Master of Medicine

Serum procalcitonin as a biomarker for differentiating between infectious and non-infectious fever after pancreas transplantation

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Ye Eun Shim

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Supervisor : Sung Shin

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Ye Eun, Shim

Department of Medicine

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This certifies that the master of medicine
of Ye Eun Shim is approved.

Committee Chair Dr. Chang-hee, Jung

Committee Member Dr. Sung Shin

Committee Member Dr. Woo-hyung, Lee

Department of Medicine

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국문요약

이식환자에서의 감염은 여러 합병증 및 사망과 직결되는 중요한 문제이며, 발열은 감염을 시사하는 중요한 징후이다. 하지만 이식환자에서의 모든 발열이 감염에 의한 것은 아니며, 아직까지는 감염에 의한 발열과 비감염성 원인에 의한 발열을 감별할 수 있는 인자로 증명된 생체표지자는 없는 상태이다. 본 연구에서는 췌장이식 환자에서 감염에 의한 발열과 비감염성 원인에 의한 발열을 감별할 수 있는 생체표지자가 있는지를 밝혀내어, 비감염성 원인에 의한 발열에서의 불필요한 항생제 사용을 줄이고자 하였으며, 혈중 Procalcitonin 이 갖는 의미에 중점을 두어 데이터를 분석하였다.

비감염성 원인에 의한 발열이란 배양검사상 음성이거나 임상적으로 감염의 징후가 없는 상태에서 발열(> 38.3 ℃)이 있는 것으로 정의하였다. 2014년 8월부터 2019년 7월까지 본원에서 췌장이식을 시행한 184명의 수혜자 중, 91명에서 한 달 이내에 발열이 있었다. 그 중 46명은 감염에 의한 발열군으로 분류되었고, 나머지 45명은 비감염성 원인에 의한 발열군으로 분류되었다. 여러 인자에 따라 두 군을 비교 분석하였고, 수술 후 발열이 시작되는 시기가 비감염성 원인에 의한 발열군(14.4 ± 3.7일)이 감염에 의한 발열군(16.5±5.8일, $P = 0.033$)보다 발열이 일찍 나타났다. 다변량 분석 결과, 두 그룹을 감별할 수 있는 인자로 혈중 최고 Procalcitonin 농도가 통계적으로 유의미했다 (OR 53.776, 95% CI: 6.824–423.776, $P < .001$). 두 군을 감별할 수 있는 혈중 Procalcitonin 의 기준점은 0.405 ng/mL (민감도, 77.1% ; 특이도 80.8%) 였으며 CRP 는 7.355 mg/dL(민감도, 66.78% ; 특이도 67.3%)였다.

결론적으로, 췌장 이식 후에 발생하는 감염성 발열과 비감염성 원인에 의한 발열을 감별하는 유용한 생체표지자로 혈중 Procalcitonin을 사용할 수 있을 것으로 생각된다. 췌장이식 환자에서 수술 후 발열이 있을 경우 경험적 항생제의 사용이 필요한지 여부를 결정하기 위해, 연속적으로 혈중 Procalcitonin 측정하는 것이 도움이 될 것이다.

Keywords: 혈중 Procalcitonin , 비감염성 원인에 의한 발열, 췌장 이식

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Introduction

Fever, a traditional clinical indicator of diseases, is one of the most common reasons for medical consultations. [1, 2] Accurate understanding of the fever and the febrile response is important for proper diagnosis, treatment, and follow-up of various illnesses and diseases. [3] Post-transplant fever is a frequently observed phenomenon in solid organ transplantation, in which the prevention, diagnosis, and management of infectious diseases are major concerns. Because fever often occurs in response to infection, empirical antibiotics are often prescribed prior to the identification of causative microorganisms. However, empirical antibiotics may cause antibiotic-associated complications (e.g., leukopenia, thrombocytopenia) and the development of drug-resistant bacteria as well as an extension of the hospitalization period and increase of medical costs.

