Inferior Vena Cava Filter is a New Additional Therapeutic Option to Reduce Mortality From Acute Pulmonary Embolism

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Background There are few reports that examine the current imaging and management techniques according to the severity of acute pulmonary embolism (APE) or that clarify whether the management strategy ameliorated the mortality from APE.

Methods and Results The study group were 456 patients with APE who were clinically diagnosed before their death. The severity at diagnosis, and the imaging and management techniques were analyzed. Mortality from APE was 0.8% in patients without shock nor right ventricular overload, 2.7% in patients with right ventricular overload without shock, 15.6% in patients with shock, and 52.4% in patients with cardiopulmonary arrest (p<0.0001). In the more severe cases, pulmonary angiography and trans-thoracic echocardiography were used more frequently, whereas both ventilation and perfusion lung scans were used less frequently. Computed tomography was used widely, regardless of the severity. Thrombolytic therapy and catheter therapy were used more frequently in the more severe cases, but an inferior vena cava filter was the only management strategy that reduced the mortality from APE.

Conclusions The severity of APE at diagnosis affected the selection of both the diagnostic techniques and the type of management. Implantation of inferior vena cava filters reduced the mortality from APE.

Key Words: Complications; Filter; Mortality; Thrombolysis

A cute pulmonary embolism (APE) is potentially fatal1–3 and although the number of cases in Japan is lower in Western countries, the incidence has been increasing in recent years.4–6 Many techniques to decrease mortality have been tried, including the use of heparin7, thrombolytic therapy8–11 surgical embolectomy, percutaneous cardiopulmonary support (PCPS)12 catheter intervention and inferior vena cava (IVC) filter.13 However, only thrombolytic therapy for hemodynamically unstable patients8 and heparin7 have been shown to effectively reduce mortality. Recently, computed tomography (CT)14 and magnetic resonance (MR) angiography15 in addition to pulmonary angiography and lung scintigraphy, have become useful tools for diagnosing APE. Kasper et al reported that APE patients with cardiogenic collapse underwent diagnostic lung scintigraphy and pulmonary angiography less frequently and thrombolytic therapy more often1 and other than that report, more information on the most suitable diagnostic imaging tests and management strategies is required to improve the treatment and outcome of APE.

In the United States, 0.1–0.5% of surviving cases of APE progressed to chronic thromboembolic pulmonary hypertension16,17 compared with approximately 30% of patients with pulmonary embolism in Japan becoming chronic.18,19 Therefore, the present study was designed to examine the influence of the selection of diagnostic methods and treatments for APE, and to clarify which are more strongly associated with reduced mortality.

Methods

Study Population The study was performed using data from the third registry (the present registry) of the Japanese Society of Pulmonary Embolism Research (JaSPER) in which 629 patients with pulmonary embolism were enrolled. The cases of APE (461 patients, 73.3%), defined as an acute onset illness of less than 2 weeks duration, were all diagnosed between November 2000 and August 2003 in the participating centers in JaSPER (Appendix 1). The diagnosis of pulmonary embolism was made by pulmonary angiography, CT, or MR angiography, which indicated vessel occlusions or intraluminal filling defects, by a lung perfusion scan that indicated the high probability of pulmonary embolism20 by trans-esophageal echocardiography or by

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autopzy.

Because APE was not diagnosed before autopsy in 5 cases, we used the data from 456 of the 461 cases of APE and the clinical characteristics are shown in Table 1. The mean age of the patients at diagnosis was 63.3±16.0 years (range 10–98). Right ventricular overload was not evaluated in 7 patients without shock and the diagnostic tests were not reported in an additional 4 patients, in total 445 patients with APE were used in the evaluation of the clinical diagnostic tests and 449 patients in that of the therapeutic management according to the severity of the disease.

All decisions regarding the diagnostic workup, treatment, and cause of death, whether for a first APE attack or recurrent APE, were made by the attendant clinicians. The steering committee took care not to influence the management strategy employed in the participating hospitals.

