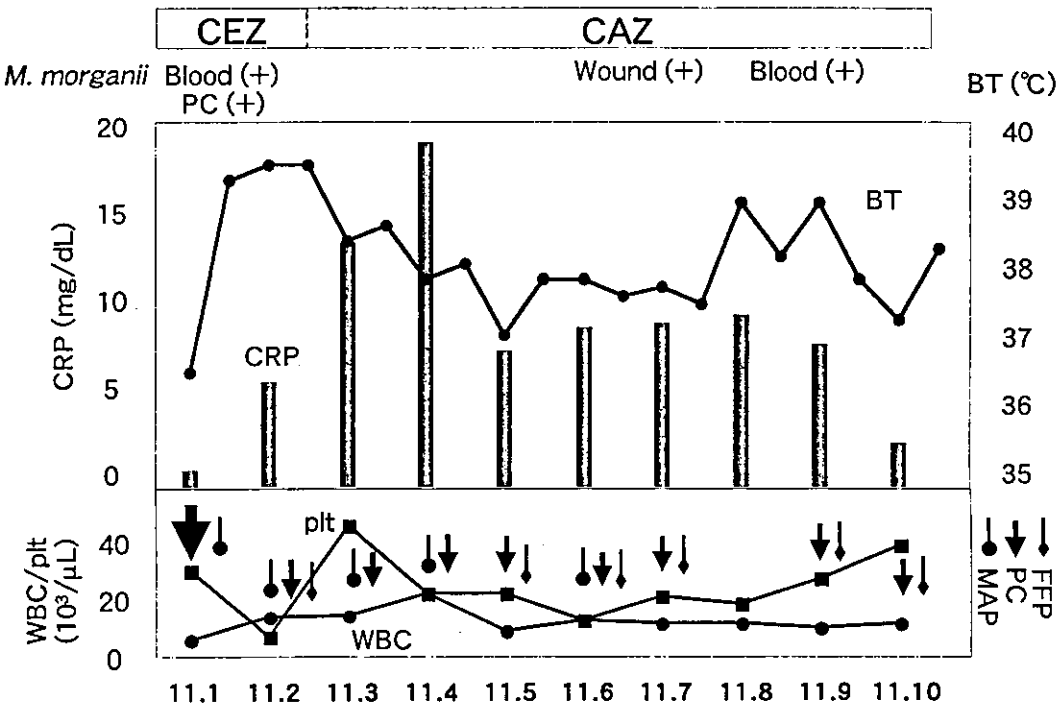


図　Fever developed and plasma CPR levels increased after platelet transfusion. *M. morganii* were detected just after the transfusion from both the patient's blood and the platelet concentrates used. *M. morganii* had not been detected before this. The patient improved two days after the transfusion, when ceftazidime was started.

で，ここに報告する．

症　例

症例は7カ月の男児．平成10年3月3日に近医で出生，出生時体重は2,568g，Apgar scoreは8点，出産は妊娠39週4日目の自然分娩であった．出生時よりチアノーゼを認め，心エコーでファロー四徴，肺動脈弁閉鎖症，大動脈管開存症と診断，プロスタグランジン E_2 療法などの保存的治療が無効なため，手術目的で4月1日に当院転入となった．入院同日に動脈管閉鎖術ならびに右室流出路形成術を施行したが心不全は改善せず，同年10月14日に右室流出路拡大術を施行した．同28日頃より播種性血管内凝固症候群（disseminated intravascular coagulation syndrome；DIC）が出現し，11月1日に血小板数が3.1万/μLに低下したため，血小板製剤（platelet concentrates；PC）を輸血した．製剤は成分採血由来10単位の濃厚血小板「日赤」であり，輸血時に白血球除去フィルター（セパセルPLX-10A-W）を使用した．

輸血開始の時点で体温36.5℃，血圧90/50，脈拍116/分，輸血開始1時間後に顔面と体幹部の紅斑様発疹に気付くも，体温36.8℃，血圧120/60，脈拍125/分と安定していたため，輸血速度を遅くして経過観察した．輸血開始2時間後に紅斑が全身に広がって悪寒と戦慄が出現，体温38.5℃，血圧80/40，脈拍170/分となったため，輸血を中止した（輸血総量35mL）．残りの製剤は無菌的に保冷庫に保存した．輸血中止1時間後，体温38.1℃，血圧75/40，脈拍172/分と改善しないため，昇圧剤投与などの対症的治療を開始し，患者自身の血液（動脈血）培養検査を提出した．抗生物質は術後から予防投与中のCefazolinを継続投与した．同日，一連の経過を主治医と当輸血・細胞療法部で相談し，製剤の一部を細菌培養検査に提出した．出庫時と回収時の2回行った製剤の肉眼的観察では，いずれも外観異常は確認出来なかった．翌々日（同3

日)に，患者血液と血小板製剤の両者で多数の *M. morganii* 菌が検出され，直ちに同菌に感受性がある Ceftazidime の投与を開始した．本患者から同菌が検出されたのはこの時が最初であった．

