年、ACE 阻害薬や ARB、β 遮断薬、アルドステロン拮抗薬、そして心臓再同期療法に比肩する治療法は登場していない。現状、今ある治療法を最大限に有効活用するのが唯一の方法であり、その為のキーワードが「早期介入」と「他臓器との関連」である。具体的には、急性心不全患者が救急外来ないし集中治療室に収容された直後から、他の臓器を考慮した評価および介入により、短期だけでなく、その先にある長期予後まで見据えた治療が理想的とされている。しかし、心不全患者は多彩な背景より発症し、病像も様々である。そのガイドライン作成には、適切な評価・層別化が前提にあり、こうした大規模な登録研究により心不全の実像を把握する必要がある。

本研究に関して、現段階では個々の臓器との関連や心機能単独指標との関連を調査するにとどまっているが、今後より集約的なデータの発信を行い、心不全診療の向上に役立つ成果の発表を行っていくこととしたい。

F. 健康危惧情報

本研究は観察研究であり、健康危惧情報は特にない。

G. 研究発表

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H. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得　なし
2. 実用新案登録　なし
3. その他　なし

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Letter to the Editor

Prognostic impact of renal and hepatic dysfunction based on the MELD-XI score in patients with acute heart failure

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The multiple organ system contributes to defining the prognosis of patients with acute heart failure (AHF). "Cardio-renal interaction" is a well-known entity [1], and clinical studies during the past decade have considered baseline renal dysfunction as one of the most important prognostic factors in hospitalized AHF patients [2]. In addition, "cardio-hepatic interactions" have been reported, and studies have demonstrated that abnormal results on liver function tests in patients with heart failure were independently related to adverse outcomes and increased risk of mortality [3,4].

The Model for End-Stage Liver Disease (MELD) scoring system has emerged as a novel parameter to evaluate both cardio-renal and cardio-hepatic interactions simultaneously. This scoring system was originally developed for patients with cirrhosis awaiting liver transplantation, and it could measure the progression of liver dysfunction based on the level of creatinine and total bilirubin and the international normalized ratio (INR) [5]. Modification of the MELD score excluding the INR (MELD-XI score) was proposed more recently, since the INR becomes dissociated from liver dysfunction in patients receiving anticoagulation therapy [6]. Previously, this scoring system has been applied and tested in patients with end-stage heart failure, such as patients with Fontan circulation requiring surgery, or those with advanced heart failure awaiting heart transplantation. In both studies, an elevated MELD-XI score was strongly associated with an increased risk of adverse outcomes; [7,8] however, the prognostic impact of the MELD-XI score has not been investigated in patients with AHF, which is more frequently encountered in clinical practice. Proving the validity of the MELD-XI score in an acute clinical situation can further enrich the information on risk stratification when these patients are hospitalized.

In the present study, we sought to investigate the prognostic impact of the MELD-XI score in AHF patients. We analyzed the data from 949 consecutive AHF cases registered in the West Tokyo Heart Failure (WET-HF) registry from April 2006 to March 2013. This database is an ongoing, prospective, multicenter registry designed to collect the clinical background and outcome data of AHF patients. Specifically, patients presenting with acute coronary syndrome were not included. The WET-HF registry included three teaching hospitals within the metropolitan Tokyo area, and participating hospitals were instructed to record and register data from consecutive hospital visits for AHF. Exclusive on-site auditing by the investigators (T.I., S.K., and Y.S.) ensured proper registration of each patient. The follow-up survey by chart review and telephone contact was performed for all patients (100%), and the mean follow-up duration was 555 ± 476 days. Within our cohort, 77 patients were excluded for the following reasons: missing baseline creatinine value and missing baseline total bilirubin value. The remaining 872 patients were included in the present analysis. Additionally, we evaluated the long-term outcomes of 820 patients after excluding those with in-hospital death (Fig. 1).

The MELD-XI score was calculated by the following formula: MELD-XI = 5.11 × Ln(total bilirubin) + 11.76 × Ln(creatinine) + 9.44. A high MELD-XI score was defined as ≥10 based on the median score. The following outcomes were evaluated: 1) in-hospital death as a short-term outcome, and 2) composite endpoints including all-cause death and re-hospitalization due to heart failure as long-term outcomes.

Differences in each variable between the patients with high (≥10) and low (<10) MELD-XI scores were evaluated using the chi-square test for categorical variables and unpaired Student's t-test for continuous

Abbreviations: AHF, acute heart failure; MELD, Model for End-Stage Liver Disease; INR, international normalized ratio; MELD-XI score, MELD score excluding the INR; WET-HF, West Tokyo Heart Failure.

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variables. Event-free survival in patients with high and low MELD-XI scores was estimated by the Kaplan–Meier method, and statistical differences were evaluated by means of the log-rank test. Logistic regression model and Cox proportional hazards models were used to compare endpoints and correct for differences in baseline variables. In these models, adjustments were made using the clinically important variables (age, sex, ischemic etiology, systolic blood pressure, and heart rate). Analyses of data were performed using statistical software SPSS version 21.0 (SPSS Japan, Tokyo, Japan). This study was approved by each ethics review board, and written informed consents were obtained from all patients.

From an analysis of 872 patients, 351 patients (40.3%) had a high MELD-XI score. Table 1 shows the baseline characteristics of those with low and high MELD-XI scores. Age, ischemic etiology, and prior hospitalization for heart failure, and hypertension or diabetes history were significantly different between the two groups. Naturally, both serum creatinine and B-type natriuretic peptide were higher in patients with a high MELD-XI score, albeit the difference in the total bilirubin level did not reach statistical significance.

Table 2 summarizes the treatment of patients. The patients with high MELD-XI scores were more likely to be administered loop diuretics or beta blockers than those with low MELD-XI scores. In addition, intravenous diuretics were more frequently administered and mechanical ventilation requiring intubation was more often needed for patients with high MELD-XI scores. At discharge, although the prescription rate of loop diuretics was similar between both groups, the dose of loop diuretics was significantly higher for patients with a high MELD-XI score than for those with low scores.

During the hospital course, there were 52 in-hospital deaths. Patients with a high MELD-XI score had higher mortality, and this association was consistent after adjusting for differences in baseline variables (odds ratio: 2.33, 95% CI: 1.28–4.27, $P = 0.006$). For long-term outcome analysis, Fig. 2 shows Kaplan–Meier survival curves for composite endpoints in patients with low and high MELD-XI scores. This curve indicated that patients with a high MELD-XI score had a significantly lower survival rate during the follow-up (log-rank test: $P < 0.001$). Cox regression analysis for composite endpoints revealed that advanced age, low systolic blood pressure, and a high MELD-XI score (hazard ratio: 1.79, 95% CI: 1.40–2.30, $P < 0.001$) were independent predictors of composite endpoints (see online-only Supplement eTable). Fig. 3 summarizes creatinine and total bilirubin values for each patient of the study cohort. This representation shows that adverse composite endpoints occurred even in patients with normal renal function complicated with hepatic dysfunction, which further signifies the importance of simultaneous cardio-renal and cardio-hepatic evaluations.