For the comparison with the mortality in the previous registries, the first (between January 1994 and October 1997; 309 APE patients) and second registries (between November 1997 and October 2000; 257 APE patients) were also used.

**Data Acquisition**

Complete information on the clinical course and the diagnostic and therapeutic modalities of the patients entered into the registry was obtained by means of a standardized questionnaire sent to the participating centers by the steering committee. Data were collected on (1) the severity of APE (Group A = cardiopulmonary arrest, Group B = shock, Group C = right ventricular overload without shock, and Group D = relatively stable state without right ventricular overload nor shock); (2) 30-day mortality after the diagnosis of APE; (3) clinical symptoms and signs of the patients at diagnosis; (4) presence of underlying diseases or predisposing factors for APE; (5) definitive diagnostic procedures given to patients; (6) treatments given to patients; and (7) bleeding complications. Shock was defined as hypotension (systolic blood pressure <90 mmHg or a decrease in systolic blood pressure of at least 40 mmHg during a period of less than 15 min) not caused by newly emerged arrhythmia, hypovolemia or sepsis, accompanied by clinical signs of organ hypoperfusion and hypoxia (eg, impaired consciousness, urine output <30 ml/h, cold and clammy extremities). Right ventricular overload was not evaluated in 7 patients without shock and the diagnostic tests were not reported in an additional 4 patients, in total 445 patients with APE were used in the evaluation of the clinical diagnostic tests and 449 patients in that of the therapeutic management according to the severity of the disease.

**Statistical Analysis**

Statistical analysis was carried out using StatView 5.0 (SAS Institute Inc, Cary, NC, USA). All continuous variables were expressed as mean±standard deviation. Non- ordinal categorical data were analyzed by chi-square statistics, and ordinal categorical data by Mann–Whitney test. We also used multiple logistic regression analysis. The results of the logistic regression models are presented as estimated odds ratios with the corresponding 95% confidence intervals (CI). Survival data were analyzed by log rank test. All significant tests were two-tailed.

**Results**

### Severity and Mortality From APE

Groups A, B, C and D consisted of 21, 77, 225 and 126 patients, respectively. In Group A, 5 patients were not diagnosed before death, and 11 patients in Group A (52.4%), 12 in Group B (15.6%), 6 in Group C (2.7%), and 1 in Group D (0.8%) died within 30 days of the diagnosis (p<0.0001) (Table 2). Cumulative survival curves are shown in Fig 1. In Group A, 2 patients showed consciousness levels of 300, 2 continued to have disturbances of mental capacity, and only 6 patients had no residual brain dysfunction 30 days after diagnosis. Mortality has reduced in recent years because of a decrement in the ratio of severe cases (cases with cardiopulmonary arrest or shock were 35.9%, 30.7% and 22.3% in the first, second and third surveys, respectively).
When analyzing after stratification, the mortality in both severe cases and less severe cases was unchanged between the 3 surveys (Table 3).

**Diagnostic Techniques**

D-dimer was examined in 80.4% of patients whose onset occurred before admission and 70.5% of patients whose onset occurred in hospital (p=0.015). A high level of D-dimer (≥500 ng/ml) was found in 95.9% of the pre-admission cases and in 96.3% of the in-hospital cases (p>0.99).

The diagnostic imaging techniques used according to the severity are shown in Table 4. Pulmonary angiography and trans-thoracic echocardiography were chosen for the more severe cases, and perfusion and ventilation lung scans were used in the less severe cases. CT was employed regardless of the severity of APE. Deep vein thrombosis (DVT) was less frequently sought in the severe patients.

**Management**

The types of management strategies according to the severity are shown in Table 5. Thrombolysis, PCPS, surgical embolectomy, cardiotonic agents, artificial ventilation and catheter therapy were used in the severe cases, but the use of heparin and IVC filters was independent of the severity.