WBC と CRP は輸血後上昇したが，同4日の 22,000/μL，17.98mg/dL をピークに改善傾向を示した．*M. morganii* 菌はさらに同7日に手術創部から，同9日に動脈血液から検出されたが，以後全て陰性化した．DIC は一時増悪傾向にあり，口腔内，上気道～気管内から粘膜出血が続いたため，濃厚赤血球 MAP，PC，新鮮凍結血漿（fresh frozen plasma；FFP)を輸血した．これらの輸血に伴う合併症はみられなかった．同 10 日に右半身痙攣が出現し，CT で左側頭葉の梗塞巣と硬膜下血腫の所見が確認された．輸血後経過を図に示す．

翌平成 11 年2月に *Escherichia Coli* による腹膜炎を併発し，敗血症性ショックのため2月 12 日に死亡した．

平成 10 年 11 月2日に採取した本患者血液を日本赤十字血液センターに提出し，抗 human leukocyte antigen（HLA）抗体を lymphocyte cytotoxicity test (LCT 法) で，抗 human platelet antigen (HPA) 抗体を mixed passive hemoagglutination test (MPHA 法) で，抗血漿蛋白抗体をオクタロニー法と enzyme-linked immunosorbent assay (ELISA 法)で行ったが，いずれも陰性であった．また本患者に投与した血小板製剤と同一献血者由来の FFP 製剤を用いた，塗沫検査，細菌培養検査，エンドスペシーによるエンドトキシンテストも全て陰性であった．

考　察

本例は血小板輸血後に敗血症性ショックを呈し，血液培養と輸血製剤培養の両者で *M. morganii* 菌が検出された1例である．血小板輸血を開始後早期に全身性の発疹様紅斑，悪寒，戦慄を伴う 38℃ 台の発熱が出現し，血圧低下，脈拍増加を認めた．患者血液と血小板製剤から同時に *M. morganii* 菌が検出され，その後さらに術創部と血液から同菌が検出された．

米国の輸血副作用報告システム[1]を用いて解析した BaCon study は，輸血後細菌感染症の現状を提供する，非常に信頼性の高い調査研究である[2]．報告によれば，輸血後細菌感染症の発症頻度はシングルドナー由来血小板製剤 100 万単位当たり 9.98 とされている．国内情報では，赤十字血液センターの医薬情報部が実施している輸血副作用調査が唯一である[3]．この 1998 年から 2001 年までの4年間の集計では，輸血後細菌感染疑いは 40 例，うち 27 例で患者検体から細菌が検出された．ただし，同一献血者由来の FFP 製剤から同一菌が検出されたのはわずか3例しかない．一方日本赤十字血液センターが行った血小板製剤の無菌試験では，10,750 回に1回陽性（陽性率 0.01%）であった[4]．本例は BaCon study の診断基準を全て満たしており，輸血後感染症が強く示唆された．

M. morganii 菌は腸内細菌科 Morganella 属の通性嫌気性グラム陰性桿菌である．鞭毛を有して運動性を示すことが特徴であり，健常人の便から検出されるが，ヒトで菌血症を起こすことは稀である[5]．重症感染症の報告は，新生児敗血症[6][7]，新生児脳膿瘍[8]，造血器腫瘍に合併した髄膜炎[9]等の免疫不全患者に限られ，輸血後感染症の報告はない．

ま と め

アフェレーシス血小板製剤の輸血後に発症し，輸血後細菌感染症の可能性が強く示唆された症例を経験した．本例は血小板輸血後の経過ならびに動脈血液培養と輸血血小板製剤培養の結果から，輸血後 *M. morganii* 感染症に伴う敗血症性ショックを起こしたものと推察された．

追記：2004 年の Transfusion Medicine に献血者由来 *M. morganii* 菌による致死的敗血症例の症例報告が掲載されたので追記致します．

謝辞：本報告に際し，輸血副作用検査にご協力いただきました日本赤十字血液センターに深謝致します．

文　献

1) Kuehnert MJ, Roth VR, Haley NR, et al.: Transfusion-transmitted bacterial infection in the United States, 1998 through 2000., Transfusion, 41: 1493—1499, 2001.
2) Roth VR, Kuehnert MJ, Haley NR, et al.: Evaluation of a reporting system for bacterial contamination of blood components in the United States.,

Transfusion, 41：1486—1492, 2001.
3) 日本赤十字血液センター医薬情報部：輸血情報 0203-70, 2003.
4) 日本赤十字血液センター医薬情報部：輸血情報 0203-69, 2003.
5) O' hara CM, Brenner FW and Miller M：Classification, identification and clinical significance of Proteus, Providencia, and Morganella., Clin Microbiol Rev, 13：534—546, 2000.
6) Rowen JL and Lopez SM：Morganella morganii early onset sepsis., Pediat Infect Dis J, 17：1176, 1998.
7) Casanova-Roman M, Sabchez-porto A and Casanova-Bellido M：Early-onset neonatal sepsis caused by vertical transmission of Morganella morganii., Scand J Infect, 34：534—535, 2002.
8) Verboon-Maciolek M, vandertop WP, Peters CB, et al.：Neonatal brain abscess caused by Morganella morganii., CID, 20：471, 1995.
9) Samonis G, Anatoliotaki M, Apostolakou H, et al.：Fatal septicemia and meningitis due to Morganella morganii in a patient with Hodgkin's disease., Scand J Infect Dis, 33：553—555, 2001.