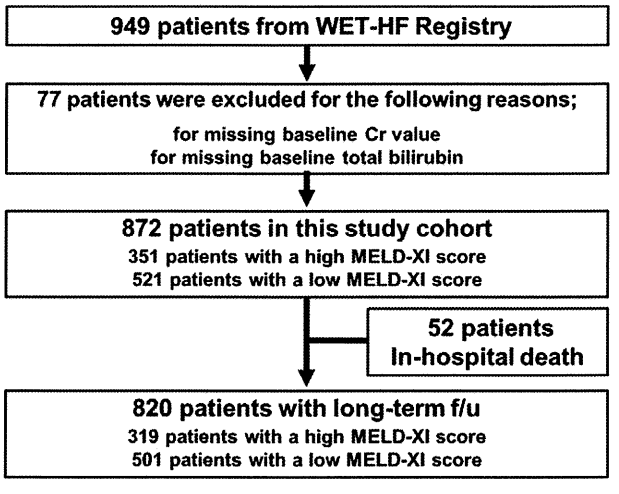

Fig. 1. Description of the patient dataset for the current analysis.

Table 1
Baseline characteristics.

	MELD-XI ≤ 10 (N = 521)	MELD-XI > 10 (N = 351)	*P*-value
Age (years)	69.5 ± 14.6	72.5 ± 13.5	0.003
Men	216 (41.5%)	91 (25.9%)	<0.001
Ischemic cause of heart failure	168 (32.2%)	138 (39.3%)	0.036
Medical history			
Prior hospitalization for heart failure	158 (30.3%)	164 (46.7%)	<0.001
Hypertension	296 (56.8%)	222 (63.2%)	0.032
Dyslipidemia	189 (36.3%)	127 (36.2%)	0.884
Diabetes mellitus	160 (30.7%)	130 (37.0%)	0.048
Atrial flutter or fibrillation	189 (36.3%)	140 (39.9%)	0.285
Clinical profile on admission			
Paroxysmal nocturnal dyspnea	138 (26.5%)	115 (32.8%)	0.046
Orthopnea	120 (23.0%)	96 (27.4%)	0.18
Rales	238 (45.7%)	181 (51.6%)	0.058
Jugular venous distension	206 (39.5%)	158 (45.0%)	0.134
Peripheral edema	261 (50.1%)	200 (57.0%)	0.056
Cold extremities	85 (16.3%)	83 (23.6%)	0.007
Heart rate (beats/min)	91.5 ± 26.8	92.1 ± 27.1	0.754
Systolic blood pressure (mm Hg)	136.2 ± 33.2	135.3 ± 36.2	0.71
Diastolic blood pressure (mm Hg)	79.2 ± 20.8	77.4 ± 20.4	0.226
B-type natriuretic peptide (pg/mL)	550 ± 623	1120 ± 1258	<0.001
Serum creatinine (mg/dL)	0.83 ± 0.18	2.41 ± 2.46	<0.001
Total bilirubin (mg/dL)	0.94 ± 0.65	1.02 ± 0.79	0.097
Outcome			
In-hospital death	20 (3.8%)	32 (9.1%)	0.002
Composite endpoint	139 (27.7%)	141 (44.2%)	<0.001

All values are expressed as mean ± SD or n (%).

The main finding of this study is that simultaneous assessment of renal and liver dysfunction according to the MELD-XI scoring system provided additional risk stratification in patients with AHF. Two distinct hemodynamic abnormalities, namely, hypoperfusion and venous congestion, broadly describe the processes underlying renal and hepatic dysfunction [1,4]. Traditionally, renal dysfunction associated with AHF has been attributed to hypoperfusion of the kidney caused by the progressive impairment of cardiac output. More recently, in an analysis from series of patients admitted for AHF, hypotension was rarely observed in patients with renal dysfunction, and the elevation of central venous pressure was more closely associated with worsening renal function rather than lower cardiac index [9]. This trend may be true in

Table 2
Medical management of patients with low or high MELD-XI scores.

	MELD-XI ≤ 10 (N = 521)	MELD-XI > 10 (N = 351)	*P*-value
In-hospital intravenous therapy			
Diuretics	255 (48.9%)	218 (62.1%)	<0.001
Vasodilator	340 (65.3%)	224 (63.8%)	0.665
Inotropes	66 (12.7%)	59 (16.8%)	0.094
In-hospital management			
NIPPV	59 (11.3%)	34 (9.7%)	0.502
Intubation	51 (9.8%)	52 (14.8%)	0.032
Revascularization therapy	83 (15.9%)	29 (8.3%)	0.001
Valve replacement	8 (1.5%)	1 (0.3%)	0.093
Medication before admission			
Loop diuretics	192 (36.9%)	194 (55.3%)	<.001
ACE-I or ARB	235 (45.1%)	167 (47.6%)	0.489
Aldactone	115 (22.2%)	88 (25.4%)	0.288
Beta blockers	203 (39.4%)	160 (46.0%)	0.058
Medication at discharge			
Loop diuretics	333 (64.8%)	235 (68.5%)	0.269
Dose of loop diuretics	26.6 ± 18.2	37.7 ± 29.9	<0.001
ACE-I or ARB	354 (67.9%)	194 (55.3%)	<0.001
Aldactone	243 (47.2%)	131 (38.2%)	0.009
Beta blockers	374 (72.5%)	230 (67.3%)	0.109

Data are expressed as mean ± SD, as number (percentage).
Abbreviations: NIPPV, non-invasive positive-pressure ventilation; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