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**Table 3** Comparison of 30-Day Mortality From Acute Pulmonary Embolism in 3 Registries

<table>
<thead>
<tr>
<th></th>
<th>First21</th>
<th>Second22</th>
<th>Third (present data)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>44/309 (14.2%)</td>
<td>31/257 (12.1%)</td>
<td>35/461 (8.0%)</td>
<td>0.01</td>
</tr>
<tr>
<td>CPA or cardiogenic shock</td>
<td>33/111 (29.7%)</td>
<td>25/79 (31.6%)</td>
<td>28/103 (27.2%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Without CPA nor shock</td>
<td>11/198 (5.6%)</td>
<td>6/178 (3.4%)</td>
<td>7/358 (2.0%)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

CPA, cardiopulmonary arrest.

**Table 4** Diagnostic Techniques Used According to Severity of Acute Pulmonary Embolism

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=21)</th>
<th>Group B (n=77)</th>
<th>Group C (n=221)</th>
<th>Group D (n=126)</th>
<th>p value</th>
<th>Unclassified (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary angiography</td>
<td>12 (57.1%)</td>
<td>32 (41.6%)</td>
<td>91 (41.2%)</td>
<td>29 (23.0%)</td>
<td>0.0003</td>
<td>1</td>
</tr>
<tr>
<td>Perfusion lung scan</td>
<td>3 (14.3%)</td>
<td>37 (48.1%)</td>
<td>134 (60.6%)</td>
<td>101 (80.2%)</td>
<td>&lt;0.0001</td>
<td>5</td>
</tr>
<tr>
<td>Ventilation lung scan</td>
<td>1 (4.8%)</td>
<td>9 (11.7%)</td>
<td>42 (19.0%)</td>
<td>31 (24.6%)</td>
<td>0.006</td>
<td>0</td>
</tr>
<tr>
<td>CT</td>
<td>9 (42.9%)</td>
<td>43 (55.8%)</td>
<td>150 (67.9%)</td>
<td>73 (57.9%)</td>
<td>0.61</td>
<td>5</td>
</tr>
<tr>
<td>MRI</td>
<td>1 (4.8%)</td>
<td>0 (0.0%)</td>
<td>2 (0.9%)</td>
<td>4 (3.2%)</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>TTE</td>
<td>12 (57.1%)</td>
<td>43 (55.8%)</td>
<td>114 (51.6%)</td>
<td>34 (27.0%)</td>
<td>&lt;0.0001</td>
<td>0</td>
</tr>
<tr>
<td>TEE</td>
<td>2 (9.5%)</td>
<td>0 (0.0%)</td>
<td>2 (0.9%)</td>
<td>1 (0.8%)</td>
<td>0.27</td>
<td>0</td>
</tr>
<tr>
<td>DVT assessment</td>
<td>11 (52.4%)</td>
<td>50 (64.9%)</td>
<td>201 (91.0%)</td>
<td>113 (89.7%)</td>
<td>&lt;0.0001</td>
<td>6</td>
</tr>
</tbody>
</table>

Deep vein thrombosis (DVT) was searched for using lower limb venous compression ultrasonography, computed tomography (CT), contrast venography, radio-isotope venography or magnetic resonance imaging (MRI). TTE, trans-thoracic echocardiography; TEE, trans-esophageal echocardiography.

