Clinical Characteristics of Acute Pulmonary Thromboembolism in Japan: Results of a Multicenter Registry in the Japanese Society of Pulmonary Embolism Research

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Summary

Background: Although the incidence of acute pulmonary thromboembolism (APTE) has been increasing in Japan, patient characteristics, management strategies, and outcome have not yet been assessed in large series.

Hypothesis: The present study was designed to investigate the current status of APTE in Japan.

Methods: Of a total of 533 registry patients with pulmonary thromboembolism, 309 with APTE were analyzed with respect to clinical symptoms and signs, predisposing factors, diagnostic procedures, estimation of deep venous thrombosis, treatment, and clinical course.

Results: Main risk factors were recent major surgery, cancer, prolonged immobilization, and obesity; only a few patients had coagulopathy and 36% were in cardiogenic shock at presentation. The majority of registry patients underwent lung scans or pulmonary angiography; 30% were diagnosed only by lung scanning. Venous ultrasonography was used in only 34 patients, while 188 patients underwent at least one diagnostic procedure for deep venous thrombosis. Thrombolysis was more frequently performed in patients with cardiogenic shock, and only a few patients received thromboembolectomy. In-hospital mortality rate was 14%. In patients with cardiogenic shock, the mortality rate was reduced by thrombolysis. The predictors of in-hospital mortality were male-gender, cardiogenic shock, cancer, and prolonged immobilization.

Conclusions: The patients in this registry had almost the same findings as those in Western patients, except for some points that had the possibility of demonstrating a difference between Westerners and Japanese in the development of APTE. These results can prove especially helpful in planning prospective, randomized trials that will clarify the impact of widely used treatment modalities on the outcome of patients with APTE.

Introduction

It is estimated that in the USA nearly 6,000,000 patients develop acute pulmonary thromboembolism (APTE), and 60,000 die of the condition each year.[1] The incidence of APTE in Japan was thought to be minimal.[2] However, the diagnosis of APTE has been increasing in Japan[3] because of the changes in lifestyle, the aging of the population, the improved clinicians' awareness of APTE, and advances in diagnostic modalities. Recent autopsy studies indicate that the incidence of APTE in Japan is comparable with that in Western countries.[4] However, the clinical experience in Japan has shown that there are ethnic differences between Japanese and Westerners in response to anticoagulation therapy. This suggests that it is inappropriate to assume that the results of Western studies are fully applicable to the clinical situation in Japan. Therefore, it may be necessary that the characteristics, management strategies, and outcome of APTE in the Japanese population are assessed in large series.

In an attempt to resolve these issues, the present registry focused on the characteristics as well as on current management strategies and the clinical outcome of Japanese patients with

APTE in a large setting of community hospitals. This report serves the following purposes: (1) to investigate the characteristics and outcome of APTE in the Japanese population, and (2) to reveal the current diagnostic procedures and the management strategies of APTE in Japan.

Methods

Study Population

The registry in the present study was conducted between January 1994 and October 1997. During this period, the 26 participating centers in the Japanese Society of Pulmonary Embolism Research (JaSPER; listed in the Appendix) registered a total of 533 consecutive Japanese patients in whom the diagnosis of pulmonary thromboembolism was made either by a pulmonary angiogram which indicated vessel occlusions or intraluminal filling defects, a lung scan which indicated high probability of pulmonary thromboembolism, or an autopsy.

All registered patients were classified by the coordinating center into three types of pulmonary thromboembolism according to their clinical courses: (1) Patients with APTE (309 patients) whose symptoms occurred suddenly and whose mean pulmonary arterial pressures were <40 mmHg even within few hours of the embolic event. (2) Patients with chronic thromboembolic pulmonary hypertension (68 patients) whose symptoms progressed gradually until they had mean pulmonary arterial pressure of >25 mmHg, which persisted for 6 months. (3) An unclassified group (154 patients) that could not be classified either to APTE or chronic thromboembolic pulmonary hypertension. For statistical evaluation, the present study considered only those patients with APTE.

All decisions concerning the diagnostic workup and treatment were made by the clinicians caring for each patient. The steering committee took every care not to influence the management strategy followed in the participating hospitals.