医薬品・医療用具等安全性情報

No.205

ダイジェスト

平成16年（2004年）9月

[厚生労働省医薬食品局]

医薬品・医療用具等安全性情報No.205が発行されました。その概要は以下のとおりです。詳細は次の雑誌に掲載されますので，関連症例等についてはこれらをご参照下さい。

日本医師会雑誌（10月１日号）（１，２のみ）	クリニカル プラクティス（11月号）
日本薬剤師会雑誌（11月号）（１，２のみ）	月刊薬事（11月号）
日本病院薬剤師会雑誌（11月号）	診療と新薬（10月号）

NTTのファクシミリ通信網サービス「Fネット」を通じ，最近１年間の「医薬品・医療用具等安全性情報」がお手元のファクシミリから随時入手できます（利用者負担）。既に，Fネットに加入されている方は，次の操作番号で目次を引き出して下さい。162# 284 03 3508 4364 01#（Fネットへの加入等についての問い合わせ先は☎0120-161-011）

なお，医薬品医療機器情報提供ホームページ（http://www.info.pmda.go.jp/）又は厚生労働省ホームページ（http://www.mhlw.go.jp/）からも入手可能です。

1．平成15年度インフルエンザワクチンの副反応の報告等について

平成15年度におけるインフルエンザワクチンの副反応の報告状況及び安全対策をまとめたので紹介する。

平成15年度のインフルエンザワクチンの推定出荷本数は，約1,463万本であり，薬事法に基づく副作用等報告による副反応は，162症例，259件（注射部位の発赤・腫脹等26件，発熱18件，ショック・アナフィラキシー様症状14件，肝機能障害12件，発疹等12件，意識消失等９件，関節痛７件，筋痛７件，ギラン・バレー症候群７件，痙攣７件，喘息６件，下痢５件，他）であった。

J Infect Chemother (2004) 10:110–114
DOI 10.1007/s10156-004-0301-y

ORIGINAL ARTICLE

Kazuhiko Sekine · Seitaro Fujishima · Naoki Aikawa

Plasma hepatocyte growth factor is increased in early-phase sepsis

Received: July 30, 2003 / Accepted: January 9, 2004

Abstract To elucidate the involvement of hepatocyte growth factor (HGF) in systemic inflammatory response syndrome (SIRS) and sepsis, we investigated the plasma levels of HGF, as well as those of various proinflammatory and anti-inflammatory cytokines, in 50 patients who visited our emergency department (ED). The patients were divided into four groups, depending on the existence of SIRS and infection: group 1 (G1), no infection and no SIRS; group 2 (G2), infection and no SIRS; group 3 (G3), no infection and SIRS; and group 4 (G4), infection and SIRS (e.g., sepsis). We found that plasma HGF levels in G4 were significantly higher than those in the groups without infection (G1 and G3). However, the correlations between HGF and other cytokines were comparatively low compared with those between any other pairs of cytokines, suggesting independent regulation of HGF production in vivo. High plasma HGF was significantly correlated with the presence of infection and with serum total bilirubin (TB) level on multivariate logistic regression analysis. Considering HGF's known functions, we speculated that high plasma HGF levels may indicate the occurrence or necessity for tissue protection and regeneration after acute systemic insults in sepsis.

Key words Hepatocyte growth factor (HGF) · Systemic inflammatory response syndrome (SIRS) · Sepsis · Tumor necrosis factor (TNF) · Interleukin-10 (IL-10) · Liver dysfunction

Introduction

Sepsis is now recognized as a systemic response to local or systemic infection,[1] and the involvement of many endogenous mediators, including cytokines, has been implicated in its pathogenesis. Among proinflammatory cytokines, tumor necrosis factor alpha (TNF alpha), interleukin-6 (IL-6), and IL-8[2–4] are well established; not only for their augmented production but also for their pathogenetic roles in inducing various local and systemic inflammation and tissue injuries. Among anti-inflammatory cytokines, IL-10 is the most potent and is well established for its negative feedback inhibitory role in the production of proinflammatory cytokines.[5]

Hepatocyte growth factor (HGF) was originally identified as human scatter factor, or tumor cytotoxic factor, and its involvement has been reported in sepsis and septic shock.[6–8] However, both its regulation of production in vivo and its correlation with other proinflammatory and anti-inflammatory cytokines are poorly understood. To clarify these points, we investigated the plasma levels of HGF and various cytokines in patients who visited our emergency department (ED).

