Table 1. Patient characteristics

	Group 1 (non-infectious, non-SIRS)	Group 2 (infectious, non-SIRS)	Group 3 (non-infectious, SIRS)	Group 4 (infectious, SIRS)
No. of patients	11	4	15	20
Age (years)	53.5 (range, 19–87)	49.5 (range, 25–90)	60.6 (range, 39–89)	63.9 (range, 22–88)
Sex: male/female	8/3	3/1	9/6	11/9
Initial vital signs, mean				
Body temperature (°C)	36.1 ± 0.7	37.4 ± 0.4	37.1 ± 0.4	39.0 ± 0.3
Pulse (beats/min)	81 ± 6	93 ± 6	92 ± 6	106 ± 5
Respiratory rate (breaths/min)	17 ± 2	18 ± 0	21 ± 1	27 ± 2
Initial blood tests				
WBC count ($\times 10^9$/l)	7.0 ± 0.5	11.5 ± 2.2	9.2 ± 1.3	10.7 ± 2.0
CRP (mg/dl)	1.29 ± 0.98	12.85 ± 10.62	1.67 ± 1.11	10.79 ± 3.02
$PaCO_2$ (Torr)	38.8 ± 1.5	Not available	34.1 ± 2.9	34.7 ± 3.0
Initial diagnosis				
Respiratory tract infection		2		7
Peritonitis		1		3
Urinary tract infection				2
Soft tissue infection				2
Gastrointestinal tract infection		1		2
Retroperitoneal abscess				2
Trauma	2		2	
Accidental hypothermia			1	
Drug intoxication (amphetamine)			1	
Neurological disease	7		7	
Non-infectious acute gastroenteritis	1		3	
Others	1		1	2
Outcome at discharge				
Survived	7	4	13	17

SIRS, systemic inflammatory response syndrome

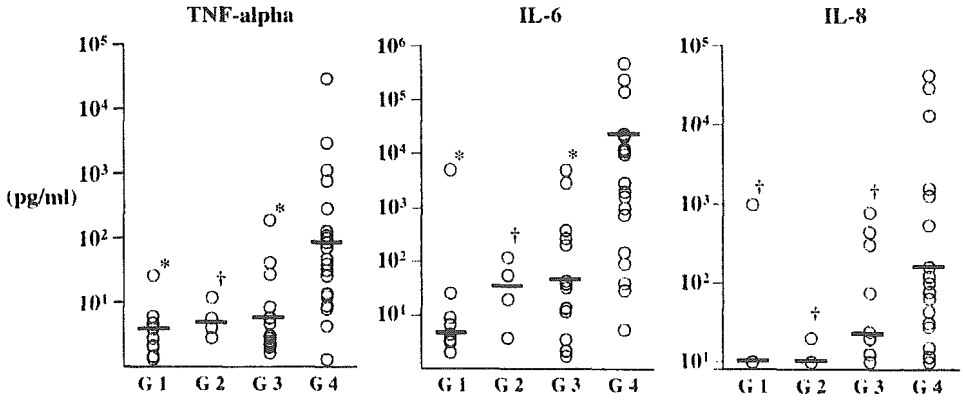

Fig. 1. Serum tumor necrosis factor-alpha (*TNF-alpha*), interleukin-6 (*IL-6*), and IL-8 levels in patients with acute illness transferred to our emergency department (ED) by ambulance. Blood was drawn from 50 patients assessed for clinical diagnosis and by Bone's criteria for systemic inflammatory response syndrome (SIRS) at the ED. Enrolled patients were divided into four groups (*G1*, no infection, without SIRS; *G2*, infection, without SIRS; *G3*, no infection, with SIRS; *G4*, infection, with SIRS). Data values are shown on a log scale. *Bars* represent medians of the groups. * $P < 0.005$; † $P < 0.05$, compared with group 4 by Fisher's protected least significant difference (PLSD) test

ence of infection, presence of SIRS, serum TB levels, and serum ALT levels. High plasma HGF was correlated with the presence of infection (OR, 54.1; 95% CI, 3.1 – 936.9; $P = 0.0061$) and serum TB level (OR, 3.9; CI, 1.01 – 15.2; $P = 0.048$), but not with other parameters. There were no correlations between plasma HGF levels and the bacterial species isolated (data not shown).

Discussion

In the present study, we examined plasma levels of HGF, as well as the levels of other proinflammatory and anti-inflammatory cytokines, in patients who visited the Keio University Hospital ED. We found that plasma HGF levels were elevated in patients with infection, especially sepsis, but the correlation with other cytokines seemed comparatively low. On further analysis of the patients, we found that HGF levels were affected by liver function.

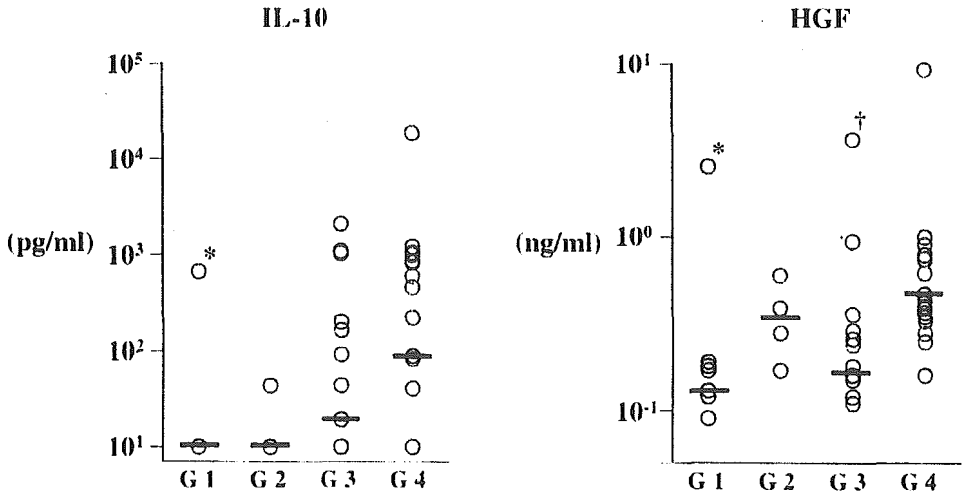

Fig. 2. Serum IL-10 and hepatocyte growth factor (*HGF*) levels in patients with acute illness transferred to our emergency department (ED) by ambulance. Blood was drawn from 50 patients assessed for clinical diagnosis and by Bone's criteria for SIRS at the ED. Enrolled patients were divided into four groups (*G1*, no infection, without SIRS; *G2*, infection, without SIRS; *G3*, no infection, with SIRS; *G4*, infection, with SIRS). Data values are shown on a log scale. *Bars* represent medians of the groups. * $P < 0.005$; † $P < 0.05$, compared with group 4 by Fisher's PLSD test

