原　著

当科における血小板減少患者の検討
—THORPⅡ Studyを行って—

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要　旨

対象は入院中に血小板数が12万/㎣未満，あるいは24時間以内に30%以上の血小板減少を認めた41名で，DIC群と非DIC群で背景，各種データ，重症度スコアを比較検討した。その結果，エントリー時の血小板数は両群間に差を認めなかったが，血小板最小値はDIC群で有意に低値であった（$p<0.01$）。DIC群はFDPが有意に高く（$p<0.05$），プロトロンビン比が有意に高値であった（$p<0.01$）が，フィブリノーゲンでは有意差を認めなかった。この結果は，2005年に発表された救急領域のDIC新診断基準と一致した。厚生省DIC診断基準と救急領域のDIC診断基準（案）を比較すると，発症からDICに陥る時期は厚生省DIC診断基準が平均2.1日であったのに対し，救急領域のDIC診断基準（案）が平均1.4日と短期間であった。死亡4例についてみると，救急領域のDIC診断基準（案）が早期にDICを診断していた。

キーワード：DIC診断基準，血小板減少症，治療，救急医療

はじめに

播種性血管内凝固症候群（disseminated-intravascular coagulation：DIC）は，その診断に厚生省特定疾患DIC調査研究班による診断基準（厚生省DIC診断基準）がひろく用いられている。しかし，救急領域で経験する外傷や敗血症，熱傷など重篤な病態では臨床症状やデータが急激に変化するため，厚生省DIC診断基準を満たす頃には予後不良となる例が少なくない[1]。今回われわれは，救急医療領域における血小板減少症に関する多施設研究　（Thrombocytopenia-Outcome-Registration Prospective Ⅱ Study：THORPⅡ Study）に参加した1施設として，当科における血小板減少患者のデータ解析から，DICの有無と凝固線溶系マーカーや重症度スコアとの関連性を比較検討した。また，救急領域のDIC診断基準（案）（救急DIC診断基準案）と厚生省DIC診断基準を比較し，その感度について検討した。

対　象

2004年7月1日より9月30日までの期間，岩手医科大学高度救命救急センター集中治療室に入院した患者285名のうち，経過中に血小板数が12万/㎣未満，あるいは24時間以内に30%以上の血小板減少を認めた41名を対象とした。男女比は30：11，平均年齢は62±20歳，転帰は生存が37例，死亡が4例であった。疾患別の内訳は外傷15例，急性冠症候群5例，消化管出血5例，脳血管障害4例，感染症3例，腹膜炎・イレウス3例，その他6例であった（**表1**）。

検討項目

①経過中，救急DIC診断基準案もしくは厚生省DIC診断基準を満たした19例をDIC群，DICを発症しなかった22例を非DIC群とし，両群間の背景，各種データ，重症度スコアを比較検討した。

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表1　対象41例の原疾患の内訳

外　傷	15例	
急性冠症候群	5例	（1例死亡）
消化管出血	5例	
脳血管障害	4例	（2例死亡）
感染症	3例	
腹膜炎・イレウス	3例	
その他	6例	（1例死亡）

②経過中，アンチトロンビンⅢ（ATⅢ）製剤，血小板輸注，新鮮凍結血漿，ヘパリン，蛋白分解酵素阻害薬，血液浄化法などの治療を要した17例を治療群，治療を行わなかった24例を非治療群とし，両群間の背景，各種データ，重症度スコアを比較検討した。

③DIC群において，厚生省DIC診断基準と救急DIC診断基準案の頻度と満たすまでの期間を比較検討した。

用いたパラメーターは，背景として年齢，集中治療室入室期間，入院後エントリーに至るまでの日数をデータとして，エントリー時の血小板数，経過中の血小板最小値，FDP，フィブリノーゲン，プロトロンビン（PT）比，ATⅢ，systemic inflammatory response syndrome（SIRS）スコア，厚生省DIC診断基準スコア，国際血栓止血学会（International Society on Thrombosis and Haemostasis：ISTH）overt-DIC診断基準スコア，救急DIC診断基準案スコアを，また重症度スコアとしてacute physiology and chronic health evaluationⅡ（APACHEⅡ）スコア，simplified acute physiology scoreⅡ（SAPSⅡ），sequential organ failure assessment（SOFA）スコア，multiple organ dysfunction syndrome（MODS）スコアを用いた。

統計学的検討

数値は平均±標準偏差で表した。2群間の比較はunpaired t-testを用いて評価し，p値が0.05未満を示したものを有意差ありと判定した。

結　果

1．DIC群と非DIC群の検討

エントリー時の血小板数は両群の間に有意差を認めなかったが，血小板最小値はDIC群5.7±3.7×$10^3/\mu L$，非DIC群8.4±2.0×$10^3/\mu L$（$p<0.01$）であった。FDPはDIC群76.6±131.7 $\mu g/mL$，非DIC群13.5±16.9 $\mu g/mL$（$p<0.05$）であったが，

