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Measuring serum and drainage fluid interleukin-6 and tumor necrosis factor-α levels for early detection of infectious complications after minimally invasive surgery for gastric cancer

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ABSTRACT

Objective: Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are inflammatory cytokines produced in response to biological invasion or infection. Their levels are elevated in the blood and locally. We examined whether measuring IL-6 and TNF-α levels in serum or drainage fluid on postoperative day (POD) 1 could detect infectious complications after minimally invasive surgery for gastric cancer.

Methods: This cohort study included 205 consecutive patients who underwent laparoscopic or robot-assisted gastrectomy for gastric cancer between November 2020 and July 2023. We measured serum and drainage fluid IL-6 and TNF-α levels on POD 1 after gastrectomy. Receiver operating characteristic (ROC) curves were created to compare the diagnostic values of each cytokine and serum C-reactive protein levels for detecting postoperative infectious complications.

Results: IL-6 and TNF-α levels in the serum or drainage fluid were significantly higher in patients with an infectious complication. In addition, drainage fluid IL-6 levels were significantly different in patients with versus without intra-abdominal abscess. In the ROC curve analysis, serum and drainage fluid IL-6 had the highest AUC values for any infectious complication and intra-abdominal abscess, respectively. POD 1 serum IL-6 level above 47 pg/mL could detect any infectious complication with sensitivity of 74.1 % and specificity of 71.8 %. POD 1 drainage fluid IL-6 level above 14,750 pg/mL had 100 % sensitivity for detecting intra-abdominal abscess with specificity of 56.0 %.

Conclusions: Measurement of IL-6 levels in blood and drainage fluid on POD 1 is valuable for early detection of postoperative infectious complications or intra-abdominal abscess after gastric cancer surgery.

1. Introduction

Gastric cancer remains one of the most common gastrointestinal malignancies; it is the fourth leading cause of cancer death worldwide [1]. For gastric cancer, surgical resection remains the only curative option, but chemotherapy and immunotherapy have been dramatically improved recently [2–4]. However, postoperative complications associated with surgery occur at a constant rate and have been shown to worsen the prognosis of patients with malignant tumors, prolong hospital stay, and decrease quality of life [5–7]. In particular, the occurrence of intra-abdominal infections has been reported to adversely affect long-term survival outcomes [8–10]. Therefore, it is very important to detect the occurrence of postoperative complications, especially intra-abdominal infections, as early as possible and to treat them appropriately.

Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are inflammatory cytokines produced in response to biological invasion or infection. Their levels are known to be elevated in the blood and in the local area [11–13]. Recently, serum cytokine levels have attracted attention as new markers that can detect postoperative infectious complications. It has been reported that serum IL-6 levels on postoperative day (POD) 1 in patients who have undergone major cancer surgery can

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detect postoperative sepsis at an early stage [14]. A retrospective study that evaluated serum IL-6 levels in 137 patients who underwent major abdominal surgery suggested that high serum IL-6 levels on POD 1 are independently associated with the occurrence of postoperative complications [15]. However, there have been few cohort studies investigating associations between serum cytokine levels and complications after gastric cancer surgery, and the significance of cytokine levels in drainage fluid remains unclear [16,17]. In addition, previous studies have mainly focused on open surgery; thus, the details of the postoperative changes in cytokine levels after minimally invasive surgery are unknown. We have routinely measured IL-6 and TNF-α levels on POD 1 both in the blood and drainage fluid from the drain placed in the abdominal cavity in patients who have undergone gastrectomy for gastric cancer since November 2020. The purpose of this study was to examine whether measuring IL-6 and TNF-α levels on POD 1 in serum or drainage fluid is sensitive for detecting infectious complications after minimally invasive surgery for gastric cancer.

2. Methods

2.1. Patients

This cohort study included consecutive patients who underwent laparoscopic or robot-assisted gastrectomy for gastric cancer at Osaka University Hospital from November 2020 to July 2023. All patients were diagnosed with adenocarcinoma of the stomach histologically. Patients with failed R2 resection were excluded from this cohort. In principle, gastrectomy type and extent of lymph node dissection were based on the Japanese Gastric Cancer Treatment Guidelines [18]. Tumor staging was performed according to the 15th edition of the Japanese Classification of Gastric Carcinoma. In all patients, a drainage tube was routinely placed in the superior border of the pancreas intraoperatively. We did not use routine prophylactic antibiotics in all cases. This study was approved by the institutional review board of Osaka University Hospital (nos. 17368 and 23232). All patients provided written informed consent for their blood and drainage fluid samples to be used in research.

2.2. Evaluation of postoperative complications

Postoperative complications were evaluated according to the Clavien–Dindo (C-D) classification [19,20]. In this study, we considered complications of C-D grade II or higher to be postoperative complications. Infectious complications included intra-abdominal abscess, pneumonia, anastomotic leak, pancreatic fistula, urinary tract infection, wound infection, cholecystitis, and catheter-related bloodstream infection.