**Table 5** Management of Acute Pulmonary Embolism

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=21)</th>
<th>Group B (n=77)</th>
<th>Group C (n=225)</th>
<th>Group D (n=126)</th>
<th>p value</th>
<th>Unclassified (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>18 (85.7%)</td>
<td>75 (97.4%)</td>
<td>213 (94.7%)</td>
<td>113 (89.7%)</td>
<td>0.13</td>
<td>5</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>13 (61.9%)</td>
<td>55 (71.4%)</td>
<td>145 (64.4%)</td>
<td>54 (42.9%)</td>
<td>&lt;0.0001</td>
<td>2</td>
</tr>
<tr>
<td>IVC filter</td>
<td>6 (28.6%)</td>
<td>23 (29.9%)</td>
<td>87 (35.7%)</td>
<td>42 (33.3%)</td>
<td>0.69</td>
<td>3</td>
</tr>
<tr>
<td>PCPS</td>
<td>11 (52.4%)</td>
<td>7 (9.1%)</td>
<td>2 (0.9%)</td>
<td>1 (0.8%)</td>
<td>&lt;0.0001</td>
<td>0</td>
</tr>
<tr>
<td>Surgical embolectomy</td>
<td>1 (4.8%)</td>
<td>6 (7.8%)</td>
<td>2 (0.9%)</td>
<td>1 (0.8%)</td>
<td>0.094</td>
<td>0</td>
</tr>
<tr>
<td>Cardiotonic agent</td>
<td>13 (61.9%)</td>
<td>18 (23.4%)</td>
<td>6 (2.7%)</td>
<td>1 (0.8%)</td>
<td>&lt;0.0001</td>
<td>0</td>
</tr>
<tr>
<td>Artificial ventilation</td>
<td>15 (71.4%)</td>
<td>14 (18.2%)</td>
<td>7 (3.1%)</td>
<td>4 (3.2%)</td>
<td>&lt;0.0001</td>
<td>0</td>
</tr>
<tr>
<td>Catheter therapy</td>
<td>4 (19.0%)</td>
<td>12 (15.6%)</td>
<td>28 (12.4%)</td>
<td>3 (2.4%)</td>
<td>0.0004</td>
<td>1</td>
</tr>
<tr>
<td>Warfarin*</td>
<td>5 (50.0%)</td>
<td>48 (73.8%)</td>
<td>189 (86.3%)</td>
<td>100 (80.0%)</td>
<td>0.28</td>
<td>7</td>
</tr>
</tbody>
</table>

IVC, inferior vena cava; PCPS, percutaneous cardiopulmonary support. *Cases who died within 30 days were excluded and this population was 419 (10 in Group A, 65 in Group B, 219 in Group C, and 125 in Group D).
Diagnosis and Treatment of Pulmonary Embolism

therapeutic strategy for this period is needed. Boettiger et al had the day when APE was diagnosed or the day after, so a mortality from APE (odds ratio 95% CI p value)

0.64 0.59–3.28
0.01 0.84–4.89
0.0001 0.0001
0.041 0.041
0.002 0.002
0.18 0.18

Discussion

The present study shows that the selection of diagnostic methods and treatment was influenced by the severity of APE, and that only inferior vena cava filters lowered the mortality from APE.

Mortality

In general, the mortality from APE has been gradually reducing, but analysis after stratification based on the severity of APE showed no difference in mortality among the 3 registries. The reason for the decreased mortality in the overall cases was that less severe cases are being diagnosed, which also implies that a substantial improvement in the mortality from APE could not be achieved during the 10-year study period. Kasper et al reported a mortality rate of 8.1% in APE with right ventricular overload (Group 1 in their report), 17% in cases with shock (Group 2 and 3), and 65% in cases of cardiogenic collapse (Group 4); and our results are consistent with their data.

As shown in Fig 1, many of the deaths occurred either on the day when APE was diagnosed or the day after, so a therapeutic strategy for this period is needed. Boettiger et al suggested that thrombolytic therapy combined with heparin might improve the mortality in patients with initial, unsuccessful treatment of cardiopulmonary arrest caused by cardiac reasons including pulmonary embolism and myocardial infarction; but negative results have been reported concerning thrombolysis for patients with cardiopulmonary arrest; and the efficacy of thrombolytic therapy in this situation remains controversial.

Detailed analysis of the clinical outcomes of the 30-day surviving patients in Group A found that only 6 (28.6% of patients diagnosed before their deaths) did not have residual cerebral damage, so preventing hypoxic injury to the cerebrum is an important problem in cases of cardiopulmonary arrest.

Diagnostic Methods

The efficacy of D-dimer for the diagnosis of APE has been established, especially as a negative predictor. Our study could not address the specificity, but the sensitivity to APE was high enough in both pre-admission and in-patients. It was to be expected that D-dimer was used more frequently in pre-admission patients than for in-patients, because D-dimer is 500 ng/ml or more in many situations.