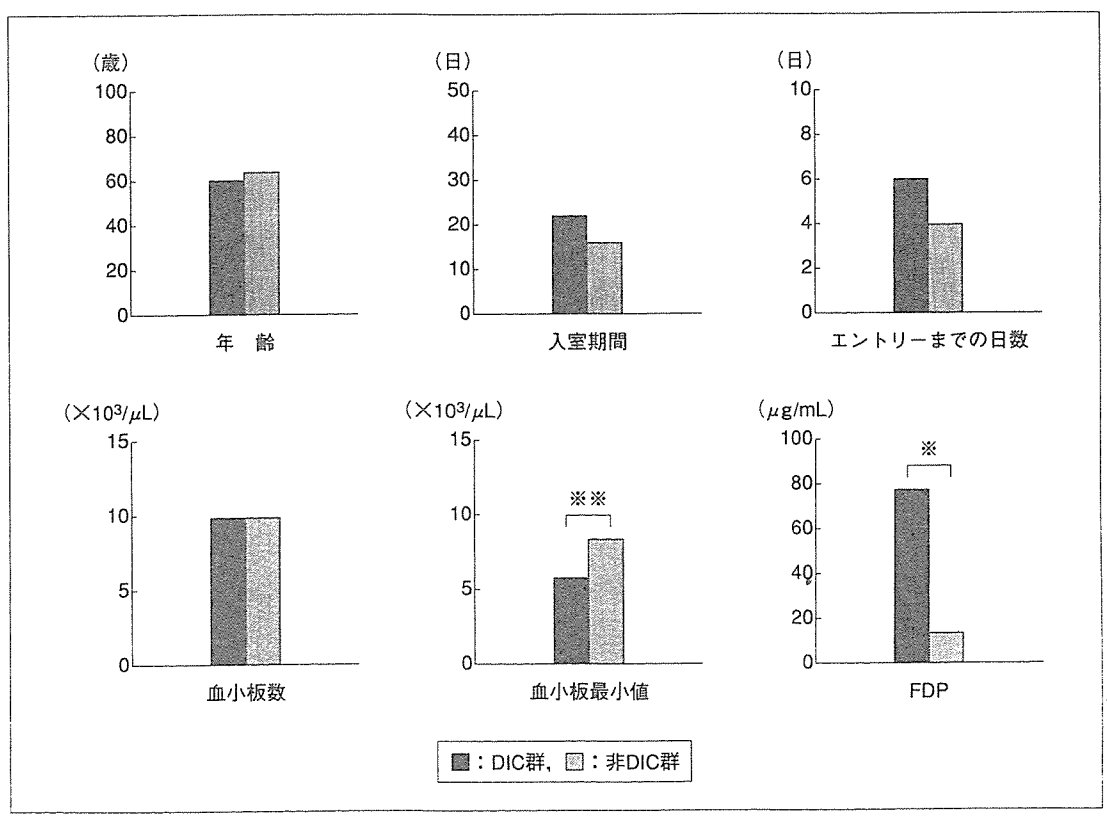

図1-1　DIC群と非DIC群の比較

※：$p<0.05$，※※：$p<0.01$

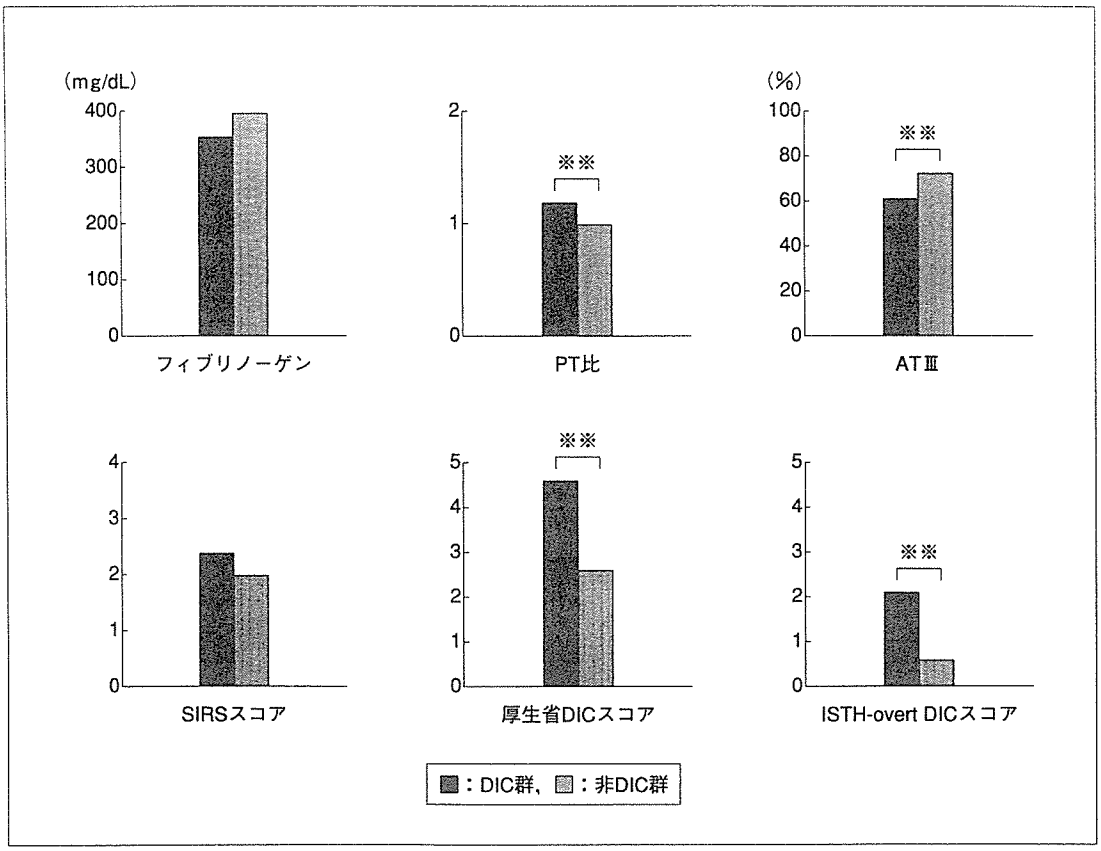

図 1 - 2　DIC 群と非 DIC 群の比較

※※：$p < 0.01$

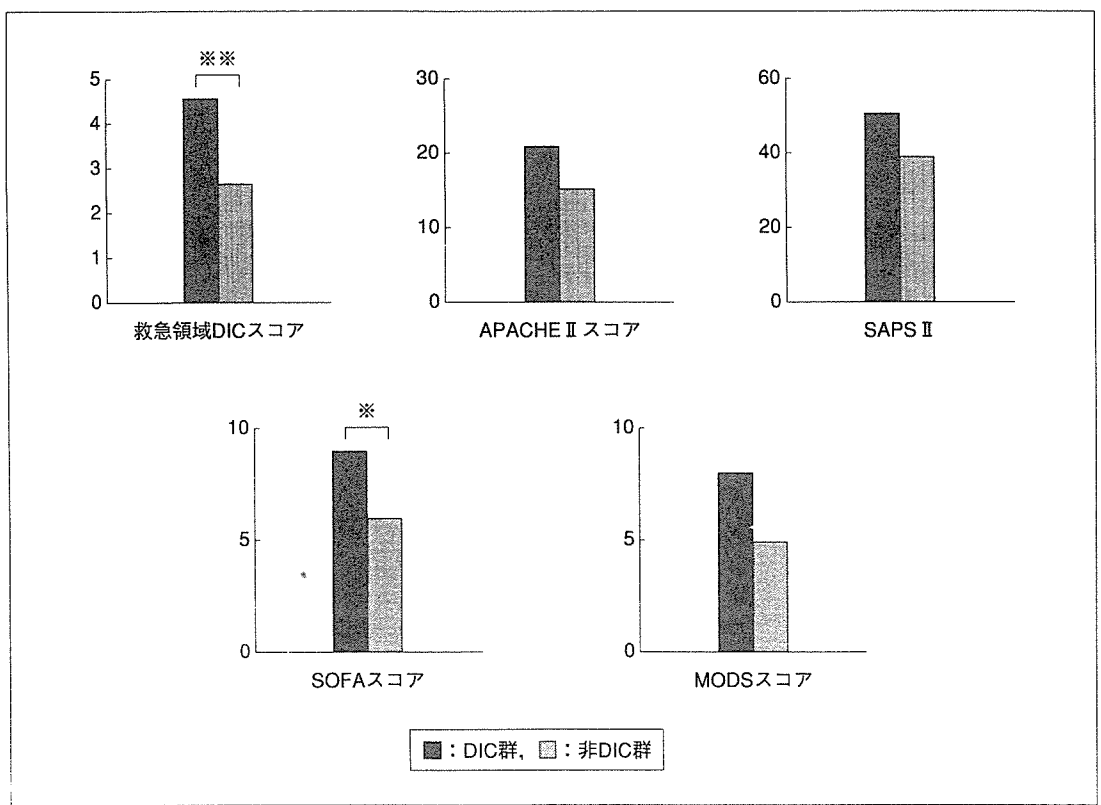

図 1 - 3　DIC 群と非 DIC 群の比較

※：$p < 0.05$，※※：$p < 0.01$

フィブリノーゲンには有意差を認めなかった。PT比はDIC群1.2±0.2，非DIC群1.0±0.1（$p<0.01$），ATⅢはDIC群61.6±13.5%，非DIC群72.3±11.0%（$p<0.01$）。厚生省，ISTH，救急領域の各DIC診断基準スコアはともにDIC群で有意に高値であった。重症度スコアはSOFAスコアがDIC群8.8±3.9，非DIC群5.9±3.6（$p<0.05$）と有意に高値であった。その他，APACHEⅡスコア，SAPSⅡ，MODSスコアはいずれもDIC群で高値を示したが有意差を認めなかった（**図1**）。

2．治療群と非治療群の検討

年齢は治療群52±19歳，非治療群69±19歳（$p<0.01$），入室期間は治療群28±30日，非治療群12±19日（$p<0.05$）と有意差を認めた。血小板数は両群の間に有意差を認めなかったが，血小板最小値は治療群5.4±2.7×$10^3/\mu L$，非治療群8.4±2.9×$10^3/\mu L$（$p<0.01$）と治療群で低値であった。FDPは治療群で高値を示したが有意差を認めなかった。各DICスコアでは治療群が高値を示したものの有意差を認めなかった。重症度スコアはMODSスコアが治療群5.8±3.5，非治療群10.0±2.4（$p<0.05$）と有意差を認めたが，他の重症度スコアでは有意差を認めなかった（**図2**）。

3．厚生省DIC診断基準と救急DIC診断基準案の比較

DIC群19例を対象に比較検討した。厚生省DIC診断基準のみ満たした症例は2例で，一方，救急DIC診断基準案のみ満たした症例は8例，両診断ともに満たした症例は9例であった（**図3**）。発症からDICに陥る時期をみると，厚生省DIC診断基準が平均2.1日に比べ，救急DIC診断基準案が平均1.4日と短期間であるが，両群間に有意差を認めなかった（**図4**）。死亡4例についてみると，厚生省DIC診断基準を早期に認めた例は1例もなく，救急DIC診断基準案を早期に認めた例が2例，同時期に両診断を満たした例が1例，両診断基準ともに満たさなかった例が1例であった（**表2**）。

考　察

2003年，救急DIC診断基準案の中間報告が救急医学会の学会通信で報告された。そこでは後ろ向き研究の結果，この診断基準案が厚生省DIC診断基準に比較してDICを感度よく，かつ早期診断できる可能性が高いことを述べている[2)]。2005年には多

