




ORIGINAL ARTICLE

Significance of blood culture testing after pancreatoduodenectomy

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Abstract

Aim: The aim of this study was to clarify the significance of blood culture testing in the postoperative period of pancreatoduodenectomy (PD), a highly invasive surgery.

Methods: Rates of blood culture sampling and positivity were investigated for febrile episodes (FEs) in patients who underwent PD (2016–2021). FEs were defined as body temperature of 38.0°C or higher occurring on or after the 4th postoperative day. Fever origin was diagnosed retrospectively, and FEs were classified as pancreatic fistula (PF)-related or PF-unrelated FEs. Factors correlated with blood culture positivity were explored.

Results: Among 339 patients who underwent PD, 99 experienced 202 FEs. Blood culture testing was performed on 160 FEs occurring in 89 patients. The sampling and positivity rates were 79.2% and 17.5%, respectively, per episode and 89.9% and 28.1%, respectively, per patient. Thirty-six FEs were classified as PF-related and 124 were classified as PF-unrelated FEs. The blood culture positivity rate was significantly lower in PF-related vs. PF-unrelated FEs (1/36 vs. 27/124, respectively, $p=0.006$). The blood culture positivity rate was significantly higher in patients with cholangitis, catheter-related blood stream infection, and urinary tract infection than PF-related FEs. Multivariate analysis showed that blood culture positivity was negatively associated with PF-related FEs and positively associated with accompanying symptoms of shivering, Pitt Bacteremia Score, and preoperative biliary drainage.

Conclusions: Patients who underwent PD showed relatively high blood culture positivity rates. Based on these results, it may be possible to distinguish PF-related and -unrelated FEs.

KEYWORDS

blood culture testing, cholangitis, fever, pancreatic fistula, pancreatoduodenectomy

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1 | INTRODUCTION

Pancreatoduodenectomy (PD) is the standard procedure for malignant and borderline malignant diseases in the periampullary region. With advances in surgical techniques and perioperative management, the postoperative mortality rate has been reduced to less than 4%, while morbidity remains high, around 40%, even in high-volume centers.¹ Postsurgical fever is a typical symptom of complications after PD. In cases of fever, blood culture testing is recommended when bloodstream infection is suspected, as in nonsurgical patients.² Following this recommendation, in our center, blood cultures have been analyzed routinely at the time of a fever of 38.0°C or higher in patients who have undergone PD. Blood culture testing has the benefit of identifying the causative infectious organisms with high accuracy, thereby limiting the use of unnecessary broad-spectrum antibiotics. On the other hand, the low positivity rate of blood culture testing possibly makes it inefficient in view of patient burden, due to venipuncture and testing costs. For such reasons, many previous reports examining the significance of blood cultures for a variety of postoperative patients have not supported routine blood culture testing.³⁻¹¹ However, it is uncertain whether such a negative attitude toward testing can be applied to the management of patients undergoing PD. In addition, PD is associated with various complications that can cause fever, including pancreatic fistula (PF), intra-abdominal abscess, ascending cholangitis, pneumonia, and catheter-related blood stream infection (CRBSI), mainly due to the complexity of the reconstruction procedure. Thus, it is possible that the significance of blood culture testing after PD is different from that of other surgeries. To the best of our knowledge, there have been no studies examining the significance of blood culture testing in postoperative patients who have undergone hepato-biliary-pancreatic surgery, including PD. The aim of this study was to clarify the significance of

blood culture testing in the postoperative period of PD, a highly invasive surgery.