Table 2. Correlations between cytokine levels in 50 patients

	Log (TNF)	Log (IL-6)	Log (IL-8)	Log (IL-10)
Log (HGF)	0.436 ($P < 0.001$)	0.592 ($P < 0.0001$)	0.531 ($P < 0.0001$)	0.615 ($P < 0.0001$)
Log (TNF)	–	0.853 ($P < 0.0001$)	0.828 ($P < 0.0001$)	0.625 ($P < 0.0001$)
Log (IL-6)	–	–	0.856 ($P < 0.0001$)	0.794 ($P < 0.0001$)
Log (IL-8)	–	–	–	0.783 ($P < 0.0001$)

Pearson's correlation coefficients, with P values in parentheses

HGF, initially identified as a potent mitogen for hepatocytes, is now well known for its protective and regenerative effects in injured tissues, such as those in the liver and lungs.[9,10] In previous reports, high plasma HGF has been reported in patients with SIRS after surgery,[6] especially hepatectomy,[11] and in patients with infectious diseases, including pneumonia.[7] In the present study, we found that plasma HGF was elevated in patients complicated with infection, especially sepsis, but that the plasma HGF levels were regulated somewhat independently of inflammatory stimuli. In conjunction with the known in vitro and in vivo functions of HGF, we speculated that HGF may be produced for tissue protection and regeneration after tissue injury. We also found that plasma HGF levels were correlated not with serum ALT, but with serum TB. The discrepancy between our findings and the past reports may be derived from differences in the study populations; namely, differences in hepatic and perihepatic operative procedures.[6,11]

In the present study, the order of the plasma levels of the proinflammatory and anti-inflammatory cytokines examined was quite similar in the four patient groups. Namely, the cytokine levels were highest in the septic group (G4), followed by the non-infectious SIRS group (G3), and the non-SIRS groups (G1 and G2). However, it is necessary to further verify our current results by enrolling a larger number of patients, especially into G2. Several reports have demonstrated strong correlations between plasma TNF alpha and IL-10 levels in septic patients,[12,13] and higher mortalities have been reported in patients with a high TNF alpha/IL-10 ratio[14,15] and a high IL-6/IL-10 ratio[16] with sepsis, as well as in patients with elevated plasma HGF with pneumonia.[7] However, neither the TNF alpha/IL-10 ratio nor the IL-6/IL-10 ratio, nor HGF were associated with poor outcomes in the current study (data not shown). The reason for this is unclear, but patients' outcomes are affected by diverse parameters, including age, comorbidity, and nutritional and immunological conditions; also, the number of patients examined here may have been too small to find correlations. In addition, blood cytokine production is dynamically regulated; so sequential measurement of plasma cytokine levels could be necessary to clarify the correlations.

Acknowledgments This study was partly supported by a Grant-in-Aid from the Ministry of Health, Labour, and Welfare of Japan (14370364).

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Long-Term Survival of Japanese Patients Transported to an Emergency Department Because of Syncope

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Study objective: Cardiovascular disease mortality is affected by ethnic differences and is lower in Japan than in Western countries. Although patients with cardiac syncope have significantly higher mortality than patients with noncardiac syncope in Western countries, no such phenomenon has been described in Japan. The aim of this study is to clarify the long-term mortality of patients with syncope who are brought to an emergency department (ED) in Japan.

Methods: This retrospective observational study was conducted on patients treated in the ED of Keio University Hospital in Tokyo. Nine hundred twelve consecutive patients who presented with syncope were identified. The patients were classified into 2 groups according to the cause of syncope: cardiac syncope and noncardiac syncope. Follow-up information about mortality was obtained from mailed questionnaires and medical records. Mortality data were analyzed using the actuarial life-table method and a Cox proportional hazards model.

Results: Follow-up information was obtained for 715 patients. The median follow-up period was 38 months, during which 63 patients died. At 5 years, the 23.1% (95% confidence interval [CI] 12.7% to 33.4%) mortality of the patients with cardiac syncope was significantly higher than the 8.2% (95% CI 5.5% to 10.9%) mortality of the patients with noncardiac syncope ($P<.0001$). The incidence of cardiac death among the patients with cardiac syncope was 17.2% (95% CI 7.8% to 26.5%) compared with 0.9% (95% CI 0% to 1.8%) in the noncardiac syncope group ($P<.0001$). Cardiac syncope was an independent predictor of overall mortality and cardiac mortality (relative risk 2.81 [95% CI 1.53 to 5.16], 18.74 [95% CI 5.90 to 59.52]).

Conclusion: Cardiac syncope is associated with higher mortality than noncardiac syncope in this Japanese patient population.

[*Ann Emerg Med.* 2004;44:215-221.]

0196-0644/$30.00

doi:10.1016/j.annemergmed.2004.02.036

Editor's Capsule Summary

What is already known on this topic

The relationship between the cause of syncope and mortality rates has only been reported in US and European societies. The incidence and patterns of cardiac disease in other countries may differ.

What question this study addressed

This study examined whether cardiac syncope in Japan has a higher rate of mortality than noncardiac syncope, as has been observed in Western countries.

What this study adds to our knowledge

Of 715 patients studied, cardiac syncope was associated with a higher mortality rate (12.9%) than noncardiac syncope in Japan. The mortality rate, however, appears to be lower than in Western countries.

How this might change clinical practice

This study reinforces the importance of attempting to identify a potential cardiac source of syncope in the emergency setting and confirms that this predicts higher mortality in a country with a different lifestyle and incidence of cardiac disease.

INTRODUCTION

Syncope is a common medical problem and accounts for 3% to 5% of all emergency department (ED) visits. The differential diagnosis is complex and extends from benign problems to severe life-threatening illness.[1-7] The discovery of cardiovascular disease during the evaluation of syncope has emerged as the most important factor for predicting the risk of death. Prognostic studies in Western countries have shown that patients with cardiac syncope have consistently higher mortality than patients with noncardiac syncope or syncope of unknown etiology.[2,4-12]

The mortality and prevalence of cardiovascular disease are affected by ethnic and geographic differences and are lower in Asian countries, including Japan, than in Western countries.[13-18] Previous studies have indicated an approximately sixfold higher coronary heart disease death rate in the United States than in Japan.[14] Consequently, the prevalence and prognosis of cardiac syncope in Asian countries may differ from its prevalence and prognosis in Western countries. However, no information on syncope in Asian countries has been reported.

The purpose of this study is to clarify long-term survival in terms of the overall and cardiac mortality of patients with syncope presenting to an ED in Japan.

MATERIALS AND METHODS

Syncope was defined as a sudden, transient loss of consciousness associated with inability to maintain postural tone that was not associated with a seizure, vertigo, dizziness, coma, shock, or other altered states of consciousness.[1,3,5-7] Patients who required pharmacologic or electrical cardioversion during their initial visit were not included. The present study was approved by the ethics committee of the ED of Keio University Hospital, Tokyo, Japan.

Patients brought to the ED of Keio University Hospital in Tokyo by ambulance with symptoms compatible with syncope between August 1988 and December 1997 were retrospectively identified for this study.

Table 1.
Characteristics of patients with syncope.