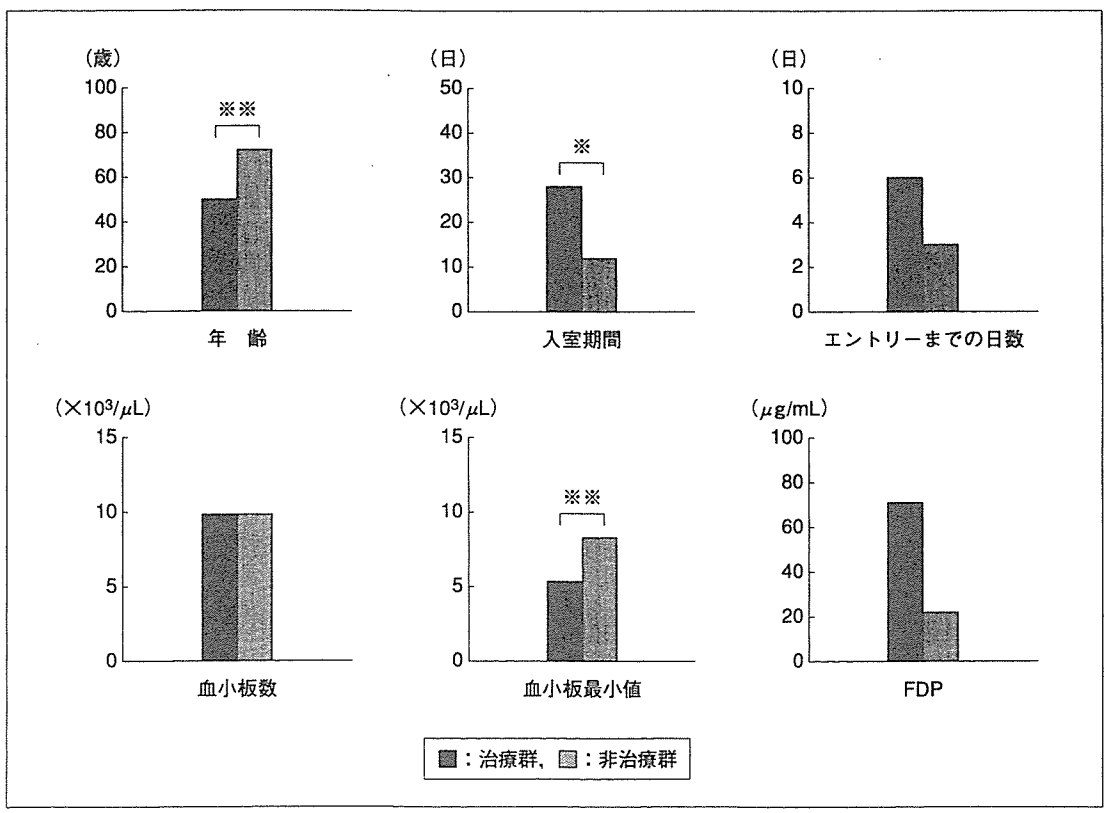

図2-1　治療群と非治療群の比較

※：$p<0.05$，※※：$p<0.01$

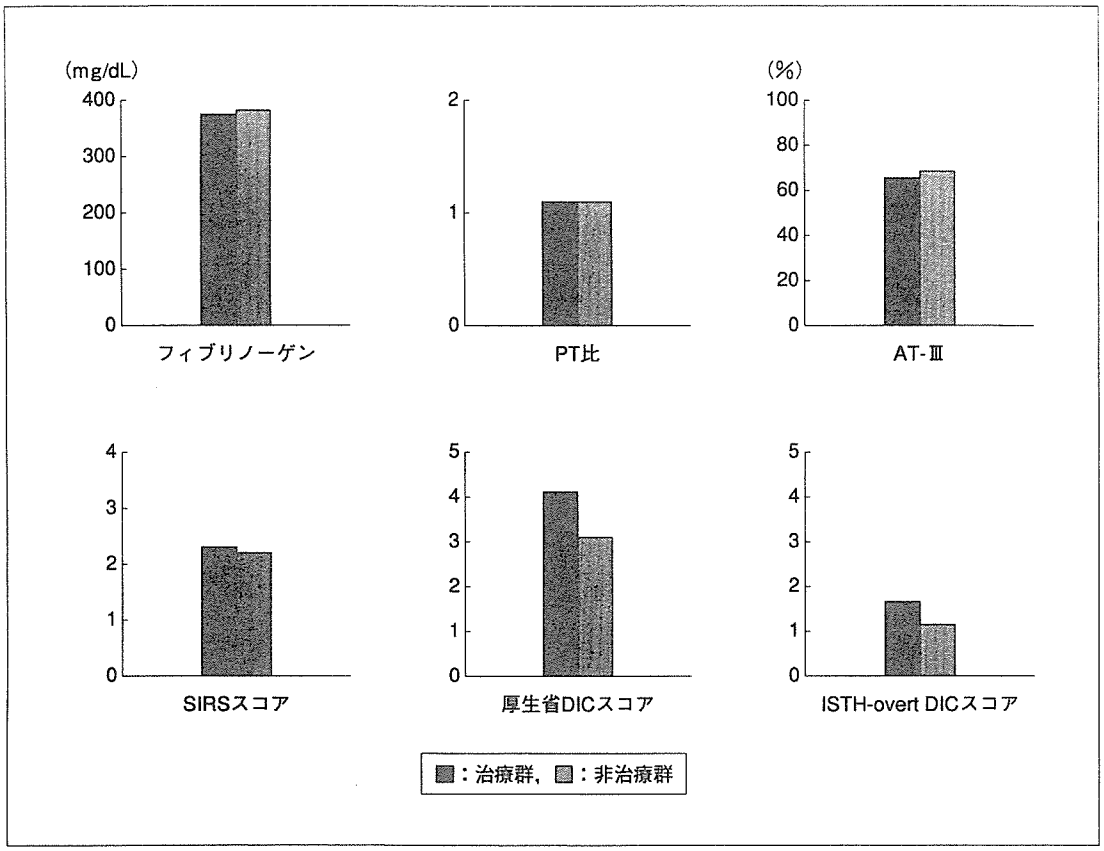

図 2 - 2　治療群と非治療群の比較

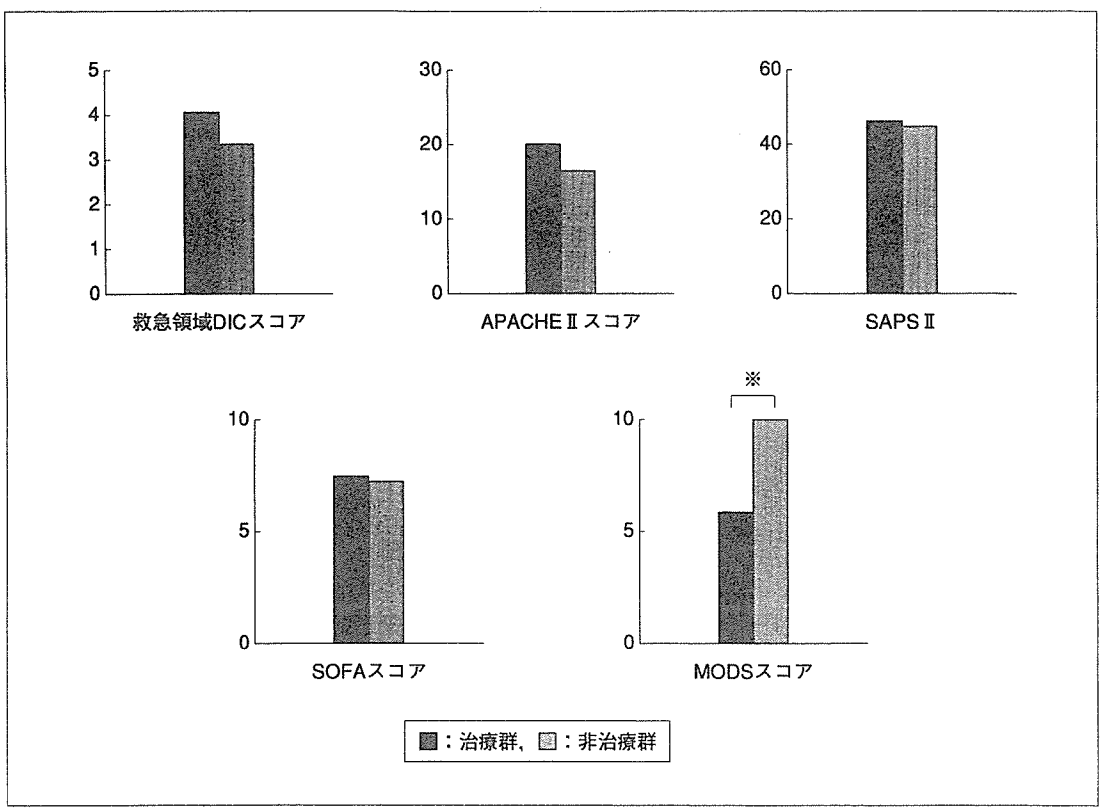

図 2 - 3　治療群と非治療群の比較

※：$p < 0.05$

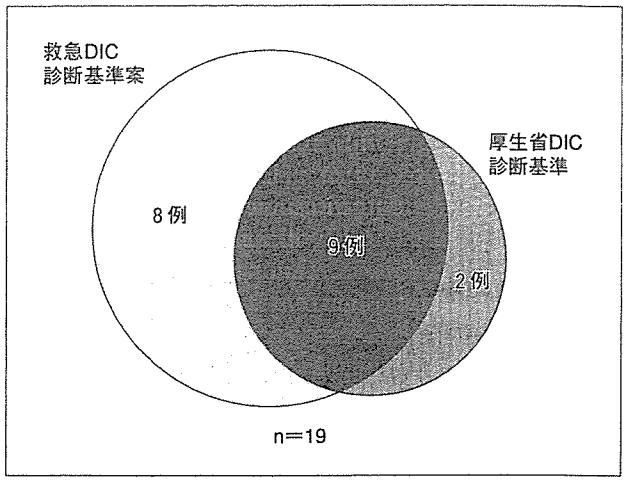

図3　厚生省 DIC 診断基準と救急 DIC 診断基準案の比較

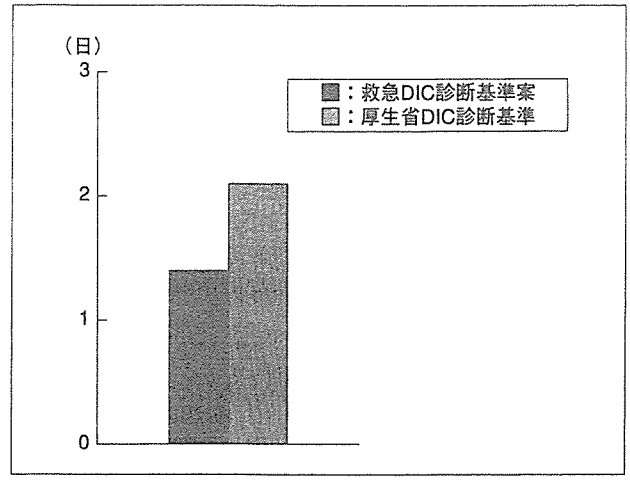

図4　発症から DIC に陥るまでの時期の比較

表2　死亡例における診断基準を満たすまでの日数の比較

		救急 DIC 診断基準案	厚生省診断基準
case 1	53歳，男性	1	1
case 2	78歳，男性	2	—
case 3	72歳，男性	1	—
case 4	87歳，女性	—	—

—：DIC を発症せず

施設共同前向き研究の結果，救急領域の DIC 新診断基準が報告された[3]。そのなかで，診断項目として血小板数のほか，血小板減少率や FDP 値，PT 比が決められている一方で，フィブリノーゲンは予後予測に役立たなかったことから診断項目から削除されている。今回のわれわれの検討では，DIC 群と非 DIC 群の血小板数はエントリー時にほぼ同値を示していたが，最小値の比較では DIC 群が有意に低値となった。このことは DIC に陥るような重症例ほど血小板減少率が大きい結果と考えられた。また，DIC 群で FDP と PT 比は有意に高値であったが，フィブリノーゲンでは有意差を認めなかった。以上より，今回のわれわれの検討結果は救急領域の DIC 新診断基準と一致していると思われた。

治療群と非治療群の検討では年齢，入室期間，血小板最小値，MODS スコアで有意差を認めた。治療群で血小板最小値が有意に低く入室期間が有意に長かった理由として，血小板が急激に減少した例ではさまざまな治療を要し，その結果，入室期間が長期に至った結果と考えられた。一方，年齢と MODS スコアで有意差を認めた理由は，最も内訳の多かった外傷患者が比較的若く，かつ多臓器不全にまで進展しなかった症例が多かったことが原因と考えられた。しかし，今回の検討ではそれぞれの治療法についての検討を行っていないため，今後症例を増やしての検討が必要と思われた。

救急 DIC 診断基準案と厚生省 DIC 診断基準の比較検討では，有意差を認めないが救急 DIC 診断基準案が早期に DIC を診断していた。また，死亡 4 症例における DIC 診断率も救急 DIC 診断基準案が厚生省 DIC 診断基準と比較して高い結果であった。前向き研究の結果では，救急 DIC 診断基準案が厚生省 DIC 診断基準や ISTH-overt DIC スコアより早期に DIC を診断しており，さらに非 DIC 症例における死亡率でも厚生省診断基準および ISTH-overt DIC スコアが救急 DIC 診断基準案に比較して高値を示したと報告されている[3]。症例数の違いはあるが，われわれの検討結果とほぼ一致した結果であった。

結　語

今回の検討は，救急領域における DIC の新診断基準に合致する結果であった。厚生省 DIC 診断基準に比べて救急 DIC 診断基準案が有用であると思われた。

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ABSTRACT

A study of the Critical Care and Emergency Center of Iwate Medical University thrombocytopenia cases —A analysis of Thrombocytopenia-Outcome-Registration Prospective (THORP) II Study—

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Study subjects were 41 in-patients whose platelet counts were less than 120,000/㎣ or decreased 30% or more within 24 hours during hospitalization. These subjects were divided into two groups of DIC group and non-DIC group, and backgrounds, various data and severity scores were compared between the two groups. At the time of admission, while there was no difference in platelet counts, the minimal platelet count was significantly lower in DIC group ($p<0.01$). In DIC group, FDP ($p<0.05$) and prothrombin ratio ($p<0.01$) were significantly higher. There was no significant difference in fibrinogen. These findings corresponded with the DIC diagnostic criteria in critical care medicine (CCM) published in 2005. In comparison between the DIC criteria by the Ministry of Health and Welfare (MHW) and DIC criteria (draft) in the CCM, the duration between onset of underlying diseases and manifestation of DIC was an average of 2.1 days by the MHW criteria and an average of 1.4 days, or shorter, by the CCM criteria (draft). In the 4 cases of deaths, DIC was diagnosed earlier by the CCM criteria (draft).