2 | METHODS

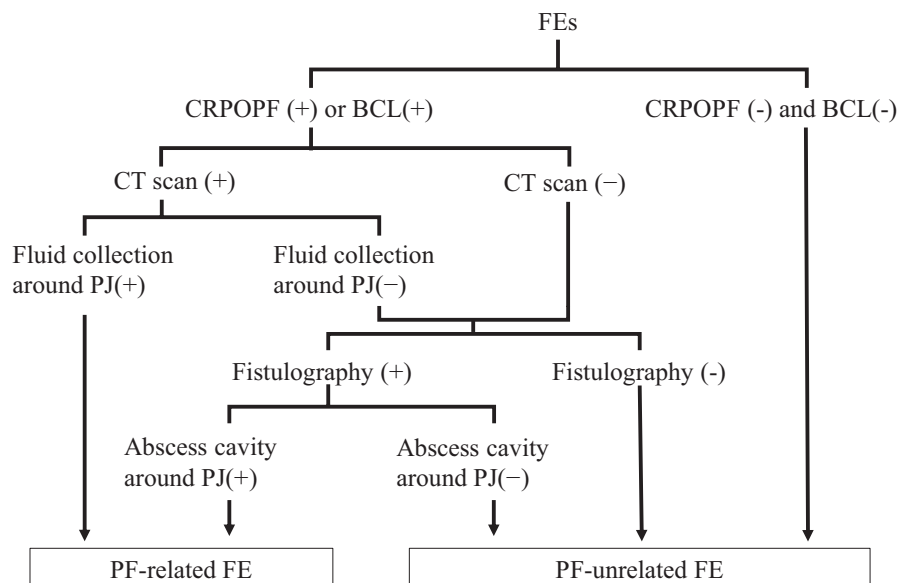
2.1 | Patients

The medical records of consecutive patients who underwent PD for diseases of the periampullary region at the Department of Gastroenterological Surgery, Aichi Cancer Center between 2016 and 2021 were reviewed retrospectively. Factors correlated with blood culture positivity were explored.

2.2 | Definitions of febrile episode (FE), fever origin, and positive blood culture

A febrile episode (FE) was defined as a fever of 38.0°C or higher that occurred during the hospitalization period from the 4th postoperative day until discharge. In our center, on principle, two sets of blood culture tests have been performed in patients with FE on or after the 4th postoperative day unless there were difficulties in collecting blood samples. Fever origins were diagnosed retrospectively in all FEs for which blood culture testing was performed. They were classified as either PF-related or PF-unrelated FEs based on a diagnostic algorithm (Figure 1). That is, among FEs occurring in patients with clinically relevant postoperative pancreatic fistula (CRPOPF) or biochemical leakage (BCL) according to the International Study Group of Pancreatic Surgery definition,¹² FEs with evidence of fluid collection around the pancreaticojejunostomy (PJ) by computed tomography (CT) or FEs with evidence of an abscess cavity around the PJ by fistulography were defined as PF-related, while the remaining FEs were defined as PF-unrelated.

FIGURE 1 Diagnostic algorithm for determining PF-related FEs. BCL, biochemical leakage; CRPOPF, clinically relevant postoperative pancreatic fistula; CT, computed tomography; FEs, febrile episodes; PF, pancreatic fistula; PJ, pancreaticojejunostomy.



Moreover, as for PF-unrelated FEs, speculated fever origin was determined retrospectively based on the findings of clinical manifestations documented in the medical record, chest X-ray and/or CT image, urinalysis, laboratory test and bacterial profiles of blood culture testing. A positive blood culture was defined as the detection of Gram-positive or -negative bacteria in one or more sets of cultures, except for skin commensals, which were regarded as contamination. Retrospective diagnosis of fever origin and interpretation of blood culture findings were performed in consultation with an infectious disease specialist (NI) and two surgeons (TA, SN). The Pitt Bacteremia Score, a previously validated scoring system based on body temperature (0, 1, or 2 points), mental status (0, 1, 2, or 4 points), blood pressure (0 or 2 points), requirement for mechanical ventilation (0 or 2 points), and recent cardiac arrest (0 or 4 points), was applied as an indicator to measure the severity of FEs.¹³ The operative complications were evaluated based on the Clavien–Dindo classification.¹⁴

2.3 | Statistical analyses

The primary endpoint of this study was blood culture positivity throughout the postoperative course. An exposure of interest was PF-related FEs. To consider the longitudinal nature of blood culture testing, we employed Generalized Estimating Equations (GEE) in the analyses.¹⁵ We evaluated the impact of PF-related FEs on blood

culture positivity by uni- and multivariable GEE models. Covariates considered in the analyses were age, gender, body mass index, presence of preoperative biliary drainage, Charlson comorbidity index, operative time, operative blood loss, maximum temperature $\geq 39.0^\circ\text{C}$, FEs that occurred on or after the 11th postoperative day, FEs with accompanying shivering symptoms, and the Pitt Bacteremia Score.