2.3. Measurement of IL-6 and TNF-α levels

All blood samples were drawn on POD 1 in all patients during routine morning blood sampling rounds, typically at 7 a.m. Similarly, drainage fluid samples were routinely collected in the morning on POD 1 at the same time. Each sample was collected in collection tubes commonly used for routine biochemical tests, yielding approximately 6 ml. Blood samples were centrifuged within 6 h after collection. All samples were stored in frozen aliquots at −80 °C, and shipped to the laboratory (SRL, Tokyo, Japan) within 4 weeks. IL-6 levels were evaluated with an electrochemiluminescent immunoassay (ECLIA). TNF-α levels were evaluated using an enzyme-linked immunosorbent assay (ELISA). C-reactive protein (CRP) levels were measured in routine perioperative laboratory tests at Osaka University Hospital. Samples that were difficult to centrifuge due to hemolysis and samples with insufficient volume were excluded.

2.4. Statistical analysis

Any cytokine level measurements beyond three times the standard deviation (SD) from the mean were considered outliers and excluded from the analysis. The relationship between infectious complications and each cytokine was assessed using the Mann–Whitney *U* test. For all tests, two-sided $P < 0.05$ was considered statistically significant. A receiver operating characteristic (ROC) curve was created to compare the diagnostic values of cytokine and CRP levels for detecting postoperative infectious complications. The cutoff value was estimated on the basis of the ROC curve and Youden's index (sensitivity + specificity − 1). Cumulative hospitalization rates were estimated using the Kaplan–Meier method and compared with the log-rank test. All analyses were performed with SPSS software, version 24.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient characteristics and postoperative complications

Of the 226 patients who met the eligibility criteria, 20 patients did not have drainage fluid cytokine measurements because of hemolysis, and 1 was excluded because no drain was placed; as a result, 205 patients were included in the analysis. Patients' background characteristics and short-term surgical outcomes are shown in Table 1.

Table 1
Background characteristics of the study patients.

Characteristics	(n = 205)
Age (years)	
Median	75
Range	37–95
Sex	
Male	127 (62.0 %)
Female	78 (38.0 %)
Body mass index at surgery (kg/m^2)	
Median	21.8
Range	14.7–33.0
Neoadjuvant chemotherapy	
Yes	28 (13.7 %)
No	177 (86.3 %)
Clinical stage	
I	111 (54.1 %)
II	41 (20.1 %)
III	47 (22.9 %)
IV	6 (2.9 %)
Surgical procedure	
Laparoscopic	124 (60.5 %)
Robot-assisted	81 (39.5 %)
Type of gastrectomy	
Total	27 (13.2 %)
Proximal	30 (14.6 %)
Distal	148 (72.2 %)
Operation time (minutes)	
Median	280
Range	150–610
Intraoperative blood loss (ml)	
Median	10
Range	0–560
Any infectious complication (≥C-D Grade II)	27[a] (13.2 %)
Intra-abdominal abscess	8 (3.9 %)
Pneumonia	8 (3.9 %)
Anastomotic leak	7 (3.4 %)
Pancreatic fistula	4 (1.9 %)
Urinary tract infection	2 (1.0 %)
Wound infection	2 (1.0 %)
Cholecystitis	1 (0.5 %)
Catheter-related bloodstream infection	1 (0.5 %)

C-D, Clavien-Dindo classification.
[a] Six patients experienced multiple complications.

Approximately half of the patients had cStage I disease and 13.7 % of patients underwent neoadjuvant chemotherapy. Approximately 60 % of patients underwent laparoscopic gastrectomy, while 40 % underwent robot-assisted gastrectomy. The most common type of gastrectomy was distal gastrectomy (72.2 %), followed by proximal gastrectomy (14.6 %). Complications of C-D grade II or higher occurred in 36 patients (17.6 %), of whom 27 patients (13.2 %) had infectious complications. The most common infectious complications were intra-abdominal abscess and pneumonia in 8 patients (3.9 %), followed by anastomotic leakage in 7 patients (3.4 %). The median Comprehensive Complications Index (CCI) in 27 patients with any infectious complication was 22.6, and in eight patients with intra-abdominal abscess, it was 37.6. None of the patients died during postoperative hospitalization.

3.2. POD 1 cytokine and CRP levels

One serum IL-6 measurement, six drainage fluid IL-6 measurements, two serum TNF-α measurements, and two drainage fluid TNF-α measurements were excluded from the analysis as outliers. On POD 1, the median serum CRP level was 3.7 mg/dL (range: 1.3–13.4). Serum IL-6 levels on the same day had a median of 28.5 pg/mL (range: 4.3–4060), while drainage fluid IL-6 levels were notably higher at 13200 pg/mL (range: 0.7–87400). Conversely, serum TNF-α levels had a median of 0.6 pg/mL (range: 0.2–17.1), with drainage fluid TNF-α levels slightly elevated at 0.9 pg/mL (range: 0.2–84.6). We compared serum CRP or cytokines levels on POD 1 with the occurrence of any infectious complication or intra-abdominal abscess. Serum CRP levels ($P = 0.003$), serum and drainage fluid IL-6 levels ($P < 0.001$ and $P = 0.003$, respectively), and serum and drainage fluid TNF-α levels ($P = 0.003$ and $P = 0.004$, respectively) were significantly higher in patients with any infectious complication (Fig. 1). In addition, only drainage fluid IL-6 levels were significantly different between patients with and without intra-abdominal abscess ($P = 0.011$) (Fig. 2).