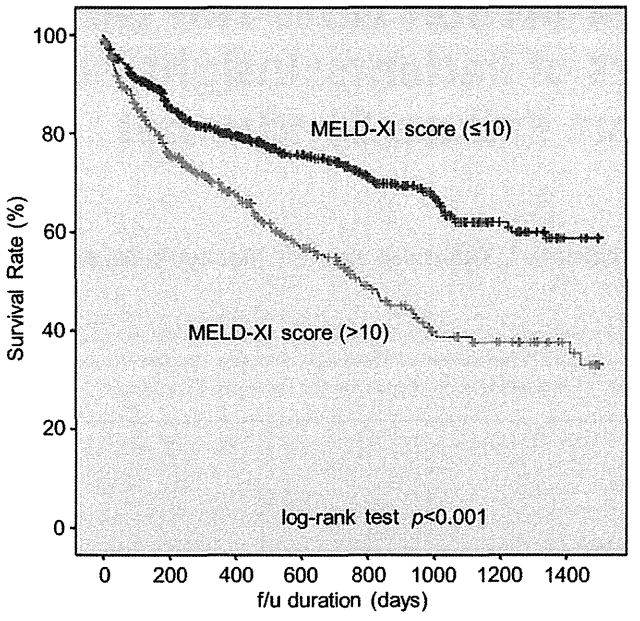

Fig. 2. Kaplan–Meier survival curves for composite endpoints in patients with low and high MELD-XI scores. Patients with a high MELD-XI score had a significantly lower survival rate during the follow-up (log-rank test: $P < 0.001$).

hepatic dysfunction complicated with AHF. Previous reports regarding the prognostic impact of the MELD-XI score on adverse cardiovascular events have been confined to situations that are more likely to be associated with venous congestion; [7,8] therefore, an elevated MELD-XI score in AHF patients could indicate patients complicated with right-sided heart failure.

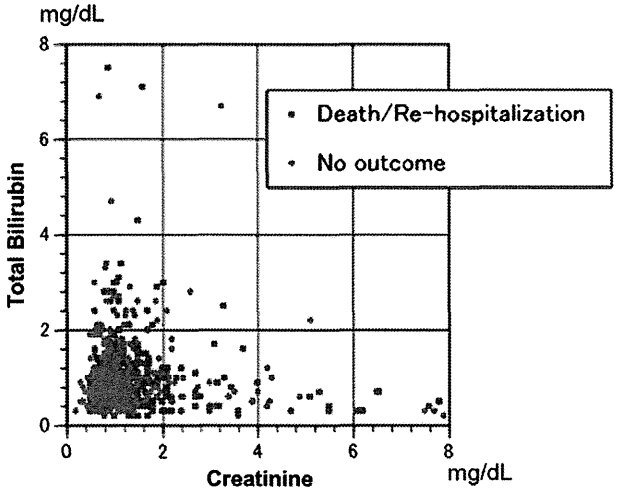

Fig. 3. Creatinine versus total bilirubin scatter plot. The red dots represent patients who did not experience the composite endpoint, while blue dots represent patients with unfavorable clinical outcomes (all-cause death and re-hospitalization for heart failure).

Unfortunately, concerning the panel of liver function tests, other hepatic makers including transaminase and gamma-glutamyltransferase (GGTP) levels were not collected in our registry. The association of elevated transaminase and increased mortality in patients with AHF has been demonstrated [4]. However, since the congestive state was more closely associated with hepato-renal dysfunction related to AHF rather than low cardiac output, hepatic makers reflecting hepatic congestion (e.g., total bilirubin) were believed to be preferable in our study. On a separate note, GGTP level could be a potential hepatic maker mainly related to hepatic congestion [10]. However, the GGTP levels were not available in our dataset, and this remains one of the important limitations of our analysis.

In conclusion, the assessment of renal and liver dysfunction according to the MELD-XI scoring system provided additional risk stratification in patients with AHF.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.08.052.

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PLOS ONE

Prognostic Impact of Renal Dysfunction Does Not Differ According to the Clinical Profiles of Patients: Insight from the Acute Decompensated Heart Failure Syndromes (ATTEND) Registry

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Abstract

Background: Renal dysfunction associated with acute decompensated heart failure (ADHF) is associated with impaired outcomes. Its mechanism is attributed to renal arterial hypoperfusion or venous congestion, but its prognostic impact based on each of these clinical profiles requires elucidation.

Methods and Results: ADHF syndromes registry subjects were evaluated (N = 4,321). Logistic regression modeling calculated adjusted odds ratios (OR) for in-hospital mortality for patients with and without renal dysfunction. Renal dysfunction risk was calculated for subgroups with hypoperfusion-dominant (eg. cold extremities, a low mean blood pressure or a low proportional pulse pressure) or congestion-dominant clinical profiles (eg. peripheral edema, jugular venous distension, or elevated brain natriuretic peptide) to evaluate renal dysfunction's prognostic impact in the context of the two underlying mechanisms. On admission, 2,150 (49.8%) patients aged 73.3±13.6 years had renal dysfunction. Compared with patients without renal dysfunction, those with renal dysfunction were older and had dominant ischemic etiology jugular venous distension, more frequent cold extremities, and higher brain natriuretic peptide levels. Renal dysfunction was associated with in-hospital mortality (OR 2.36; 95% confidence interval 1.75–3.18, $p<0.001$), and the prognostic impact of renal dysfunction was similar in subgroup of patients with hypoperfusion- or congestion-dominant clinical profiles (p-value for the interaction ranged from 0.104–0.924, and was always >0.05).

Conclusions: Baseline renal dysfunction was significantly associated with in-hospital mortality in ADHF patients. The prognostic impact of renal dysfunction was the same, regardless of its underlying etiologic mechanism.

Citation: Inohara T, Kohsaka S, Sato N, Kajimoto K, Keida T, et al. (2014) Prognostic Impact of Renal Dysfunction Does Not Differ According to the Clinical Profiles of Patients: Insight from the Acute Decompensated Heart Failure Syndromes (ATTEND) Registry. PLoS ONE 9(9): e105596. doi:10.1371/journal.pone.0105596

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Data Availability: The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. Data are from the ATTEND registry. In this study, the data was collected from multiple institutions in Japan, and the IRB approval was obtained individually from each site. Therefore, the full set of data cannot be made available to public. The reader may contact the corresponding author to request the data.

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Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Despite advances in pharmacological and mechanical therapies, acute decompensated heart failure (ADHF) remains one of the most frequently encountered and life-threatening cardiovascular conditions [1]. The EuroHeart Failure Survey, which included 11,327 patients with ADHF, showed that post-discharge mortality rates reached 8.1% and 20.5% within 3 months and 1 year, respectively [2].

Baseline renal dysfunction is one of the most important predictors of short- and long-term cardiovascular outcomes in patients with ADHF [3–5]. Although several mechanisms coexist in the deterioration of renal function among ADHF patients [6,7], two hemodynamic mechanisms, renal arterial hypoperfusion and renal venous congestion, broadly describe the processes underlying renal dysfunction. Traditionally, renal dysfunction associated with ADHF has been attributed to hypoperfusion of the kidney caused by the progressive impairment of cardiac output [8]. However, recent studies have demonstrated that hypotension is rarely observed in patients with renal dysfunction [9], and that the elevation of central venous pressure (CVP) is more closely associated with worsening renal function than the cardiac index [10]. This suggests that in patients with ADHF admitted to hospital, renal dysfunction is more dependent on venous congestion than on the impairment of cardiac output.