The chi-square test or Fisher's exact probability test was performed for categorical variables. The Mann–Whitney U test was applied for comparison of continuous variables. All analyses were carried out with STATA version 16 (STATA Corporation, College Station, TX, USA) or SPSS version 21.0 software (IBM, Armonk, New York, USA).

3 | RESULTS

During the study interval, 339 patients who underwent PD were identified in the institutional database. Among them, 99 patients experienced 202 FEs. On a per-episode basis, blood culture testing was performed in 160 of the 202 FEs (sampling rate per episode = 79.2%). Among them, two sets of blood culture testing were performed in 144 cases while single testing was performed in remaining 16. Bacterial species were detected in 33 episodes. Of those episodes, 28 were diagnosed as blood culture positive and five episodes were excluded, as they were determined to be contamination. The blood culture positivity rate per episode was 17.5%. Detected bacterial

Classification of bacteria	Identified isolates	Number
Gram-positive cocci	<i>Enterococcus faecalis</i>	7
	<i>Enterococcus faecium</i>	
	<i>Staphylococcus caprae</i>	
	<i>Staphylococcus epidermidis</i>	
	<i>Staphylococcus haemolyticus</i>	
	<i>Streptococcus sanguis</i>	
	<i>Peptostreptococcus</i> species	
Gram-positive bacilli	<i>Corynebacterium</i> species	1
Gram-negative cocci	<i>Veillonella</i> species	1
Gram-negative bacilli	<i>Acinetobacter baumannii</i>	20
	<i>Acinetobacter junii</i>	
	<i>Aeromonas hydrophila</i>	
	<i>Bacteroides</i> species	
	<i>Klebsiella aerogenes</i>	
	<i>Escherichia coli</i>	
	<i>Klebsiella pneumoniae</i>	
	<i>Prevotella buccae</i>	
	<i>Pseudomonas aeruginosa</i>	
	<i>Raoultella planticola</i>	
<i>Sallmonella</i> species		
Fungi	<i>Candida albicans</i>	2
	<i>Candida parapsosis</i>	

TABLE 1 Bacterial species detected in positive blood cultures.

species included gram-negative bacilli in 20, gram-positive cocci in seven, fungi in two, gram-positive bacilli in one, and gram-negative cocci in one episode (some overlap was present, see Table 1). On a patient population basis, at least a single blood culture test was performed in 89 of the 99 patients (sampling rate per patient=89.9%). Among them, two sets of blood culture testing were performed in 77 while single testing was performed in remaining 12. At least a single positive blood culture was confirmed in 25 patients (positivity

rate per patient=28.1%). Detailed background factors of 89 patients who underwent blood culture testing were summarized in Table 2.

3.1 | PF-related and PF-unrelated FEs

Fever origin was retrospectively analyzed for 160 FEs in 89 patients in which blood culture testing was performed (Figure 2). Among them, CRPOPF (88 FEs in 46 patients) or BCL (29 FEs in 15 patients) was evident in 117 FEs in 61 patients. Blood culture testing was positive in 18 of 117 FEs that occurred in patients with CRPOPF or BCL and 10 of 43 FEs that occurred in patients without ($p=0.249$). Of the 117 FEs, 28 FEs with fluid collection around the PJ were diagnosed by CT and eight FEs with an abscess cavity around the PJ were diagnosed by fistulography and defined as PF-related episodes. Ultimately, there were 36 PF-related and 124 PF-unrelated FEs.

Blood cultures were positive in one of 36 for PF-related FEs and 27 of 124 PF-unrelated FEs ($p=0.006$). The only PF-related FE for which a blood culture was positive was a unique one that showed evidence of communication between the abscess cavity around the PJ and the portal vein on fistulography.

