

[ ORIGINAL ARTICLE ]

# Clinical Characteristics of Heart Failure from Case Reports Presented at the Regional Meeting of the Japanese Society of Internal Medicine

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## Abstract:

**Objective** To examine case reports presented at the Regional Meeting of the Japanese Society of Internal Medicine in order to clarify the underlying disease and prognosis of heart failure, which is often caused by non-cardiovascular diseases.

**Methods** We examined 49,693 case reports from the Japanese Society of Internal Medicine database. A total of 2,893 reports were included after excluding 46,022 reports that did not include the term “heart failure” and 778 reports with no indications of symptoms of heart failure. We assessed each patient’s basal disease, and according to the abstracts, we reported their prognosis as dead or alive.

**Results** Of the 2,893 reports included, 1,952 (67.5%) and 941 (32.5%) had cardiovascular and non-cardiovascular diseases as the causes, respectively; these cases were attributed to 725 different diseases, 196 (27.0%) and 529 (73.0%) of which were cardiovascular and non-cardiovascular diseases, respectively. In addition, 91 different side effects were identified. The percentage of cases of heart failure-related mortality was significantly higher among the patients with non-cardiovascular diseases than in those with cardiovascular diseases (17.8% vs. 10.8%;  $p < 0.001$ ). Of the diseases reported as causes of heart failure in more than 10 reports, pulmonary tumor thrombotic microangiopathy (87%), multiple myeloma (50%), and amyloidosis (47%) accounted for the highest percentages of heart failure-related mortality.

**Conclusion** Because heart failure is often caused by non-cardiovascular diseases, a broad study of case reports on internal medicine is important for cardiologists.

**Key words:** heart failure, case report, internal medicine

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## Introduction

Heart failure (HF), a cardiac disease, is an important concern owing to its high prevalence and associated mortality. There are more than 6.5 million adults with HF in the United States (1). In Japan, the number of patients with HF is expected to reach 1.2 million by 2020 (2).

HF is often caused by ischemic heart disease, hypertension, or valvular disease (3-5). However, many cases of HF are also caused by systemic diseases and malignant tumors.

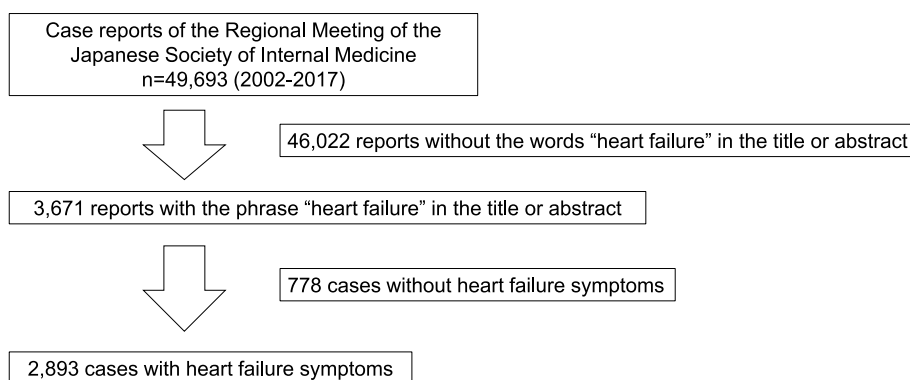
Hence, patients with HF are likely to be examined by both cardiologists and non-cardiologists at hospitals or clinics. For example, there are various symptoms and causes of Takotsubo cardiomyopathy, and case reports have been published from different types of hospital and clinical departments. Thus, non-cardiologists must understand HF, and cardiologists must be aware of the underlying non-cardiovascular diseases that can lead to HF.

Learning the differential diagnoses of HF will help both cardiologists and non-cardiologists. The studies conducted by Harrison (6), Goldman-Cecil (7), and Braunwald (8) pro-

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**Figure 1.** Flowchart of the search for case reports on heart failure.

vide a systematic understanding of HF. However, these studies cannot be expected to have completely described the diversity of HF cases; furthermore, frequent updates are difficult to carry out.

The Taiwan National Health Insurance Program is a nationwide initiative; its database contains detailed background characteristics of patients with HF (9). However, in the database, it is unclear what percentage of cases was compiled by non-cardiologists. Consequently, we sought to clarify the nature of the underlying diseases and HF-related fatalities by analyzing case reports presented at the Japanese Society of Internal Medicine. Of note, these reports originated from both cardiovascular and non-cardiovascular departments.