Patients, materials, and methods

Patients and clinical data

The study was conducted at the ED of Keio University Hospital, Tokyo, Japan. We prospectively enrolled 50 patients, whose parameters for systemic inflammatory response syndrome (SIRS) criteria were assessed at the ED according to the initial diagnosis and data. Informed consent was obtained from patients or family members before enrollment in the study.

SIRS was defined as the presence of two or more of the following criteria: temperature less than 36°C or more than 38°C; heart rate more than 90 beats/min; respiratory rate more than 20 breaths/min or $PaCO_2$ less than 32 Torr (4.27 kPa); and white blood cell (WBC) count more than 12000 cell/mm^3 or more than 10% immature forms. Additional clinical data concerning basic demographics, comorbidity, and culture results were also collected.

K. Sekine · S. Fujishima (✉) · N. Aikawa
Department of Emergency and Critical Care Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
Tel. +81-3-3225-1323; Fax +81-3-3353-2232
e-mail: fujishim@sc.itc.keio.ac.jp

Diagnosis of infection was made based on fever, clinical signs and symptoms, and radiographic imagings; respiratory tract infection was diagnosed by productive cough and infiltrative shadows on chest X-ray; peritonitis and soft-tissue infections were diagnosed by local pain and tenderness; urinary tract infection was diagnosed by flank pain, tenderness, and pyuria; gastrointestinal tract infection was diagnosed by abdominal pain, vomiting, and diarrhea; and retroperitoneal abscess was diagnosed by flank pain, tenderness, and abdominal computed tomography (CT) scan.

Patients enrolled at the ED were divided into four groups. Group 1 (G1) were subjects with an acute illness but having no evidence of infection and not fulfilling the SIRS criteria; group 2 (G2) had clinical symptoms or signs of infection, but did not fulfil the SIRS criteria; group 3 (G3) had no signs of infection, but fulfilled the SIRS criteria; and group 4 (G4) showed clinical symptoms or signs of infection and fulfilled the SIRS criteria (sepsis, following the definition of American College of Chest Physicians/Society of Critical Care Medicine [ACCP/SCCM]). As soon as a diagnosis and ward allocation was determined, venous blood was collected in sterile polypropylene tubes, containing ethylenediamine tetraacetic acid (EDTA), and immediately centrifuged at 1500*g* at 4°C for 10 min. The plasma was divided into individual aliquots and stored at −70°C until the assays were performed.

Assays for TNF alpha, IL-6, IL-10, and HGF

Sandwich enzyme-linked immunosorbent assays (ELISAs) were used to measure cytokines. The kits used for the assays were: TNF alpha (R&D Systems, Minneapolis, MN, USA), IL-6 (R&D Systems), IL-8 (TFB Tokyo, Japan), IL-10 (Wako Pure Chemical Industries, Tokyo, Japan), and HGF (Otsuka Pharmaceutical, Tokyo, Japan). The investigator performing the assays was blinded to the identity of each specimen and the clinical scenario. The investigator performing screening, enrolling, phlebotomy, and chart review was blinded to the results of the individual assays.

Statistical analysis

Cytokine levels were quite variable among patients, and seemed to follow a log-normal distribution. Thus, the log-transformed value of each cytokine level was used for statistical analysis; the unpaired *t*-test was used for comparison of two groups, Fisher's protected least significant difference (PLSD) test was used for multiple comparisons, the χ^2 test was used for proportional comparisons, and Pearson's test was used for correlation. To compare the slope of the regression lines, we performed covariance analysis with interaction with the logarithmic transformation of the variables. We further studied the association of high HGF levels with several independent variables, including age, sex, presence of SIRS or infection, serum total bilirubin (TB), and serum alanine aminotransferase (ALT) by using multivariate logistic regression analysis. Results of logistic regression were indicated with odds ratios (ORs), 95% confidence intervals (CIs), and *P* values. Differences were considered statistically significant at $P < 0.05$. Values for continuous variables were reported as means ±SEM.

Results

Table 1 provides the clinical description of the study population classified into the respective groups. Of the 50 patients, 26 were admitted to the intensive care unit, and 9 died. In one-third of the patient deaths, the cause was due to the failure of more than two vital organs; namely, multiple organ dysfunction syndrome. There were no significant differences in the survival rate among the four groups examined. The patients in non-infectious groups (G1 and G3) died mostly from exacerbation of the major illness which existed on admission. In two comatose patients, however, the cause of death was bacterial pneumonia acquired after admission.

Positive culture results in more than one clinical specimen were obtained in 15 patients (62.5%) in the groups with infection (G2 and G4) at the time of admission. The bacteria isolated were as follows: *Staphylococcus aureus* in 4 patients, *Escherichia coli* in 4, *Bacteroides fragilis* in 2, *Staphylococcus species* in 1, *Streptococcus pneumoniae* in 1, *Streptococcus species* in 1, *Pseudomonas aeruginosa* in 1, and *Klebsiella oxytoca* in 1. There were no specific correlations between the site of infection and bacterial species. Although the most frequent focus of infection was the respiratory tract, there was no significant difference in the rate of respiratory tract infections between G2 and G4 (2/4 vs 7/20; $P = 0.48$). Nine patients with positive blood cultures, were included in G4, with the most frequent focus being the respiratory tract, followed by the urinary tract, retroperitoneum, peritoneal cavity, and undetermined (3, 2, 2, 1, and 1 patient, respectively).