Only few studies have reported the distinctive characteristics of non-infectious fever compared with infectious fever in solid organ transplantation. Recently, we reported that approximately 37% of the cases of post-transplant fever following pancreas transplant with anti-thymocyte globulin induction were culture-negative, and that the increases in white blood cell (WBC) count, C-reactive protein (CRP), and serum amylase were less prominent in cases with culture-negative fever than those with culture-positive fever. [4] An important limitation of our previous study was that the level of serum procalcitonin was only assessed during the last two years out of the total study period of 10 years, thereby limiting its clinical significance. Thereafter, according to the recommendation of our infectious disease specialist (S-H.K.), we retrospectively collected the laboratory data including serum procalcitonin in order to identify the potential biomarkers for discriminating between infectious and non-infectious fever after pancreas transplantation.

The purpose of this study was to compare the usefulness of serum levels of procalcitonin and CRP as a biomarker for differentiating infectious fever from non-infectious fever occurring after pancreas transplantation.

Patients and methods

Study population and Definition of fever

This was a retrospective cohort study based on the electrical medical records of Asan Medical Center (Seoul, Korea) and was carried out in accordance with the STROBE guidelines for the reporting of observational studies. The institutional review board of Asan Medical Center approved this study(Approval number : 2015-0541). We identified patients who underwent pancreas transplantation at our center between August 2014 and July 2019 and analyzed those who developed fever, which was defined as a body temperature of above 38.3 on two measurements taken within 24 hours [5]. If the body temperature rose above 38.3 again within 48 hours, we regarded that the fever persisted. Infrared radiated devices were used to measure the tympanic membrane temperature.

Classification of fever

From the electronic medical record, we collected the data on demographics including the type of fever, fever characteristics (i.e., timing of the onset after surgery, number of episodes, duration, onset, and peak body temperature), laboratory data (i.e., WBC count, lowest absolute neutrophil count, serum amylase and lipase, C-reactive protein[CRP], and procalcitonin), microbiologic data (i.e., cultures from blood, urine, sputum, and intra-abdominal drainage catheter, *Clostridium difficile* polymerase chain reaction [PCR], cytomegalovirus [CMV] DNA PCR), and radiologic findings such as X-ray and computerized tomography (CT).

Infectious fever was differentiated from non-infectious fever
by using the following definition:

i) New growth of microbial species from blood, urine, sputum, or drainage during the fever or within a week.

ii) Presence of CMV syndromes such as neutropenia or thrombocytopenia, and the detection of CMV viremia in PCR. [6]

iii) Watery diarrhea with positive results on *C.difficile* toxin assay or PCR

iv) Complicated fluid collection on CT taken after fever.

Classification of fever was performed by a research resident (Y.E.S.). A masked review was performed by two infectious disease specialists (S-O.L., S-H.K.) to categorize the type of fever and the results were compared with those of the research resident for consensus.

Immunosuppressive and prophylactic regimen

Immunosuppressants were administered in a method similar to a previously published protocol.[4] Rabbit antithymocyte globulin (thymoglobuline, ATG) was used as induction therapy, in which the total dose of ATG was 4.5–5.0 mg/kg regardless of the type of transplant. The first dose (1–1.5mg/kg) was administered intraoperatively and was followed by a second dose (1–1.5mg/kg) on consecutive postoperative days. The dose was reduced to half in cases with a leukocyte count of 2000–3000/mm^3 or a platelet count of 50,000–70,000/mm^3. All patients intraoperatively received 500 mg prednisolone, which was tapered and weaned within a week after transplantation for those who had simultaneous pancreas-kidney (SPK) transplantation and maintained for others. In addition, tacrolimus and mycophenolate mofetil was used as that maintenance therapy. For bacterial prophylaxis, ampicillin/sulbactam was administered for one week after transplantation. To prevent *Pneumocystis jirovecii* pneumonia, oral sulfamethoxazole/trimethoprim was administered for six months. CMV blood PCR was performed every week for CMV monitoring. Valganciclovir was prescribed for CMV prophylaxis for six months only in cases of CMV-negative recipient and CMV-positive donor.

Statistical analysis

Categorical variables are presented as absolute and relative frequencies. Quantitative variables are presented as mean and standard deviation(SD). Univariate comparisons between subgroups were performed using the Student's *t*-test or Mann-Whitney U- test for quantitative variables. Categorical variables were compared using the chi-squared test. After univariate analysis, variables significantly associated with non-infectious fever were entered into a stepwise logistic regression model for multivariate analysis. In the univariate analysis, variables were selected using a forward stepwise approach with $P < .1$ as the limit for selecting variables for entry into the model. A P-value $< .05$ was considered as a statistically significant value.