## Materials and Methods

The Japanese Society of Internal Medicine holds regional meetings in Japan (e.g. in the Kanto region, Kinki region, etc.) nine times a year. Since 1946, 1,000 case reports have been presented at these meetings. Since 2002, reports presented at regional meetings across Japan have been published on the conference website, and the total number of reports in the conference database now exceeds 49,000.

Using an editing tool for abstracts (Shourei-Kun; [https://www.naika.or.jp/info/info\\_kensaku/](https://www.naika.or.jp/info/info_kensaku/)), we examined 49,693 case reports from the Japanese Society of Internal Medicine database deposited from 2002 to 2017. We excluded 46,022 reports that did not include the phrase “heart failure” based on a simple text search. After peer-reviewing the abstracts, we also excluded 778 reports with no reported symptoms of HF. We also determined the basal disease, reporting department, and prognosis for the remaining 2,893 cases with HF (5.8% of 49,693 case reports; Fig. 1). The prognosis was classified as dead or alive, according to the abstracts.

The cases originated across the following 10 department types: 1) cardiology, 2) allergy and rheumatology, 3) general internal medicine, 4) infectious disease, 5) hematology, 6) respiratory medicine, 7) gastroenterology, 8) neurology, 9) nephrology, and 10) endocrinology and metabolism. We further classified the cases into the following 18 categories: 1) cardiovascular disease, 2) congenital heart disease, 3) cardiac tumor, 4) connective tissue diseases, 5) infectious dis-

eases, 6) hematological diseases, 7) respiratory diseases, 8) gastrointestinal hepatic, biliary and pancreatic diseases, 9) neurological diseases, 10) kidney diseases, 11) endocrine diseases, 12) malignant tumors, 13) hematological malignancies, 14) inflammatory disorders, 15) systemic disorders, 16) genetic disorders, 17) side effects, and 18) others. Supplementary material 1 presents the cases classified under connective tissue diseases, systemic disorders, and genetic disorders. We subsequently combined categories 1)-3) as cardiovascular disease cases and categories 4)-18) as non-cardiovascular disease cases.

We used an unpaired *t*-test and analysis of variance (ANOVA) to evaluate and compare, respectively, the percentage of fatal HF cases among the case reports originating from the cardiovascular and non-cardiovascular departments. We analyzed all data using the Statistical Package for the Social Sciences software program (SPSS v.16.0; Chicago, USA).  $p < 0.05$  was considered statistically significant.

## Results

Of the 2,893 total case reports on HF, 1,952 (67.5%) and 941 (32.5%) originated from cardiovascular and non-cardiovascular departments, respectively (Table 1). The etiology was cardiovascular disease in 1,181 cases (40.8%) and non-cardiovascular disease in 1,712 (59.2%).

Table 2 presents the underlying diseases for more than 10 cases. Amyloidosis and sarcoidosis were the major underlying non-cardiovascular diseases, whereas ischemic heart disease, dilated cardiomyopathy, Takotsubo cardiomyopathy, and infective endocarditis were the major underlying cardiovascular diseases. Fig. 2 presents the underlying diseases (total 30) and the originating department of each case of Takotsubo cardiomyopathy; although the reports were mostly from cardiology departments (68.1%), the major underlying causes were endocrine disease (20.2%), infectious disease (13.0%), respiratory disease (7.2%), and nervous disease (7.2%).

In all, 725 diseases were identified, including 196 (27.0%) types of cardiovascular disease and 529 (73.0%) types of non-cardiovascular diseases. In addition, 91 different side effects were identified (Fig. 3). Fig. 4 shows the

**Table 1. Case Reports of Heart Failure Classified by Department of Origin.**

Department	Number of reports	Case reports with the phrase "heart failure" in the title or abstract	Cases of heart failure
Cardiology	7,761	2,285	1,952 (67.5)
Allergy and rheumatology	3,983	132	111 (3.8)
General internal medicine	423	16	13 (0.4)
Infectious diseases	3,952	114	64 (2.2)
Hematology	4,728	170	126 (4.4)
Respiratory medicine	5,685	201	144 (5.0)
Gastroenterology	8,419	160	69 (2.4)
Neurology	4,634	89	50 (1.7)
Nephrology	3,535	203	132 (4.6)
Endocrinology and metabolism	6,573	301	232 (8.0)
Total	49,693	3,671	2,893 (100)