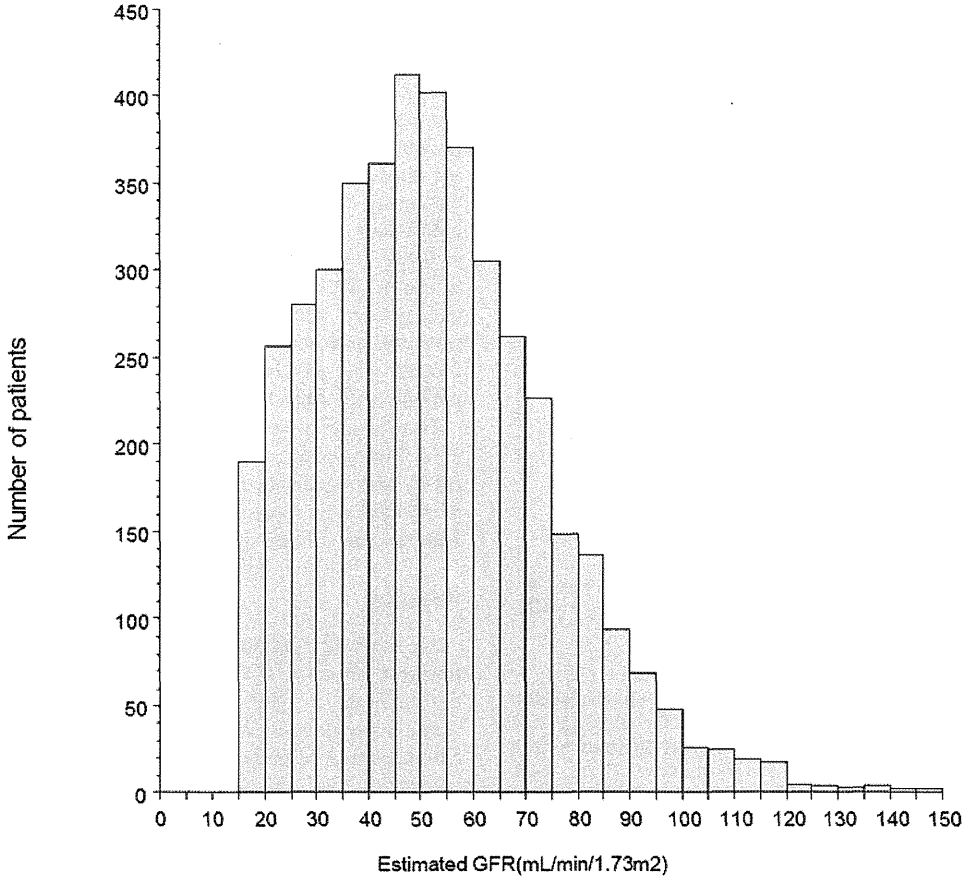

Figure 1. Distribution of estimated glomerular filtration rates levels on admission to hospital. GFR, glomerular filtration rate.
doi:10.1371/journal.pone.0105596.g001

The contributions of renal hypoperfusion and congestion to renal dysfunction have not been thoroughly investigated. Hemodynamic profiles can be assessed by measuring blood pressure, performing physical examinations, and by measuring laboratory markers [11,12], and these parameters are used to assess the mechanisms underlying renal dysfunction. This study aimed to clarify differences in the prognostic impact of renal dysfunction on in-hospital mortality in patients admitted with ADHF, based on the underlying hemodynamic mechanisms.

Methods

Data sources

The study was conducted in accordance with the Declaration of Helsinki and the Japanese ethical guidelines for clinical studies. The study protocol was registered to the University Hospital Medical Information Network (UMIN 000000736), and approved by the ethics committee at each site.

The Acute Decompensated Heart Failure Syndromes (ATTEND) registry is a nationwide, multicenter, prospective cohort study that focuses on ADHF in Japan. The details of this cohort study have been reported previously [13]. In brief, patients hospitalized for ADHF who met the modified Framingham criteria, were eligible for the study. The ATTEND registry enrolled patients from April 2007 to December 2011 in 52 hospitals throughout Japan. Approximately 200 variables were collected on admission for each patient, and clinical variables included the patient's history, physical examination results, echocardiographic data, and laboratory data. Patients aged <20 years and those not considered suitable for the study by attending physicians were excluded. The present study also ruled out acute coronary syndrome. In-hospital mortality was defined as (1) death from any cause, (2) death from cardiac causes, including sudden cardiac death and heart failure death, and (3) death from cerebral or vascular causes. Death was considered cardiac-related (defined as heart failure death, sudden death, or other cardiac death), unless a specific non-cardiac cause was identified by the primary physicians. The end-point classification committee, comprising two experienced cardiologists who were not study investigators, reviewed the data and, if any problems were encountered, they asked the primary physician to confirm the cause of death. Finally, the committee categorized each event for use in the present analysis. All data are managed at an independent biostatistics and data center (STATZ Institute, Inc., Tokyo, Japan). In this study, the data was collected from multiple institutions in Japan, and the IRB approval was obtained individually from each sites. Therefore, the full set of data cannot be made available to public. The reader may contact the corresponding author to request the data.

Study population

After excluding patients who were on hemodialysis or who had stage 5 chronic kidney disease (defined as an estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m^2) and were supported by intracardiac balloon pumping or percutaneous cardiopulmonary support, the remaining 4,321 subjects were analyzed in this study.

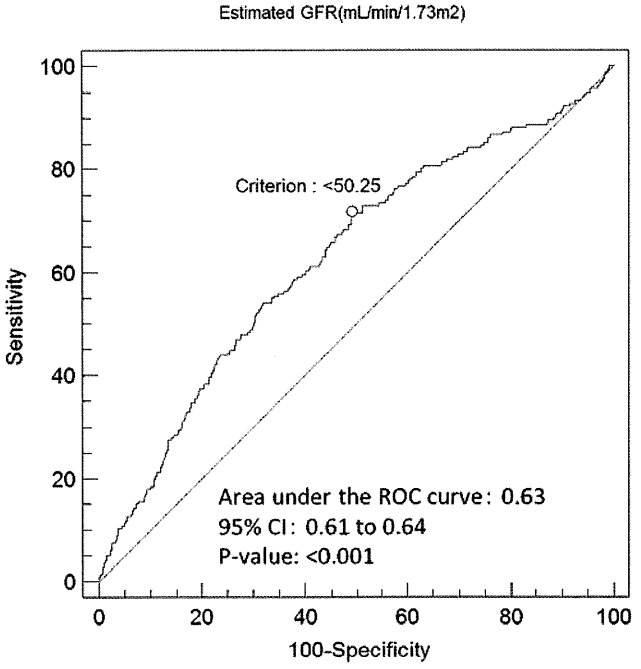

Figure 2. Evaluation of the receiver operating characteristic curve for renal dysfunction. The area under the curve was 0.63 (95% confidence interval = 0.61–0.64, $p<0.001$), and the cut-off value for the greatest sensitivity and specificity was 50.25 mL/min/1.73 m^2. GFR, glomerular filtration rate; CI, confidence interval; ROC, receiver operating characteristic.
doi:10.1371/journal.pone.0105596.g002