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA) and R version 3.3.1 (Bell Laboratories/ Translucent Technologies; Murray Hill, NJ, USA).

Results

Baseline characteristics

A total of 184 patients underwent pancreas transplantation at our center during the study period, of whom 106 developed fever within one-month post-transplant. Out of the 106 patients with febrile episodes, 15 patients were excluded either due to basiliximab induction (n = 3), no results for serum procalcitonin (n = 7), or had an indeterminate fever that could not be classified as either infectious or non-infectious (n = 5). As a result, 91 patients were finally included in the analysis and were categorized into the infectious fever group (n = 46) and the non-infectious fever group (n = 45) (Figure 1).

Among the 91 recipients, 44 (48%) were male and the mean age was 37.2±10.8 years (Table 1). The mean body mass index (BMI) was 21.87±3.49 kg/m^2 and 71 (78%) recipients had type 1 diabetes mellitus. The types of pancreas transplantation were as follows: SPK (n = 42), simultaneous deceased donor pancreas and living donor kidney (SPLK; n = 8), pancreas after kidney transplant (PAK; n = 7), and pancreas transplant alone (PTA; n = 34). Exocrine enteric drainage was performed in 54 (59%) recipients and the mean dose of anti-thymocyte globulin was 4.64±0.54 mg/kg.

The mean age of the deceased donors was 29.7±11.7 years, and 64 (70.3%) were male. The mean BMI was 22.17±3.43 kg/m^2, the mean cold ischemic time was 358.4±120.4 minutes, and the mean weight of the pancreas graft was 190.0±45.2 g. The mean warm ischemic time was 26.0±6.5 minutes, and it was significantly higher in the infectious fever group than non-infectious fever group (27.7±7.3 vs 24.4±5.0, P=0.015).