		Cause of Syncope			Follow-up Information	
			Noncardiac			
Characteristic	**Total (n=715)**	**Cardiac (n=71)**	**Total (n=644)**	**Unknown (n=329)**	**Dead (n=63)**	**Alive (n=652)**
Median age, y (range)	58 (10–91)	68 (20–91)	56 (10–91)	42 (10–91)	77 (37–91)	51 (10–91)
Male sex, No. (%)	392 (54.8)	47 (66.2)	345 (53.6)	118 (35.9)	42 (66.7)	350 (53.7)
Medical history						
Syncope	281 (39.3)	19 (26.8)	262 (40.7)	94 (28.6)	22 (34.9)	259 (39.7)
Hypertension	186 (26.0)	23 (32.4)	163 (25.3)	58 (17.6)	21 (33.3)	165 (25.3)
Cardiovascular disease	102 (14.3)	36 (50.7)	66 (10.2)	13 (4.0)	19 (30.2)	83 (12.7)
Coronary heart disease	56 (7.8)	26 (36.6)	30 (4.7)	6 (1.8)	8 (12.7)	48 (7.4)
Diabetes mellitus	43 (6.0)	10 (14.1)	33 (5.1)	9 (2.7)	7 (11.1)	36 (5.5)
Stroke	35 (4.9)	8 (11.3)	27 (4.2)	12 (3.6)	8 (12.7)	27 (4.1)
Renal insufficiency	13 (1.8)	4 (5.6)	9 (1.4)	3 (0.9)	2 (3.2)	11 (1.7)
Neoplastic disease	22 (3.1)	5 (7.0)	17 (2.6)	4 (1.2)	5 (7.9)	17 (2.6)
Cardiac syncope	71 (9.9)	—	—	—	18 (28.6)	53 (8.1)

Patients underwent a basic evaluation in the ED, consisting of (1) a complete medical history and physical examination performed by emergency physicians; (2) a 12-lead ECG; (3) prolonged ECG monitoring at the bedside in selected patients or ambulatory ECG monitoring in patients with suspected cardiac cause of syncope; (4) a baseline laboratory evaluation, including a CBC count and measurements of electrolyte, blood urea nitrogen, creatinine, glucose, and cardiac biomarker levels; and (5) active standing test of blood pressure and pulse rate for 10 minutes to evaluate orthostatic intolerance, including vasovagal syncope or orthostatic hypotension.[19] An electroencephalogram and computed tomographic scans of the head were not part of the basic evaluation for these patients. Extensive consultations with neurologists and cardiologists were used in the evaluation of selected patients with syncope.

Follow-up information about mortality was obtained from mailed questionnaires filled out by the patients themselves or by their families and from their medical records. The cause of death was assigned on the basis of information obtained from the family and the patient's medical records. The following were specified as cardiac causes of death: atherosclerotic heart disease, including myocardial infarction and coronary artery disease; valvular heart disease; congestive heart failure; pulmonary hypertension; and congenital heart disease. Patients were considered to have died suddenly if unexpected death occurred within 24 hours of the onset of the symptoms.

The causes of syncope were classified into 2 groups: cardiac causes and noncardiac causes. Assignment of the cause to these groups was based on previous reports (Figure E1 available online at http://www.mosby.com/

Table 2.
Patient distribution according to cause of syncope.

Cause of Syncope	Patients, No. (%) (n=715)
Cardiac cause	71 (9.9)
Arrhythmias	32 (4.5)
Atrioventricular conduction system disease	10 (1.4)
Ventricular tachycardia	7 (1.0)
Atrial fibrillation	6 (0.8)
Prolonged QT interval	5 (0.7)
Sick sinus syndrome	4 (0.6)
Structural cardiac or cardiopulmonary disease	39 (5.5)
Myocardial infarction/ischemia	29 (4.1)
Pulmonary embolism	4 (0.6)
Noncardiac cause	644 (90.1)
Neurally mediated syncope	261 (36.5)
Vasovagal syncope	219 (30.6)
Situational syncope	21 (2.9)
Carotid sinus syncope	21 (2.9)
Orthostatic hypotension	153 (21.4)
Autonomic failure	22 (3.1)
Drugs and alcohol	110 (15.4)
Volume depletion	21 (2.9)
Unknown cause	230 (32.2)

Table 3.
Cause of death in 63 cases.

	Cause of Syncope			
		Noncardiac Syncope, No. (%)		
Cause of Death	Cardiac Syncope, No. (%) (n=18)	Total (n=45)	Unknown cause (n=14)	Total, No. (%) (n=63)
Cardiac death	13 (72.2)	5 (11.1)	1 (7.1)	18 (28.6)
Sudden death	6 (33.3)*	0	0	6 (9.5)
Heart failure	5 (27.8)	3 (6.7)	1 (7.1)	8 (12.7)
Acute myocardial infarction	1 (5.6)	2 (4.4)	0	3 (4.8)
Pulmonary embolism	1 (5.6)	0	0	1 (1.6)
Noncardiac death	4 (22.2)	34 (75.6)	10 (71.4)	38 (58.5)
Cancer	0	15 (33.3)	4 (28.6)	15 (23.8)
Pneumonia	0	4 (8.9)	1 (7.1)	4 (6.3)
Trauma	4 (22.2)	3 (6.7)	1 (7.1)	7 (11.1)
Stroke	0	3 (67)	2 (14.3)	3 (4.8)
Renal failure	0	3 (6.7)	1 (7.1)	3 (4.8)
Miscellaneous	0	6 (13.3)	1 (7.1)	6 (9.5)
Unidentified	1 (5.6)	6 (13.3)	3 (21.4)	7 (11.1)

*The diagnosis of the cause of syncope was ventricular tachycardia in 2 cases, prolonged QT in 1 case, hypertrophic myocardiopathy in 1 case, old myocardial infarction in 1 case, and angina in 1 case.

AnnEmergMed).[5,9,20,21] Then the patients were classified into 2 groups, cardiac syncope group and noncardiac syncope group.

The statistical analysis, including calculation of median values and ranges, was performed using Stat View 5.0J software (SAS, Inc., Cary, NC). Mortality data were analyzed by using actuarial life-table methods. The Mantel-Cox statistic was used to determine the statistical significance of differences between the groups. We used a Cox proportional hazards model with backward elimination procedure to identify multivariate predictors of 5-year mortality among age, sex, cardiac syncope, history of hypertension, diabetes, stroke, renal failure, neoplastic disease, ischemic heart disease, and arrhythmias.

RESULTS

Among the 26,198 patients brought to the ED by ambulance, 912 (3.5%) consecutive patients with a history consistent with syncope were eligible. In this study, patients were limited to those transported by ambulance because most walk-in patients in Japan visit outpatient clinics, not the ED. Of these 912 patients, 197 were excluded because of incomplete follow-up data. Of the 197 patients excluded from this analysis, 34 had incomplete diagnostic data in their medical records, 34 had missing patient records, and 129 had no follow-up data. The reason that follow-up was not obtained was inability to contact by mail or lack of a repeated visit to Keio University Hospital. The characteristics of the 715 (78%) remaining patients are shown in Table 1.

The patient distribution according to cause of syncope is shown in Table 2. The prevalence of cardiac syncope was 9.9%, whereas the most common cause of syncope was neurally mediated syncope.