3.2 | Speculated origins of PF-unrelated FEs

Among 124 PF-unrelated FEs, there were 82 FEs of cholangitis, 13 FEs of intra-abdominal abscess (except the PJ site), 11 FEs of respiratory infection, six FEs of CRBSI, five FEs of liver abscess, three FEs of post-transhepatic arterial embolization fever, two FEs of urinary tract infection, one FE of enterocolitis, and one FE of wound

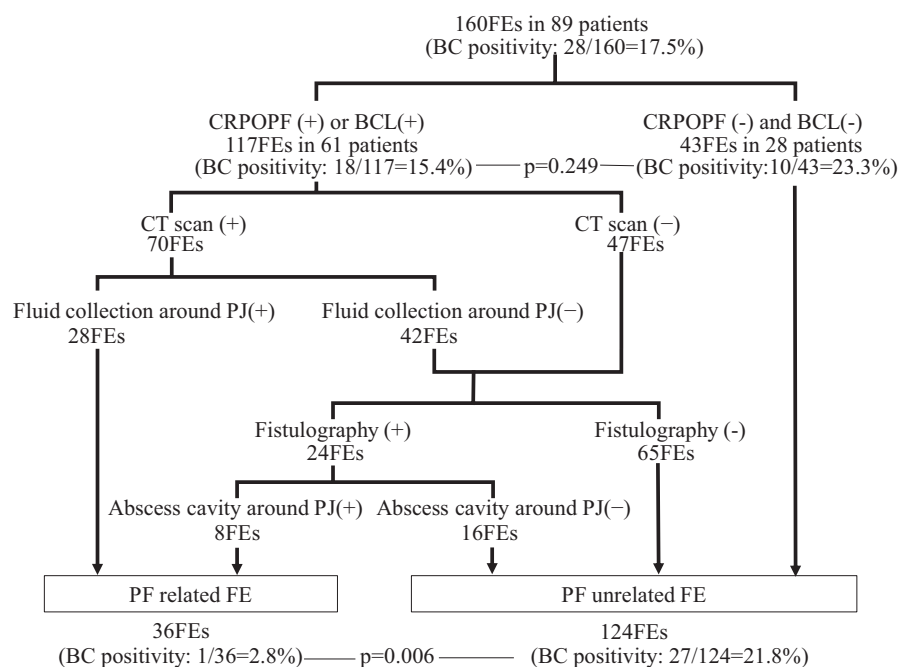
TABLE 2 Detailed background factors of patients who underwent blood culture testing.

	<i>n</i> = 89
Age, years*	70 (33–84)
Male gender	61 (68.5)
Body mass index, m/kg ² *	22.6 (16.5–40.7)
ASA-PS*	2 (1–3)
ASA-PS \geq 3a	8 (9.0)
Charlson comorbidity index*	1 (0–7)
Pathology=PDAC	30 (33.7)
Presence of preoperative biliary drainage	30 (33.7)
Concomitant resection of portal vein	20 (22.5)
Operative time, min*	428 (193–923)
Total blood loss, mL*	490 (60–3500)
Pancreatic fistula	46 (51.7)
Clavien–Dindo \geq grade 3a	56 (62.9)
Mortality	0 (0)

Note: Values in parentheses are percentages unless indicated otherwise. Abbreviations: ASA-PS, American Society of Anesthesiologists physical status; PDAC, pancreatic invasive ductal adenocarcinoma.

*Values are median (range).

FIGURE 2 PF-related and PF-unrelated FEs. BC, blood culture; BCL, biochemical leakage; CRPOPF, clinically relevant postoperative pancreatic fistula; CT, computed tomography; FEs, febrile episodes; PF, pancreatic fistula; PJ, pancreaticojejunostomy.



infection (Figure 3). The blood culture positivity rate was significantly higher in cholangitis (17/82), CRBSI (5/6), and urinary tract infection (2/2) than in PF-related FEs (1/36).