3.3. ROC curve analysis

We analyzed ROC curves of cytokine and serum CRP levels on POD 1 to identify the best diagnostic markers for any infectious complication or intra-abdominal abscess (Fig. 3). The highest area under the curve (AUC) value of the ROC curve for any infectious complication was for serum IL-6 (0.732), followed by serum CRP (0.688). On the other hand, the highest AUC value of the ROC curve for intra-abdominal abscess was drainage fluid IL-6 (0.768), followed by serum TNF-α (0.716). When the POD 1 serum IL-6 cutoff value for detecting any infectious complication was determined as 47 pg/mL based on the Youden index, sensitivity and specificity were 74.1 % and 71.8 %, respectively (Table 2). Likewise, when the POD 1 drainage fluid IL-6 cutoff value for detecting intra-abdominal abscess was determined as 14,750 pg/mL, sensitivity and specificity were 100 % and 56.0 %, respectively. The high serum IL-6 group had significantly longer postoperative hospital stays than the low serum IL-6 group (log-rank $P < 0.001$). Similarly, the high drainage fluid IL-6 group had significantly prolonged postoperative hospital stays than the low drainage fluid IL-6 group (log-rank $P < 0.001$) (Fig. 4).

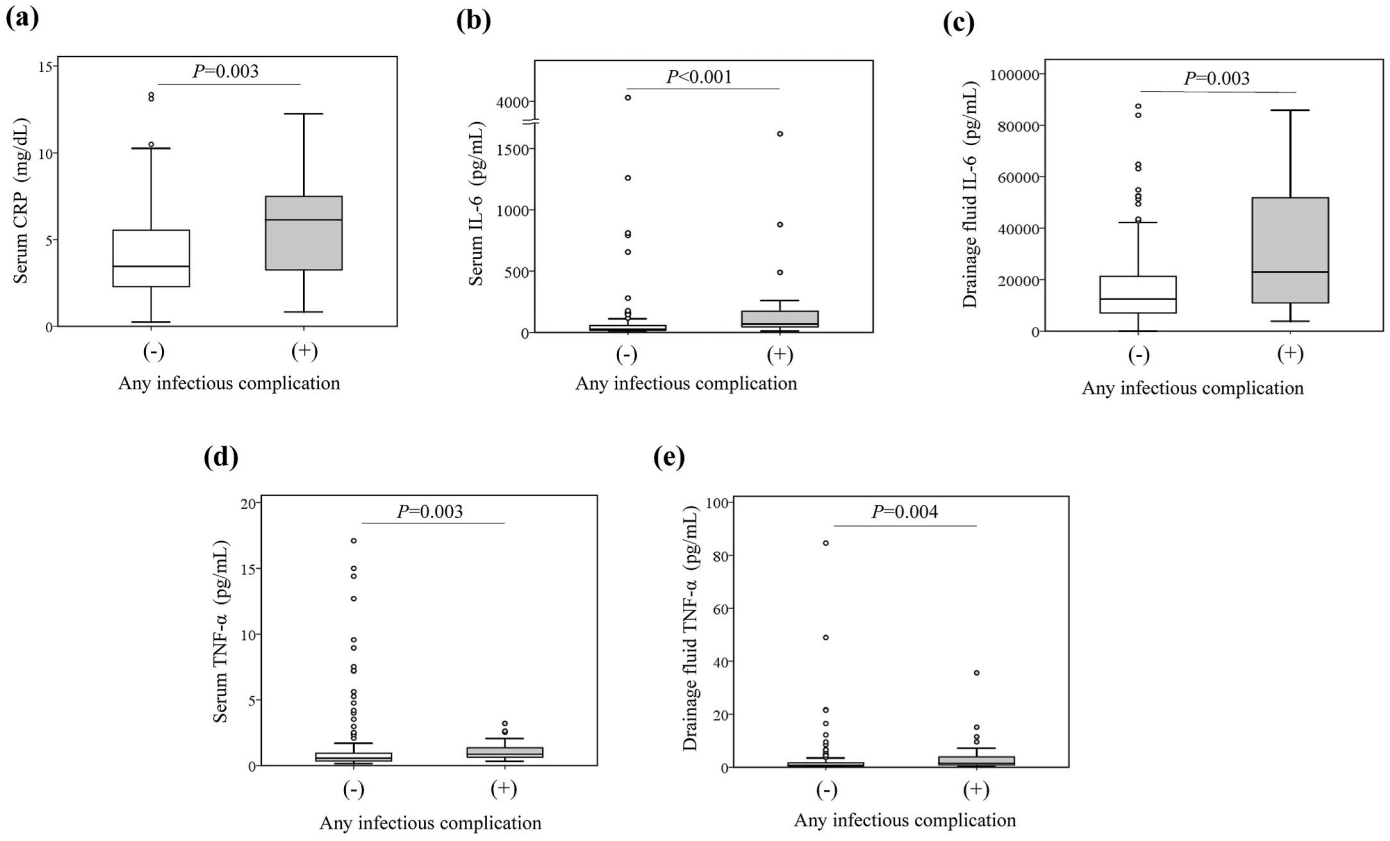

Fig. 1. C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels on postoperative day 1 in patients with versus without any infectious complication

Boxplots show (a) CRP, (b) serum IL-6, (c) drainage fluid IL-6, (d) serum TNF-α, and (e) drainage fluid TNF-α levels in patients with versus without any infectious complication. Boxplots indicate the first, second (median), and third quartiles. Bars show the lowest data points within 1.5 times the interquartile range (IQR) value from the lower quartile boundary or the highest data points within 1.5 times the IQR value from the upper quartile boundary. Circles indicate values that were more than 1.5 times the interquartile range (IQR) value, beyond the boundary between the lower or upper quartile points.