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SURGERY TODAY

Group IIA-Soluble Phospholipase A_2 Levels in Patients with Infections After Esophageal Cancer Surgery

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Abstract

Purpose. To examine the changes in blood-soluble phospholipase A_2-IIA levels caused by surgical stress and postoperative infections.

Methods. We retrospectively analyzed a prospective database of 40 patients who underwent esophagectomy for esophageal cancer. Nine of these patients had a postoperative infection (E Inf(+) group), and 31 did not have a postoperative infection (E Inf(−) group). The blood $sPLA_2$-IIA level was measured using a radioimmunoassay, and whole blood was stimulated with lipopolysaccharide (LPS) to examine the $sPLA_2$-IIA production.

Results. In the E Inf(−) group, the blood $sPLA_2$-IIA levels peaked on postoperative day (POD) 3 then decreased gradually thereafter. Receiver-operator characteristic statistics based on the $sPLA_2$-IIA values on POD 5, which are used to classify postoperative infectious complications, revealed an area under the curve of 0.789. However, stimulation of peripheral blood cells with LPS did not induce the production of $sPLA_2$-IIA.

Conclusion. During the early postoperative phase, blood $sPLA_2$-IIA levels increase according to the surgical stress. Soluble PLA_2-IIA may be produced at the site of infection or in the liver, but not in the circulating blood. Sustained elevation of the serum $sPLA_2$-IIA level, observed even after POD 3, seems to represent a response to postoperative infection.

Key words Phospholipase A_2 · Esophageal cancer · Surgical stress · Postoperative infection

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Introduction

Phospholipase A_2 (PLA_2) hydrolyzes the acyl ester bond at the sn-2 position of glycerophospholipids on the cell membrane, to release arachidonic acid.[1] Phospholipase A_2 activity serves as the rate-limiting factor for the production of inflammatory lipid mediators such as prostaglandins and leukotrienes by the arachidonic acid cascades.[2] Secretory and cystosolic forms of PLA_2 have been described. Secretory PLA_2 ($sPLA_2$), is known to have ten subtypes,[3] one of which, groupIIA $sPLA_2$ ($sPLA_2$-IIA), is produced in platelets, neutrophils, spleen, and liver.[4] Elevated blood $sPLA_2$-IIA levels are found in patients with inflammatory conditions such as sepsis, acute pancreatitis, myocardial infarction, and multiple trauma.[5–7] The blood PLA_2-IIA levels have been reported to be correlated with the severity of organ failure[8] in inflammatory conditions. In acute respiratory distress syndrome (ARDS), $sPLA_2$-IIA is involved in the degradation of pulmonary surfactant.[9–11] Moreover, an increased blood $sPLA_2$-IIA level is an important indicator of a host defensive reaction, which serves a bactericidal role in the presence of infection.[11]

We conducted this study to examine changes in the blood levels of interleukin (IL)-6, IL-8, and $sPLA_2$-IIA caused by surgical stress in patients undergoing surgery for esophageal cancer, and to analyze changes in the blood levels of $sPLA_2$-IIA in association with postoperative infections.

Subjects and Methods

The protocol of this prospective, observational cohort study was approved by our institutional review board. The study commenced in June 1996 and continued for 6 years, ending in November 2002.

Protocol

The subjects were a consecutive 150 patients with esophageal cancer who underwent resection of the thoracic segment of the esophagus after right thoracotolaparotomic manipulation, combined with excision of the cervical, mediastinal, and abdominal lymph nodes. Anastomosis of the cervical segment of the esophagus to the stomach was done via a posterior mediastinal route in all patients. The following patients were excluded from the study: those who did not give informed consent; those who had been treated preoperatively by chemotherapy, radiotherapy, or immunotherapy; those aged over 76 years old; those with preoperative coexisting disorders such as liver cirrhosis, insulin-dependent diabetes mellitus, a creatinine clearance below 60 ml/min, a percent vital capacity below 80%, and forced expiratory volume in 1 s ($FEV_{1.0}$%) below 70%; and those with double cancer. The interval from diagnosis to operation was less than 3 weeks, and oral or enteral feeding was continued until the day before the surgery in all patients.

Blood loss was replaced by an appropriate volume of bank blood. For postoperative alimentation, glucose was infused intravenously at the rate of 5 g/h. On postoperative day (POD) 3, enteral administration of nutrients via the jejunostomy was started at an initial rate of 5 kcal/kg per day, then gradually increased to the full requirement of 30 kcal/kg per day by POD 10–14.[11] All patients received prophylactic mechanical ventilation and intravenous Cefazolin sodium.[11] The blood $sPLA_2$-IIA levels in patients who underwent open surgery for colonic cancer (colon group) served as a control.

Definition of Postoperative Infectious Complications

The definition of infection within 7 days of surgery for esophageal cancer was derived from the Centers for Disease Control and Prevention (CDC) guidelines.[13] Pneumonia, urinary tract infection, blood infection, intraperitoneal abscess, and empyema were included as postoperative infections, whereas superficial incision site infections were excluded. The presence of infection was diagnosed by physicians certified by the Japan Infection Control Doctors' Association, independently of the intensive care unit (ICU) staff. The diagnosis was made retrospectively on the basis of ICU records and bacteriological test results. When making this diagnosis, the examiner was given no information about the $sPLA_2$-IIA or cytokine levels in the patient. The patients were divided into an infection group (E Inf(+) group) and a non-infection group (E Inf(–) group).

Blood Sampling and Assay

Blood specimens were collected from the patients on the day before the surgery (PRE), at the end of the intrathoracic manipulation during the operation (OP), 1 h after the operation (D0), and at 07:00 h each day from POD 1 (D1) until POD 7 (D7). Each blood sample was immediately centrifuged, and the separated plasma samples were stored frozen at –80°C until the assay. Peripheral blood IL-6 and IL-8 levels were measured by enzyme-linked immunosorbent assay (R & D Systems, Minneapolis, MN, USA). The $sPLA_2$-IIA was measured by radioimmunoassay (RIA) using anti-$sPLA_2$-IIA monoclonal antibody, as described previously.[14] The minimum detectable levels of IL-6, IL-8, and $sPLA_2$-IIA were 0.7 pg/ml, 18 pg/ml, and 3.7 ng/ml, respectively. Hematological, serum biochemical, and blood gas analyses were conducted at the central laboratory of our hospital.

The $sPLA_2$-IIA production in whole blood after esophageal cancer surgery was examined. Two 3-ml specimens of peripheral blood were collected from each patient in ethylenediamine tetraacetic acid-containing blood collection tubes. Each blood specimen was incubated with 1 ml (1 mg) of lipopolysaccharide (LPS; derived from *Escherichia coli* 0111, Sigma, St. Louis, MO, USA) or 1 ml of normal saline at 37°C for 24 h. The concentration of $sPLA_2$-IIA in the culture supernatant was measured by RIA. The difference in the $sPLA_2$-IIA levels between the LPS-stimulated culture and the normal saline culture was deemed as the amount of $sPLA_2$-IIA produced in the blood.

Statistical Analysis

The differences in the clinical characteristics of the patients were analyzed by the chi-square test or Fisher's exact test. Chronological changes in the laboratory data were analyzed by analysis of variance (ANOVA) for repeated measures. When a significant difference was found by ANOVA, the differences at various times were examined by Student's *t*-test. To evaluate the pathophysiologic predictors of postoperative infection, a series of logistic regression models and a receiver-operator characteristics (ROC) curve were used. A P value of less than 0.05 was considered significant. All statistical analyses were performed on a personal computer using the statistical package SPSS for Windows, Advanced Statistics 11.0 J (SPSS, Chicago, IL, USA).

Results

Background Variables

A total of 40 patients who underwent surgery for esophageal cancer and 10 who underwent surgery for

Table 1. Clinical characteristics of patients

	E Inf(−) group ($n = 31$)	E Inf(+) group ($n = 9$)	P Value	Colon group ($n = 10$)
Sex (%)			NS[a]	
Male	28 (94)	9 (100)		8 (80)
Female	3 (6)			2 (20)
Age (years)	64 ± 7	62 ± 8	NS[b]	60 ± 8
pTNM stage[c], n (%)			NS[a]	
Stage I	4 (13)	1 (11)		
Stage II	10 (32)	3 (33)		3 (30)
Stage III	17 (55)	5 (56)		7 (70)
Duration of surgery (min)	339 ± 49	330 ± 33	NS[b]	205 ± 41
Operative blood loss (ml)	647 ± 286	696 ± 314	NS[b]	225 ± 143

Mean ± SD. NS, not significant
[a] Fisher's exact test
[b] Unpaired t-test
[c] UICC classification[19]

Table 2. Postoperative complications (within 28 days)

	E Inf(−) group ($n = 31$)	E Inf(+) group ($n = 9$)
Organ system complications, n (%)		
Cardiovascular failure[a]	4 (13)	2 (22)
Respiratory failure[b]	6 (19)	5 (56)
Hepatic failure[c]	7 (23)	2 (22)
Surgical complications, n (%)		
Anastomotic leakage	0	2 (22)
Infectious complication		
within 7 days	0	9 (100)
within 8–28 days	3 (10)	2 (22)
Death	0	0

[a] Requiring dopamine or dobutamine >6 μg/kg/min or occurrence of arrhythmia which requires medication
[b] $PaO_2/FiO_2 < 250$
[c] Total bilirubin level >2.0 mg/dl

Table 3. Postoperative infectious complications within 7 days

Site	Number (%)
Pyothorax	2 (22)
Pneumonia	4 (44)
Bloodstream infection	3 (33)

colonic cancer (colon group) were enrolled in this study.