Data Acquisition

Complete information on the clinical course and the diagnostic and therapeutic management of the patients entering the registry was obtained by means of a standardized questionnaire sent to the participating centers by the steering committee. Data were collected on (1) clinical symptoms and signs of the patients at diagnosis; (2) presence of underlying diseases or predisposing factors for APTE; (3) definitive diagnostic procedures given to patients (pulmonary angiography, lung scan, and autopsy), and auxiliary diagnostic measures (esophageal echocardiography, contrast computed tomographic scan, and magnetic resonance imaging); (4) presence of deep venous thrombosis (DVT) and diagnostic procedures (contrast venography, venous ultrasonography, and radionuclide venography); (5) treatment given to patients (anticoagulation, thrombolysis, pulmonary thromboembolectomy, catheter interventional therapy, and inferior vena cava filter implantation); and (6) in-hospital and out-of-hospital clinical course.

Statistical Analysis

All continuous variables were reported as mean ± 1 standard deviation. Comparisons of proportion were made by chi-square statistics or, when appropriate, by Fisher's exact test. Multiple logistic regression was used to investigate the independent effect of clinical characteristics and thrombolytic therapy on in-hospital mortality in APTE. The results of the logistic regression models are presented as estimated odds ratios (ORs) with the corresponding 95% confidence intervals (CIs). All significant tests were two-tailed, with p<0.05 considered as statistically significant.

Results

The clinical characteristics of 309 patients with APTE (187 women and 122 men) are shown in Table I. The mean age of the patients at diagnosis was 60 ± 15 years (range 15–87 years), with 137 (44%) aged ≥65 years (Fig. 1). The mean time interval between the onset of symptoms and the diagnosis of APTE was 5 ± 10 days; 2 ± 5 days in patients with cardiogenic shock and 6 ± 10 days in patients without cardiogenic shock. Ninety-eight patients (32%) were diagnosed 3 days or longer after the onset of symptoms. Most patients (80%) had dyspnea or chest pain at diagnosis, and 39% of patients had cardiogenic shock or loss of consciousness. The frequencies of cough, hemoptysis, and fever in patients without cardiogenic shock (11, 6, and 13%, respectively) occurred twice as often as in those with cardiogenic shock. Many patients had recent ma-

TABLE I   Clinical characteristics at diagnosis in 309 study patients

Characteristics	No. of patients (%)
Age ≥65 years	137 (44)
Sex (female/male)	187/122 (1.5/1)
Dyspnea	205 (66)
Chest pain	141 (46)
Palpitation	59 (19)
Syncope	62 (20)
Cardiogenic shock	111 (36)
Recent major operation	110 (36)
Recent major trauma or fracture	29 (9)
Cancer	70 (23)
Prolonged immobilization	71 (23)
Deep venous thrombosis	99 (32)
Obesity (BMI ≥25.3)	106 (34)
Coagulopathy	17 (6)
Protein C deficiency	0
AT III deficiency	4
Lupus anticoagulant	10
Onset in hospital/out of hospital	154/145 (1.1/1)
Presence of definitive trigger	108 (34)
Standing up or walking	62
Urination or defecation	24

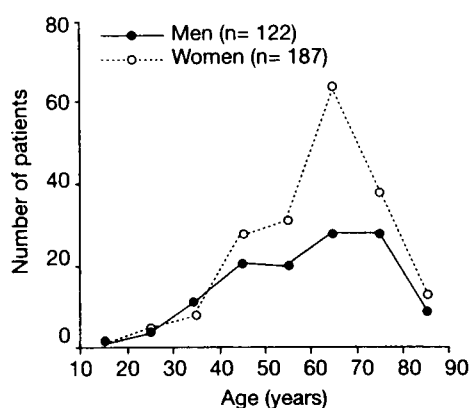Abbreviations: AT = antithrombin, BMI = body mass index.

FIG. 1   Distribution of disease by age and gender in 309 consecutive patients with a diagnosis of acute pulmonary thromboembolism from 1994 to 1997.

jor surgery, cancer, prolonged immobilization, or obesity as risk factors for venous thromboembolism, while only a few had a coagulopathy. One-half of the registry patients developed APTE out of hospitals; of these, 85 (55%) had no obvious risk factors. A definitive trigger event for APTE occurred in 108 patients, and a few patients developed APTE after urination or defecation.

Diagnostic Strategies

The frequencies with which definitive diagnostic methods of APTE were used are shown in Table II. The majority of registry patients underwent lung scans or pulmonary angiography: lung scans in 229 patients, angiography in 140 patients, and at least one of these imaging studies in 277 patients. Only 18% of registry patients underwent either esophageal echocardiography, contrast computed tomography scans, or magnetic resonance imaging as auxiliary diagnostic measures. Few patients were diagnosed at autopsy.