Figure 1. Patient selection flow

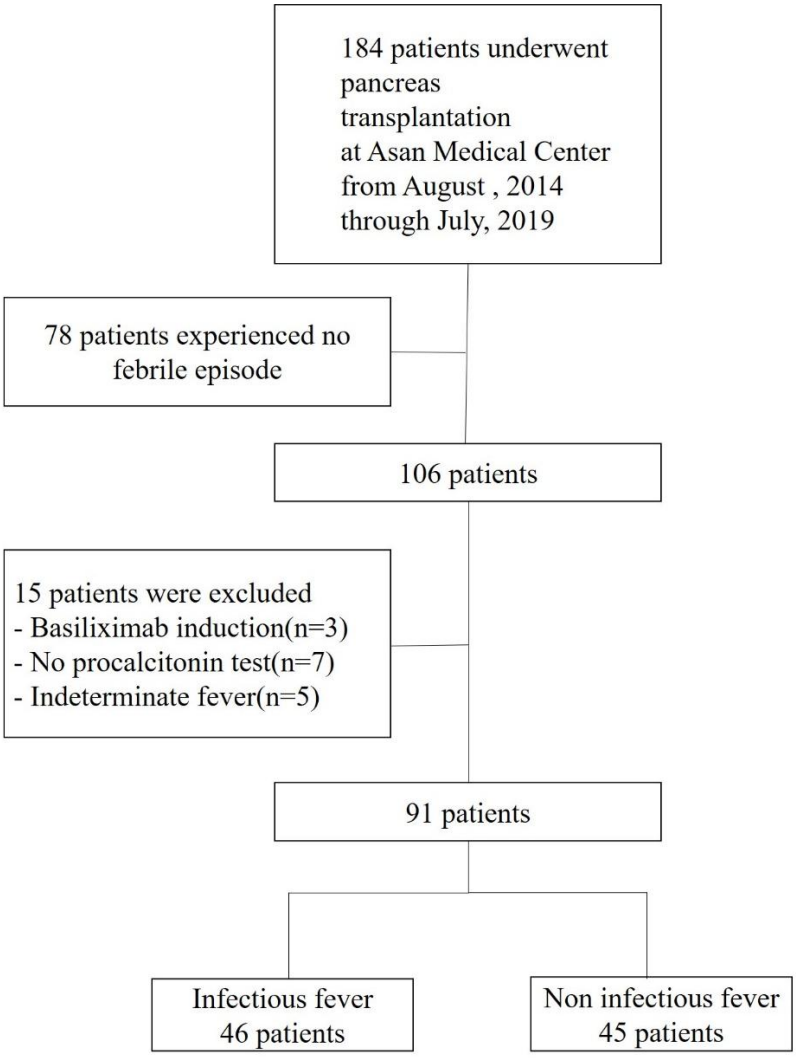


Table 1. Baseline characteristics according to the cause of post-transplant fever

Variables	**All patients**	**Infectious**	**Non-Infectious**	**P-value**
	(n = 91)	**(n = 46)**	**(n = 45)**	
Recipient characteristics				
Mean age, y (SD)	37.2(10.8)	36.5(10.7)	37.8(11.1)	0.571
Male gender, n (%)	44(48.4)	22(47.8)	22(48.9)	0.919
Type 1 DM , n (%)	71(78)	34(73.9)	37(82.2)	0.339
Body mass index, kg/m^2 (SD)	21.87(3.49)	22.02(3.18)	21.72(3.82)	0.691
Onset of DM, y (SD)	19.7(10.0)	18.9(9.3)	20.6(10.8)	0.416
Duration of DM, y (SD)	17.5(9.3)	17.2(7.7)	17.8(10.8)	0.769
Amount of insulin requirement, units/day (SD)	40.8(25.5)	41.7(29.9)	39.9(20.4)	0.589
HbA1c, % (SD)	8.34(1.80)	8.71(1.93)	7.96(1.59)	0.055
Transplant type, n (%)				0.287
Simultaneous pancreas kidney	42(46.2)	23(50.0)	19(42.2)	
Simultaneous deceased donor pancreas and living donor kidney	8(8.8)	2(4.3)	6(13.3)	
Pancreas after kidney	7(7.7)	5(10.9)	2(4.4)	
Pancreas transplant alone	34(37.4)	16(34.8)	18(40.0)	

Enteric drainage, n (%)	54(59.3)	30(65.2)	24(53.3)	0.249
HLA mismatch, n (SD)	3.8(1.3)	3.6(1.2)	4.0(1.3)	0.102
Retransplant, n (%)	4(4.4)	2(4.3)	2(4.4)	0.982
Dose of anti-thymocyte globulin, mg/kg (SD)	4.64(0.54)	4.63(0.69)	4.65(0.33)	0.563
Donor characteristics				
Mean age, y (SD)	29.7(11.7)	31.5(11.5)	27.8(11.7)	0.135
Male gender, n (%)	64(70.3)	35(76.1)	29(64.4)	0.224
Body mass index, kg/m^2 (SD)	22.17(3.43)	22.37(3.59)	21.95(3.29)	0.562
Cold ischemic time, m (SD)	358.4(120.4)	359.1(116.4)	357.6(125.7)	0.953
Warm ischemic time, m (SD)	26.0(6.5)	27.7(7.3)	24.4(5.0)	0.015
Weight of pancreas graft, mg (SD)	190.0(45.2)	192.9(42.3)	187.1(48.4)	0.541

DM, Diabetes mellitus

Comparison of clinical and laboratory variables between infectious and non-infectious fever groups

A total of 45 recipients were diagnosed with non-infectious fever. There were no significant differences in the baseline characteristics according to the cause of post-transplant fever except warm ischemic time of graft. (Table 1). The length of stay was longer in the infectious fever group (38.1±14.3 days) than non-infectious fever group(31.7±12.0 days, $P = 0.003$). (Table 2). The onset of fever was somewhat earlier in the non-infectious fever group (14.4±3.7 post-transplant days) compared with the infectious fever group (16.5±5.8 post-transplant days; $P = .033$). The peak fever was slightly higher in the infectious fever group

(38.78±0.52) compared with the non-infectious fever group (38.57±0.37□; *P* = .032), while there was no significant difference in the duration of fever. The two groups did not show significant differences in the WBC count at the onset of fever and the peak of fever as well as in the increases in the WBC count from the onset of fever to the peak.