Evaluation of renal function

The National Kidney Foundation advocates estimating the GFR by using the Modification of Diet in Renal Disease (MDRD) formula to detect the early stages of renal dysfunction [14]. On the basis of this recommendation, renal function in this study was evaluated by estimating the GFR, which was calculated using the abbreviated MDRD study equation:

$$eGFR = 186 \times (Serum\ creatinine\ in\ mg/dL)^{-1.154} \times (age\ in\ years)^{-0.203} \times (0.742, if\ female)$$

The distribution of eGFRs is shown in Figure 1. An evaluation of the receiver operating characteristic curve determined that the optimal cut-off value for renal dysfunction was estimated as a GFR ≤50 mL/min/1.73 m^2 (Figure 2), and the area under the curve was 0.63 (95% confidence interval [CI] = 0.61–0.64, $p<0.001$).

Assessing renal dysfunction mechanisms

Renal dysfunction as it relates to hypoperfusion, which is usually caused by a low-output status, was defined as the presence of cold extremities, a low left ventricular ejection fraction (LVEF) of ≤ 40%, a low mean blood pressure (mBP) of ≤100 mmHg [15], or a low proportional pulse pressure (PPP) of ≤40% [16]. In contrast, renal dysfunction as it relates to congestion was defined as the presence of peripheral edema or jugular venous distension (JVD), or elevated brain natriuretic peptide (BNP) levels of >677 pg/mL [17]. The cutoff values of mBP, PPP, and BNP were determined according to the respective median values.

Statistical analysis

All data are expressed as means ± standard deviations or medians with the interquartile ranges. The receiver operating characteristic curve for renal dysfunction was used to evaluate the optimal cut-off value. Differences in each variable between patients with and without renal dysfunction were evaluated using the chi-square test or Fisher's exact test for categorical variables, and using Student's unpaired *t*-test or Mann-Whitney U test for continuous variables. A logistic regression model was used to evaluate the influence of renal dysfunction on in-hospital mortality. In the logistic regression models, the covariates were age, gender, etiology (ischemic or non-ischemic), systolic blood pressure, and heart rate. The covariates incorporated into these models were clinically associated with in-hospital mortality in patients with ADHF.

Data analyses were performed using SAS, software version 9.1 (SAS Institute Inc., Cary, North Carolina). All p-values were two-sided, and significance was defined as $p<0.05$. All analyses were performed at an independent biostatistics and data center (STATZ Institute, Inc., Tokyo, Japan).

Results

Of the 4,321 patients hospitalized with ADHF, renal dysfunction was present in 2,150 (49.8%) patients and was determined on the basis of a GFR cut-off value of ≤50 mL/min/1.73 m^2. Table 1 presents a comparison of the demographic and baseline characteristics of patients with and without renal dysfunction. In comparison with those patients without renal dysfunction, patients with renal dysfunction were older, they were more likely to have an ischemic etiology and to have histories of hospitalization for heart failure, and they were more likely to have risk factors for cardiovascular disease, which included hypertension, dyslipidemia, and diabetes mellitus. On admission to hospital, physical findings, including JVD and cold extremities, were more frequently observed in patients with renal dysfunction than in patients without renal dysfunction. Patients with renal dysfunction had significantly lower blood pressures and heart rates, and significantly higher plasma BNP levels, compared with those without renal dysfunction.

Before admission to the hospital and with the exception of digitalis, most types of medication, including diuretics, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, calcium-channel blockers, beta blockers, nitrate, and statins, were more frequently used by patients with renal dysfunction than those without renal dysfunction. Although vasodilator use was similar in both groups during hospitalization, the use of intravenous diuretics and inotropes was significantly higher in patients with renal dysfunction. Non-pharmacologic management, including non-invasive or invasive positive-pressure ventilation, was similar for both groups, except for the application of revascularization therapy, which was more commonly used in patients without renal dysfunction (Table 2).

The all-cause death rate was significantly higher in patients with renal dysfunction at 6.8% compared with 3.0% for those without renal dysfunction. Furthermore, cardiac death rates were significantly higher in patients with renal dysfunction compared with those without renal dysfunction (4.8% vs. 2.1%, respectively, $p<0.001$) (Figure 3). Logistic regression analysis demonstrated that the presence of renal dysfunction was an independent predictor of all-cause death after adjustment for associated factors (OR: 2.36, 95% CI: 1.75–3.18, $p<0.001$).

To evaluate the prognostic impact of renal dysfunction in the context of the two underlying hemodynamic mechanisms, we

Table 1. Baseline characteristics of patients with and without renal dysfunction.