Evaluation of Deep Venous Thrombosis

Seventy-three patients (24%) had signs of DVT, and 188 patients underwent at least one diagnostic procedures for DVT. Contrast venography was performed in most of these

TABLE II   Diagnostic workup

Diagnostic methods	No. of patients (%)
Lung scan	229 (74)
Pulmonary angiography	140 (45)
Esophageal echocardiography	2 (1)
Contrast computed tomography	43 (14)
Magnetic resonance imaging	7 (2)
Autopsy	12 (4)

Total study population was 309 patients.

patients, while venous ultrasonography was performed in only 34 patients. These procedures were performed in 52 of the 111 (47%) patients with cardiogenic shock, and in 136 of 198 (69%) patients without cardiogenic shock. In the above 188 DVT examinations, 98 instances of DVT were detected. Of the 62 patients who had clinical signs of DVT, DVT was detected by these diagnostic procedures in 57 (92%) patients, while of the 126 patients without signs of DVT, it was not detected in 87 (69%) patients (Table III).

Treatment of Acute Pulmonary Thromboembolism

Almost all patients with APTE received specific treatment (Table IV). Intravenous heparin was the most widely used treatment (74%). In all, 155 (50%) patients underwent thrombolytic treatment. Excluding the patients who were diagnosed at autopsy, thrombolysis was more frequently performed in patients with cardiogenic shock (68%) than in those without cardiogenic shock (40%, p < 0.0001). More aggressive therapeutic procedures, such as catheter interventional therapy or emergency surgical thromboembolectomy, were performed only in isolated cases. Percutaneous cardiopulmonary support was performed in five patients with circulatory collapse, with only one survival.

TABLE III   Evaluation of deep venous thrombosis

	No. of patients (%)
Signs of DVT	73 (24)
Diagnostic procedures for DVT	188 (61)
Contrast venography	152
Venous ultrasonography	34
Radionuclide venography	25
Detection of DVT in diagnostic procedures	98 [a] (52)
Detection of DVT in patients with signs of DVT	57 [b]
Nondetection of DVT in patients without signs of DVT	87 [c]

Total study populations were 309, [a] 188, [b] 62, and [c] 126 patients.
Abbreviation: DVT = deep venous thrombosis.

TABLE IV   Treatment of acute pulmonary thromboembolism

Treatment	No. of patients (%)
Heparin anticoagulation	230 (74)
Thrombolysis	155 (50)
Patients with cardiogenic shock	75 [a] (68)
Patients without cardiogenic shock	80 [b] (40)
Surgical thromboembolectomy	7 (2)
Catheter interventional therapy	17 (6)
Inferior vena cava filter	57 (18)
Percutaneous cardiopulmonary support	5 (2)

Total study population were 309, [a] 111, [b] 198 patients.

TABLE V In-hospital and out-of-hospital mortality

	No. of patients (%)
Overall in-hospital mortality	44 (14)
Mortality with cardiogenic shock	33 [a] (30)
with thrombolysis	15 [b] (20)
without thrombolysis	18 [c] (50)
Mortality without cardiogenic shock	11 [d] (6)
with thrombolysis	6 [e] (8)
without thrombolysis	5 [f] (4)
Out-of-hospital mortality	7 [g] (3)

Total study populations were 309, [a]111, [b]75, [c]36, [d]198, [e]180, [f]118, and [g]206 patients.

After the diagnosis of venous thromboembolism, an inferior vena cava filter was implanted in only 57 patients, including 16 patients who had neither clinical signs nor laboratory confirmation of DVT.

In-Hospital and Out-of-Hospital Mortality

The overall in-hospital mortality rate was 14%. There was a substantial increase in the mortality rate from 6% in patients without cardiogenic shock at presentation to 30% in patients who presented with cardiogenic shock (p<0.0001). Excluding the patients who were diagnosed at autopsy, the mortality rate in patients with cardiogenic shock was 20%. In the patients who presented with cardiogenic shock, the mortality rate with and without thrombolytic therapy was 20 and 50%, respectively (p<0.005). In patients who presented without shock, there was no significant difference in mortality rate between those with (8%) and without (4%) thrombolytic therapy (Table V).

Multiple logistic regression analysis demonstrated that the in-hospital mortality was independently associated with the following clinical characteristics at presentation: male gen-

der (OR 2.36; 95% CI 1.07–5.21; p = 0.0034), cardiogenic shock (OR 10.00; 95% CI 4.21–23.72; p < 0.00001), cancer (OR 4.92; 95% CI 1.88–12.89; p = 0.0012), and prolonged immobilization (OR 7.59; 95% CI 2.83–20.36; p = 0.00006) (Table VI).