The peak level of CRP during fever was significantly higher in the infectious groups compared with the non-infectious group (10.5±7.97 vs 6.92±4.60 mg/dL; *P* =.030), while there was no significant difference in serum CRP levels at the onset of fever (Figure 2A). Similarly, the peak level of serum procalcitonin during fever was significantly higher in the infectious fever group compared with the non-infectious fever group (0.94±1.07 vs 0.26±0.26 ng/mL, *P* =.022) (Figure 2B). There were no significant differences in the levels of serum amylase and lipase between the two groups.

Table 2. Comparison of clinical and laboratory variables between infectious and non-infectious fever groups

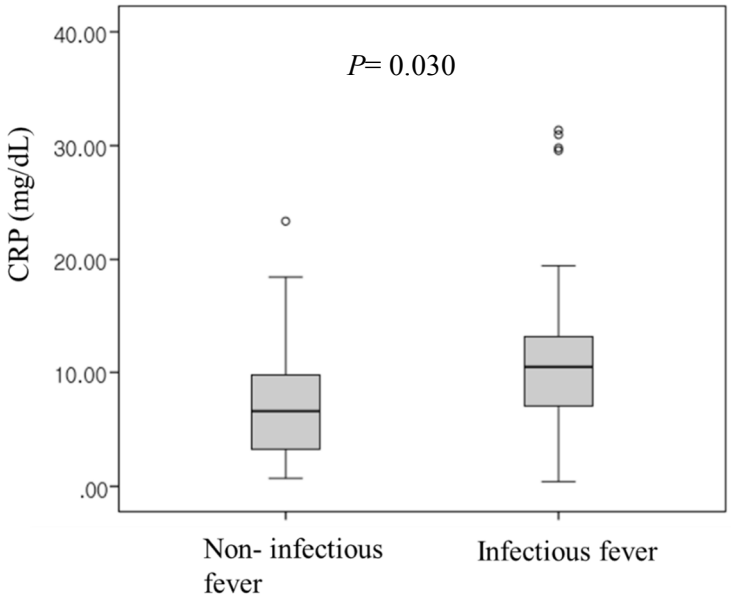
Variables	**All patients (n = 91)**	**Infectious (n = 46)**	**Non-infectious (n = 45)**	**P-value**
Clinical data				
Length of stay, days (SD)	34.9(13.5)	38.1(14.3)	31.7(12.0)	0.003
Body temperature at peak, (SD)	38.68(0.46)	38.78(0.52)	38.57(0.37)	0.032
Duration of fever, days (SD)	4.4(3.6)	4.8(3.8)	3.9(3.4)	0.245
onset of fever, post-transplant days (SD)	15.4(4.9)	16.5(5.8)	14.4(3.7)	0.033

Laboratory data				
onset WBC†, /uL (SD)	7.29(3.59)	7.69(4.18)	6.88(2.85)	0.576
peak WBC, /uL(SD)	9.62(5.27)	10.46(5.85)	8.76(4.51)	0.275
delta WBC	2.33(3.58)	2.77(3.82)	1.88(3.30)	0.264
onset CRP‡, mg/dL (SD)	3.23(4.07)	4.14(5.29)	2.31(1.87)	0.210
peak CRP, mg/dL (SD)	8.73(6.73)	10.5(7.97)	6.92(4.60)	0.030
delta CRP, mg/dL (SD)	5.49(5.14)	6.42(5.93)	4.54(4.04)	0.167
onset Procalcitonin, ng/mL (SD)	0.25(0.38)	0.32(0.51)	0.18(0.15)	0.229
peak Procalcitonin, ng/mL (SD)	0.59(0.83)	0.94(1.07)	0.26(0.26)	0.022
Serum amylase, U/L (SD)	90.8(46.1)	92.4(45.7)	89.2(47.9)	0.568
Serum lipase, U/L (SD)	83.9(72.0)	84.4(68.7)	83.4(75.9)	0.864

† WBC, white blood cell; ‡ CRP, C-reactive protein

Figure 2. Comparison of serum CRP (A) and procalcitonin (B) levels between the non-infectious and infectious fever groups. CRP, C-reactive protein

A.



B.

