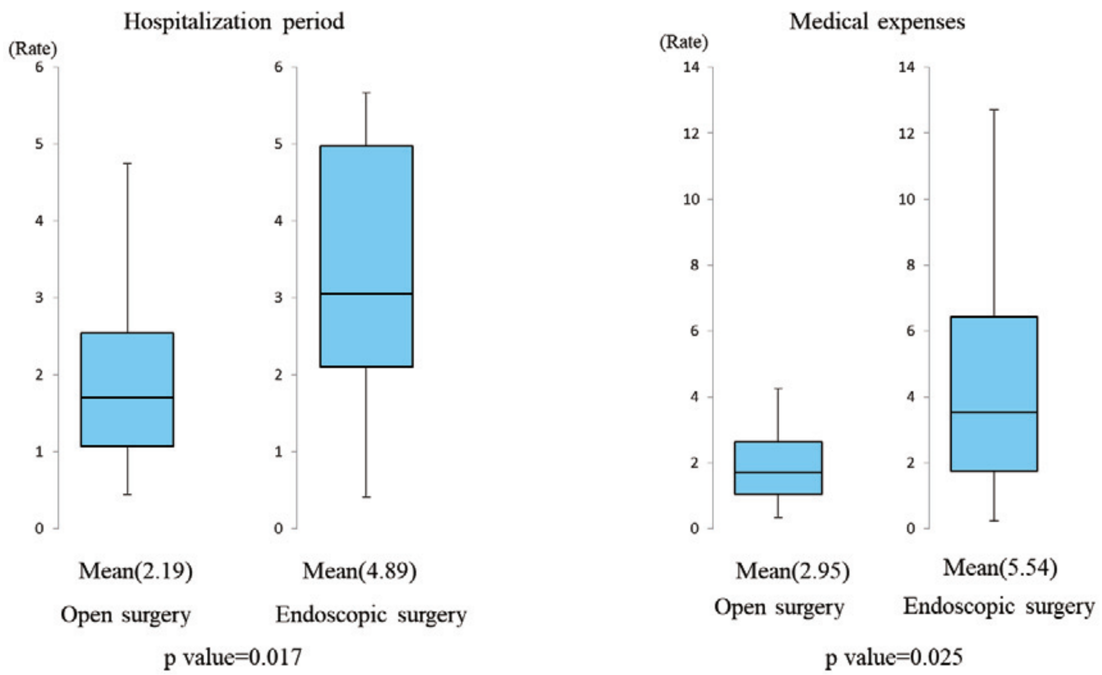

Fig 3. Rate of increase in duration of hospitalization and medical expenses for patients undergoing endoscopic and open surgeries.

diseases, PRTI are recognized as postoperative aspiration pneumonia, with measures such as breathing training and depressurization via nasogastric tubes considered effective[16]. In Japan, researchers have started reporting risk factors related to postoperative pneumonia after colorectal cancer surgery in persons aged 80 years or older[17]. Postoperative complications clearly prolonged postoperative hospitalization and increased medical expenses incurred by patients.

Studies in Western countries have examined SSI-related increases in medical expenses[2,3]. In Japan, 1 report suggested that the duration of postoperative hospitalization and medical expenses increased by 2.3 and 2.6 times, respectively, after incident postoperative SSI[4]. However, no studies have assessed prolongation of postoperative hospitalization and the increase in medical expenses after development of PRTI. In the present study, the duration of postoperative hospitalization was extended by a factor of 2.4, and postoperative medical expenses by a factor of 2.2, after PRTI. When analyzed by diagnostic category, post-PRTI costs for prescriptions were 2.3 times those of non-PRTI patients; the other multiples, in relation to the non-PRTI group, were 3.8 for injection costs, 4.0 for treatments, 2.3 for examinations, 2.8 for image diagnoses, 3.3 for other costs, and 1.9 for hospitalizations. Although the costs for surgery/anesthesia were 1.7 times those of the non-PRTI group, the difference was not significant, probably because PRTI, unlike SSI, required fewer repeat surgeries, thus resulting in a lower multiple, as compared with other diagnostic categories.