	Total	eGFR >50 mL/min/1.73 m^2	eGFR ≤50 mL/min/1.73 m^2	
	(N = 4,321)	(n = 2,171)	(n = 2,150)	p-value
Mean age (years)	73.3±13.6	70.2±14.4	76.5±11.9	<0.001
Men, n (%)	2,501 (57.9)	1,300 (59.9)	1,201 (55.9)	0.007
Ischemic cause of HF, n (%)	1,283 (29.7)	564 (26.0)	719 (33.4)	<0.001
Medical history				
Prior hospitalization for HF, n (%)	1,521 (35.2)	576 (26.5)	945 (44.0)	<0.001
Hypertension, n (%)	2,980 (69.0)	1,417 (65.3)	1,563 (72.7)	<0.001
Dyslipidemia, n (%)	1,558 (36.1)	736 (33.9)	822 (38.2)	0.003
Diabetes mellitus, n (%)	1,391 (32.2)	667 (30.7)	724 (33.7)	0.036
Smoking, n (%)	1,840 (42.6)	990 (45.6)	850 (39.5)	<0.001
Atrial flutter or fibrillation, n (%)	1,745 (40.4)	849 (39.1)	896 (41.7)	0.096
Chronic respiratory disease, n (%)	538 (12.5)	263(12.1)	275 (12.8)	0.501
Stroke/transient ischemic attack, n (%)	611 (14.1)	261 (12.0)	350 (16.3)	<0.001
Pacemaker/ICD, n (%)	380 (8.8)	142 (6.5)	238 (11.1)	<0.001
Cardiac resynchronization therapy, n (%)	86 (2.0)	24 (1.1)	62 (2.9)	<0.001
Clinical profile on admission				
Paroxysmal nocturnal dyspnea, n (%)	2,288 (53.0)	1,161 (53.5)	1,127 (52.4)	0.609
Orthopnea, n (%)	2,717 (62.9)	1,368 (63.0)	1,349 (62.7)	0.795
Rales, n (%)	3,075 (71.2)	1,548 (71.3)	1,527 (71.0)	0.938
Third heart sound, n (%)	1,518 (35.1)	745 (34.3)	773 (36.0)	0.35
Jugular venous distension, n (%)	2,246 (52.0)	1,088 (50.1)	1,158 (53.9)	0.005
Peripheral edema, n (%)	2,887 (66.8)	1,423 (65.5)	1,464 (68.1)	0.075
Cold extremities, n (%)	917 (21.2)	409 (18.8)	508 (23.6)	<0.001
EF≤40%, n (%)	2,301 (53.3)	1,181 (54.4)	1,120 (52.1)	0.158
NYHA functional class				
I, n (%)	74 (1.7)	40 (1.8)	34 (1.6%	0.458
II, n (%)	706 (16.3)	372 (17.1)	334 (15.5)	
III, n (%)	1,657 (38.3)	825 (38.0)	832 (38.7)	
IV, n (%)	1,834 (42.4)	909 (41.9)	925 (43.0)	
Mean heart rate (beats/min)	99.0±29.3	102.9±29.4	95.0±28.7	<0.001
Mean systolic blood pressure (mmHg)	146.1±35.8	147.4±34.8	144.8±36.7	0.016
Mean diastolic blood pressure (mmHg)	83.1±22.4	85.4±21.7	80.9±23.0	<0.001
Median B-type natriuretic peptide (pg/mL)	677 (350–1,220)	562 (298–981)	848 (439–1,490)	<0.001
Mean blood urea nitrogen (mg/dL)	25.2±18.6	18.7±15.5	31.8±19.2	<0.001
Mean serum creatinine (mg/dL)	1.15±0.52	0.80±0.18	1.50±0.51	<0.001
Mean eGFR (mL/min/1.73 m^2)	51.9±21.6	68.9±15.9	34.8±9.7	<0.001
Mean serum sodium (mEq/L)	139.4±4.3	139.6±4.2	139.3±4.3	0.023
Mean hemoglobin (g/dL)	12.2±2.6	12.7±2.4	11.6±2.7	<0.001
Median total bilirubin (mg/dL)	0.8 (0.5–1.1)	0.8 (0.6–1.2)	0.7 (0.5–1.1)	<0.001

Data are expressed as mean ± standard deviation, as number (percentage), or as median (interquartile range).
eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; EF, ejection fraction; NYHA, New York Heart Association.
doi:10.1371/journal.pone.0105596.t001

performed logistic regression analyses on subgroups of patients with or without hypoperfusion-dominant characteristics (e.g., patients with cold extremities, low LVEFs, low mBPs, or low PPPs) and on subgroups of patients with or without congestion-dominant characteristics (e.g., edema, JVD or high BNP levels). As shown in Table 3, all-cause mortality was consistently higher in patients with renal dysfunction. The prognostic impact of renal dysfunction quantified using ORs, was similar across all of the subgroups, regardless of whether the clinical signs of hypoperfusion or congestion were present (Figure 4). The p-value for the interaction ranged from 0.104–0.924 and was always >0.05.

Discussion

The major finding from this study was that renal dysfunction was significantly associated with an increased risk of in-hospital mortality in patients admitted with ADHF. Furthermore, this

Table 2. Management of patients with and without renal dysfunction.

	Total	eGFR>50 mL/min/1.73 m^2	eGFR≤50 mL/min/1.73 m^2	
	(N=4,321)	(n=2,171)	(n=2,150)	p-value
Intravenous therapy				
Diuretics, n (%)	3,306 (76.5)	1,622 (74.7)	1,684 (78.3)	0.005
Vasodilators, n (%)	3,392 (78.5)	1,708 (78.7)	1,684 (78.3)	0.781
Inotropes, n (%)	676 (15.6)	290 (13.4)	386 (18.0)	<0.001
In-hospital management				
Oxygen supplementation, n (%)	2,736 (63.3)	1,361 (62.7)	1,375 (64.0)	0.355
NIPPV, n (%)	1,012 (23.4)	501 (23.1)	511 (23.8)	0.592
Intubation, n (%)	259 (6.0)	117 (5.4)	142 (6.6)	0.094
Revascularization, n (%) therapy	348 (8.1)	202 (9.3)	146 (6.8)	0.002
Valve replacement, n (%)	98 (2.3)	66 (3.0)	32 (1.5)	<0.001
Outpatient medications before admission				
Loop or thiazide diuretics, n (%)	2,037 (47.1)	779 (35.9)	1,258 (58.5)	<0.001
ACE-I or ARB, n (%)	2,043 (47.3)	854 (39.3)	1,189 (55.3)	<0.001
Calcium-channel blockers, n (%)	1,192 (27.6)	528 (24.3)	664 (30.9)	<0.001
Beta blockers, n (%)	1,428 (33.0)	571 (26.3)	857 (39.9)	<0.001
Digitalis, n (%)	556 (12.9)	288 (13.3)	268 (12.5)	0.432
Nitrate, n (%)	726 (16.8)	286 (13.2)	440 (20.5)	<0.001
Amiodarone, n (%)	188 (4.4)	53 (2.4)	135 (6.3)	<0.001
Statins, n (%)	993 (23.0)	430 (19.8)	563 (26.2)	<0.001
Length of hospital stay (days)				
Median (interquartile range)	20 (13–30)	19 (13–28)	21 (13–33)	<0.001
Mean ± SD	27±34	25±28	29±39	<0.001

Data are expressed as mean ± standard deviation (SD), as number (percentage), or as median (interquartile range).
eGFR, estimated glomerular filtration rate; NIPPV, non-invasive positive-pressure ventilation; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker.
doi:10.1371/journal.pone.0105596.t002

adverse effect of renal dysfunction on short-term outcomes remained the same, regardless of the underlying hemodynamic mechanism. The present study confirms previous findings from studies performed in Western countries that reported an association between baseline renal dysfunction and an increased risk of short-term mortality in patients admitted with ADHF [3,4].