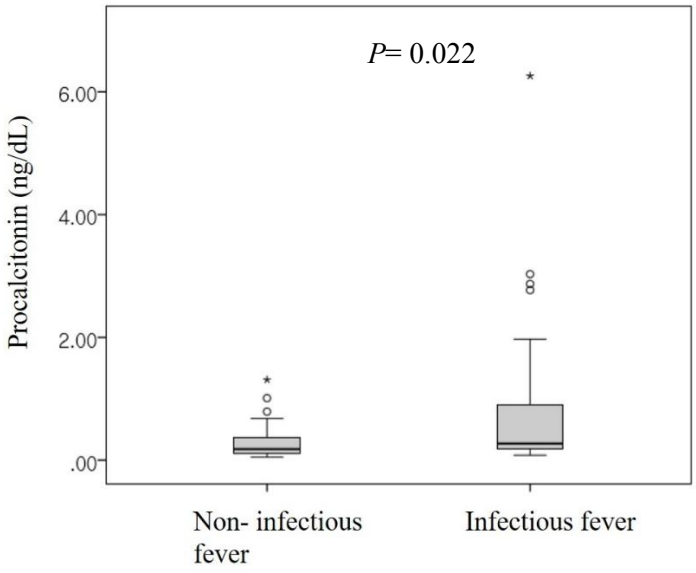
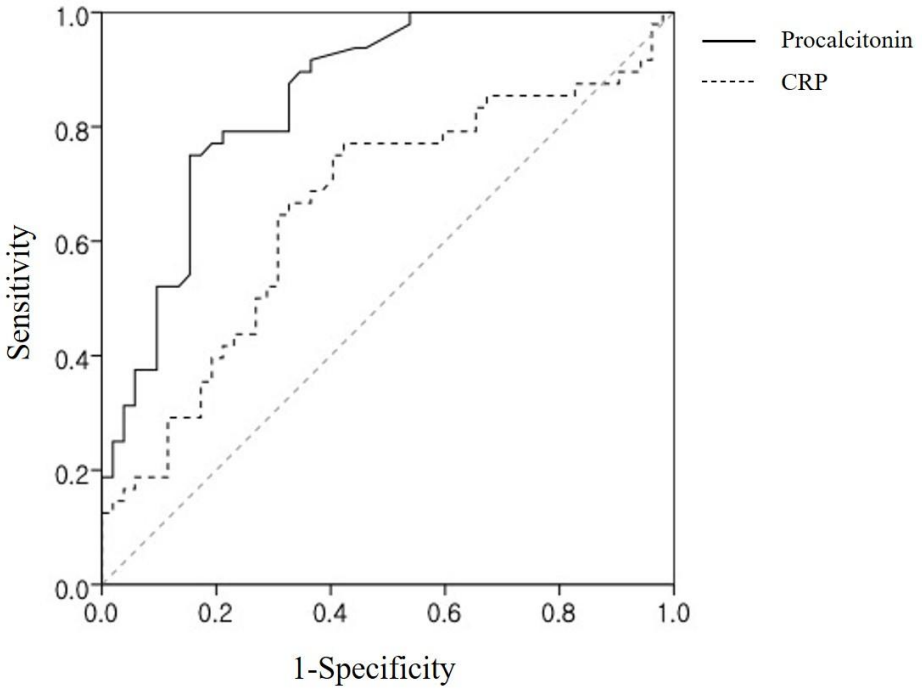


Table 3. Multivariate logistic regression analysis of factors associated with non-infectious fever

Variables	**OR_{unadj}**	**OR_{adj}**[‡]	**95% CI**[§]	**p-value**
peak CRP[¶], mg/dL	1.111	1.059	0.956 – 1.173	0.270
peak procalcitonin, ng/mL	62.182	53.776	6.824-423.776	<0.001

[†] odds ratio unadjusted; [‡] odds ratio adjusted; [§]confidence interval; [¶] C-reactive protein

Figure 3. Receiver operating characteristics curves for serum procalcitonin and CRP levels in differentiating the non-infectious fever group from the infectious fever group



Differentiating variables for non-infectious fever and the cut-off value for serum procalcitonin