The E Inf(+) group consisted of 9 patients diagnosed as having a postoperative infection within 7 days after esophagectomy and the E Inf(−) group consisted of the remaining 31 patients with no evidence of infection after esophagectomy (Table 1). There were no significant differences between the Inf(+) and Inf(−) groups in clinical characteristics or postoperative complications, apart from the early infectious complications (Tables 2 and 3). The primary infections were the pyothorax in 4 (22%) patients, pneumonia in 2 (44%), and septicemia in 3 (33%). The background variables for the colon group are also shown in Table 1. There were no postoperative complications, including infection, in this control group.

Changes in the Serum $sPLA_2$-IIA Level

The serum $sPLA_2$-IIA levels did not change significantly after surgery in the colon group (repeated-measures one-way ANOVA; $P = 0.1153$). Among the patients who underwent surgery for the treatment of esophageal cancer, the $sPLA_2$-IIA level began to increase on POD 1. In the E Inf(−) group, the $sPLA_2$-IIA peaked on POD 3, then decreased gradually thereafter. In the E Inf(+) group, the $sPLA_2$-IIA level was significantly higher than that in the E Inf(−) group from POD 5 onward.

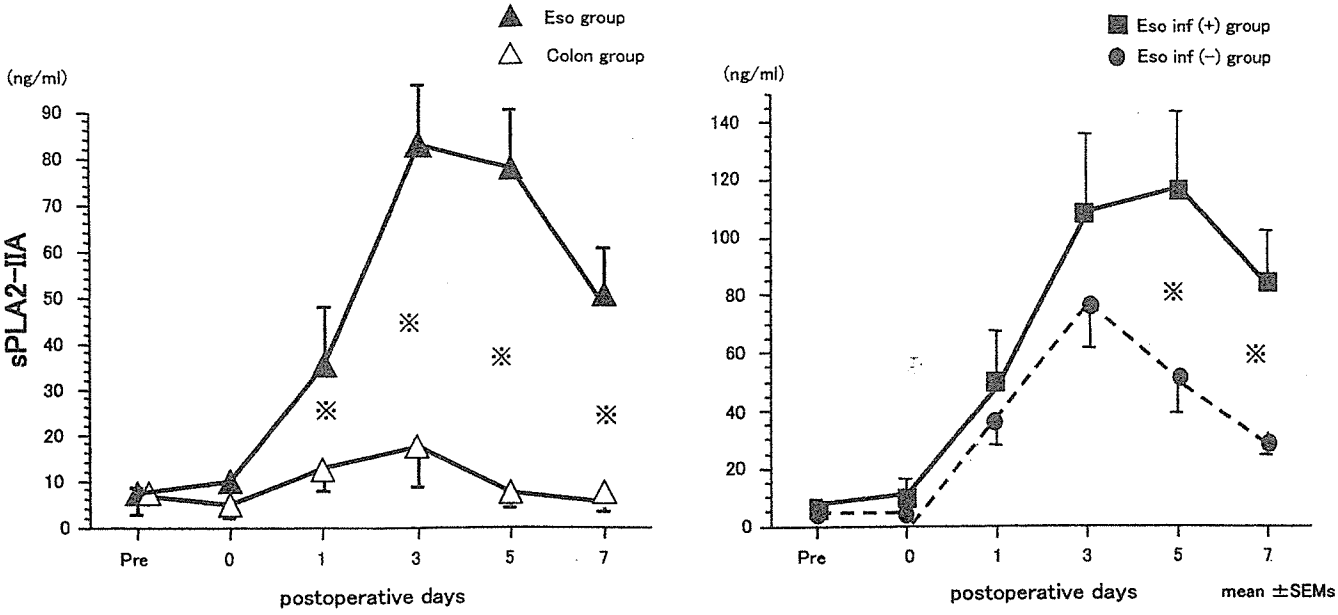

Fig. 1. Postoperative changes in serum soluble phospholipase A_2-IIA (*$sPLA_2$-IIA*) levels after esophagectomy (*Eso*) and colectomy (*left*), and in the postesophagectomy infection (*Eso inf*(+)) and non-infection (*Eso inf*(−)) groups (*right*). The serum $sPLA_2$-IIA levels did not change significantly after colectomy (repeated-measures one-way analysis of variance; $P = 0.1153$). The postoperative increases in the serum $sPLA_2$-IIA levels were significantly higher in the infection group than in the noninfection group ($P < 0.01$, ANOVA). $^{*}P < 0.05$, unpaired *t*-test

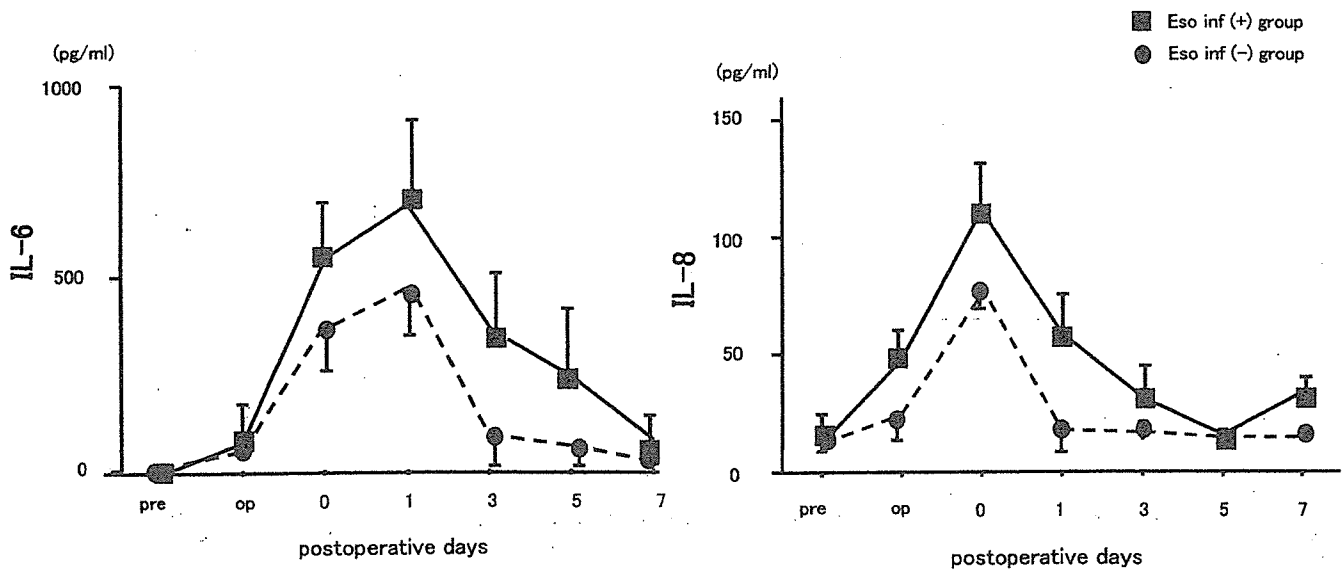

Fig. 2. Postoperative changes in plasma interleukin-6 (*IL-6*) and the interleukin-8 (*IL-8*) levels in the infection (*Eso inf*(+)) and noninfection (*Eso inf*(−)) groups. There were no remarkable differences in the IL-6 and IL-8 levels between the two groups

Changes in the Serum IL-6 and IL-8 Levels

The serum IL-6 level peaked between the period immediately after surgery and POD 1, then decreased gradually thereafter, and did not increase significantly again. The serum IL-8 levels were not significantly different between the E Inf(+) group and the E Inf(−) group. There was no significant correlation between the serum $sPLA_2$-IIA level and the serum CRP, IL-6, or IL-8 levels, the respiratory coefficient, or the serum total bilirubin level at any time of measurement (data not shown).

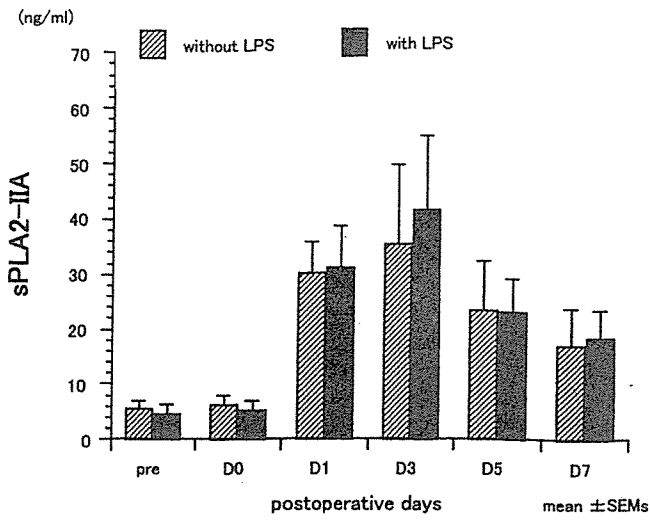

Fig. 3. Soluble phospholipase A_2-IIA (*$sPLA_2$-IIA*) production in lipopolysaccharide (*LPS*)-stimulated whole blood after esophagectomy. Postoperative production of $sPLA_2$-IIA was not detected in LPS-stiumlated whole blood at any time

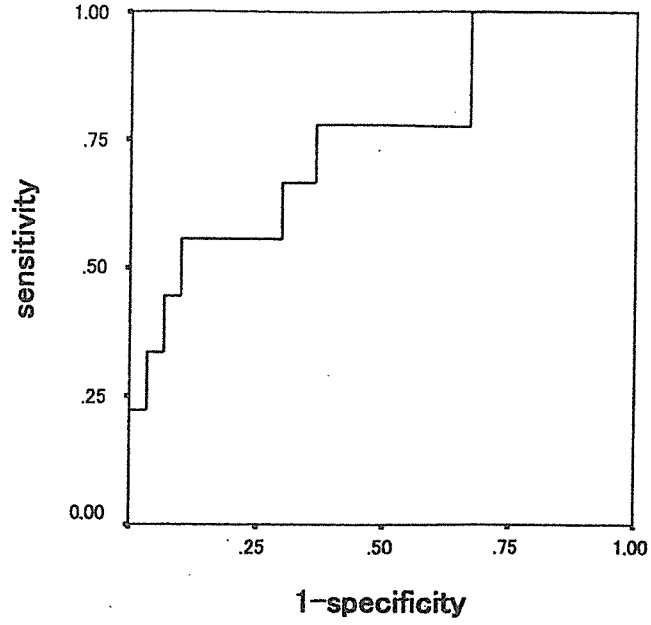

Fig. 4. Receiver operating characteristics (ROC) analysis of postoperative $sPLA_2$-IIA levels, measured on postoperative day 5, for the diagnosis of postoperative infection within 7 days. The area under the curve of the ROC curve was 0.756

The $sPLA_2$-IIA Production in Whole Blood After Esophagectomy

$sPLA_2$-IIA production in whole blood was examined after esophagectomy in 16 patients. Stimulation of whole blood specimens with LPS did not induce $sPLA_2$-IIA production at any time of measurement (Fig. 3).