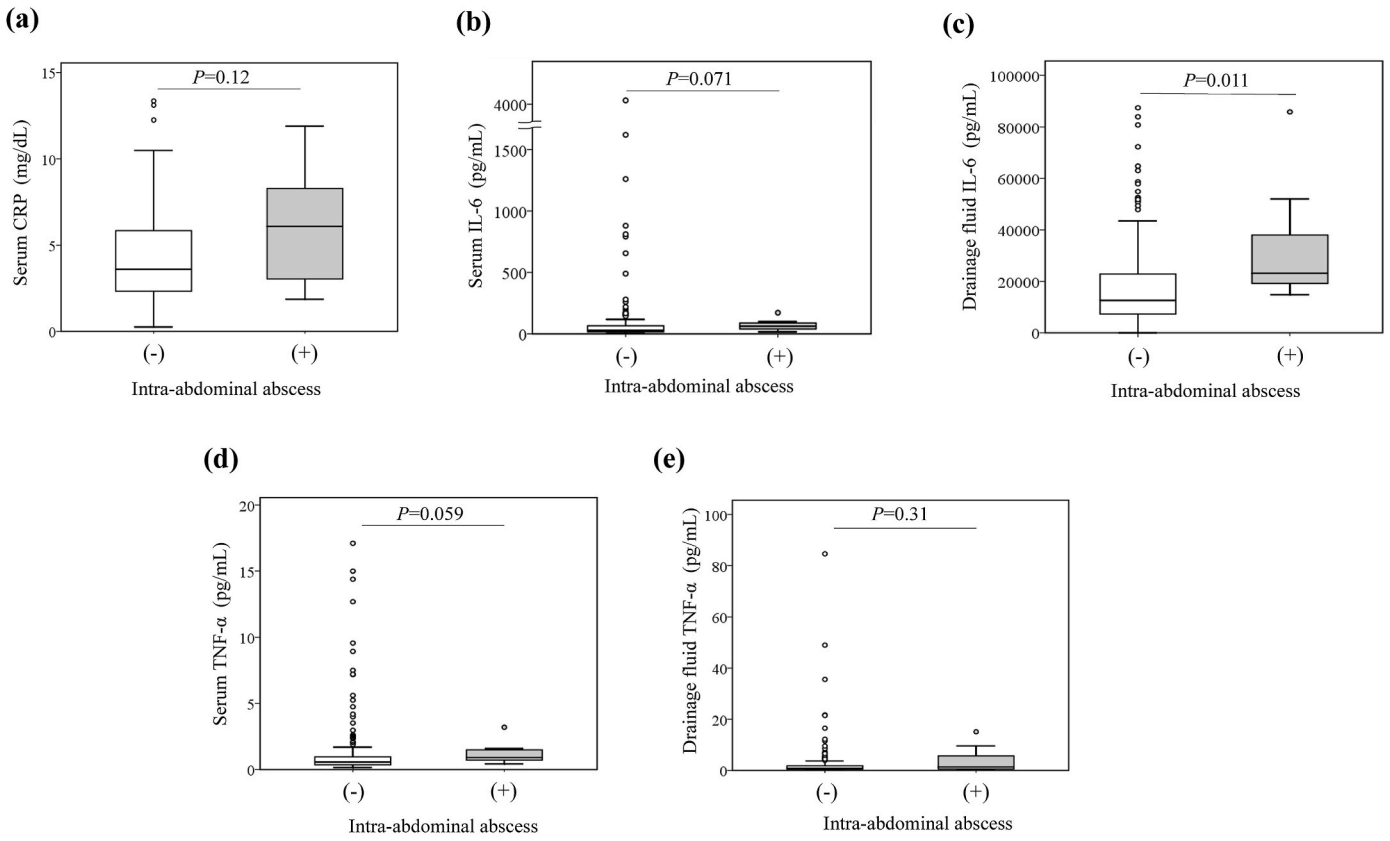

Fig. 2. C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels on postoperative day 1 in patients with versus without intra-abdominal abscess
Boxplots show (a) CRP, (b) serum IL-6, (c) drainage fluid IL-6, (d) serum TNF-α, and (e) drainage fluid TNF-α levels in patients with versus without intra-abdominal abscess. Boxplots indicate the first, second (median), and third quartiles. Bars show the lowest values within 1.5 times the interquartile range (IQR) value from the lower quartile boundary or the highest data points within 1.5 times the IQR value from the upper quartile boundary. Circles indicate values that were more than 1.5 times the IQR value, beyond the lower or upper quartile points.