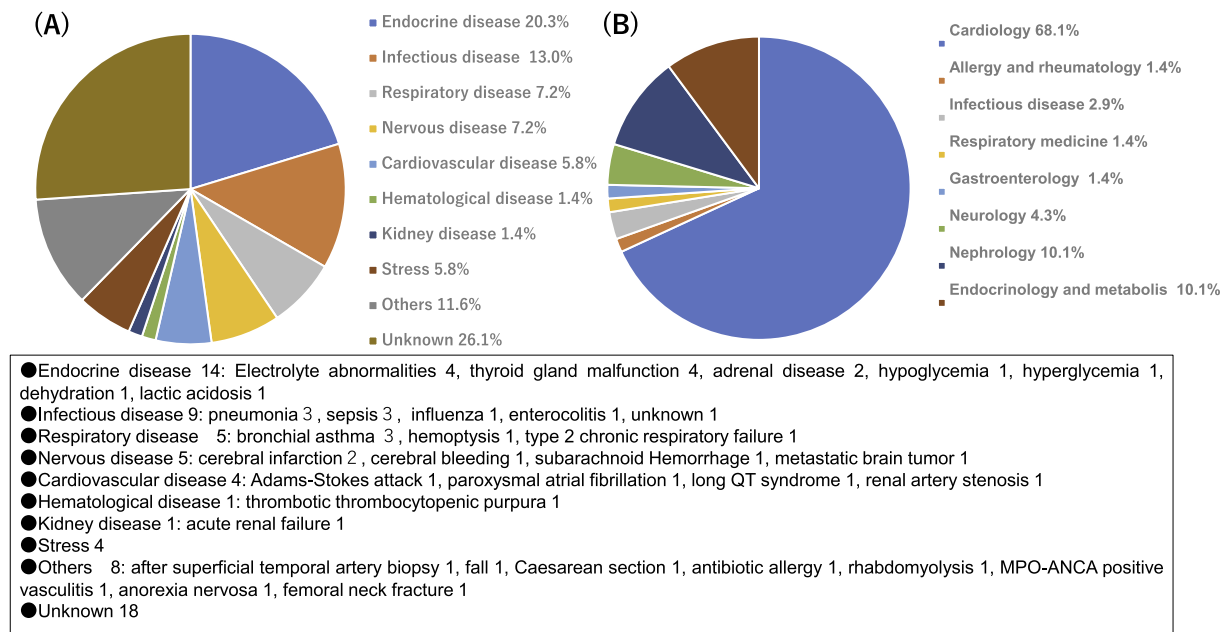
Data is shown as number or percentage of originating department in cases of heart failure.