The levels of TNF alpha, IL-6, IL-8, IL-10, and HGF in the four groups are shown in Figs. 1 and 2. The levels of TNF alpha, IL-6, and IL-8 in G4 (sepsis) were significantly higher than those in the other groups (Fig. 1). IL-10 was detectable in 1/11 patients (9.1%) in G1, 1/4 (25%) in G2, 8/15 (53%) in G3, and 13/20 (65%) in G4; and the IL-10 levels in G1 were significantly different from those in G4. Plasma HGF levels in G4 were also significantly higher than those in the non-infectious groups (G1 and G3), but were not higher than those in G2.

Because the functional roles of HGF have not been clarified in SIRS and sepsis, we analyzed the correlations between HGF levels and levels of other cytokine (Table 2). Although significant linear correlations were found in all pairs of cytokines examined, the correlation coefficients between HGF and the other cytokines were lower than those between other pairs.

Next, all patients were divided into two subgroups, depending on HGF levels higher ($n = 16$) or lower ($n = 34$) than the upper limit of the normal range (0.39 ng/ml) and were analyzed by multivariate logistic regression for the contribution of six independent parameters: age, sex, pres-

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 ($\times 10^3$/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

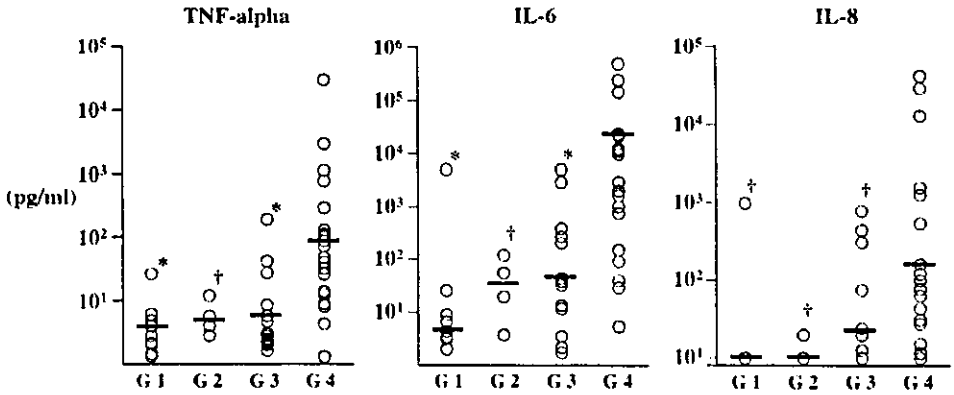


Fig. 1. Serum tumor necrosis factor-alpha (*TNF-alpha*), interleukin-6 (*IL-6*), and IL-8 levels in patients with acute illness transferred to our emergency department (ED) by ambulance. Blood was drawn from 50 patients assessed for clinical diagnosis and by Bone's criteria for systemic inflammatory 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.

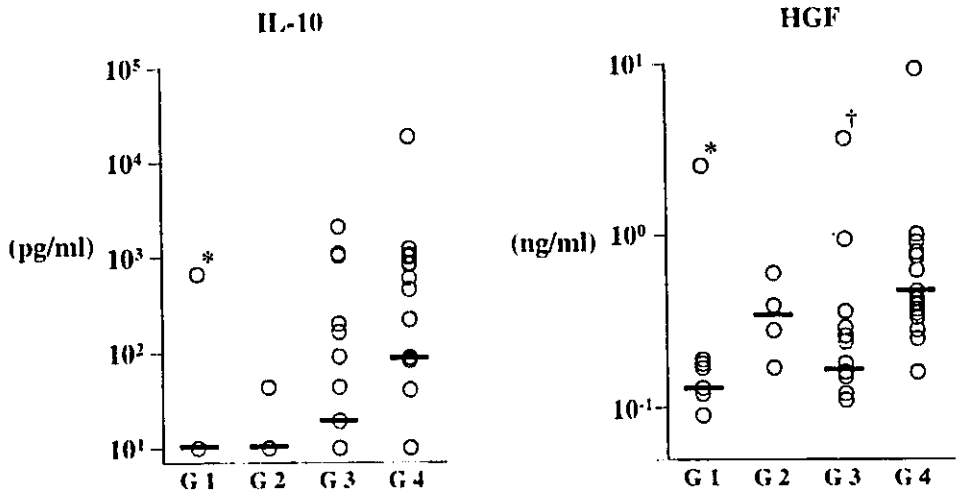


Fig. 2. Serum IL-10 and hepatocyte growth factor (*HGF*) levels in patients with acute illness transferred to our emergency department (ED) by ambulance. Blood was drawn from 50 patients assessed for clinical diagnosis and by Bone's criteria for SIRS at the ED. Enrolled patients were divided into four 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).