The median follow-up period was 38 months (range 0 to 132 months; 6 patients died within 1 month). During the follow-up period, 63 patients died; 6 sudden cardiac deaths were observed (Table 3). Actuarial life-table analysis revealed a cumulative overall mortality of 9.9% (95% confidence interval [CI] 7.2% to 12.6%) at 5 years, with an overall incidence of cardiac death of 2.7% (95% CI 1.3 to 4.1%). At 5 years, the 23.1% (95% CI 12.7% to 33.4%) mortality of the cardiac syncope group was also significantly higher than the 8.2% (95% CI 5.5% to 10.9%) mortality in the noncardiac syncope group ($P<.0001$; Figure 1). At 5 years, the incidence of cardiac death in the cardiac syncope group was 17.2% (95% CI 7.8% to 26.5%) as opposed to 0.9% (95% CI 0% to 1.8%) in the noncardiac syncope group ($P<.0001$; Figure 2). The Cox proportional hazards analysis indicated cardiac cause of syncope as an independent predictor of overall and cardiac mortality (Table 4). In Table 5, the prevalence of arrythmias is described for this population.

Figure 1.

Comparison of overall mortality. Closed circles indicate the cumulative mortality of the patients with cardiac syncope, and open circles indicate that of the patients with noncardiac syncope. Overall mortality analyzed by the actuarial life-table method shows higher mortality in the patients with cardiac syncope (P<.0001). The number of patients evaluated at each 6-month point follows: 561, 547, 527, 472, 419, 371, 330, 286, 256, and 223 patients.

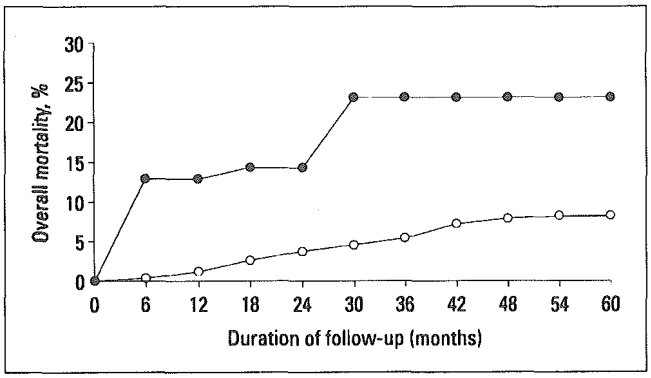
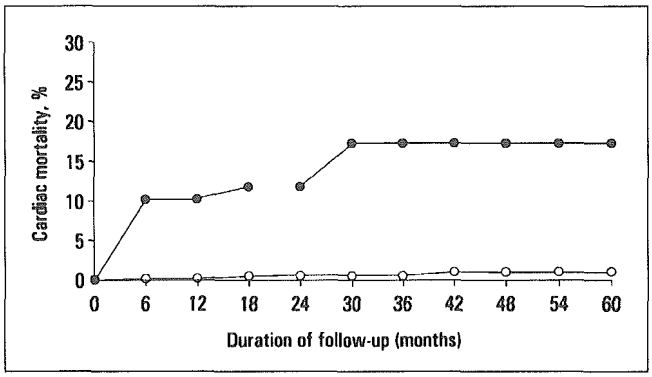


Figure 2.

Comparison of cardiac mortality. Closed circles indicate the cumulative mortality of the patients with cardiac syncope, and open circles indicate that of the patients with noncardiac syncope. Cardiac mortality analyzed by the actuarial life-table method shows higher mortality in the patients with cardiac syncope (P<.0001). The number of patients evaluated at each 6-month point follows: 561, 547, 527, 472, 419, 371, 330, 286, 256, and 223 patients.



LIMITATIONS

There are potential limitations for this study. Because the cohort consisted of retrospectively identified patients with syncope who were brought to an academic ED in Tokyo by ambulance and the follow-up data were collected from only 78% of the patients initially enrolled, the cohort was highly selected. The Japanese emergency medical system is also quite different from that found in Western countries; however, its impact on the present study is likely minimal because all patients identified for this trial are limited to those transported by ambulance to the hospital. Furthermore, the cause of death was assigned on the basis of information obtained from the family and medical records, which can understate or overstate the proportion of patients with a presumed cardiac cause of their syncope or death. Finally, generalization of the findings to Asian countries other than Japan may require further studies in other Asian cohorts.

Table 4.
Relative risk for 5-year overall mortality and cardiac mortality.

Predictors	Overall Mortality, Relative Risk (95% CI)	Cardiac Mortality, Relative Risk (95% CI)
Cardiac syncope	2.81 (1.53–5.16)	18.74 (5.90–59.52)
Age	1.09 (1.06–1.12)	1.03 (0.995–1.07)

DISCUSSION

The results of this study reveal a prevalence of cardiac syncope of 9.9% and higher mortality for patients with cardiac syncope than for patients with noncardiac syncope among patients brought to an ED in Japan. Cardiac syncope is an independent predictor of mortality for patients presenting to the ED with syncope. These findings are compatible with those in Western countries. Despite possible selection bias because of the inclusion of patients arriving only by ambulance to the ED, the findings may be important because evidence from similar studies in Western countries has now been confirmed in an Asian population for the first time.

Although poor prognosis in patients with cardiac syncope is observed in Japan, mortality in the described cohort is lower than in previous reports from Western countries. Previous prognostic studies have indicated that patients with cardiac syncope have a higher 1-year mortality rate, ranging from 18% to 33%.[2,4,8,10] In this study, the 1-year mortality of the patients with cardiac syncope was only 12.9% (Figure 1). This disparity in prognosis may be attributable to ethnic and geographic differences in mortality and prognosis of cardiovascular disease. Cardiovascular disease mortality has been reported to be lower in the Japanese population than in Western countries,[15,17,18] and the prognosis for Japanese patients with cardiovascular disease is better than in Western countries.[22,23] Kapoor and Hanusa[24] noted that syncope itself is not a risk factor for increased overall or cardiac mortality and that underlying heart disease is a risk

Table 5.
Comparison of prevalence of syncope.

Studies	Country	No. of Patients: Initially Enrolled Patients (% Lost to Follow-up)	No. of Patients: Age, Mean (SD)	Cause of Syncope, %: Cardiac: Total	Cardiac: Arrhythmias	Vasovagal	Unknown
ED-based studies							
Present study	Japan	912 (22)	52 (22)	9.9	4.5	30.6	32.2
Day et al[4]	US	198 (7)	44	9	—	40	13
Kapoor et al[2]	US	204 (42)	56 (20)	26	20	5	46
Martin et al[8]	US	170 (11)	41	4	—	37	38
Eagle et al[10]	US	176 (6)	54 (23)	9	7	45	39
Sarasin et al[25]	Switzerland	650 (8)	60 (23)	11	7	37	14
Crane[11]	UK	210 (10)	55 (25)	7	—	37	40
Framingham Heart Study							
Soteriades et al[12]	US	822 (12)	51 (14)	10	—	21	37

US, United States; **UK**, United Kingdom.

factor regardless of whether patients have syncope. Therefore, the mortality of Japanese patients with non-cardiac syncope would be expected to be relatively low.