ROC Curve

ROC analysis using the $sPLA_2$-IIA values on POD 5 to determine if there was a postoperative infectious complication revealed an area under the curve of 0.756 (95% confidence interval 0.568–0.943) (Fig. 4).

Discussion

Soluble PLA_2-IIA is an enzyme that catalyzes the degradation of arachidonic acid. It plays a role in inflammatory reactions and organ failure, particularly acute lung injury,[5–8] and also serves as a bactericidal mediator in the presence of infection.[11] We examined the changes in the $sPLA_2$-IIA levels induced by surgical stress, and the time course of changes after the onset of postoperative infection.

This study yielded the following findings:

1. The blood $sPLA_2$-IIA level increased as the surgical stress became greater in the absence of postoperative complications, but decreased to baseline levels after POD 3 in patients without infection
2. The peak blood level of $sPLA_2$-IIA was reached later than the peak blood levels of cytokines
3. Stimulating circulating blood cells with LPS did not induce $sPLA_2$-IIA production
4. In the presence of postoperative infection, the blood $sPLA_2$-IIA levels were increased, but the blood cytokine levels were not

Moreover, $sPLA_2$-IIA increased to a significantly higher level after esophagectomy than after colectomy, which suggests that in the absence of postoperative complications, the increase in the blood $sPLA_2$-IIA level is correlated with the degree of surgical stress.

Local responses to surgical stress differ remarkably from the systemic responses. In general, local inflammatory mediator levels are high, and this local inflammatory response predominates over local anti-inflammatory responses. After esophagectomy, the IL-8 level in bronchoalveolar lavage fluid was several hundred-fold higher than the blood IL-8 level.[16] On the other hand, the anti-inflammatory systemic responses predominate to suppress the inflammatory responses, thus suppressing the immune functions.[17]

Abe et al.[15] reported that the $sPLA_2$-IIA level in the ascitic fluid peaked 12 h after gastrectomy, earlier than when the serum $sPLA_2$-IIA level peaked. At that time of measurement, the $sPLA_2$-IIA level in the ascitic fluid was not correlated with that in the serum. Thus, they concluded that the serum $sPLA_2$-IIA level did not origi-

nate as a spillover of the $sPLA_2$-IIA released at the local site of stress. In the present study, stimulation of peripheral blood cells with LPS did not induce the production of $sPLA_2$-IIA. This supports the report by Abe et al. that although the neutrophils in ascitic fluid expressed $sPLA_2$-IIA mRNA and produced $sPLA_2$-IIA, peripheral blood neutrophils did not express $sPLA_2$-IIA mRNA.[15] These findings suggest that the postoperative $sPLA_2$-IIA level in the peripheral blood does not reflect the local inflammatory responses or the responses of circulating blood cells. Considering the previous findings that the liver is also a source of $sPLA_2$-IIA,[4] the increase in the $sPLA_2$-IIA level in the blood under surgical stress seems to have a significance equivalent to that of the acute-phase reactants produced by the liver. Tumor necrosis factor, IL-1, and IL-6 induce $sPLA_2$-IIA synthesis and secretion in various cells.[3] It is generally recognized that measurement of the cytokine-producing capacity in LPS-stimulated whole blood provides an estimate of the patient's immune capacity.[17] Although LPS stimulation in the blood of patients with esophageal cancer results in the production of many cytokines, it does not seem to result in the production of $sPLA_2$-IIA. The detailed mechanism of production and the cellular source of $sPLA_2$-IIA needs to be studied further.

In the absence of postoperative infection, the blood $sPLA_2$-IIA level gradually increased until POD 3, and thereafter returned to the baseline. However, in patients complicated by postoperative infection, the blood $sPLA_2$-IIA level continued to increase even after POD 3. It is well known that for several days after major surgery, the immune responses to infection are reduced. During this period, called the "immunoparalysis" period,[17] the levels of inflammatory cytokines in the peripheral blood do not increase, even in the presence of infection. However, in this study we found that the $sPLA_2$-IIA level did increase in response to infection. Since there was no correlation between organ failure and the serum $sPLA_2$-IIA level in the postoperative period (data not shown), we cannot rule out the possibility that the increased blood $sPLA_2$-IIA level serves as a favorable host defense response to infection. However, considering the finding of previous reports, excessive production of $sPLA_2$-IIA may cause tissue injury when a serious infection causes more stress than the surgery. Several investigators have reported that the detrimental activities of $sPLA_2$-IIA induce organ failure, especially ARDS.[5-8]

The $sPLA_2$-IIA inhibitors may be effective against ARDS if infection is absent or under control, as in the animal model of pulmonary edema induced by oleic acid. However, the precise antibacterial functions of $sPLA_2$-IIA under immunocompromised conditions are still unclear. Thus, the possible diverse roles played by $sPLA_2$-IIA under different conditions should be investigated.

In conclusion, the results of this study suggest that measuring serum $sPLA_2$-IIA levels may assist in the early diagnosis of postoperative infections, even in patients with systemic inflammation in response to a highly invasive surgical procedure. Further investigation is needed to establish the diagnostic value of measuring the serum $sPLA_2$-IIA level.

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ORIGINAL ARTICLE

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Multicenter prospective study of procalcitonin as an indicator of sepsis

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Abstract The clinical significance of serum procalcitonin (PCT) for discriminating between bacterial infectious disease and nonbacterial infectious disease (such as systemic inflammatory response syndrome (SIRS)), was compared with the significance of endotoxin, β-D-glucan, interleukin (IL)-6, and C-reactive protein (CRP) in a multicenter prospective study. The concentrations of PCT in patients with systemic bacterial infection and those with localized bacterial infection were significantly higher than the concentrations in patients with nonbacterial infection or noninfectious diseases. In addition, PCT, endotoxin, IL-6, and CRP concentrations were significantly higher in patients with bacterial infectious disease than in those with nonbacterial infectious disease ($P < 0.001$, $P < 0.005$, $P < 0.001$, and $P < 0.001$, respectively). The cutoff value of PCT for the discrimination of bacterial and nonbacterial infectious diseases was determined to be 0.5 ng/ml, which was associated with a sensitivity of 64.4% and specificity of 86.0%. Areas under the receiver operating characteristic curves (POCs) were 0.84 for PCT, 0.60 for endotoxin, 0.77 for IL-6, and 0.78 for CRP in the combined group of patients with bacterial infectious disease and those with nonbacterial infectious disease, and the area under the ROC for PCT was significantly higher than that for endotoxin ($P < 0.001$). In patients diagnosed with bacteremia based on clinical findings, the positive rate of diagnosis with PCT was 70.2%, while that of blood culture was 42.6%. PCT is thus essential for discriminating bacterial infection from SIRS, and is superior in this respect to conventional serum markers and blood culture.

Key words Procalcitonin · Bacterial infection · Sepsis · SIRS

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Introduction

Although the monitoring of parameters of infectious diseases, such as body temperature, heart rate, respiratory rate, leukocyte count, and C-reactive protein (CRP) concentration has been routinely performed, these parameters often provide information that is inadequate for the discrimination of bacterial and nonbacterial infections and for diagnosis. Blood culture is a very specific and confirmatory method for the detection of septicemia, but test results are not available within 24 h; physicians must, in the meantime, decide whether the patient needs antibiotic treatment. In addition, the sensitivity of blood culture is low.[1] For patients with a slight possibility of bacterial infection, physicians tend to prescribe antibiotics so as not to miss severe infections such as septicemia. A rapid and reliable test to rule out bacterial infections would thus be very useful for knowing the suitable indications for antibiotics, and this could also have an impact on both the length of hospital stay and total medical costs.[2,3]

Procalcitonin (PCT) is a 13-kDa 116-amino acid prohormone of calcitonin. Under physiological conditions, hormonally active calcitonin is produced and secreted in the C cells of the thyroid gland after the specific intracellular proteolytic processing of the prohormone PCT. Calcitonin is secreted into the circulation, and its plasma half-life is only a few minutes. In 1993, Assicot et al.[4] reported increased PCT concentrations in patients with sepsis and infection. Further clinical studies indicated that bacterial inflammation and sepsis, but not viral infections or autoimmune disorders, could induce high concentrations of serum PCT.[5–8] The origin of PCT in these conditions is thought to be extrathyroidal.[4] In severe bacterial infections or sepsis, specific proteolysis fails, and high concentrations of the precursor protein of PCT accumulate in plasma.[9] Nylen et al.[10] suggested a biological role of PCT as a mediator of inflammation. PCT has a half-life of approximately 24–30 h in the circulation.[9] However, all of the reports described above originate from Europe, and there could be ethnic differences between European populations and the Japanese population. Therefore, a multicenter, prospective study was carried out in Japan to assess the diagnostic efficiency of PCT in distinguishing bacterial infection from other infectious diseases, systemic inflammatory response syndrome (SIRS), and related conditions.

Subjects, materials, and methods

Subjects

Serum specimens were collected prospectively by seven Japanese hospitals from October 2000 through December 2001. All patients gave their informed consent according to the regulations of each hospital. Two hundred and forty-five patients diagnosed with infectious diseases, suspected of having infectious diseases, and diagnosed with noninfectious diseases were enrolled in the study, with the addition of 20 healthy volunteers. Inclusion criteria were more than one of the following results: (1) body temperature less than 36°C or more than 37.5°C; (2) white blood cell count less than 4000 or more than 9000/mm^3; and (3) elevated CRP greater than 0.3 mg/dl. The patients were divided into five groups by the results of blood culture.

Systemic bacterial infection group

In this group, at least one blood culture was positive for pathogenic bacteria. A causative bacterium was identified by the physicians in charge. Coagulase-negative *Staphylococcus* spp. and *Bacillus* spp. may or may not have been considered as pathogenic bacteria, depending on the judgment of physicians in charge.