Only 7 of 206 patients (3%) who survived to discharge and could be followed up were dead after hospital discharge.

Discussion

Patients with venous thromboembolic disease are seen by a variety of medical specialists, including general physicians, surgeons, obstetricians, hematologists, radiologists, and chest physicians. Because thromboembolic disease forms only a small part of the practice of most of these clinicians, it is difficult for them to keep abreast of advances that are important for optimal patient care, especially in Japan where thromboembolic disease is relatively uncommon. Therefore, it is important to provide clinicians with information required to manage venous thromboembolic problems. Recently, although some Japanese studies showed that the number of patients with the diagnosis of APTE has increased considerably, those studies dealt with too few patients to reach significant conclusions.[3] The present Japanese multicenter study of APTE was large enough to make clearer the characteristics of APTE in Japan.

Western studies have demonstrated that the proportion of APTE increases progressively with age, reaching its peak in the seventh decade.[5] The age distribution in our case series was similar to Western studies, but their peak of age was in the sixth decade. One of the reasons may be that Japanese clinicians had a lower interest in making an accurate diagnosis as patients reached age ≥70 because some Japanese autopsy studies showed that the highest incidence of APTE was in the seventh decade.[4]

Reports in Western countries indicated that APTE occurs more often in men than in women.[5, 6] In this patient population, however, the prevalence of APTE in women was higher

TABLE VI Predictors of in-hospital mortality in acute pulmonary thromboembolism [a]

Characteristics	Odds ratio	95% CI	p Value
Age ≥65 years	1.60	0.74–3.47	0.24
Male	2.36	1.07–5.21	0.0034
Cardiogenic shock	10.00	4.21–23.72	<0.00001
Recent major operation	0.41	0.16–1.04	0.061
Recent major trauma or fracture	2.25	0.71–7.13	0.17
Cancer	4.92	1.88–12.89	0.0012
Prolonged immobilization	7.59	2.83–20.36	0.00006
Obesity (BMI≥25.3)	1.27	0.51–3.17	0.61
Onset out of hospital	1.64	0.59–4.59	0.35
Thrombolytic therapy	0.78	0.35–1.72	0.54

Total study opoulation was 309 patients.

[a] Values shown were derived by a logistic regression analysis.

Abbreviations: BMI = body mass index, CI = confidence interval.

than in men. The female/male ratio in the general Japanese population was 0.96, and few Japanese women used oral contraceptives. Furthermore, excluding women who had malignancy or surgery of the breast, uterus, or ovary, the female/male ratio in our patients was 1.26. These results suggest that Japanese women had an increased risk of APTE.

Unfortunately, the time interval between the onset of symptoms and the diagnosis of APTE was still rather long in the present registry, especially in patients without cardiogenic shock at presentation. The low incidence of patients who had symptoms for < 3 days (30%) confirms the low level of awareness and recognition of this disease process by the patients and/or physicians. This delay in arriving at the clinical diagnosis of APTE is probably responsible for some of the early case fatalities. The clinical diagnosis of APTE is highly nonspecific because the clinical features may be simulated by many cardiorespiratory or musculoskeletal disorders. Therefore, the clinical suspicion of APTE seems to be the most important factor in the early diagnosis. Although recent autopsy studies indicate that the incidence of APTE in Japan is comparable with that in Western countries,[4] the clinical diagnosis of APTE in Japan was approximately 200th of the rate in the United States according to a 1999 report.[7] The ratio of correct diagnosis of patients with APTE may be still low in Japan.

In the present study, the most common frequent symptoms were dyspnea (66%) and chest pain (49%); moreover, the combination of dyspnea and chest pain was rather common (32%). These results were similar to other reports;[8] however, the symptoms causing suspicion of minor degrees of APTE, such as cough, hemoptysis, or fever, were quite low in our registry. Because recurrences which occurred with minor degrees of APTE, where the diagnosis was delayed, often became fatal,[9] the diagnosis of a minor degree of APTE also seems to be important.

The incidence of patients with cardiogenic shock in this registry (36%) was similar to other Japanese reports,[10] but was only approximately 10% in Western studies.[11] The underdiagnosis of minor degrees of APTE could account for the higher ratio of cardiogenic shock in Japan.