**Table 2. Underlying Diseases Implicated in More than 10 Cases.**

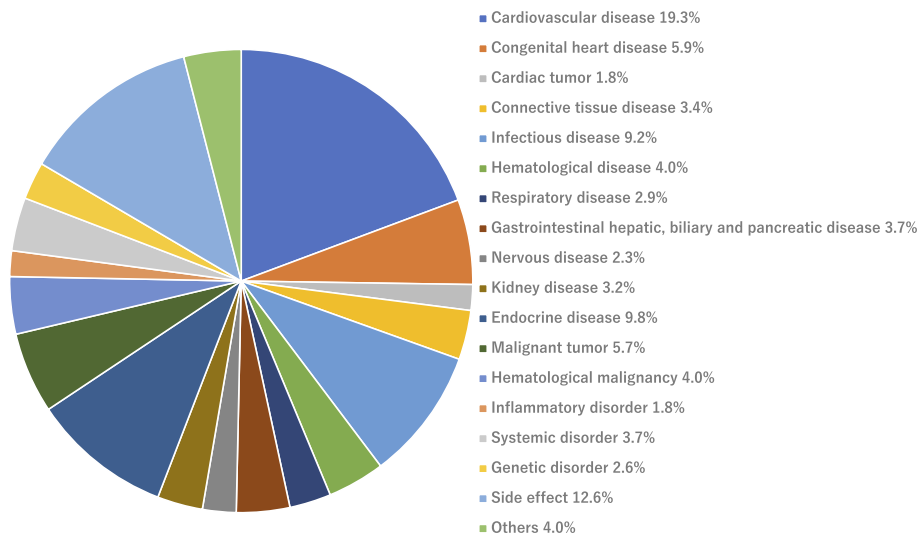
Disease	Number		
Amyloidosis	155	Hypertrophic obstructive cardiomyopathy	19
Ischemic heart disease	112	Acromegaly	19
Infectious endocarditis	89	Hyperthyroidism	17
Dilated cardiomyopathy	71	Multiple myeloma	16
Takotsubo myopathy	69	Vasospastic angina	16
Sarcoidosis	66	Acute myocarditis	16
Acute myocardial infarction	65	Fulminant myocarditis	16
Vitamin B1 deficiency	44	Hypertensive heart disease	16
Thyroid crisis	43	Polymyositis	15
Systemic lupus erythematosus	35	Pulmonary tumor thrombotic microangiopathy	15
Graves' disease	35	Malignant hypertension	14
Aortic valve stenosis	34	Anthracycline-associated	13
Eosinophilic myocarditis	34	Pulmonary hypertension	12
Atrial fibrillation	32	Trastuzumab-associated	12
Constrictive pericarditis	31	Corrected transposition of the great arteries	12
Non-compaction	31	Sjögren's syndrome	11
Peripartum cardiomyopathy	30	Rheumatoid arthritis	11
Hyperthyroidism	30	Tuberculous pericarditis	11
Malignant lymphoma	29	Cushing's syndrome	11
Mitochondrial disease	28	Lung cancer	11
Systemic scleroderma	26	Crow-Fukase's syndrome	11
Aortitis syndrome	24	Acute coronary syndrome	10
Obesity hypoventilation syndrome	23	After mitral valve replacement	10
Mitral regurgitation	22	Dermatomyositis	10
Pheochromocytoma	20	Sleep apnea syndrome	10
Renal artery stenosis	19	Fabry disease	10

percentage of fatal HF cases according to the originating department. The percentages of fatal HF cases were high among the reports originating from the hematology (27.0%), respiratory medicine (30.6%), and gastroenterology (27.7%) departments. The percentage of fatal HF cases was significantly higher among reports originating from non-cardiovascular departments than among those originating from cardiovascular departments (17.8% vs. 10.8%, respectively;  $p < 0.001$ ). The diseases implicated in more than 10

cases were pulmonary tumor thrombotic microangiopathy (PTTM; 87%), multiple myeloma (50%), and amyloidosis (47%). These diseases accounted for the highest percentages of HF-related mortality. The number of reported PTTM cases (by year) is presented in Table 3. Although PTTM is associated with a high mortality rate, surviving cases were reported in 2012 and 2017.



**Figure 2.** Causes of diseases (A) and the originating departments (B) for the case reports on Takotsubo cardiomyopathy.



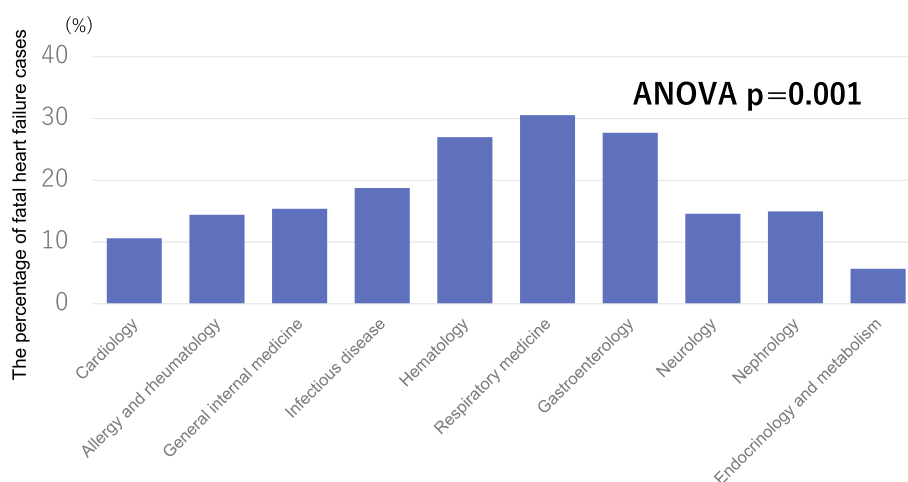
**Figure 3.** The number of diseases identified in 18 categories.