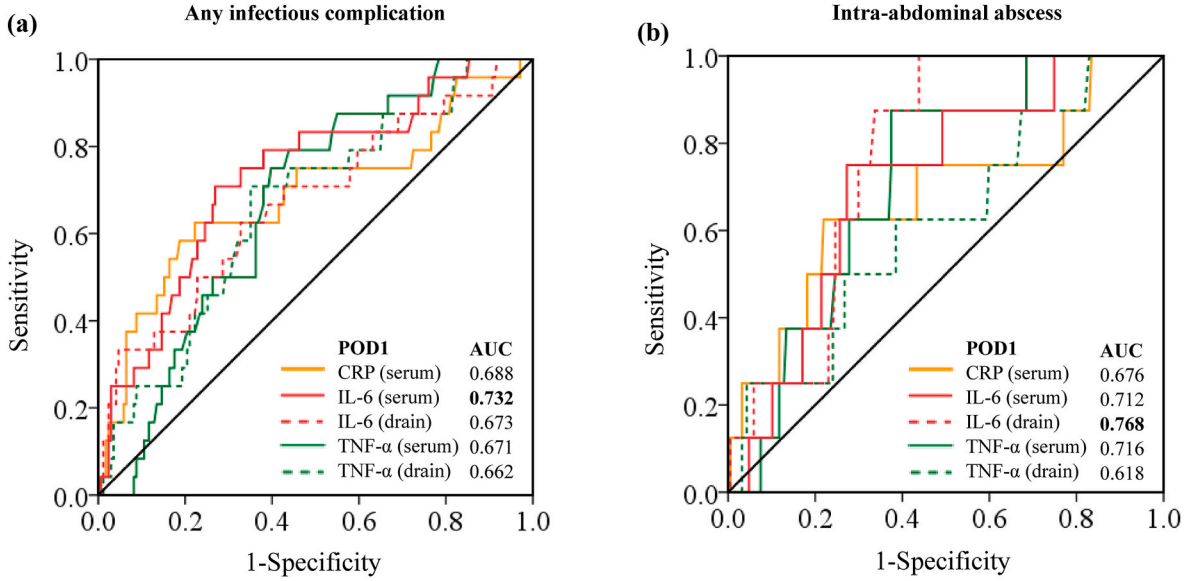

Fig. 3. Receiver operating characteristic (ROC) curves of C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels on postoperative day 1 for (a) any infectious complication or (b) intra-abdominal abscess
Area under the curve (AUC) values for each factor in the ROC curve are also presented.

Table 2
Diagnostic values of serum and drainage fluid interleukin-6 (IL-6) levels for any infectious complication or intra-abdominal abscess.

Serum IL-6	Any infectious complication		Sensitivity 74.1 %
	(+)	(−)	Specificity 71.8 %
≥47 pg/mL	20	50	PPV 28.6 %
<47 pg/mL	7	127	NPV 94.8 %
Drain IL-6	Intra-abdominal abscess		Sensitivity 100 %
	(+)	(−)	Specificity 56.0 %
≥14,750 pg/mL	8	84	PPV 8.7 %
<14,750 pg/mL	0	107	NPV 100 %

PPV, positive predictive value; NPV, negative predictive value.

4. Discussion

This cohort study examined whether cytokine levels in serum or drainage fluid after gastric cancer resection could detect postoperative infectious complications as early as possible. POD I serum IL-6 level above 47 pg/mL could detect any infectious complication after gastric cancer surgery with sensitivity of 74.1 % and specificity of 71.8 %. In addition, POD 1 drainage fluid IL-6 level above 14,750 pg/mL had 100 % sensitivity for detecting intra-abdominal abscess with specificity of 56.0 %. The high IL-6 group required significantly longer hospitalization after surgery than the low IL-6 group. Serum CRP level, which is more widely used in clinical practice, did not surpass these results.

IL-6 is a cytokine with multiple types of activity. It is synthesized locally during the early stages of inflammation and then translocated via the bloodstream to the liver, where it induces the synthesis of acute phase proteins such as serum amyloid A, fibrinogen, and hepcidin [12,13]. It has been known that serum IL-6 levels increase prior to a rise in body temperature and serum acute-phase protein levels in aseptic surgical procedures [21]. Furthermore, polymorphisms in the genes encoding IL-6 and TNF-α are associated with the development of postoperative complications after lung resection [22].

Therefore, several studies have investigated the usefulness of serum IL-6 as a diagnostic marker of postoperative complications [23–25]. Rettig et al. evaluated serum IL-6 levels in 137 patients undergoing major abdominal surgery. They reported that a POD 1 serum IL-6 cutoff value of 432 pg/mL has specificity of 70 % and sensitivity of 64 % for detecting all complications [15]. Szczepanik et al. also evaluated serum IL-6 levels in 99 patients undergoing gastrectomy for gastric cancer. They reported that a POD 1 serum IL-6 level above 288.7 pg/mL is an independent diagnostic marker of infectious complications [16]. In our study, we found that POD 1 serum IL-6 level yielded the most accurate detection of infectious complications, consistent with previous reports. Our cutoff value (47 pg/mL) for serum IL-6, which was determined based on the Youden index with ROC curve analysis, was considerably lower than in previous reports, probably due to the use of laparoscopic or robot-assisted surgery in our cohort. IL-6 can also be released from damaged cells due to non-infectious trauma, directly or indirectly promoting inflammation [21]. With the increasing adoption of minimally invasive surgery, it is possible that the serum IL-6 levels in our study might be lower than those reported in previous studies. Since minimally invasive surgery is becoming increasingly mainstream worldwide, we believe that our cutoff values would be more useful in clinical practice.