The prevalence of arrhythmias in the present study was also lower than in previous studies (Table 5).[2,10,25] The difference is mainly attributable to the smaller proportion of patients with associated ventricular tachycardia, which was the diagnosis reported to be the most common cardiac cause of syncope (11%) by Kapoor et al[2,26] and Kapoor,[20] but represented the cause of syncope in only 1.0% of the cases in our study (Table 2). The lower prevalence of ventricular tachycardia may also have been related to the lower mortality of cardiac syncope in the present study.

The incidence of cardiovascular disease in Japan is also lower than in Western countries[15]; however, this study showed proportions of patients with cardiac causes of syncope comparable to those in ED-based studies in Western countries (Table 5).[2,4,8,10-12,25] Although the true reason for the comparable proportions is unknown, differences in emergency medical systems between Japan and Western countries may be a contributing factor.[27] In Japan, EDs have a different selection of patients compared with Western countries. In Japan, unless patients are transported to a hospital by ambulance, most patients visit outpatient clinics rather than walking into EDs to be evaluated. Therefore, all of the patients in our study of syncope were brought to the ED by ambulance. Because there has been no similar study reported to date that classified the transportation characteristics of syncope patients to the ED, we are unable to compare our results with previous studies based on patients transported to the hospital only by ambulance. We can only speculate, therefore, that the proportion of patients with relatively severe conditions, such as cardiac syncope, was higher in our cohort than for walk-in patients who may have visited outpatient clinics in Japan.

The cardiac syncope survival curve in this present study plateaued after 3 years, indicating that there was no substantial difference in mortality between the 2 groups after 3 years (Figures 1 and 2). The studies by Kapoor et al[2] and Kapoor[20] also reported a similar pattern in survival curves. These findings suggest that cardiac deaths related to cardiac syncope occur within 3 years after the syncopal episode, thereby indicating that a minimum follow-up period of 3 years is needed in future prognosis studies of patients with syncope.

In conclusion, cardiac syncope was an independent predictor of mortality after ED visits associated with syncope in Japan. These findings are similar to those in Western countries.

Author contributions: MS, SH, and KS conceived the idea and design of the study. SH and NA supervised the conduct of the study and data collection. MS, SH, KS, and IN collected and managed patients' data. MS analyzed the data statistically and drafted the manuscript. NA chaired the data oversight committee. SH takes responsibility for the paper as a whole.

Received for publication September 30, 2003. Revisions received November 19, 2003, and February 9, 2004. Accepted for publication February 23, 2004. Available online July 26, 2004.

Presented at the Society for Academic Emergency Medicine annual meeting, Atlanta, GA, May 2000.

The authors report this study did not receive any outside funding or support.

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診　　断

SIRS・sepsisの重症度評価

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Evaluation of severity for systemic inflammatory response syndrome and sepsis

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Abstract

Systemic inflammatory response syndrome (SIRS) is defined by four simple clinical and laboratory indices and now widely accepted for diagnosing sepsis. However, since the SIRS criteria include patients with a wide range of severity, other parameters are necessary to evaluate the severity and outcome of the patients.

In this review, we discussed several methods to estimate the severity of SIRS, such as number of positive SIRS indices among four, duration of SIRS, plasma IL-6 and procalcitonin, etc.

Key words: severity, evaluation, SIRS, sepsis

はじめに

SIRS (systemic inflammatory response syndrome: 全身性炎症反応症候群) はsepsisおよびその関連病態の定義を整理し，多施設共同研究を推進する必要性から1990年代初頭に米国胸部医学会/米国集中治療医学会の合意委員会で提唱された概念である[1]．基礎疾患にかかわらず重症患者が高率に全身性の過剰炎症状態を呈し，これが多臓器機能不全 (multiple organ dysfunction syndrome: MODS) の誘因になるという一連の病態解明が，SIRSという概念が生まれる素地を作った．

SIRSは感染症のみならず，外傷，熱傷，急性膵炎，出血性ショックなど様々な侵襲病態により惹起され，その診断基準は純粋に臨床項目のみでなされる．すなわち，**図1**[2]に示した診断基準のうち2項目以上を満たした場合SIRSと診断される．このうち呼吸項目に関しては，人工呼吸管理中の場合は，呼吸数が20回/min未満の設定であっても呼吸状態が異常であるとの解釈からカウントし，逆に激しい運動や精神的動揺，過換気症候群などによる一過性反応の場合はカウントしない．

SIRS診断基準の各項目は軽症でも基準を満たす場合が多く，感染症では特に基準を満たす (すなわちsepsis) ことが多い．MODSを併発する患者の多くがSIRS基準を満たす一方，SIRS患者では非SIRS患者に比しMODSの発症率は高いとはいえ，ごく一部である．すなわち，SIRSの診断基準はクリアーカットであるものの，患者の重症度把握には他の評価方法が必要

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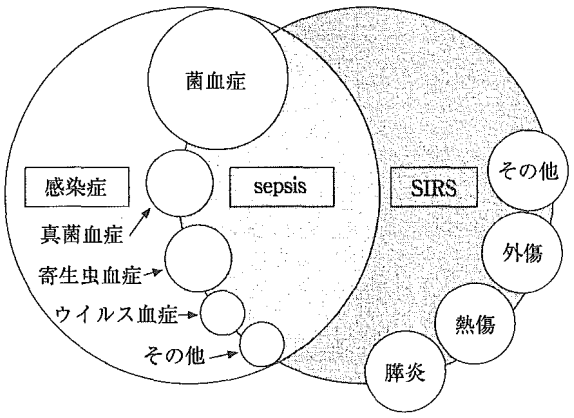

SIRSの診断基準

1. 体　温：<36℃または38℃<
2. 脈　拍：90回/分<
3. 呼吸数：20回/分<
   $PaCO_2$<32 mmHg
4. ＷＢＣ：12,000/mm³<または
   <4,000/mm³または
   10％<の未成熟細胞
   の存在

2つ以上を満たすとき，SIRSと診断する．

図1　SIRSの概念と診断基準[2]
SIRS: systemic inflammatory response syndrome

である．

本稿では，代表的な重症度評価法について概説する．

I. SIRS項目，他の臨床指標値からの重症度評価

SIRS診断基準4項目のうち陽性項目数が多いほど，救急外来からの入院率，死亡率ともに有意に高くなる[3]．その4項目のうち非感染性SIRSでは頻脈[4]，感染性SIRS(すなわちsepsis)では白血球や体温異常など感染の指標[5]がMODSへの進展率や死亡率に関与する．

侵襲が中等度までの手術・外傷・感染などではSIRS徴候は侵襲に対する正常な生体反応としてとらえられる．この反応は感染防御・創傷治癒に必要不可欠であり，合併症がなければ通常2-3日で消退する．重症感染症，重症熱傷など侵襲の程度が過大な場合や，十分に制御できない感染症など侵襲の持続期間が長い場合に，各種炎症性サイトカインが継続的かつ過剰に産生される状態，すなわちサイトカイン・ストームを呈することとなる．したがってSIRS状態が3-4日以上持続したり，再燃したりする場合は，MODSへ進展する可能性が高くなり，SIRSの持続日数はsevere SIRSの簡便なwarning signとなり得る．