3.3 | Factors correlating with blood culture positivity

When covariates were compared between FEs with positive and negative blood cultures, the rate of PF-related FEs was significantly lower in positive vs. negative blood cultures, while the rates of FEs with maximum temperature $\geq 39.0^{\circ}\text{C}$, FEs that occurred on or after the 11th postoperative day, FEs with accompanying shivering symptoms, and FEs with a higher Pitt Bacteremia Score were significantly higher in positive vs. negative blood culture episodes (Table 3).

When covariates were compared between patients with positive and negative blood cultures, there were no statistically significant differences (Table S1).

Multivariate analysis showed that blood culture positivity was positively associated with accompanying symptoms of shivering, Pitt Bacteremia Score, and preoperative biliary drainage and negatively associated with PF-related FEs (Table 4).

4 | DISCUSSION

To the best of our knowledge, 10 publications have examined the significance of blood culture collection for postoperative patients^{3-11,16} (Table 5). Among them, four described patients who underwent orthopaedic surgery, three unspecified general surgery, two gynecological surgery, and one colorectal surgery, and none of them studied postoperative patients who had undergone PD. In previous studies, blood culture positivity rates were low, ranging from 0%–16.5% per patient and 0%–7.9% per episode. Thus, most of the publications did not support routine blood culture collection at the time of fever considering the high cost and the invasiveness associated with venipuncture.³⁻¹¹ In contrast, we demonstrated that the positivity rate

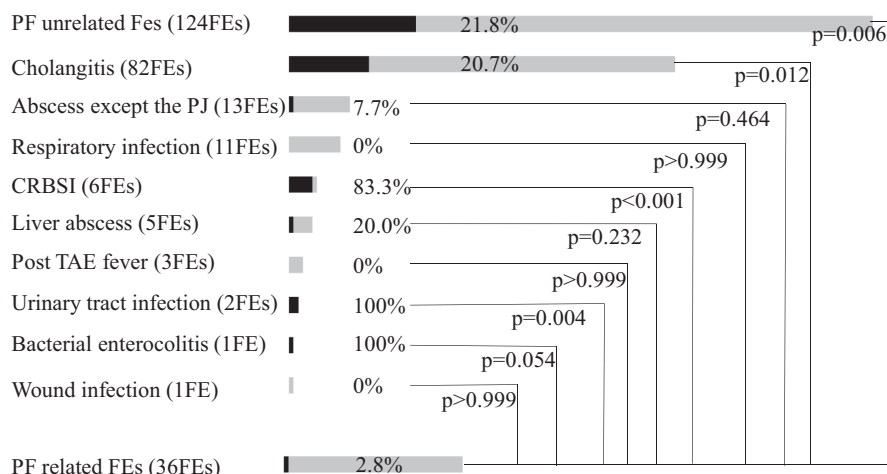


FIGURE 3 Correlation between speculated fever origin and blood culture positivity rate. The rate of positive blood cultures was significantly higher in patients with cholangitis, CRBSI, and urinary tract infection than in patients with PF-related FEs. PF, pancreatic fistula; FEs, febrile episodes; PJ, pancreaticojejunostomy; CRBSI, catheter related blood stream infection; TAE, transhepatic arterial embolization.

TABLE 3 Comparison between positive blood culture and negative blood culture episodes.

	Positive blood culture episodes (n = 28)	Negative blood culture episodes (n = 132)	p
PF-related FEs	1	35	0.006
FEs with maximum temperature $\geq 39.0^{\circ}\text{C}$	16	27	<0.001
FEs that occurred on or after the 11th POD	26	89	0.005
FEs with accompanying shivering symptoms	20	38	<0.001
Pitt Bacteremia Score*	2 (0–3)	0 (0–6)	<0.001

Abbreviations: FE, febrile episode; PF, pancreatic fistula; POD, postoperative day.

*Values are median (range).

TABLE 4 Predictive factors for positive blood culture.