References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
2. Damas P, Reuter A, Gysen P, Demonty J, Lamy M, Franchimont P. Tumor necrosis factor and interleukin-1 serum levels during severe sepsis in humans. Crit Care Med 1989;17:975–8.
3. Hack CE, De Groot ER, Felt-Bersma RJ, Nuijens JH, Strack Van Schijndel RJ, Eerenberg-Belmer AJ, et al. Increased plasma levels of interleukin-6 in sepsis. Blood 1989;74:1704–10.
4. Fujishima S, Sasaki J, Shinozawa Y, Takuma K, Kimura H, Suzuki M, et al. Serum MIP-1 alpha and IL-8 in septic patients. Intensive Care Med 1996;22:1169–75.
5. Marchant A, Deviere J, Byl B, De Groote D, Vincent JL, Goldman M. Interleukin-10 production during septicaemia. Lancet 1994;343: 707–8.
6. Sakon M, Kita Y, Yoshida T, Umeshita K, Gotoh M, Kanai T, et al. Plasma hepatocyte growth factor levels are increased in systemic inflammatory response syndrome. Surg Today 1996;26:236–41.
7. Nayeri F, Nilsson I, Skude G, Brudin L, Soderstrom C. Hepatocyte growth factor (HGF) in patients with pneumonia: a comparison between survivors and non-survivors. Scand J Infect Dis 1998;30: 405–9.
8. Nayeri F, Nilsson I, Brudin L, Fryden A, Soderstrom C, Forsberg P. High serum hepatocyte growth factor levels in the acute stage of community-acquired infectious diseases. Scand J Infect Dis 2002; 34:127–30.
9. Yanagita K, Matsumoto K, Sekiguchi K, Ishibashi H, Niho Y, Nakamura T. Hepatocyte growth factor may act as a pulmotrophic factor on lung regeneration after acute lung injury. J Biol Chem 1993;268:21 212–7.
10. Okajima A, Miyazawa K, Naitoh Y, Inoue K, Kitamura N. Induction of hepatocyte growth factor activator messenger RNA in the liver following tissue injury and acute inflammation. Hepatology 1997;25:97–102.
11. Namekata K, Takamori S, Kojima K, Beppu T, Futagawa S. Significant changes in the serum levels of IL-6, h-HGF, and type IV collagen 7S during the perioperative period of a hepatectomy: relevance to SIRS. Surg Today 2000;30:403–9.
12. Gomez-Jimenez J, Martin MC, Sauri R, Segura RM, Esteban F, Ruiz JC, et al. Interleukin-10 and the monocyte/macrophage-induced inflammatory response in septic shock. J Infect Dis 1995; 171:472–5.
13. Marchant A, Alegre ML, Hakim A, Pierard G, Marecaux G, Friedman G, et al. Clinical and biological significance of interleukin-10 plasma levels in patients with septic shock. J Clin Immunol 1995;15:266–73.
14. Oberholzer A, Oberholzer C, Moldawer LL. Interleukin-10: a complex role in the pathogenesis of sepsis syndromes and its potential as an anti-inflammatory drug. Crit Care Med 2002;30: S58–63.
15. van Dissel JT, van Langevelde P, Westendorp RG, Kwappenberg K, Frolich M. Anti-inflammatory cytokine profile and mortality in febrile patients. Lancet 1998;351:950–3.
16. Taniguchi T, Koido Y, Aiboshi J, Yamashita T, Suzaki S, Kurokawa A. Change in the ratio of interleukin-6 to interleukin-10 predicts a poor outcome in patients with systemic inflammatory response syndrome. Crit Care Med 1999;27:1262–4.

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

Masaru Suzuki, MD
Shingo Hori, MD
Iwao Nakamura, MD
Kyoko Soejima, MD
Naoki Aikawa, MD, FACS

From the Department of Emergency Medicine, School of Medicine, Keio University, Tokyo, Japan.

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.