Serum CRP levels might not be suitable for early detection of infectious complications because CRP is usually produced in the liver with IL-6 stimulation and rises later than IL-6, which indicates that the most sensitive period for serum CRP levels to detect infectious complications is POD 3–5 [26–28]. Therefore, measuring serum IL-6 levels on POD 1 can enable earlier detection of infectious complications compared to routine blood tests. This can assist in devising strategies such as additional imaging studies and early initiation of antibiotic treatment.

There were few studies on cytokines in drainage fluid from abdominal surgery. Similar to our results, a previous study reported that IL-6 levels are higher in drainage fluid than in blood after hepatic resection [29]. In thoracic surgery, cytokine levels in postoperative pleural effusions have been reported to be higher than in blood [30,31], suggesting that local cytokine production as a result of thoracic surgery is much higher than after abdominal surgery. In our study, drainage fluid IL-6 on POD 1 could detect intra-abdominal abscess with higher sensitivity than serum IL-6 because lipopolysaccharide from gram-negative rods reacts with Toll-like receptors in intra-abdominal tissues, resulting in local IL-6 production and higher IL-6 levels in ascites fluid. Procalcitonin is also widely recognized as an early predictive marker for infection. However, in a previous report of colorectal surgery, procalcitonin was measured daily until POD 4, and the highest area under the ROC curve for intra-abdominal infection was found on POD 4 [26]. Postoperative intra-abdominal abscess is usually treated with antibiotics and drainage [32,33]. Recent studies have suggested that earlier treatment of intra-abdominal infections leads to better outcomes [34]. We believe that the findings of our study will be useful in clinical practice to enable early detection and treatment of intra-abdominal abscess. In addition, the placement of drainage tubes after gastric cancer surgery remains controversial. There has been a report of complications due to drain placement [35]. These results will also encourage the removal of drain tubes early during the postoperative course, leading to enhanced recovery after surgery (ERAS).

In our study, serum and drain drainage fluid TNF-α were not as sensitive for postoperative infectious complications. Several studies have reported measuring TNF-α levels in the drainage fluid of patients after colorectal cancer surgery is helpful for detecting anastomotic

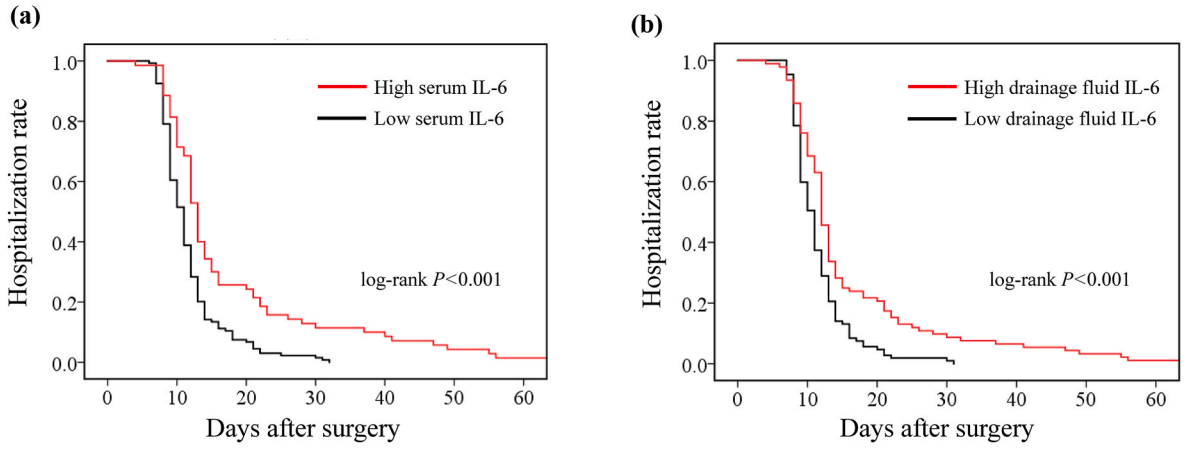

Fig. 4. Kaplan–Meier curves for postoperative hospital stay by interleukin-6 (IL-6) level in (a) serum or (b) drainage fluid on postoperative day 1.

leakage [36,37]. The other study has reported no statistically significant differences between patients with and without complications [38], which indicates a consensus has not been reached. Moreover, TNF-α has been reported to increase from POD 4 onward in the presence of complications [15]. Thus, it might be inappropriate as a marker for early detection of postoperative infectious complications.

This study has several limitations. First, despite collecting patient samples prospectively, it remains a retrospective investigation conducted at a single facility. Furthermore, the incidence of complications was lower than that in Western institutions [39,40]. Therefore, further research is necessary to assess whether our findings can be extrapolated to Western institutions. Second, each cytokine was measured only on POD 1. Therefore, longitudinal changes could not be tracked. However, previous studies have demonstrated that preoperative IL-6 levels were too low to predict surgical site infection, and that POD 1 exhibited the highest sensitivity in tracking the changes of IL-6 levels over time after surgery [15,24,25]. Third, intake–output balance due to intraoperative anesthesia management might vary depending on the duration of surgery and surgical technique, which might increase or decrease the volume of intraperitoneal drainage fluid after surgery and dilute cytokine levels.