	OR	95% CI	p
PF-related FE	0.065	0.006–0.744	0.028
Maximum temperature $\geq 39.0^{\circ}\text{C}$	1.824	0.539–6.169	0.334
FEs that occurred on or after the 11th POD	3.094	0.509–18.825	0.220
FEs with accompanying shivering symptoms	4.148	1.274–13.506	0.018
Pitt Bacteremia Score	2.287	1.257–4.161	0.007
Age	1.035	0.978–1.094	0.235
Male gender	0.735	0.210–2.577	0.630
Body mass index	1.102	0.973–1.248	0.125
Presence of preoperative biliary drainage	4.361	1.294–14.698	0.018
Charlson comorbidity index	1.014	0.703–1.461	0.942
Operative time	0.998	0.990–1.006	0.585
Operative blood loss volume	1.001	0.995–1.002	0.285

Abbreviations: CI, confidence interval; FE, febrile episode; POD, postoperative day; OR, odds ratio.

of blood cultures in postoperative patients who had undergone PD was 28.1% per patient and 17.5% per episode. Admittedly, it is not possible to simply compare positive blood culture rates across studies, but the higher positive rates in our study are possibly due to the high invasiveness of the procedure. Blood culture tests, if the results are positive, enable the appropriate use of antibiotics based on the sensitivity of the cultured organisms. In this sense, compared to the previously reported postoperative patients, patients who have undergone PD represent a population more likely to benefit from blood culture and to use antibiotics properly.

In the current study, the two leading causes of postoperative fever were cholangitis and PF-related FEs. Compared with bile duct infection in non-surgical patients, postoperative cholangitis after PD is difficult to diagnose, because most cases represent reflux cholangitis without biliary obstruction, and consequently are rarely accompanied with blood test abnormalities, such as elevated hepatobiliary enzymes, other than fever. Therefore, in postoperative management, making a discriminative diagnosis between cholangitis and PF-related fever is not always straightforward. We showed that the blood culture positivity rate was significantly lower for PF-related FEs than for PF-unrelated FEs (the majority of which was cholangitis). Moreover, multivariate analysis also revealed that PF-unrelated FEs were an independent predictor of blood cultures positivity. The higher rate of positive blood cultures in cholangitis is presumably due to the direct reflux of intestinal bacteria into hepatic sinusoidal capillaries.¹⁷ On the other hand, as for PF-related FEs, pancreatic juice leaking into the abdominal cavity, even if sterile, can induce chemical inflammation of the peritoneum. Even when accompanied by bacterial infection, the inflammation is

mainly in the peritoneum, and there is little possibility of bacterial reflux into the blood vessels. This may be the reason for the low rate of blood culture positivity in PF-related FEs. In this study, the only case in which a blood culture was positive for a PF-related FE was a unique one that showed evidence of communication between the intra-abdominal abscess and the portal vein on fistulography. Regarding the treatment of cholangitis and an infected pancreatic leak, both commonly require administration of antibiotics, while most cases of pancreatic leak require modification or addition of drainage. In most cases, the differential diagnosis between cholangitis and pancreatic leakage is faster using value of drain amylase and findings of CT or fistulography than waiting for blood culture results. However, even in a limited number of cases, when a CT finding shows a small fluid collection in a location that is difficult to puncture, physicians often have a difficult time deciding whether to carry out drainage at the risk of puncture. In this study, we demonstrated that the results of blood culture may be helpful in determining the treatment strategy in such limited cases.

Besides the low positivity rate, the high contamination rate is also problematic for blood culture testing. A review by Dargere et al.¹⁸ reported that contaminants cause unnecessary antibiotic administration and prolonged hospitalization. To avoid such a contamination, at least two sets of blood draws of sufficient volume from multiple sites are recommended for each febrile episode.¹⁹ However, the high cost and the distress of venipuncture resulting from blood collection cannot be dismissed in postoperative patients who have undergone PD and are experiencing frequent recurring fevers. In the current study, as well as in PF-unrelated fever, multivariate analysis identified several predictors of positive blood cultures, including the presence of accompanying shivering, preoperative biliary drainage, and Pitt Bacteremia Score. Based on these results, in the future, the omission of routine blood culture collection for each febrile episode should be considered, especially for patients with low blood culture positivity. Further large multicenter studies should be conducted to increase the number of cases and to identify patient populations for which blood culture collection can be omitted.