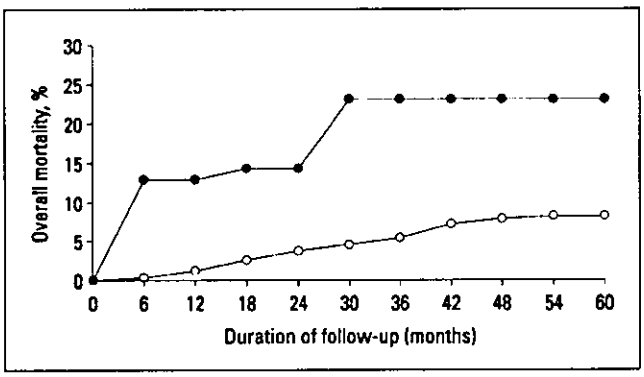
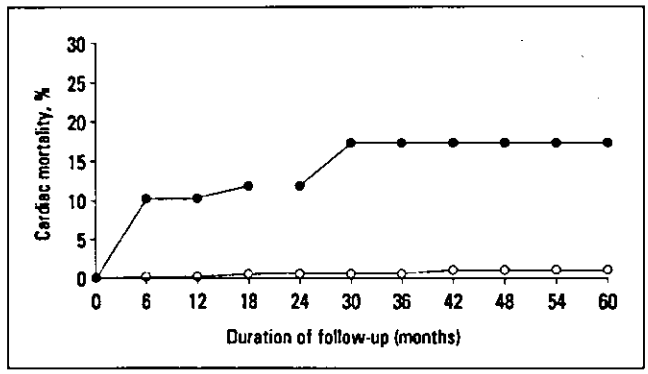


Figure 2.
Comparison of cardiac mortality. Closed circles indicate the cumulative mortality of the patients with cardiac syncope, and open circles indicate that of the patients with noncardiac syncope. Cardiac mortality analyzed by the actuarial life-table method shows higher mortality in the patients 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.

Address for reprints: Shingo Hori, MD, 35 Shinanomchi, Shinjukuku, Tokyo 160-8582, Japan; 81-3-3225-1323, fax 81-3-3353-2232; E-mail shingo@ sc.itc.keio.ac.jp.

REFERENCES

1. Kapoor WN. Current evaluation and management of syncope. *Circulation.* 2002;106: 1606-1609.
2. Kapoor WN, Karpf M, Wieand S, et al. A prospective evaluation and follow-up of patients with syncope. *N Engl J Med.* 1983;309:197-204.
3. Hori S. Diagnosis of patients with syncope in emergency medicine. *Keio J Med.* 1994;43:185-191.
4. Day SC, Cook EF, Funkenstein H, et al. Evaluation and outcome of emergency room patients with transient loss of consciousness. *Am J Med.* 1982;73:15-23.
5. Brignole M, Alboni P, Benditt D, et al. Guidelines on management (diagnosis and treatment) of syncope. *Eur Heart J.* 2001;22:1256-1306.
6. Linzer M, Yang EH, Estes NA, et al. Diagnosing syncope, part 2: unexplained syncope: Clinical Efficacy Assessment Project of the American College of Physicians. *Ann Intern Med.* 1997;127:76-86.
7. Linzer M, Yang EH, Estes NA, et al. Diagnosing syncope, part 1: value of history, physical examination, and electrocardiography: Clinical Efficacy Assessment Project of the American College of Physicians. *Ann Intern Med.* 1997;126:989-996.
8. Martin GJ, Adams SL, Martin HG, et al. Prospective evaluation of syncope. *Ann Emerg Med.* 1984;13:499-504.
9. Martin TP, Hanusa BH, Kapoor WN. Risk stratification of patients with syncope. *Ann Emerg Med.* 1997;29:459-466.
10. Eagle KA, Black HR, Cook EF, et al. Evaluation of prognostic classifications for patients with syncope. *Am J Med.* 1985;79:455-460.
11. Crane SD. Risk stratification of patients with syncope in an accident and emergency department. *Emerg Med J.* 2002;19:23-27.
12. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med.* 2002;347:878-885.
13. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations: monitoring trends and determinants in cardiovascular disease. *Lancet.* 1999;353:1547-1557.
14. Saito I, Folsom AR, Aono H, et al. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. *Int J Epidemiol.* 2000; 29:837-844.
15. Robertson TL, Kato H, Rhoads GG, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: incidence of myocardial infarction and death from coronary heart disease. *Am J Cardiol.* 1977;39: 239-243.
16. Robertson TL, Kato H, Gordon T, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: coronary heart disease risk factors in Japan and Hawaii. *Am J Cardiol.* 1977;39:244-249.
17. World Health Organization. *World Health Statistics Annual 1995.* Geneva, Switzerland: World Health Organization; 1996.
18. Department of Economic and Social Affairs. *2000 Demographic Year Book Fifty-Second Issue.* New York, NY: United Nations; 2002.
19. Bloomfield DM, Sheldon R, Grubb BP, et al. Putting it together: a new treatment algorithm for vasovagal syncope and related disorders. *Am J Cardiol.* 1999;84:330-390.