In conclusion, this study demonstrated that measuring cytokine levels in blood and drainage fluid is valuable for early detection of postoperative infectious complications and intra-abdominal abscess. We plan to conduct long-term follow-up investigations in the future that examine the relationship between cytokines and long-term prognosis.

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Disclosures

The authors declare that they have no conflicts of interest.

Author contributions

Study concept and design: T Itami, Y Kurokawa, R Yoshioka; Data acquisition: T Itami, R Yoshioka; Quality control of data and algorithms: Y Kurokawa, T Saito, K Yamamoto, T Takahashi; Data analysis and interpretation: all authors; Statistical analysis: T Itami; Manuscript preparation: T Itami, Y Kurokawa, R Yoshioka; Manuscript editing: T Saito, K Yamamoto, T Takahashi, K Momose, K Yamashita, K Tanaka, T Makino, K Nakajima, H Eguchi, Y Doki; Manuscript review: all authors.

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2021 May;71(3):209–49.
[2] Yanagimoto Y, Kurokawa Y, Doki Y. Essential updates 2021/2022: perioperative and surgical treatments for gastric and esophagogastric junction cancer. Ann Gastroenterol Surg 2023 Sep;7(5):698–708.
[3] Kurokawa Y, Kawase T, Takeno A, Furukawa H, Yoshioka R, Saito T, et al. Phase 2 trial of neoadjuvant docetaxel, oxaliplatin, and S-1 for clinical stage III gastric or esophagogastric junction adenocarcinoma. Ann Gastroenterol Surg 2023 Mar;7(2):247–54.
[4] Hashimoto T, Kurokawa Y, Mori M, Doki Y. Update on the treatment of gastric cancer. JMA J. 2018 Sep 28;1(1):40–9.
[5] Kataoka K, Takeuchi H, Mizusawa J, Igaki H, Ozawa S, Abe T, et al. Prognostic impact of postoperative morbidity after esophagectomy for esophageal cancer: exploratory analysis of JCOG9907. Ann Surg 2017 Jun;265(6):1152–7.
[6] Artinyan A, Orcutt ST, Anaya DA, Richardson P, Chen GJ, Berger DH. Infectious postoperative complications decrease long-term survival in patients undergoing curative surgery for colorectal cancer: a study of 12,075 patients. Ann Surg 2015 Mar;261(3):497–505.
[7] Kurokawa Y, Yamashita K, Kawabata R, Fujita J, Imamura H, Takeno A, et al. Prognostic value of postoperative C-reactive protein elevation versus complication occurrence: a multicenter validation study. Gastric Cancer 2020 Sep;23(5):937–43.
[8] Tokunaga M, Tanizawa Y, Bando E, Kawamura T, Terashima M. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. Ann Surg Oncol 2013 May;20(5):1575–83.
[9] Tokunaga M, Kurokawa Y, Machida R, Sato Y, Takiguchi S, Doki Y, et al. Impact of postoperative complications on survival outcomes in patients with gastric cancer: exploratory analysis of a randomized controlled JCOG1001 trial. Gastric Cancer 2021 Jan;24(1):214–23.
[10] Alonso S, Pascual M, Salvans S, Mayol X, Mojal S, Gil MJ, et al. Postoperative intra-abdominal infection and colorectal cancer recurrence: a prospective matched cohort study of inflammatory and angiogenic responses as mechanisms involved in this association. Eur J Surg Oncol 2015 Feb;41(2):208–14.
[11] Dimopoulou I, Armaganidis A, Douka E, Mavrou I, Augustatou C, Kopterides P, et al. Tumour necrosis factor-alpha (TNFalpha) and interleukin-10 are crucial mediators in post-operative systemic inflammatory response and determine the occurrence of complications after major abdominal surgery. Cytokine 2007 Jan;37(1):55–61.
[12] Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harbor Perspect Biol 2014 Sep 4;6(10):a016295.
[13] Heinrich PC, Castellt JV, Andust T. Interleukin-6 and the acute phase response. Biochem J 1990;265(3):621–36.
[14] Mokart D, Merlin M, Sannini A, Brun JP, Delpero JR, Houvenaeghel G, et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth 2005 Jun;94(6):767–73.
[15] Rettig TCD, Verwijmeren L, Dijkstra IM, Boerma D, van de Garde EMW, Noordzij PG. Postoperative interleukin-6 level and early detection of complications after elective major abdominal surgery. Ann Surg 2016 Jun;263(6):1207–12.
[16] Szczepanik AM, Scislo L, Scully T, Walewska E, Siedlar M, Kolodziejczyk P, et al. IL-6 serum levels predict postoperative morbidity in gastric cancer patients. Gastric Cancer 2011 Aug;14(3):266–73.
[17] Zhang Z, Weng B, Qiu Y, Feng H, Zhang R, Zhang J, et al. Effect of perioperative interleukin-6 and tumor necrosis factor-α on long-term outcomes in locally advanced gastric cancer: results from the CLASS-01 trial. J Immunol Res 2022 Jul 8;2022:7863480.
[18] Japanese Gastric Cancer Association. Japanese gastric cancer treatment Guidelines 2021 (6th edition). Gastric Cancer 2023 Jan;26(1):1–25.
[19] Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004 Aug;240(2):205–13.
[20] Katayama H, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, et al. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. Surg Today 2016 Jun;46(6):668–85.
[21] Nishimoto N, Yoshizaki K, Tagoh H, Monden M, Kishimoto S, Hirano T, et al. Elevation of serum interleukin 6 prior to acute phase proteins on the inflammation by surgical operation. Clin Immunol Immunopathol 1989 Mar;50(3):399–401.
[22] Shaw AD, Vaporciyan AA, Wu X, King TM, Spitz MR, Putnam JB, et al. Inflammatory gene polymorphisms influence risk of postoperative morbidity after lung resection. Ann Thorac Surg 2005 May;79(5):1704–10.
[23] Yu Q, Cen C, Gao M, Yuan H, Liu J. Combination of early Interleukin-6 and -18 levels predicts postoperative nosocomial infection. Front Endocrinol 2022 Oct 10;13:1019667.
[24] Xie T, Zhao C, Ding C, Zhang L, Cheng M, Chun C, et al. Postoperative interleukin-6 predicts intra-abdominal septic complications at an early stage after elective intestinal operation for crohn's disease patients. Inflamm Bowel Dis 2018 Aug 16;24(9):1992–2000.
[25] Kimura F, Shimizu H, Yoshidome H, Ohtsuka M, Kato A, Yoshitomi H, et al. Increased plasma levels of IL-6 and IL-8 are associated with surgical site infection after pancreaticoduodenectomy. Pancreas 2006 Mar;32(2):178–85.
[26] Facy O, Paquette B, Orry D, Binquet C, Masson D, Bouvier A, et al. Diagnostic accuracy of inflammatory markers as early predictors of infection after elective colorectal surgery: results from the IMACORS study. Ann Surg 2016 May;263(5):961–6.
[27] Giaccaglia V, Salvi PF, Antonelli MS, Nigri G, Pirozzi F, Casagranda B, et al. Procalcitonin reveals early dehiscence in colorectal surgery: the PREDICS study. Ann Surg 2016 May;263(5):967–72.
[28] Warschkow R, Beutner U, Steffen T, Müller SA, Schmied BM, Güller U, et al. Safe and early discharge after colorectal surgery due to C-reactive protein: a diagnostic meta-analysis of 1832 patients. Ann Surg 2012 Aug;256(2):245–50.
[29] Kimura F, Miyazaki M, Suwa T, Itoh H, Ambiru S, Shimizu H, et al. Hyperactive cytokine response after partial hepatectomy in patients with biliary obstruction. Eur Surg Res 1998;30(4):259–67.
[30] Delko T, Watson DI, Beck-Schimmer B, Immanuel A, Hussey DJ, Zingg U. Cytokine response in the pleural fluid and blood in minimally invasive and open esophagectomy. World J Surg 2019 Oct;43(10):2631–9.
[31] Breunig A, Gambazzi F, Beck-Schimmer B, Tamm M, Lardinois D, Oertli D, et al. Cytokine & chemokine response in the lungs, pleural fluid and serum in thoracic surgery using one-lung ventilation. J Inflamm 2011 Nov 11;8:32.
[32] Bassetti M, Eckmann C, Giacobbe DR, Sartelli M, Montravers P. Post-operative abdominal infections: epidemiology, operational definitions, and outcomes. Intensive Care Med 2020 Feb;46(2):163–72.
[33] Zhao N, Li Q, Cui J, Yang Z, Peng T. CT-guided special approaches of drainage for intraabdominal and pelvic abscesses: one single center's experience and review of literature. Medicine 2018 Oct;97(42):e12905.
[34] Sartelli M, Catena F, Ansaloni L, Coccolini F, Corbella D, Moore EE, et al. Complicated intra-abdominal infections worldwide: the definitive data of the CIAOW Study. World J Emerg Surg 2014 May 14;9:37.