The present study revealed that the selection of diagnostic methods depended on the severity of APE with respect to some imaging techniques, but not with others. Pulmonary angiography and trans-thoracic echocardiography were more frequently used for the more severe cases, probably because aggressive catheter interventional therapy can follow pulmonary angiography, and trans-thoracic echocardiography can be performed anywhere within a short time. Both ventilation and perfusion lung scans were performed less frequently in the severe cases, which was comparable to previously reported data. There are special situations in Japan in which radioisotopes can be used in restricted areas, and only in an emergency in a very limited number of institutions. On the other hand, CT was widely used to

Table 6 Bleeding Complications

<table>
<thead>
<tr>
<th></th>
<th>Heparin alone (n=160)</th>
<th>With thrombolysis (n=269)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>1 (0.6%)</td>
<td>9 (3.3%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Need for blood transfusion</td>
<td>5 (3.1%)</td>
<td>19 (7.1%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Other minor hemorrhage</td>
<td>5 (3.1%)</td>
<td>18 (6.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Total bleeding complications</td>
<td>11 (6.9%)</td>
<td>46 (17.1%)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 7 Relation Between 30-Day Mortality and Management in the Acute Phase

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65 years</td>
<td>0.59</td>
<td>0.24–1.45</td>
</tr>
<tr>
<td>Male</td>
<td>1.30</td>
<td>0.51–3.28</td>
</tr>
<tr>
<td>Heparin</td>
<td>0.84</td>
<td>0.15–4.89</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>0.81</td>
<td>0.32–2.01</td>
</tr>
<tr>
<td>IVC filter</td>
<td>0.16</td>
<td>0.04–0.64</td>
</tr>
<tr>
<td>Group A*</td>
<td>192</td>
<td>20.7–1,781</td>
</tr>
<tr>
<td>Group B*</td>
<td>27.9</td>
<td>3.4–231</td>
</tr>
<tr>
<td>Group C*</td>
<td>4.3</td>
<td>0.36–37.1</td>
</tr>
</tbody>
</table>

Multiple logistic regression analysis was used to estimate the influence of management on mortality. *Compared with Group D. CI, confidence interval.
diagnose APE regardless of the severity of the disease. Helical CT can provide immediate images and has similar diagnostic power to pulmonary angiography, which is the gold standard for the diagnosis of APE. Both MR and trans-esophageal echocardiography were used less frequently, and their use did not relate to the severity of APE.

Management

The management of APE was also affected by the initial severity. Heparin and IVC filters were used regardless of the severity, in addition to warfarin in the 30-day surviving cases. In the present study, IVC filters were used more frequently in patients with venous thrombus than in those without, whereas thrombolytic therapy, PCPS, surgical embolectomy, cardiotoxic agents, artificial ventilation, and catheter therapy were used more frequently in the more severe cases. Thrombolysis can reduce mortality in cases with unstable hemodynamics and decreases the need for additional therapy and recurrent pulmonary embolism in the acute phase. Our previous study showed that, in patients with right ventricular afterload stress, better outcomes were observed in the thrombolytic group than in the anticoagulation group, although the difference did not reach statistical significance. Therefore, thrombolytic therapy in severe cases may be recommended, although Aklog et al showed that surgical embolectomy was a viable alternative to thrombolytic therapy, which has a risk of fatal bleeding complications. However, the indications for surgical embolectomy still remain to be determined.

We were not able to confirm that heparin and thrombolytic therapy reduced the 30-day mortality from APE, but it was decreased by IVC filter implantation, which implies that IVC filters prevent recurrent pulmonary embolism in the acute phase, thereby saving lives. Contraindications for or complications of anticoagulation accounted for 57.9% of the indications for IVC filters in the report by Athanasoulis et al, and these indications have been widely accepted, although IVC filters have been used in patients without those indications; however, the prophylactic use of IVC filters in patients with high risk of APE or venous thrombosis, or as an ancillary treatment for patients using anticoagulant and/or thrombolytic agents remains controversial. In our study, the use of IVC filters was independent of the use of heparin or warfarin in the 30-day surviving cases, but was higher in patients administered thrombolytic agents. Much of the indication for IVC filters in our study was ancillary to other types of treatment, and our data suggested that such use of IVC filters effectively reduced the mortality from APE.