Localized bacterial infection group

In this group, there was clinical evidence of local infection, defined as positive culture(s) of nonblood specimens, such as spinal fluid, ascites, pleural fluid, sputum, bronchoalveolar lavage, urine, and pus, and/or the presence of a clinical focus of infection, such as fecal peritonitis, a wound with purulent discharge, or pneumonia. Also included in this group were patients with positive serological antibody tests for *Mycoplasma*, *Chlamydia*, and *Streptolysin*.

Nonbacterial infection group

In this group, viral or fungal infection was diagnosed by cultures or serum antibody titers.

Suspected bacterial infection group

In this group, the physician in charge suspected a bacterial infection but could not confirm it by laboratory testing. This group was not included in the statistical analysis.

Noninfectious disease group

In this group, blood culture or other specimens were negative. In addition, there was no clear clinical evidence of bacterial infection and the physician in charge did not suspect it.

The healthy volunteers were not included in the statistical analysis.

The average, median, and range of age in the 176 patients in the four groups shown in Table 1 (102 men and 74 women) were 37.3, 47.5, and 0.1–92 years, respectively. The numbers of patients with systemic bacterial infection, localized bacterial infection, nonbacterial infection, suspected bacterial infection, and noninfectious disease, and the healthy volunteers were 20, 70, 26, 69, 60, and 20, respectively. Data analysis was performed for the groups with systemic bacterial infection, localized bacterial infection, nonbacterial infection, and noninfectious disease. Table 1 summarizes the underlying diseases for these four groups.

PCT assay

Serum PCT concentrations were measured by immunoluminometric assay (LUMI test PCT; Brahms Diagnostica, Berlin, Germany).[11] The luminometer used was an Autolumat LB953 (Berthord, Bad Wildbad, Germany).

Serological assays

Endotoxin and (1–3)-β-D-glucan (β-D-glucan) were measured by kinetic turbidimetric *Limulus* tests; the Wako Endotoxin-single test, and Wako β-Glucan test (Wako Pure Chemical Industries, Osaka, Japan).[12–14] The serum interleukin (IL)-6 concentration was determined by enzyme-linked immunosorbert assay (ELISA; human IL-6 ANALYZA Immunoassay Kit; TECHNE, Minneapolis, MN, USA). Other conventional markers were tested and blood cultures were performed at each hospital using commercially available kits and instruments.

Table 1. Patients' underlying diseases

Underlying disease		PCT value (ng/ml)			
		Systemic and localized bacterial infection groups combined		Nonbacterial infection and Non-infectious group combined	
	n	*n*	Range	*n*	Range
Circulatory disease	38	10	0–10.08	28	0–1.70
Respiratory disease	10	5	0–21.04	5	0–0.42
Gastroenterological disease	14	11	0.60–373.46	3	0–0.91
Hepatobiliary disease	7	4	0–205.79	3	0–0.41
Renal disease	3	2	2.02–212.18	1	0.33
Neurological disease	3	3	0–7.98	0	–
Diabetes mellitus	7	6	0.34–82.29	1	0
Malignant disease	6	3	0.42–1.73	3	0
Trauma	15	10	0–82.48	5	0–0.38
Burns	7	7	0–34.53	0	–
Kawasaki disease	12	1	4.89	11	0–1.91
Others	17	7	0–20.59	10	0–8.72
None	37	21	0–93.29	16	0–3.67
Total	176	90		86	

Statistical analysis

The statistical significances of differences were determined using the Mann-Whitney *U*-test and receiver operating characteristic (ROC) analysis, carried out with StatFlex Ver. 5.0 (AHTEKKU, Osaka, Japan). *P* values of less than 0.05 were considered significant.

Results

Serum PCT, endotoxin, β-D-glucan, IL-6, and CRP concentrations in patient groups

The patterns of distribution of PCT, endotoxin, IL-6, and CRP concentrations in the systemic bacterial infection group, localized bacterial infection group, nonbacterial infection group, and noninfectious disease group are shown in Fig. 1. The median ages of the patients with nonbacterial and suspected bacterial infections were lower than those of the other groups (Table 2). Previous studies have reported that there were no differences in PCT values by age,[15,16] with the exception of neonates.[17] Table 3 summarizes serum concentrations of PCT, endotoxin, IL-6, and CRP in patients in the five groups and in the healthy volunteers. Table 4 shows statistical analysis using the criteria for the diseases. Serum PCT concentrations were significantly higher in both the systemic bacterial infection and localized bacterial infection groups than in both the nonbacterial infection and noninfectious disease groups ($P < 0.05$). Serum PCT concentrations did not differ significantly between the systemic bacterial infection and localized bacterial infection groups ($P = 0.770$). The systemic bacterial infection and localized bacterial infection groups were therefore combined as the bacterial infectious disease group. In the same fashion, no significant difference in serum PCT concentration was observed between the nonbacterial infection group and the noninfectious disease groups ($P = 0.174$), and the nonbacterial infection and noninfectious disease groups were therefore combined as the nonbacterial infectious disease group. The patterns of distribution of PCT, endotoxin, IL-6, and CRP concentrations for these two groups are shown in Fig. 2. Serum PCT, endotoxin, IL-6, and CRP concentrations were significantly higher in the bacterial infectious disease group than in the nonbacterial infectious disease group ($P < 0.001$, $P < 0.005$, $P < 0.001$, and $P < 0.001$).

Cutoff value and diagnostic accuracy of serum PCT concentration

Table 5 shows the sensitivity, specificity, positive predictive values, and negative predictive values for the serum markers. When 0.5 ng/ml was used as the cutoff value for PCT, the sensitivity, specificity, positive predictive value, and negative predictive value were 64.4%, 86.0%, 82.9%, and 69.8%, respectively. Figure 3 presents the receiver operating characteristic curves of four serum markers used to discriminate the bacterial infectious disease group from the nonbacterial infectious disease group. The area under the receiver operating characteristic curve (AUC) for PCT was 0.84, which was significantly higher than that for endotoxin (0.60; $P < 0.001$), and tended to be higher than those for IL-6 (0.77; $P = 0.22$) and CRP (0.78; $P = 0.32$).

Sensitivities of serum markers for the type of infection

Table 6 shows the sensitivities of PCT, endotoxin, β-D-glucan, IL-6, and CRP with regard to the type of infection determined by culture. The difference in PCT serum con-

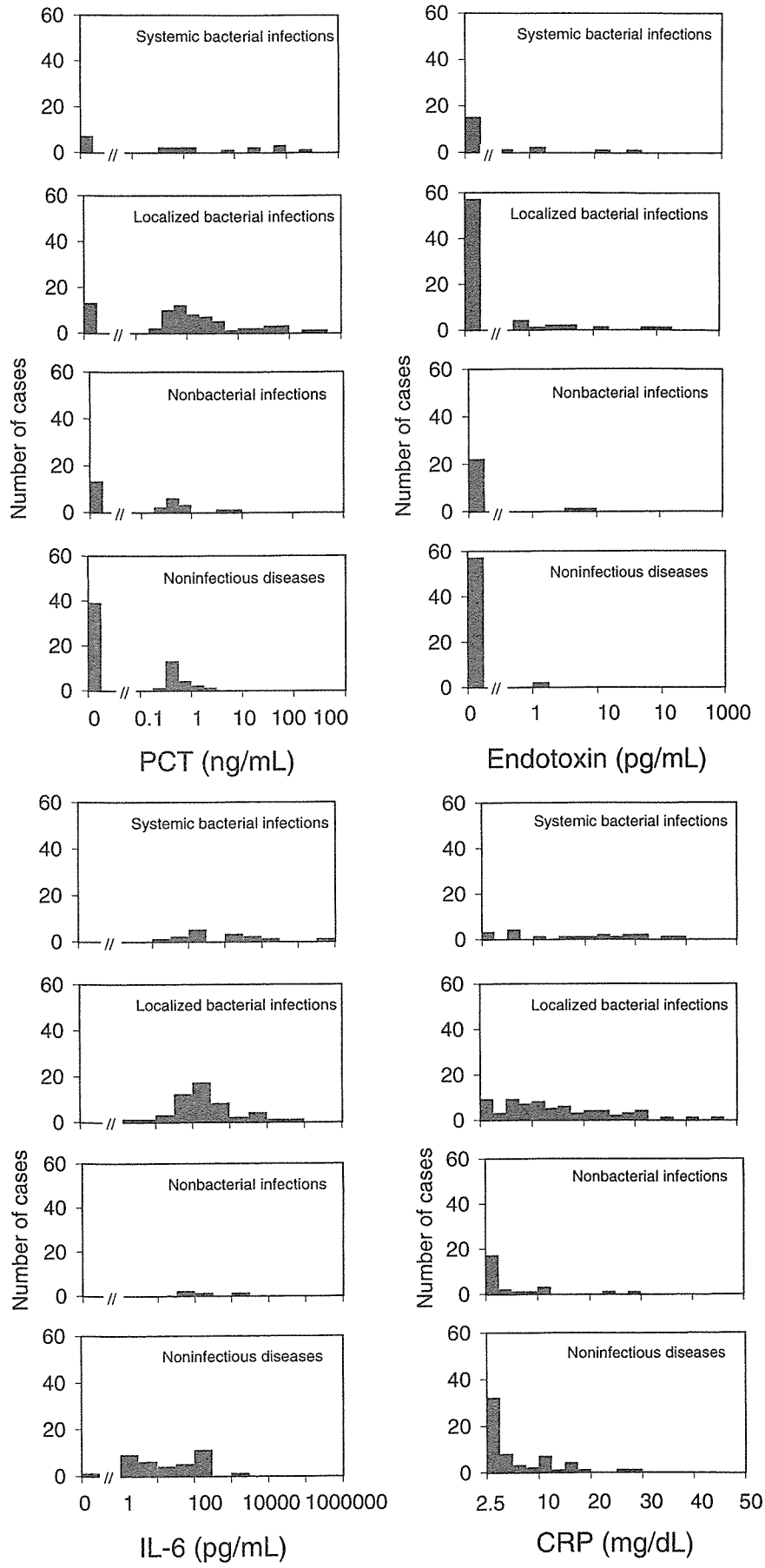

Fig. 1. Distribution patterns of procalcitonin (*PCT*), endotoxin, interleukin-6 (*IL-6*) and C-reactive protein (*CRP*) in patients with systemic bacterial infections, localized bacterial infections, nonbacterial infections, and noninfectious diseases