20. Kapoor WN. Evaluation and outcome of patients with syncope. *Medicine (Baltimore).* 1990;69:160-175.
21. Kapoor WN, Peterson J, Wieand HS, et al. Diagnostic and prognostic implications of recurrences in patients with syncope. *Am J Med.* 1987;83:700-708.
22. Yano K, Grove JS, Reed DM, et al. Determinants of the prognosis after a first myocardial infarction in a migrant Japanese population: the Honolulu Heart Program. *Circulation.* 1993;88:2582-2595.
23. Kambara H, Nakagawa M, Kinoshita M, et al. Long-term prognosis after myocardial infarction: univariate and multivariate analysis of clinical characteristics in 1,000 patients: Kyoto and Shiga Myocardial Infarction (KYSMI) Study Group. *Clin Cardiol.* 1993;16:872-878.
24. Kapoor WN, Hanusa BH. Is syncope a risk factor for poor outcomes? Comparison of patients with and without syncope. *Am J Med.* 1996;100:646-655.
25. Sarasin FP, Louis-Simonet M, Carballo D, et al. Prospective evaluation of patients with syncope: a population-based study. *Am J Med.* 2001;111:177-184.
26. Kapoor WN, Smith MA, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med.* 1994;97:78-88.
27. O'Malley RN, O'Malley GF, Ochi G. Emergency medicine in Japan. *Ann Emerg Med.* 2001;38:441-446.

日本臨牀　第62巻・第12号（平成16年12月号）別刷

特集：SIRS・sepsisの最前線

SIRS·sepsisの重症度評価

栗原智宏　　藤島清太郎　　相川直樹

診　　断

SIRS·sepsisの重症度評価

栗原智宏　藤島清太郎　相川直樹

Evaluation of severity for systemic inflammatory response syndrome and sepsis

Tomohiro Kurihara, Seitaro Fujishima, Naoki Aikawa
Department of Emergency and Critical Care Medicine,
Keio University School of Medicine

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

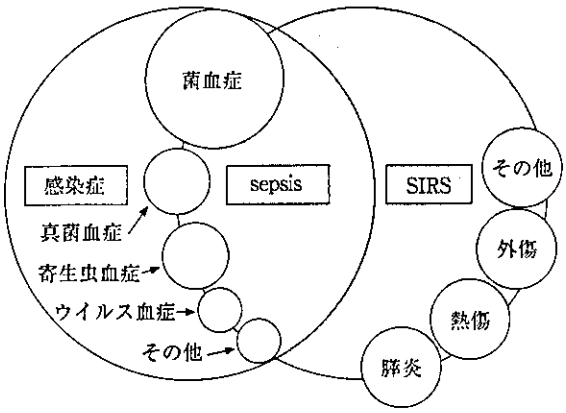
SIRS (systemic inflammatory response syndrome: 全身性炎症反応症候群) はsepsisおよびその関連病態の定義を整理し，多施設共同研究を推進する必要性から1990年代初頭に米国胸部医学会/米国集中治療医学会の合意委員会で提唱された概念である[1]．基礎疾患にかかわらず重症患者が高率に全身性の過剰炎症状態を呈し，これが多臓器機能不全 (multiple organ dysfunction syndrome: MODS) の誘因になるという一連の病態解明が，SIRSという概念が生まれる素地を作った．

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

慶應義塾大学医学部救急医学

0047-1852/04/¥50/頁/JCLS



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-

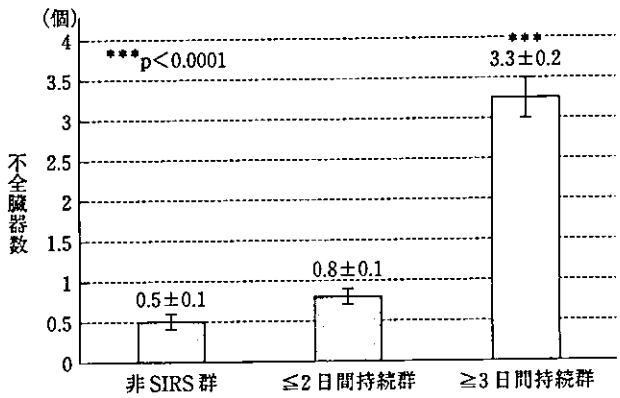


図2 SIRS期間と不全臓器数[6]

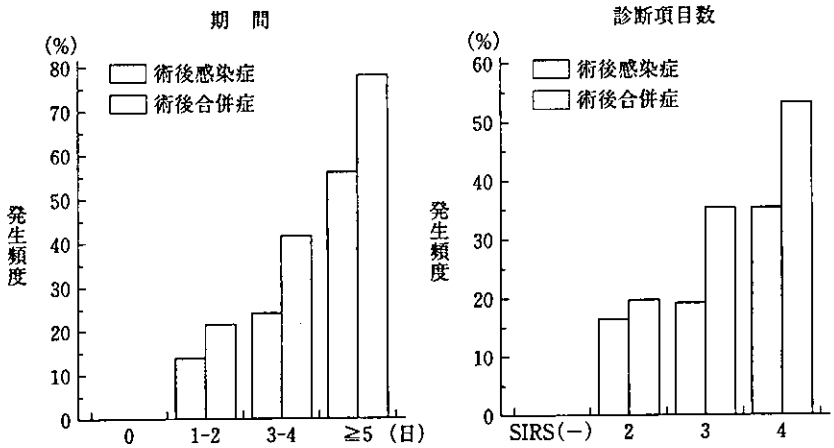


図3 SIRSと術後感染症および合併症発生頻度との関係[7]

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-