One third of our patients had triggers for development of APTE, such as urination or defecation (24 patients), the reason for which may be found in the Japanese discharge style in which venous return is disturbed because their legs are acutely bent. Another Japanese study showed that 88% had triggers for development of APTE, and in 42% they developed after urination or defecation, especially among patients who experienced sudden death.[12] Therefore, we would like to call attention to the triggers for the development of APTE so that early diagnosis may be promoted.

The main risk factors for APTE identified in the present registry were similar to other reports.[13] Although coagulopathy such as activated protein C resistance is found in at least half of all Western patients with idiopathic venous thrombosis, only a minority of patients in the present registry had classic coagulation protein deficiencies such as antithrombin III. No patients had activated protein C resistance (which has never been found in Japanese subjects).[14] However, since 58% of outpatients in our registry had no known risk factors for ve-

nous thromboembolism, we may assume that unknown risk factors for venous thrombosis exist in Japanese people.

Recent reports recommend a more flexible diagnostic algorithm instead of the traditional rigid approach of lung scanning followed by pulmonary angiography.[15] In the present study, although many patients underwent pulmonary angiography, approximately 30% were diagnosed by lung scans without pulmonary angiography. These results seem to reflect the expansion of the above new diagnostic trends in Japan.

Only a few of our patients were diagnosed as having APTE at autopsy, although another Japanese study reported that many patients with APTE who died suddenly were diagnosed at autopsy.[12] Without autopsies, it is probable that many patients who died suddenly due to APTE were regarded as unknown deaths due to unknown causes.

The frequency of a search for DVT in the present study was 69% in clinically stable patients, but remained relatively high even in patients with cardiogenic shock. This practice suggests the development of the concern of Japanese clinicians for the presence of a significant peripheral venous clot burden and assessing the risk of recurrent APTE. However, although the sensitivity of the signs for DVT was high (92%), the specificity was not as high (69%) in the present study. Moreover, in most contemporary studies of ambulatory patients with symptoms compatible with DVT, the diagnosis of DVT is confirmed in only approximately one-third even when reliable objective tests are performed.[16] These results suggest that a clinical suspicion of DVT should always be confirmed by objective tests. In the present registry, venous ultrasonography was performed in only 18% of patients who underwent diagnostic procedures for DVT, while contrast venography was performed in 81%. Venous ultrasonography is now the diagnostic method of choice in most patients with clinically suspected DVT because the negative predictive value of a negative venous ultrasound is > 99%.[17] Although the utility of venous ultrasonography has been reported by other Japanese studies,[18] we found that venous ultrasonography was not popular with most Japanese clinicians.

Results from trials of APTE patients with either hemodynamic stability or instability at presentation suggest that they may benefit from thrombolytic therapy.[19] However, there has been no large randomized, controlled trial of thrombolytic therapy in Japan. From the results of the present study, multiple logistic regression analysis did not demonstrate a reduction of in-hospital mortality associated with thrombolytic therapy. However, in-hospital mortality was markedly reduced among those patients with cardiogenic shock at presentation who received thrombolysis, although there was no significant difference in the mortality in those without cardiogenic shock. These results indicate that thrombolytic therapy is effective for APTE patients, especially in those with cardiogenic shock, although this therapy is not yet approved for patients with APTE in the Japanese national health insurance, and APTE is regarded as an indication for thrombolytic therapy.

In this registry, only seven patients underwent pulmonary thromboembolectomy because Japanese clinicians probably believed that the mortality for thromboembolectomy was

excessive; consequently, there are only a few reports of small series of thromboembolectomies.[20, 21] However, in patients without circulatory collapse, the mortality of thromboembolectomy is not very high.[22] To maximize the likelihood of survival, it is crucially important to decide quickly whether to proceed with pulmonary thromboembolectomy, without waiting until the patient develops circulatory collapse. Although only 16 of our patients underwent catheter interventional therapy, this procedure has been recently performed more frequently in some centers in Japan.[23] This approach would decrease the fatal outcome in patients in whom thrombolytic therapy is contraindicated or not effective.

The implantation of inferior vena cava filters has been viewed largely as an alternative therapy when anticoagulation therapy fails or is contraindicated. In the present study, there were not many cases of implantation of inferior vena cava filters. Although the insertion of inferior vena cava filters is increasing, their indication is not yet clear in Japan.