## Discussion

HF case reports accounted for 5.8% of all internal medicine case reports. Of the 2,893 cases of HF, 40% were caused by cardiovascular diseases; however, the underlying cardiovascular disease was identified in only 20% of all cases.

We assessed all cases of HF in our conference database to determine the different underlying diseases. It has recently become possible to perform the differential diagnosis of HF using information available on the Internet (e.g. websites like UpToDate.com.) and in medical textbooks (e.g. those authored by Harrison, Goldman-Cecil, Braunwald,

etc.) (6-8). The leading textbooks are growing thicker each year with the increase in knowledge concerning these diseases, making the Internet increasingly useful for its convenience and ease of access. However, the information available on the Internet is not always up-to-date due to delays in publication; furthermore, racial differences in the available sources may exist. In Japan, Takotsubo cardiomyopathy is a cause of HF, and in recent years, this disease has been frequently reported and garnered substantial attention (10). However, because there are several causes of Takotsubo cardiomyopathy, the relevant reports have originated from different types of hospitals and clinical departments. In the present study, we identified 725 separate disease designations. It is thus impractical to describe all of the potential underlying



**Figure 4.** The percentage of fatal heart failure cases.

**Table 3.** Reported Number of Pulmonary Tumor Thrombotic Microangiopathies by Year.

Year	Alive report	Death report
2006	0	1
2007	0	0
2008	0	0
2009	0	0
2010	0	1
2011	0	2
2012	1	2
2013	0	1
2014	0	1
2015	0	3
2016	0	1
2017	1	1

ing diseases in a single textbook. However, using case reports from the Regional Meeting of the Japanese Society of Internal Medicine database, we were able to investigate the details of the underlying diseases in recent cases of HF, including Takotsubo cardiomyopathy. The side effects of various therapeutic drugs could also be quickly checked using this database.

We found that a high percentage of HF-related mortality was attributable to PTTM, multiple myeloma, and amyloidosis. The differential diagnosis is therefore extremely important for clinicians. Both amyloidosis and sarcoidosis are systemic diseases. When non-cardiologists diagnose a systemic disease, they should pay attention to HF. Cardiologists should be able to properly diagnose and treat HF associated with systemic diseases. In the present study, PTTM was the underlying cause of HF-related mortality in many early autopsy reports; however, surviving cases have recently been reported. The first report of a patient with PTTM was published in 1990 (11), and the first such report in Japan was published in 1995 (12). The recently increasing PTTM incidence may be due to an improved disease understanding.

Further reports of detailed autopsy investigations in HF may help improve the quality of the diagnosis, treatment, and prognosis for rare diseases that cause HF.

In the present study, we attempted to elucidate the different etiologies of HF based on a large database of case reports. Of note, case reports (by their nature) often depict special or rare cases, so the disease frequencies and severities determined purely from case reports may differ from the actual status. However, the enumeration of many differential diagnoses is advantageous for the accurate diagnosis of HF etiologies and for identifying the underlying diseases most commonly associated with high mortality. In the future, by continued the annual updating of case reports, the number of diseases associated with HF will continue to increase, and the expanding database will improve our ability to differentially diagnose patients and determine the prognosis of HF.

## Conclusion

Many cases of HF are caused by non-cardiovascular diseases. To improve our ability to clinically diagnose HF, it is necessary to examine the underlying non-cardiovascular diseases of HF. A broad study of case reports on internal medicine is important for cardiologists.

### Author's disclosure of potential Conflicts of Interest (COI).

Hisahiko Sato: Stock ownership or options, Precision. Kazuomi Kario: Honoraria, Daiichi Sankyo, Omron Healthcare and Takeda; Research funding, A&D, Bayer Yakuhin, Boehringer Ingelheim, Daiichi Sankyo, EA Pharma, Fukuda Denshi, Medtronic, Mitsubishi Tanabe Pharma Corporation, Mochida Pharmaceutical, Omron Healthcare, Otsuka, Pfizer, Takeda and Teijin Pharma.

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