In the multivariate analysis, peak procalcitonin was a significant factor for differentiating between the infectious fever group and the non-infectious fever group (odds ratio [OR] 53.776, 95% confidence interval [CI]: 6.824–423.776, $P < .001$) (Table 3). When we analyzed the receiver operating characteristics curves for serum procalcitonin and CRP levels in differentiating the infectious fever group from the non-infectious fever group, the area under the curve was 0.853 (95% CI, 0.780–0.926) for procalcitonin and 0.667 (95% CI, 0.549–0.785) for CRP. The best cut-off value for differentiating between the two groups was 0.405 ng/mL for serum procalcitonin (sensitivity, 77.1%; specificity, 80.8%) and 7.355 mg/dL for serum CRP (sensitivity, 66.7%; specificity, 67.3%) (Figure 3), respectively.

Causes and Etiologies of infectious fever

The causes and etiologies of infectious fever after pancreas transplantation are listed in Table 4. Urinary tract infection (43.5%) was the most frequent cause of infectious fever, and bacteria (65.2%) were the most predominant microorganism that caused infectious fever.

Table 4. Causes and etiologies of infectious fever after pancreas transplantation

Causes	Etiologies	Incidences
Urinary tract infection	Escherichia coli	6
	Klebsiella pneumoniae	5
	Enterococci	5
	Pseudomonas aeruginosa	1
	Enterobacter cloacae	1

	Stenotrophomonas maltophilia	1
	Citrobacter freundii	1
	Aeromonas hydrophilia / Comamonas acidovorans	1
Pneumonia	RSV	1
	Influenza	2
	Unknown	1
Viral infection	CMV syndrome	4
Bacteremia of unknown origin	Enterococci	1
Postsurgical infection	Staphylococcus epidermidis	2
	Klebsiella pneumonia	1
	Staphylococcus aureus	1
	Enterococcus faecium	1
	Escherichia coli	1
	Unknown	5
Gastrointestinal infection	Clostridium difficille	5
Total		46

Causes of non-infectious fever

The causes of non-infectious fever after pancreas transplantation are listed in Table 5. Although the causes of fever for 13 patients were identified, but it was difficult to find those for 32 patients. Possible causes for non-infectious fever with unknown etiologies are such as hidden infection , anti-thymocyte globulin related fever, rheumatologic disorder, etc.

Table 5. Causes of non-infectious fever after pancreas transplantation

Causes	Incidences
Hematoma	7
Transfusion reaction	3
Transplant rejection	2
Contrast reaction	1
Unknown	32
Total	45

Conclusion

In our study, about half of febrile episodes occurring within one month after pancreas transplantation were due to non-infectious causes. Similar to our previous report [4], the mean onset of non-infectious fever was approximately two weeks post-transplant, which was earlier than that of infectious fever. Importantly, our results showed that serum procalcitonin may be effective for differentiating infectious fever from non-infectious fever. Although there was a significant difference in the level of serum CRP between the infectious and non-infectious fever groups, only the level of serum procalcitonin turned out to be significantly

associated with infectious fever in multivariate analysis. It is noteworthy that serum procalcitonin was prospectively measured in recipients who had fever after pancreas transplantation to validate the ability of serum procalcitonin for differentiating infectious fever from non-infectious fever after pancreas transplantation. To our knowledge, this is the first study to investigate the diagnostic usefulness of serum procalcitonin for distinguishing infectious fever from non-infectious fever after pancreas transplantation.

So far, non-infectious fever was clinically diagnosed after the exclusion of infectious fever. There have been only few reports that suggested reliable laboratory biomarkers to help the differentiation of infectious fever from non-infectious fever after pancreas transplantation. Misdiagnose of a non-infectious fever may lead to overuse or misuse of antibiotics, especially during the immediate posttransplant period after solid organ transplantation. Therefore, it is necessary to find laboratory biomarkers that can distinguish infectious fever from non-infectious fever. Procalcitonin is the 116 amino acid polypeptide precursor of calcitonin and a calcium regulatory hormone produced by the C cells of the thyroid gland. [7, 8] Procalcitonin is generally undetectable in healthy people, and increases in cases of systemic bacterial infection. [7, 9] In this study, serum procalcitonin level had a higher sensitivity and specificity than did CRP level for distinguishing infectious fever from non-infectious fever. Our study is consistent with a recent report in which fifty-six patients with systemic inflammatory responses including malignancy, drug-induced inflammation, and allergy had a significantly lower incidence of high procalcitonin levels than did the bacterial infection group. [10] According to a meta-analysis, procalcitonin and CRP have different kinetics and profiles even though they are both released in infectious diseases and non-infectious inflammatory disease. [11] The kinetics of CRP is slower than that of procalcitonin, and the levels are not likely to increase further as the severity of infection progresses; on the other hand, the levels of serum procalcitonin increase according to the severity of sepsis. [11] And there is a meta analysis that elevated serum procalcitonin is associated with a increased risk of mortality in pneumonia.[19]