実際，Sunら[3]はSIRS持続日数が3日未満であった群の死亡率は6.1％であったのに対し，3日以上SIRSが持続した患者の死亡率は44.3％と有意に高かったと報告しており，Gandoら[6]もSIRSが3日以上持続する場合には不全臓器数が増加すると報告している(**図2**)．また芳賀らも，SIRSの陽性項目が多いほど，また持続期間が長いほど術後感染症や合併症が多くなると報告している(**図3**)[7]．

感染症が原因となって起こるSIRSはsepsisと定義され，sepsisのうち臓器機能障害・循環不全(乳酸アシドーシス・乏尿・急性意識障害など)あるいは低血圧を合併するものがsevere sepsis，更にsevere sepsisのうちで適切な輸液管理でも低血圧が持続する状態がseptic shockと定義されている．カテコールアミンなどにより血圧が維持されている状態でも臓器機能障害・循環不全がある場合にはseptic shockと定義される．

sepsisの定義を非感染性SIRSに応用して，臓器機能障害・循環不全あるいは低血圧を合併するものをsevere SIRSと定義しようとする提案[8]もあるが一般的には受け入れられてはいない．

また，APACHEスコアと組み合わせてsevere SIRSをとらえようとする試みもなされている[3,9]．

II. 臨床検査値による重症度評価

CRP高値(≧5 mg/dl)，血小板減少(≦12万/μl)など通常検査で測定できる値を用いてse-

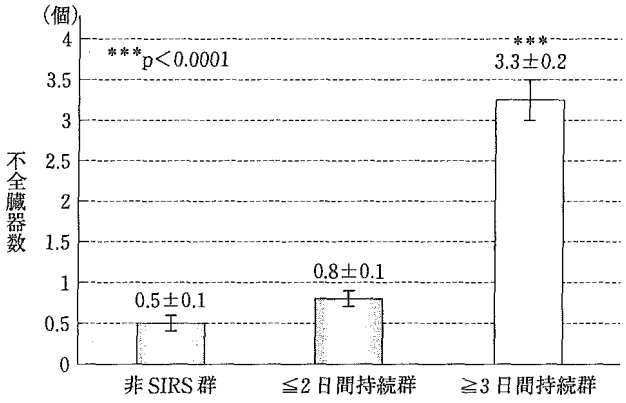

図2 SIRS期間と不全臓器数[6]

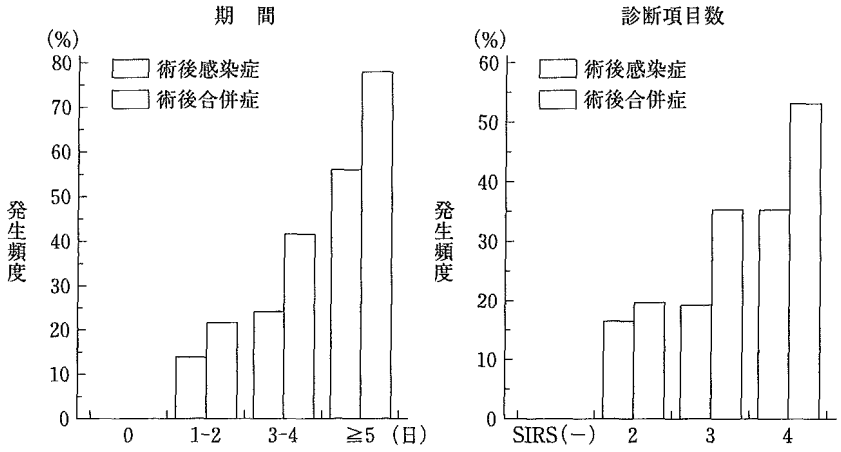

図3 SIRSと術後感染症および合併症発生頻度との関係[7]

vere SIRSを定義し，これによる予後の評価を試みた報告もある[4]．CRPなどの急性相蛋白は主にIL-6刺激によって肝臓で産生され，血中濃度はIL-6よりやや遅れて侵襲2-3日後にピークに達する．一般検査で測定可能な項目ではあるが，後述するIL-6同様，非特異的な炎症反応の指標である．また侵襲により血中濃度が増加する好中球エラスターゼはSIRS診断項目の陽性数が多いほど高値であるとの報告もあり，重症度評価に応用できる可能性がある(図4)[10]．

細菌感染症が原因のsepsisの重症度評価として，現在認可準備中のプロカルシトニン(procalcitonin: PCT)が注目されている．PCTはカルシトニンの前駆蛋白で，感染症，特に細菌感染下で各種細胞から産生が亢進する．遠藤らによると，sepsis群の外傷群との比較では，CRPやIL-6，TNF-αには有意差を認めず，PCTのみ前者で有意に高値をとり，またPCTはsepsis群に比べてsevere sepsis群，septic shock群で有意に高値であった[11]．MullerらもPCTがCRPやIL-6，乳酸に比べて感受性，特異性ともに高いことから細菌感染症の診断に有用であると報告している[12]．つまり，PCTは細菌感染症の早期診断と重症度評価に有用な指標として期待されている．現在，プロカルシトニンは化学発光免疫測定法によって検出が可能になっているが，更にベッドサイドで可能なプロカルシトニンの簡便な定性反応キットの開発が進められており，早期の臨床応用が期待される．

その他，sepsis患者の重症度と単球のHLA-

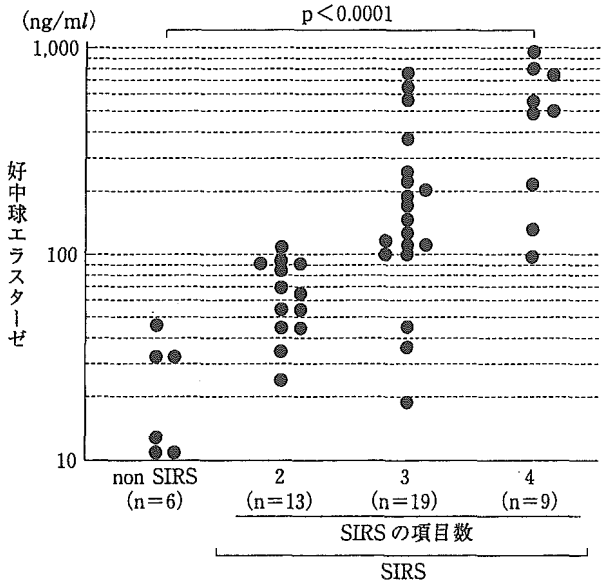

図4　SIRS項目数と好中球エラスターゼ値[10]

DR発現がよく相関し，短時間に結果が得られるため臨床的に有用であるとの報告もあるが，flow cytometerという高価な機器を用いて，採血後すぐに解析する必要があるため，利用できる施設は限られるであろう[13]．