[35] Wang Z, Chen J, Su K, Dong Z. Abdominal drainage versus no drainage post gastrectomy for gastric cancer. Cochrane Database Syst Rev 2011 Aug 10;(8):CD008788.
[36] Fouda E, El Nakeeb A, Magdy A, Hammad EA, Othman G, Farid M. Early detection of anastomotic leakage after elective low anterior resection. J Gastrointest Surg 2011 Jan;15(1):137–44.
[37] Yamamoto T, Umegae S, Matsumoto K, Saniabadi AR. Peritoneal cytokines as early markers of peritonitis following surgery for colorectal carcinoma: a prospective study. Cytokine 2011 Feb;53(2):239–42.
[38] Bertram P, Junge K, Schachtrupp A, Götze C, Kunz D, Schumpelick V. Peritoneal release of TNFalpha and IL-6 after elective colorectal surgery and anastomotic leakage. J Invest Surg 2003 Mar-Apr;16(2):65–9.
[39] Uttinger KL, Diers J, Baum P, Pietryga S, Baumann N, Hankir M, et al. Mortality, complications and failure to rescue after surgery for esophageal, gastric, pancreatic and liver cancer patients based on minimum caseloads set by the German Cancer Society. Eur J Surg Oncol 2022 Apr 1;48(4):924–32.
[40] Triemstra L, de Jongh C, Tedone F, Brosens LAA, Luyer MDP, Stoot JHMB, et al. The Comprehensive Complication Index versus Clavien-Dindo grading after laparoscopic and open D2-gastrectomy in the multicenter randomized LOGICA-trial. Eur J Surg Oncol 2023 Dec;49(12):107095.