The efficacy of IVC filters needs to be assessed in terms of short-term and long-term results. Our study showed the short-term efficacy of IVC filters in reducing mortality, but did not deal with long-term effects. A randomized control study in patients with acute venous thrombosis showed that IVC filters prevented acute pulmonary re-embolism, but did not reduce mortality from APE. Moreover, in that study IVC filters increased the incidence of DVT 2 years after implantation, although less than 40% of the subjects were symptomatic cases of APE and cases requiring treatment with thrombolytic agents were excluded. White et al showed that IVC filters increased the 1-year cumulative rate of re-hospitalization because of venous thrombosis in patients with primary pulmonary embolism. These findings indicate that the efficacy of IVC filters is reduced in the long-term and therefore the temporary or retrievable type should be chosen, if possible.

We first documented that IVC filters reduced the mortality from APE in the acute phase, but many studies have attempted to assess management strategies and could not demonstrate the efficacy of IVC filters on mortality. Our results on IVC filters may have been influenced by the high rate of severe cases in which thrombolytic agents were used and by the higher rate of IVC filter use compared with those previous reports.

There are only 16 prospective studies on IVC filters from 1975 to 2000 and among these, only 1 randomized control study. Generally, the quality of the literature on IVC filters is low and more detailed studies are needed to address the types of patients that would benefit from filter implantation, what type of filter would be best, and whether combined treatment using IVC filters and thrombolytic therapy is superior to the use of either alone.

Conclusions

In the present study the severity of APE at diagnosis affected the selection of both diagnostic and management techniques. Only implantation of IVC filters reduced the mortality from APE, at least in the short term.

References


**Appendix 1**

The following physicians and centers participated in JaSPER: Second Department of Internal Medicine, Akita University, Akita; Department of Radiology, Graduate School of Medicine, Chiba University, Chiba; Department of Cardiology and Pneumology, Dokkyo University School of Medicine, Mibu; Department of Pulmonary Medicine, Fukushima Medical University, Fukushima; Ichinomiya City Hospital, Ichinomiya; Izumi City Hospital, Osaka; Department of Surgery, Jichi Medical School, Minamikawachi; Department of Thoracic and Cardiovascular Surgery, Kanazawa Medical University, Ishikawa; Department of Medicine, Keio University, Tokyo; Department of Anesthesiology, Kitazato University, Sagamihara; Division of Cardiovascular and Respiratory Medicine, Graduate School of Medicine, Kobe University, Kobe; Metropolitan Hiroo General Hospital, Tokyo; Mie Prefectural General Medical Center, Yokkaichi; The First Department of Internal Medicine, Mie University, Tsu; Masashino Red Cross Hospital, Musashino; Second Department of Internal Medicine, Nagasaki University, Nagasaki; Department of Anesthesiology, Nara Medical School, Kashihara; Nara Red Cross Hospital, Nara; Intensive and Coronary Care Unit, Nippon Medical School, Tokyo; Saka General Hospital, Shiojima; Sasebo City General Hospital, Sasebo; Seirei Mikatahara General Hospital, Hamamatsu; Sendai Open Hospital, Sendai; Department of Respiratory Internal Medicine, Showa University Fujisawa Hospital, Showa University, Yokohama; Department of Cardiology, St Marianna University School of Medicine, Kawasaki; Tachikawa Kyosai Hospital, Tachikawa; Department of Cardiology, Toho University Omori Hospital, Toho University, Tokyo; Respiratory Center, Toho University Omori Hospital, Toho University Tokyo; Department of Cardiovascular Medicine, Graduate School of Medicine, Tohoku University, Sendai; Tokyo Teishin Hospital, Tokyo; Toranomon Hospital, Tokyo; Division of Organ Regeneration Surgery, Tottori University, Yonago; Department of Cardiovascular Surgery, Graduate School of Medicine, University of Tokyo, Tokyo; The First Department of Internal Medicine, Yamagata University, Yamagata.