III. サイトカインによる重症度評価

各種サイトカインの中でも，SIRS項目の異常を誘導する作用はTNF-αやIL-1が最も強く，PGE_2の産生を介して発熱や低体温，頻脈，多呼吸を誘発する．また好中球に関しては，直接血管内皮細胞への接着能を亢進して初期の白血球減少を生じさせる一方で，IL-8やG-CSFの産生を介してその後の白血球増多症へも寄与している．一方，IL-6には，直接SIRS項目の異常を惹起する作用はないが，TNF-α，IL-1および細菌内毒素などにより産生が誘導され，血中濃度が侵襲後速やかに上昇し，かつ持続するため，各種臨床試験などで重症度評価によく用いられる．

血中IL-6値は小手術では極めて低いが，侵襲の大きな手術では高値を示すなど，手術侵襲ともよく相関する．非感染性SIRSが多い外傷においてもIL-6は重症度を表すinjury severity score(ISS)と相関する．感染やショック，再手術などの侵襲が加わり，侵襲が持続，遷延化するとIL-6の高値持続や再上昇がみられ，北村らはSIRS発症3日後にIL-6＞800 pg/mlの患者が，MODSに移行する可能性が高いとしている[5]．このようにIL-6は生体への侵襲度を比較的よく反映するものの，少なくとも我が国では簡便に測定できず，臨床応用に至っていないのが現状である．

おわりに

集中治療を要する患者の多くは一過性に過剰炎症状態となり，SIRS基準を満たす場合が多く，SIRS基準によって重症度，すなわちMODS発症率，予後を評価するにはかぎりがある．日常の患者管理に際し，治療追加や変更の必要性を見極めるために，患者の重症度を常に把握している必要があり，実際多くの臨床医は，無意識のうちにこれを行っているのかもしれない．しかし，病態が増悪しつつある患者を早期に発見し適切に対応するためには，本稿に述べたような各種指標値を用いた客観的な重症度評価法の確立が是非とも必要である．

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序：SIRS, sepsis, 敗血症の病態解明とsepsisに対する新規治療法の開発

相川直樹　藤島清太郎

Understanding the pathogenetic mechanisms of SIRS and sepsis and development of innovative therapies of sepsis

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Abstract

The concept of systemic inflammatory response syndrome (SIRS) was introduced in 1992 to define and objectively diagnose sepsis. Over the last decade, the definition of sepsis has been used for inclusion criteria of multicenter trials to develop innovative therapies of sepsis. With the recent understanding of the pathogenetic mechanisms of sepsis, many drugs have been tested, but only two drugs (activated protein C and neutrophil-elastase inhibitor) have been approved for clinical use in sepsis or SIRS. Further understanding of basic pathophysiology of SIRS and sepsis holds promise to develop a new therapeutic strategy to improve survival of patients with SIRS and sepsis.

Key words: SIRS, sepsis, cytokine storm, innovative therapy

はじめに

SIRS は systemic inflammatory response syndrome の略で，1991年に米国で開催された American College of Chest Physicians と Society of Critical Care Medicine の Consensus Conference（合意会議）で初めて提唱された臨床概念である．この会議を主導し，SIRSの考えを創造したのは後述する Roger Bone 教授であった．

sepsis の定義に関する合意内容が，1992年6月に両学会の機関誌である Chest[1] と Critical Care Medicine[2] に同時掲載され，SIRSの概念が広く注目されるようになり，今日まで，多くの研究によりその病態が解明されてきている．両機関誌の論文の表題が“Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis”となっているように，そもそも SIRS は sepsis の定義統一のために導入された概念である[3]．

SIRSの概念導入により sepsis が共通の定義（sepsis＝感染症を原因とする SIRS）で認識され，その簡便な診断基準により，ベッドサイドで sepsis が迅速に診断されるようになったことから，sepsis の新規治療法の多施設臨床治験が円滑に進むようになった．これを基に開発された SIRS や sepsis 新規治療薬が臨床応用されるようになるまでには長い年月を要したが，一つの臨床概念の導入が医療を変え得ることのモデルとなった．

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I. SIRSに基づいたsepsisの定義

1. sepsisの定義

このように，SIRSはsepsisとその関連病態の定義を統一する必要性から生まれた概念である．1980年代後半の北米において，sepsisやこれに伴うショック(septic shock)，多臓器不全(septic MOF)に対する新しい治療法として大量コルチコステロイドや抗エンドトキシン抗体などの新薬開発が盛んに行われるようになった．しかし当時はsepsisの定義が統一されていなかったために混乱が生じていた．

医師によってsepsisの定義や解釈が異なることは，臨床現場での混乱を招くばかりでなく，sepsisの多施設臨床治験におけるsepsis患者の選択基準設定に大きな支障であった．このような背景から，sepsisをめぐる用語の統一が求められていた[4]．

sepsisを'重症の全身症状を有する感染症'とすることにはほとんど異論はなかったが，sepsisの条件として，血液培養による病原菌検出を求めるべきか[5]，重症の全身症状とは，具体的に何の症状とし，どの程度の重症度とするかについては様々な意見があった．このような状況にあって，Boneはsepsisの定義を統一すべきであると主張して[6]，合意会議の議長として指導的役割を発揮した．

Boneは当初，自分が主張していた"sepsis syndrome"なる用語[7]を提唱しようとしたが，認められず，結局は，'感染症が原因となってSIRSとなっている状態'をsepsisとすることとなった．

2. SIRSの概念の導入と治験への影響

ここで，sepsisとsepsisでない感染症とを区別する'重症の全身症状'をどのように規定するかについては，全身性炎症を反映する4項目；体温(発熱または低体温)，心拍数(頻脈)，呼吸数(頻呼吸)あるいは$PaCO_2$($PaCO_2$低下)，末梢血白血球数(白血球増多または白血球減少)あるいは白血球分画(未熟顆粒球増加)のうち2項目以上に異常のある状態とし，これをSIRSとした．

SIRSの診断基準に必要な4項目の兆候や検査項目は，半世紀以上にわたって臨床現場で一般に用いられているものである．1992年の医療水準を考えると，sepsisを診断する根拠となる全身性炎症の診断には，例えばCRP，プロカルチトニン，インターロイキン6などの検査値をも取り入れれば，診断の精度が更によくなるとも考えられる．しかし，合意会議で提唱した診断基準は，上記の検査結果を待たなくとも，ベッドサイドで簡便かつ迅速に診断できるという点で，特にsepsisの新規治療薬の臨床治験の患者選択には有用となった．治験への組み入れ患者数が多くなるばかりでなく，sepsisの治療を早期に開始できることにより，治験薬の効果がより強く発揮されることが期待された．

一方，頻脈や頻呼吸は，炎症以外でも出現する兆候であり，これらで診断されるsepsis患者は，多様な病態からなる患者集団となることも指摘される[8,9]．このような多様な感染患者集団を対象とした治験では，治験薬の効果のみならず様々な要因が経過に影響し，そのノイズのために治験薬の有効性や安全性が正しく評価されないというジレンマもある．