The in-hospital mortality rate in this patient cohort with cardiogenic shock was 30%, which is in accordance with the high mortality rates (18–33%) reported by other investigators in patients with massive APTE.[24, 25] However, the mortality rate was 20% in our patients with cardiogenic shock when we excluded those diagnosed at autopsy. Without cardiogenic shock, the mortality rate was 6% which is in accordance with the low mortality rates (8 and 9.5%) of hemodynamically stable patients included in the Urokinase in Pulmonary Embolism Trial[26] and the Prospective Investigation of Pulmonary Embolism Diagnosis trial,[27] respectively. Furthermore, the out-of-hospital mortality was very low in this registry. These results suggest that, when correctly diagnosed and treated, patients with APTE could have a good outcome in Japan. However, a current problem of APTE in Japan is the high frequency of sudden death. One Japanese study reported that approximately 20% of patients with APTE had a sudden death within 1 h from symptom onset.[12]

In the present study, in-hospital mortality was independently associated with male gender, cardiogenic shock, cancer, and prolonged immobilization. This information may be important for risk stratification as well as for the identification of potential candidates for more aggressive treatment. Recently, the use of percutaneous cardiopulmonary support for patients with APTE, whose respiratory as well as circulatory conditions are unresponsive to cardiopulmonary resuscitation, is on the increase in Japan.[28] Although this technique was performed in only five patients in our series, percutaneous cardiopulmonary support may reduce the mortality rate in APTE with circulatory collapse.

Conclusions

The present registry demonstrated the characteristics, management strategies, and outcome of patients with APTE in Japan. Our patients had almost the same findings as those in Western patients, except for some points that had the possibility of revealing differences between Westerners and Japanese

in the development of APTE. Although the time interval between the onset of symptoms and the diagnosis of APTE was rather long, the patients who were correctly diagnosed and treated had a good outcome. The predictors of in-hospital mortality were male gender, cardiogenic shock, cancer, and prolonged immobilization. Thrombolysis was found to be effective in patients with APTE. Although clinicians have been taking an increasing interest in DVT, venous ultrasonography was not as often performed. These results can prove especially helpful in planning prospective, randomized trials that will clarify the impact of widely used treatment modalities on the outcome of patients with APTE.

Appendix

The following physicians and centers participated in JaSPER:

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Chiba University, Chiba; Takaaki Nakamoto: Department of Cardiology and Pneumology, Dokkyo University School of Medicine, Mibu; Norifumi Nakanishi: Department of Internal Medicine, National Cardiovascular Center, Osaka; Takeshi Nakano: The First Department of Internal Medicine, Mie University, Tsu; Masayuki Nakata: The First Department of Internal Medicine, Toho University, Tokyo; Akihiro Niwa: Musashino Red Cross Hospital, Musashino; Satoshi Ogawa: Department of Medicine, Keio University, Tokyo; Hitoshi Ohteki: Saga Prefectural Hospital Koseikan, Saga; Seiji Ougi: The Second Department of Surgery, Tottori University, Yonago; Kazuyoshi Sakai: Tosei General Hospital, Seto; Tetsuo Sato: Department of Pulmonary Diseases/Infectious Diseases, Jikei University, Tokyo; Tetsuo Shibata: Ichinomiya City Hospital, Ichinomiya; Kunio Shirato: The First Department of Internal Medicine, Tohoku University, Sendai; Takahito Sone: Ogaki Municipal Hospital, Ogaki; Takashi Sueda: Prefectural Hospital of Hiroshima, Hiroshima; Tsuneaki Sugimoto: Kanto Central Hospital, Tokyo; Hajime Suzuki: Department of Respiratory Internal Medicine, Showa University Fujisawa Hospital, Showa University, Yokohama; Shinichi Takamoto: Department of Cardiovascular Surgery, University of Tokyo, Tokyo; Morimasa Takayama: Intensive and Coronary Care Unit, Nippon Medical School, Tokyo; Kan Takeda: Department of Radiology, Mie University, Tsu; Seiya Tsuchiya: Handa City Hospital, Handa; Junichi Udo: The First Department of Surgery, Kumamoto University, Kumamoto; Michio Yamakido: The Second Department of Internal Medicine, Hiroshima University, Hiroshima; Kiyoshi Yoshida: Department of Cardiology, Kawasaki Medical School, Kurashiki; Junichi Yoshikawa: The First Department of Internal Medicine, Osaka City University, Osaka; Masahiro Yoshinaga: Imperial Cooperated Saiseikai Izumio Hospital, Osaka; Chikao Yutani: Department of Pathology, National Cardiovascular Center, Osaka; Hideo Wada: The Second Department of Internal Medicine, Mie University, Tsu; Sachiro Watanabe: Gifu Prefectural Gifu Hospital, Gifu.

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