We hypothesized that the rates of increase in duration of hospitalization and medical expenses would be higher for PRTI than for SSI; however, no substantial differences were noted in these rates[4]. The SSI study was conducted from 2006 to 2008, while the present study analyzed data from 2014 to 2016. Therefore, differences in drug prices and other medical expenses make direct comparison unfeasible. Moreover, the surgeon who performed the initial surgery may not have been responsible for the patient until the time of hospital discharge, and patients stabilized with procedures such as tracheotomy may have been transferred to another hospital, thus prolonging hospitalization. In such cases, extension of hospitalization may have incurred relatively low medical costs. Therefore, postoperative medical expenses did not increase as expected.

Elective endoscopic surgery is widely performed to treat diseases of the digestive organs. The present comparison of endoscopic and open surgeries revealed that patients who developed PRTI after open surgery had longer hospitalizations and higher medical expenses. The rate of increase was approximately 160%. In contrast, patients undergoing endoscopic surgery had an approximately 370% increase in duration of hospitalization and total medical expenses, which was significantly greater than the increase in the open surgery group. In general, endoscopic surgery results in fewer postoperative complications. Therefore, if complications do not occur, patients who have undergone endoscopic procedures tend to be discharged from hospital earlier and incur lower medical expenses than do patients who have undergone open surgery procedures. Among the present non-PRTI patients, the mean hospitalization period was 12.5 days in the endoscopic surgery group and 19.0 days in the open surgery group. Although the difference was not significant, patients in the open surgery group were hospitalized longer. Potential differences in preoperative conditions between surgery groups may have resulted in the higher rate of increase in duration of hospitalization and medical expenses in PRTI patients in the endoscopic surgery group.

The number of esophageal surgery pairs was 12, which was the most frequent surgery performed. Studies of data from large databases of esophageal surgeries in Japan[18], the US[19], and the UK[20] showed no advantage of endoscopic surgery with respect to postoperative complications but indicated that operation time was longer and repeat surgery more frequent. Postoperative mortality was inversely related to the annual number of esophageal surgeries performed[21,22]. Endoscopic surgery can result in postoperative complications, particularly in patients with esophageal diseases. From the perspective of hospitalization period and total medical expenses, endoscopy is not very advantageous and may in fact aggravate PRTI complications and increase the duration of hospitalization and medical expenses after surgery. Endoscopic surgery for diseases other than esophageal disease is less likely to cause complications; however, few studies have evaluated post-PRTI prognosis and outcomes[17]. Therefore, prospective studies with a larger number of cases are necessary.

Variable-matching analysis was used in this study. To focus on the different attributes of PRTI cases, PRTI and non-PRTI cases were paired, and differences in evaluation items were analyzed between pairs. With this method, an increased number of matched variables led to failure to identify some patients with PRTI, thus resulting in fewer registered cases. In addition, retrospective observation may not be sufficiently thorough to extract all PRTI cases. Furthermore, the present definitions of PRTI are unlike those of SSI, which are more carefully established and may therefore differ in relation to the subjective assessment and diagnosis of observers. However, despite these limitations, duration of postoperative hospitalization and medical expenses were significantly higher in the PRTI group. Therefore, our results clearly demonstrate the increased burdens on PRTI patients and healthcare systems. Oral care, pain management, and breathing exercises are reported to be effective measures for preventing PRTI[16]. In addition to PRTI (a type of RI), urinary tract infection, *Clostridioides difficile* enteritis, and catheter infection have serious effects on the quality of life of patients undergoing surgical treatment. Additional studies of these important complications of RI will likely increase awareness.

This study had limitations that warrant mention. It was limited to expenses related to medical care; hence, outcomes of surgical patients, as determined by the Clavien-Dindo classification, were not investigated. Furthermore, data were collected at centers affiliated with the Japan Society for Surgical Infection, which emphasizes management of perioperative infections. Therefore, the present findings may not accurately reflect conditions throughout Japan. A nationwide study is therefore necessary.

In conclusion, we conducted a retrospective analysis of data from a multicenter joint study of the effects of postoperative PRTI on postoperative duration of hospitalization and medical expenses. Incident PRTI was associated with increased duration of hospitalization and higher medical expenses, and thus greater medical and economic burdens on patients and the healthcare system.

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