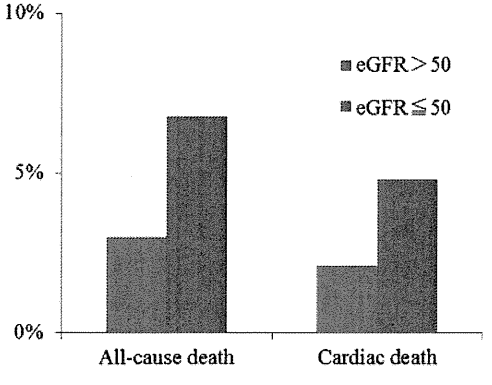

Figure 3. Relationship between the baseline estimated glomerular filtration rates and in-hospital mortality. eGFR, estimated glomerular filtration rate.
doi:10.1371/journal.pone.0105596.g003

While various mechanisms have been proposed for renal dysfunction in patients admitted with ADHF, these mechanisms fall into two broad categories from the perspective of hemodynamics, namely renal hypoperfusion and renal congestion. A scientific statement to assess and grade congestion in acute heart failure has been proposed by the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology [17]. Thus, if peripheral edema, JVD, and elevated BNP levels are the variables associated with congestion, then cold extremities and low LVEFs, mBPs, and PPPs could be the variables associated with hypoperfusion, because this type of renal dysfunction is attributed to reduced systemic perfusion. Using these definitions for each clinical profile, we demonstrated that, contrary to common belief, the typical physical findings indicative of renal hypoperfusion and renal congestion, including cold extremities and JVD, were more frequently observed in patients with renal dysfunction on hospitalization.

Traditionally, a reduction in renal blood flow, namely renal hypoperfusion, has been considered the main cause of renal dysfunction associated with ADHF. Although the precise mechanism that connects cardiac output with renal blood flow remains unclear in the context of ADHF, it is hypothesized that neurohormonal activation, for example via the renin-angiotensin system, results in afferent vasoconstriction, thereby reducing renal blood flow and hence the effective volume of circulating fluid, as is expected in patients with ADHF [7]. In contrast, recent studies have highlighted the association between an increased CVP and

Table 3. All-cause mortality in different patient subgroups.

		Normal Renal Function			Renal Dysfunction		
		eGFR>50 mL/min/1.73 m^2			eGFR≤50 mL/min/1.73 m^2		
		No. of patients	No. of Events	No. of Events (%)	No. of Patients	No. of Events	No. of Events (%)
Total		2171	65	3.0%	2150	146	6.8%
Age (years)	≤75	1259	18	1.4%	850	21	2.5%
	>75	912	47	5.2%	1300	125	9.6%
Gender	Women	871	30	3.4%	949	76	8.0%
	Men	1300	35	2.7%	1201	70	5.8%
mBP (mmHg)	≤100	940	43	4.6%	1115	112	10.0%
	>100	1218	21	1.7%	1024	32	3.1%
PPP	≤42	1114	42	3.8%	955	67	7.0%
	>42	11044	22	2.1%	1184	77	6.5%
JVD	Absent	917	24	2.6%	815	42	5.2%
	Present	1088	37	3.4%	1158	97	8.4%
Edema	Absent	724	16	2.2%	663	41	6.2%
	Present	1423	46	3.2%	1464	102	7.0%
Cold extremities	Absent	1663	35	2.1%	1551	81	5.2%
	Present	409	26	6.4%	508	59	11.6%
BNP (pg/ml)	≤677	1182	28	2.4%	822	40	4.9%
	>677	830	35	4.2%	1175	97	8.3%
LVEF (%)	≤40	1181	39	3.3%	1120	77	6.9%
	>40	960	25	2.6%	993	67	6.7%

Abbreviation; eGFR, estimated glomerular filtration rate; mBP, mean blood pressure; PPP, proportional pulse pressure; JVP, juglur venous distension; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.
doi:10.1371/journal.pone.0105596.t003

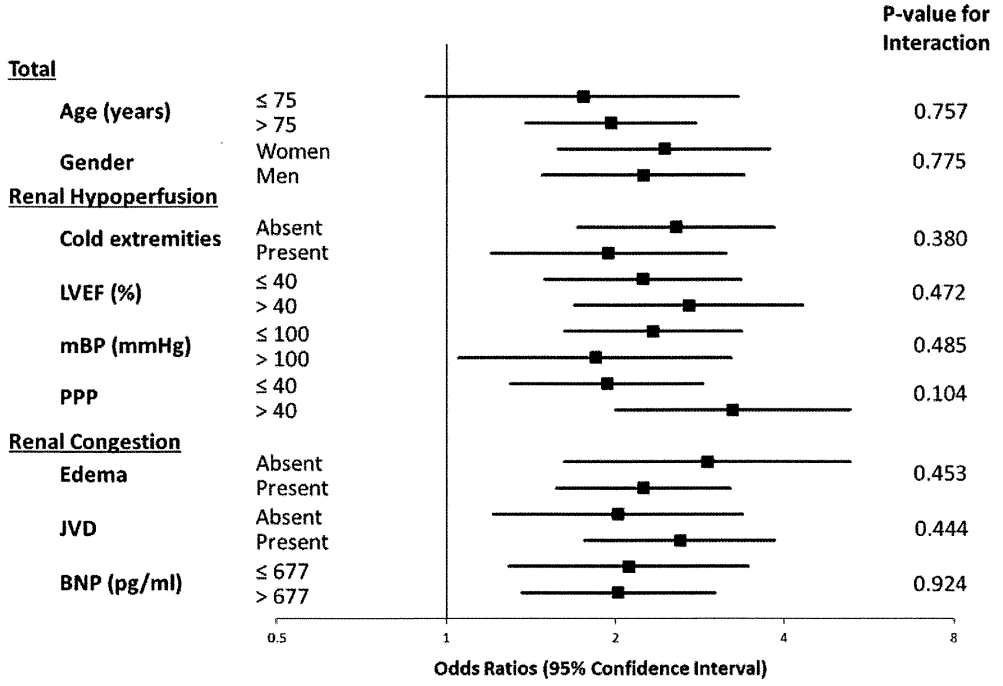

Figure 4. The prognostic impact of renal dysfunction in the prediction of all-cause mortality in relation to the underlying etiologic mechanisms. LVEF, left ventricular ejection fraction; mBP, mean blood pressure; PPP, proportional pulse pressure; JVD, jugular venous distension; BNP, brain natriuretic peptide.
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renal dysfunction or renal congestion. According to this hypothesis, elevated CVP is directly transmitted to the renal vein and increases renal perfusion pressure, which raises the interstitial intrarenal pressure and causes tubule collapse, leading to a decrease in GFR [18]. The association between a higher CVP and decreasing GFR has been demonstrated in several studies [10,19–21]. Our study suggests that the resulting renal dysfunction could impact on patient outcomes, regardless of the etiology underlying the renal dysfunction.