In our previous study, we showed that the increases in WBC count, CRP, and serum amylase were less prominent in non-infectious fever compared with infectious fever. [4] However, these laboratory characteristics did not have sufficiently strong sensitivity and specificity, and thus had limited clinical application. Therefore, by using retrospectively collected data, our current study revealed that serum procalcitonin is an effective indicator for distinguishing infectious fever from non-infectious fever after pancreas transplantation, with a better sensitivity and specificity than do serum CRP and WBC.

Several studies suggested the cut-off values of serum procalcitonin for the diagnosis of sepsis, [12-18] which ranged from 0.6 to 5 ng/mL. Of these studies, three showed high sensitivity, specificity, positive predictive value, and negative predictive value. [13, 16, 17] In our study, the best cut-off value of serum procalcitonin for differentiating infectious fever from non-infectious fever was 0.405 ng/mL, with a sensitivity of 77.1% and a specificity of 80.8%, which is close to the lower limit of positive procalcitonin test (0.5 ng/mL). Our study has a relatively lower cut-off value for serum procalcitonin because we also included recipients with less severe degrees of infection.

There are several limitations to our study. This was a retrospective study in a single center. In addition, the small number of enrolled patients limits a wide clinical application of the cut-off value of serum procalcitonin. Also, sample size was too small for dividing with severity of infectious disease, it was difficult to find relationship with serum procalcitonin level and severity of infectious disease. A multicenter study is needed to determine the best cut-off value for the differentiation between infectious and non-infectious fever after pancreas transplantation. Lastly, we only measured serum procalcitonin at the onset of fever and the peak of fever. Serial measurements of serum procalcitonin should be carried out in a future study.

In conclusion, serum procalcitonin was a more reliable biomarker than serum CRP for differentiating infectious fever from non-infectious fever occurring after pancreas

transplantation. When post-transplant fever occurs in a pancreas transplant recipient, serial measurements of serum procalcitonin may be helpful for determining the need for empirical antibiotics.

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Abstract in English

Infectious diseases have been regarded as major problem in solid organ transplantation recipients, resulting in substantial morbidity and mortality, and fever has been regarded as important sign for infectious diseases. But, in fact, having a fever doesn't always signal infection. Laboratory biomarkers that can differentiate non-infectious fever from infectious fever after pancreas transplantation have yet to be discovered. Non-infectious fever was defined as the presence of fever (> 38.3) in the absence of a documented clinical diagnosis of infection or a positive culture.

Among 184 consecutive recipients, a total of 91 recipients developed fever within one-month post-transplant, of whom 46 had infectious fever and 45 had non-infectious fever at our center between August 2014 and July 2019. The onset of fever was earlier in the non-infectious fever group (14.4±3.7 post-transplant days) compared with the infectious fever group (16.5±5.8 post-transplant days; $P = .033$). Multivariate analysis showed that serum procalcitonin at the peak of fever could significantly differentiate infectious fever from non-infectious fever (OR 53.776, 95% CI: 6.824–423.776, $P < .001$). The area under the curve for differentiating between the two groups was 0.853 (95% CI, 0.780–0.926) for procalcitonin and 0.667 (95% CI, 0.549–0.785) for CRP. The best cut-off values of serum procalcitonin and CRP were 0.405 ng/mL (sensitivity, 77.1%; specificity, 80.8%) and 7.355 mg/dL (sensitivity, 66.7%; specificity, 67.3%), respectively.

Serum procalcitonin may be useful for differentiating non-infectious fever from infectious fever after pancreas transplantation