3. Sepsisと敗血症の区別

合意会議によるsepsisの定義に従えば，感染症でSIRSとなればsepsisとなり，血中に病原微生物が存在しなくても'sepsis'とされる．例えば，急性気管支炎で38℃以上の発熱と白血球数12,000/mm^3以上とがあれば，血液培養が陽性でなくてもsepsisとされる．sepsisは邦語では敗血症と訳されるが，我が国ではこのような気管支炎を敗血症とはしない．

一方，邦語の'敗血症'は，一般に'重症の全身症状を伴う菌血症(あるいは真菌血症)'と定義されている[10]．特に内科領域や感染症領域で'敗血症'とするには，血液培養陽性が必要となる．抗菌薬が'敗血症'の適応を取得する場合にも，血中分離菌の推移が検討された症例が求められている[11]．

したがって，合意会議でのSIRSから定義される'sepsis'の登場により，'sepsis'と我が国で用いられている'敗血症'との間に乖離が生じ

てしまった．そのため，sepsisを敗血症と訳してしまうと，大きな混乱が生じる．そこで，著者は1992年以降の欧米の定義による'sepsis'は'セプシス'として，'敗血症'と区別するべきであると主張している[11,12]．

II. 病態の理解に基づく新規治療法

1. SIRSとsepsisの病態

sepsisを定義するために導入されたSIRSではあるが，SIRSの診断基準を満たす全身性炎症は外傷，熱傷，急性膵炎，ショックなどの非感染性侵襲でも惹起される．すなわち，エンドトキシンや外毒素などの病原微生物由来の物質のほかに，組織損傷やトロンビン形成，アノキシアなど種々の要因が全身性炎症の原因となり，原因が何であっても，同一の非特異的な全身性炎症が引き起こされる機序として，炎症性サイトカインをはじめとした種々のメジエータが関与することが知られてきた．

本特集では，その病態に関する最新の知見がまとめられており，その詳細は割愛するが，SIRSでは侵襲に対して，まずpivotal cytokinesとしてTNF-α (tumor necrosis factor-alpha: 腫瘍壊死因子)とIL-1(interleukin-1)の産生が増加し，主としてautocrine，paracrineであるべきサイトカインが，あたかもendocrineのごとく全身的に作用して，他のサイトカインやメジエータの産生を誘導し，全身性炎症反応のカスケードが広まることが病態の根源にある．敗血症のように高度の侵襲が持続する難治性重症感染症や，手術，外傷に続く感染のような繰り返す侵襲(two-hit)では，炎症性サイトカインの誘導・産生の制御機構が破綻し，種々のサイトカインが血中に高濃度出現，重症sepsisや多臓器不全(MODS)となる．sepsisでは種々のサイトカインが血中に高濃度出現することが知られており[13,14]，このような状態を，著者は'サイトカイン・ストーム'と称している[15,16]．

本特集では，SIRSとsepsisの複雑な病態生理学的機序についてproteomicsからgenomicsに至るまで多面的に解説されており，この数年にかけて膨大な情報が集約されてきたことがわかる．

2. 病態機序の理解に基づく新規治療法

多くの病態が解明されてきたとはいっても，SIRSとsepsisの病態は複雑多様であり，我々の知らない部分もいまだに多い．しかしながら，病態の理解に基づいた新規治療法が，最近になってようやく臨床応用されるようになった．この分野を研究している者として，大変勇気付けられる．

臨床医が病態生理を研究する目的にはいろいろあろうが，病態生理の研究成果が新規治療法の開発につながり，それにより患者が救命できることを目標にしている者も多い．抗菌薬療法が進歩した21世紀の今日でも，sepsisはまれな病態ではなくその死亡率は高く[17]，抗菌薬療法や感染対策に加えて，種々の新規治療法が開発されてきた．

合意会議で定義された重症sepsisの診断基準は，これらの開発において患者選択基準として使われてきたが，多くの臨床治験が失敗してきた中で[18]，新たにリコンビナント活性プロテインCが重症sepsisの死亡率を著明に減少させることが証明され[19]，欧米で認可され現在臨床現場で広く使われている．我が国でも，SIRSとALI(acute lung injury)の診断基準を用いて臨床治験が進められたエラスターゼ阻害薬が市場に登場した．

sepsisを定義するために創られたSIRSなる概念が，薬剤の適応症となるまでに12年を要したが，SIRSとsepsisの病態の理解は，今後も急速に進むことと思う．その成果が，新たな治療法導入につながり，sepsisの治療成績が目覚ましく向上する日も近いことと思う．

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図説

高サイトカイン血症の病態生理

Pathophysiology of hypercytokinemia

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SIRS(systemic inflammatory response syndrome)は，各種感染症や重症外傷，熱傷により惹起される全身性炎症反応である(図 1)[1]．SIRS 状態にある患者体内では，様々な炎症性，抗炎症性サイトカインが過剰に産生，放出され，これらが病態の形成に重要な役割を担っている(図 2)[2]．近年，サイトカインの概念は拡大傾向にあり，DNA 結合蛋白の一種である HMGB-1，可溶性受容体などもそれぞれ炎症性，抗炎症性サイトカインと認識されつつある．サイトカインは，各々特異的な受容体に結合し，paracrine, autocrine に標的細胞を活性化し，刺激伝達系酵素のリン酸化などを介して，様々な機能を発揮する(図 3)．ここでは好中球を例として，受容体(図 4)と，刺激時に放出されるメディエータ(図 5)を示した[3]．好中球は，サイトカインなどのメディエータによって活性化されると，接着分子を介して臓器内の微小血管内皮細胞に付着した後，血管外へ遊走し，組織内で上記傷害物質を放出して，急性肺傷害などの臓器不全を誘発する(図 6)．その中でも好中球エラスターゼは代表的な傷害物質であるが，近年同酵素に各種の細胞機能調節作用があることが明らかとなっている(図 7)[4]．

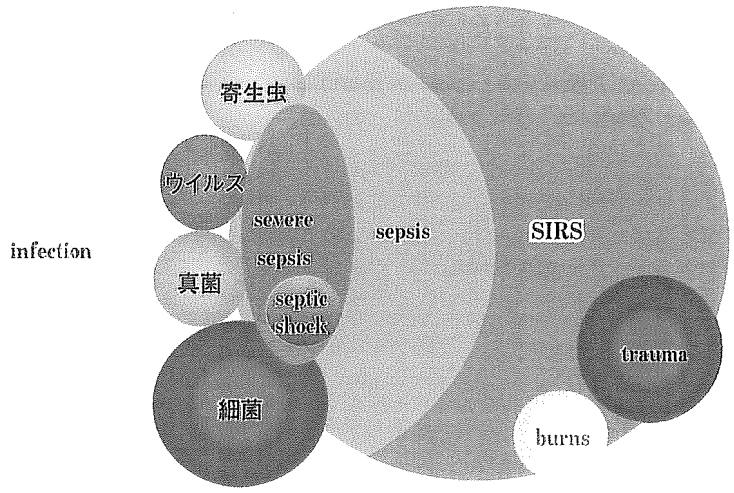

図 1　SIRS の概念と sepsis

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