Our study has several limitations. First, it was a retrospective study; thus, blood cultures were not collected from all febrile patients or at all febrile episodes. However, considering the fact that the previously reported blood culture collection rate was 36.5%–44.1% per patient,^{8,9} our collection rate was rather high (per patient, 89.9%; per order, 79.2%). Therefore, our finding of a higher blood culture positivity rate after PD is considered reliable. Second, there are no clearly defined criteria for diagnosis of the cause of postoperative fevers. CT imaging or fistulography was not performed for all postoperative FEs. As a consequence, the cause of fever was determined retrospectively. However, most postoperative complications often have causes that are not obvious in the onset phase but become apparent over time. In this sense, the present study, being a retrospective study, is likely to have yielded the correct diagnosis. Third, examining the risk of postoperative blood culture-positive occurrence, as in this study, involves difficulties in statistical analysis. For example, suppose that

TABLE 5 Studies reporting positive blood culture test rates for postoperative patients.

Year	Author	Surgical procedure	No. of pts examined	No. of BC orders	Positive rate (per patient)	Positive rate (per episode)
1996	Henke et al. ¹¹	Burn, general surgery, trauma	121	1040	6.6%	7.9%
1997	Swisher et al. ¹⁰	Hysterectomy	62	41	0%	0%
1998	Fanning et al. ⁹	Gynecological surgery	77	NA	0%	0%
2007	Bindelglass et al. ⁸	Arthroplasty	71	NA	0%	0%
2009	Anderson et al. ⁷	Arthroplasty	50	102	0%	0%
2010	Ward et al. ⁵	Arthroplasty	71	NA	5.6%	NA
2010	Lee et al. ⁶	Surgery in general	150	NA	6.0%	NA
2012	Vijayasegaran et al. ⁴	Arthroplasty	101	141	2.0%	1.4%
2018	Copeland-Helperin et al. ³	Surgery in general	746	1780	5.8%	4.0%
2020	Watt et al. ¹⁵	Colorectal surgery	3390	NA	16.5%	NA
2024	Aritake et al.	Pancreatoduodenectomy	99	160	28.1%	17.5%

Abbreviations: BC, blood culture; NA, not available; Pts, patients.

a 72-year-old male patient experienced two febrile episodes postoperatively, the first of which was 38.3°C PF-related episode (blood culture negative), and the second of which was 39.5°C cholangitis (blood culture positive). To identify the risk factors for blood culture positivity, it is necessary to separately consider patient-specific factors (in this case, 72-year-old/male) and episode-specific factors (in this case, fever $\geq 39.0^\circ\text{C}$ vs. $< 39.0^\circ\text{C}$ /PF related vs. PF unrelated). In current study, we found several factors, including PF-unrelated FEs, to have a statistically significant correlation with blood culture positivity in the per episode analysis, while no factors were identified in the per patient analysis. We believe that some of aforementioned statistically difficulty due to longitudinal nature of blood culture positivity have been overcome by applying Generalized Estimating Equations (GEE) as a multivariate analysis method.

In conclusions, due to the high positivity rate identified in this study, patients who have undergone PD are likely to benefit from postoperative blood culture testing in terms of appropriate use of antibiotics. Based on the testing result, it is possible to distinguish PF-related and -unrelated FEs.

AUTHOR CONTRIBUTIONS

Aritake and Natsume designed the study and wrote the initial draft of the manuscript. Naoya Itoh, Matsuo, and Shimizu contributed to interpretation of the data and critical revision of the manuscript for important intellectual content. All the other authors (Asano, Okuno, Seiji Ito, Komori, Abe) contributed to the data collection and interpretation and critically reviewed the manuscript. All the authors have read and approved the final version of the manuscript and have agreed to be accountable for the study, ensuring that any questions related to the accuracy or integrity of any part of the work are resolved.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

ETHICS STATEMENT

Approval of the research protocol: This study was approved by the Ethics Review Committee of Aichi Cancer Center (approval number: R021175).

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study. Alternatively, opt-out approach was used with the permission of the Ethics Review Committee.

Registry and the Registration No. of the study/trial: This research conforms to the provisions of the Declaration of Helsinki.

Animal Studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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