Table 2. Patient demographics

	n	Sex	Age (years)
		Male/Female	Median (range)
Systemic bacterial infection	20	7/13	58 (1–81)
Localized bacterial infection	70	44/26	53 (0.1–92)
Nonbacterial infection	26	13/13	4 (0.1–72)
Suspected bacterial infection	69	45/24	5 (0.1–85)
Noninfectious disease	60	38/22	48 (0.1–87)
Healthy volunteers	20	16/4	22 (22–27)

Table 3. Serum concentrations of PCT, endotoxin, IL-6 and CRP in patients with systemic bacterial infection, localized bacterial infection, nonbacterial infection, suspected bacterial infection, and noninfectious diseases, and healthy volunteers

	n	PCT (ng/ml)	Endotoxin (pg/ml)	IL-6 (pg/ml)	CRP (mg/dl)
		Median (range)	Median (range)	Median (range)	Median (range)
Systemic bacterial infection	20	0.66 (0.00–212.18)	0.0 (0.0–39.4)	199.5 (22.3–592000.0)	20.0 (0.1–38.2)
Localized bacterial infection	70	0.94 (0.00–373.46)	0.0 (0.0–135.4)	141.2 (1.6–38922.0)	11.9 (0.2–46.7)
Nonbacterial infection	26	0.16 (0.00–8.72)	0.0 (0.0–7.0)	152.6 (54.3–2550.0)	1.9 (0.3–28.4)
Suspected bacterial infection	69	0.38 (0.00–85.93)	0.0 (0.0–29.1)	17.1 (10.3–1086.0)	2.5 (0.1–26.8)
Noninfectious disease	60	0.00 (0.00–1.91)	0.0 (0.0–1.3)	17.1 (0.0–1350.0)	2.1 (0.0–28.1)
Healthy volunteers	20	0.00 (0.00–0.00)	0.0 (0.0–0.6)	1.8 (1.5–4.5)	0.1 (0.0–0.1)

Table 4. Statistical analysis according to the disease criteria

	p value			
	PCT	Endotoxin	IL-6	CRP
Systemic bacterial infection vs localized bacterial infection	0.770	0.469	0.131	0.244
Systemic bacterial infection vs nonbacterial infection	0.026	0.149	0.317	<0.001
Systemic bacterial infection vs noninfectious disease	<0.001	0.004	<0.001	<0.001
Localized bacterial infection vs nonbacterial infection	<0.001	0.323	0.766	<0.001
Localized bacterial infection vs noninfectious disease	<0.001	0.011	<0.001	<0.001
Nonbacterial infection vs noninfectious disease	0.174	0.317	0.104	0.756

centrations between Gram-negative and Gram-positive bacterial infections was not significant (13.79 ± 28.18 ng/ml for Gram-negative and 9.91 ± 35.20 ng/ml for Gram-positive bacterial infections; $P = 0.673$). The sensitivity of PCT for mixed Gram-negative and Gram-positive bacterial infections was 64.3% (9/14 cases). The sensitivities of PCT and endotoxin for Gram-negative bacterial infections in systemic infections were 100% (3/3) and 67% (2/3), respectively. On the other hand, the sensitivities of PCT and endotoxin for localized Gram-negative bacterial infections were 50% (6/12) and 0% (0/12), respectively. In a patient with confirmed fungal infection, the PCT result was negative, below the cutoff value. Four of 24 samples from patients with viral infections (16.7%) exhibited PCT concentrations exceeding the cutoff value. One patient with malaria showed a high PCT concentration, of 8.7 ng/ml.

Sensitivity of serum PCT compared with blood culture

The sensitivities of serum PCT and blood culture were compared in the combined systemic bacterial infection group and the localized bacterial infection group. The sensitivity of PCT was 70.2% (33/47 cases) in this combined group, but it was 42.6% (20/47 cases) for blood culture.

Discussion

Sepsis can be difficult to distinguish from other, noninfectious, conditions in critically ill patients admitted with clinical signs and symptoms of various acute inflammatory diseases. This issue is of paramount importance, given that therapies and outcomes differ greatly between patients with and those without bacterial sepsis. Blood culture is the most reliable method of detecting bacterial infections. However, more than 3 days is required to obtain results, and the positive detection rate is low. Although CRP and IL-6 have been suggested to be good indicators of sepsis, elevated CRP and IL-6 concentrations can also be found following surgical procedures and in patients with nonbacterial or noninfectious inflammation alone. Thus, there is an unmet need for clinical tools that distinguish bacterial infections from other inflammatory diseases.

The diagnostic and prognostic importance of PCT in severe inflammatory diseases was first reported for a series of patients with burns, in 1992.[18] Serum PCT values were less than 0.1 ng/ml in healthy individuals, but were markedly increased, mostly as a result of induced extrathyroidal production, in patients with severe infection. However, the roles of PCT and the origin of its production, as well as the

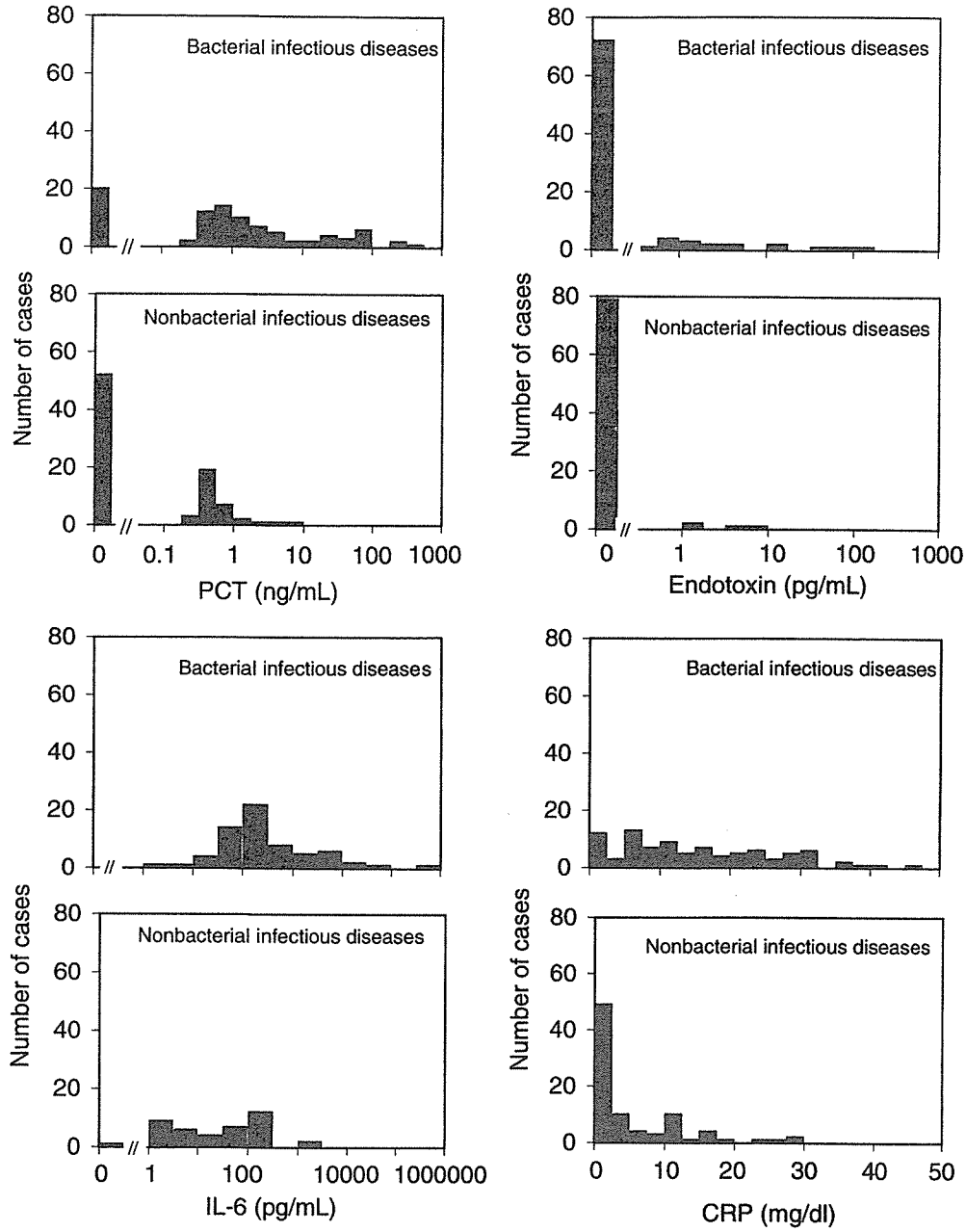

Fig. 2. Distribution patterns of PCT, endotoxin, IL-6, and CRP in patients with bacterial infectious diseases and those with nonbacterial infectious diseases

Table 5. Sensitivity, specificity, positive predictive value and negative predictive value of PCT, endotoxin, IL-6, and CRP in patients with bacterial infectious diseases and those with nonbacterial infectious diseases

	Cutoff value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PCT	0.5 ng/ml	64.4% (58/90)	86.0% (74/86)	82.9% (58/70)	69.8% (74/106)
PCT	2.0 ng/ml	34.4% (31/90)	97.7% (84/86)	93.9% (31/33)	58.7% (84/143)
Endotoxin	1.0 pg/ml	14.6% (13/89)	95.2% (79/83)	76.5% (13/17)	51.0% (79/155)
IL-6	10 pg/ml	96.9% (63/65)	39.0% (16/41)	71.6% (63/88)	88.9% (16/18)
IL-6	100 pg/ml	70.8% (46/65)	65.9% (27/41)	76.7% (46/60)	58.7% (27/46)
CRP	0.3 mg/dl	97.8% (88/90)	9.3% (8/86)	53.0% (88/166)	80.0% (8/10)
CRP	5.0 mg/dl	83.3% (75/90)	68.6% (59/86)	73.5% (75/102)	79.7% (59/74)

mechanism underlying PCT induction, are still not well known. Recent findings suggest that sources of PCT may include hepatic cells and monocytes/macrophages.[19,20] PCT is consistently increased after endotoxin injection, suggesting an association of endotoxin with septic shock and high PCT serum concentration.[21] Tumor necrosis factor (TNF) and IL-6 concentrations peaked before the appearance of PCT, suggesting that proinflammatory cytokines may play a