In our study, patients' clinical presentation parameters and vital signs were primarily used to differentiate the underlying etiologic mechanisms of renal dysfunction; however, novel biomarkers could differentiate these mechanisms in more objective and reproducible fashion. Several novel biomarkers are emerging, and we evaluated their potential in the clinical settings. Among these biomarkers, soluble suppression of tumorigenicity 2 (sST2) could be a leading candidate. sST2, a member of the interleukin (IL)-1 receptor family, has been established as a predictor of mortality in the long-term follow-up of ADHF patients [22,23]. As sST2 is a biomarker for cardiac remodeling and fibrosis, it may be more prominent in patients with hypoperfusion than in those with congestion.

Hypoperfusion has traditionally been considered the predominant cause of renal dysfunction in patients with ADHF [8]. However, a recent study reported that venous congestion may also be an important hemodynamic factor in this condition [10], and its impact has received strong attention. In turn, our study found the adverse impact of renal dysfunction on in-hospital outcomes to be consistent regardless of etiology. This finding has established the prognostic importance of renal dysfunction complicated with ADHF under any circumstances. Furthermore, our study also reconfirmed the adverse impact of renal dysfunction on in-hospital outcomes in the Asian population who have completely different clinical characteristics compared with the Western population. Previously, we demonstrated the key differentiating characteristics of heart failure patients in Western countries as compared with those in Asian countries [13]. Notably, we found an increased prevalence of patients with de novo heart failure and non-ischemic etiology in Japan versus in Western countries. Additionally, the length of hospital stay for this category of patients was much longer in Japan than in Western countries, probably owing to the differences in health insurance systems. All these complicating factors could potentially have mitigated the effect of eGFR.

Study Limitations

Our study has several limitations. Firstly, the calculation of the GFR was originally developed for use in patients with chronic kidney disease whose renal functions are relatively stable; the applicability of this calculation for patients with ADHF has not been sufficiently validated. However, previous studies have demonstrated an association between reduced GFRs and adverse outcomes in patients with ADHF [24–26]. Our intent was to estimate the level of renal dysfunction in our study population, rather than to determine the precise renal function levels of these patients. Secondly, it could be argued that an invasive approach, such as right heart catheterization, should have been used to evaluate patients' hemodynamic profiles more precisely. However, we believe that evaluations based on accessible and non-invasive clinical measures, including vital signs, physical findings, laboratory markers, and echocardiograms, are relevant to clinical decision making. Furthermore, these non-invasive parameters reflect values assessed with an invasive modality, and they are considered sufficient substitutes for a more invasive approach [15–17]. Moreover, analyses based on these clinical measures may be more practical for patient assessments and more applicable in routine practice. Third, we could not evaluate the associations between renal dysfunction and long-term outcomes, because long-

term follow-up data were not available for this study. Further study is needed regarding long-term assessments. Finally, hospital stays were much longer in the ATTEND registry than those reported from Western countries, which is associated with Japan's health insurance system [13], and in-hospital mortality in the data within the ATTEND registry might differ from its counterparts in other countries. However, a previous analysis of data from the ATTEND registry has shown that most sudden cardiac deaths occurred within 14 days of admission [27], therefore a hospital stay of less than 7 days might be too short to accurately evaluate short-term outcomes. From this perspective, our results may reflect short-term mortality more precisely.

Conclusions

In conclusion, baseline renal dysfunction was significantly associated with in-hospital mortality in patients admitted with ADHF. The prognostic impact of renal dysfunction was the same, regardless of its underlying etiologic mechanism.

Supporting Information

Appendix S1 ATTEND Study Investigators.
(DOC)

Acknowledgments

We wish to extend our appreciation to the investigators of the ATTEND registry, who are listed in Appendix S1.

Disclaimer: All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Author Contributions

Conceived and designed the experiments: TI SK NS KK TK MM TT. Performed the experiments: NS KK TK MM TT. Analyzed the data: TI SK NS. Contributed reagents/materials/analysis tools: NS KK TK MM TT. Contributed to the writing of the manuscript: TI SK NS.

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CHEST

Incidence and Prognostic Significance of Myocardial Late Gadolinium Enhancement in Patients With Sarcoidosis Without Cardiac Manifestation

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BACKGROUND: Cardiac death is the leading cause of mortality associated with sarcoidosis in Japan. However, the involvement of sarcoidosis infiltration often remains undetected. Recently, late gadolinium enhancement with cardiovascular MRI (LGE-CMR) imaging has been introduced for the detection of myocardial infiltrative disease, as it enables the detection of even minor myocardial damage. We investigated the incidence and prognostic value of LGE-CMR in patients with extracardiac sarcoidosis without cardiac manifestations.

METHODS: Sixty-one consecutive patients who met the histologic and clinical criteria for sarcoidosis, and who did not have signs or symptoms of cardiovascular involvement, were prospectively recruited. LGE-CMR was performed at the time of enrollment, and patients were classified into positive or negative late gadolinium enhancement groups based on the findings. The study end point was a composite of all-cause death, symptomatic arrhythmia, and heart failure necessitating admission.

RESULTS: Patients were predominantly middle aged (57 ± 15 years) and female (66%), and most had stable disease activity that did not require treatment with immunosuppressants. LGE-CMR detected cardiac involvement in eight patients (13%). Interventricular septal thinning detected by echocardiography was an independent predictor of LGE-CMR-detected cardiac involvement. During the follow-up period of 50 ± 12 months, no significant difference in adverse events was noted between patients in the LGE-CMR-positive and LGE-CMR-negative groups.

CONCLUSIONS: LGE-CMR detected cardiac involvement in 13% of patients with sarcoidosis without cardiac manifestation, but both patients with and without LGE had relatively low event rates.

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ABBREVIATIONS: ACE = angiotensin-converting enzyme; CAD = coronary artery disease; CMR = cardiovascular MRI; CRP = C-reactive protein; IVS = interventricular septum; JMHW = Japanese Ministry of Health and Welfare; LGE = late gadolinium enhancement; LGE-CMR = late gadolinium enhancement with cardiovascular MRI; LVEF = left ventricular ejection fraction; PES = programmed electric stimulation; SSFP = steady-state free precession

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Sarcoidosis is a multiorgan disorder of unknown etiology that is characterized by granulomatous formation.[1] Although the disease is thought to have low mortality and a benign prognosis, cardiac involvement may worsen the prognosis, as it leads to left ventricular dysfunction, congestive heart failure,[2] and life-threatening cardiac arrhythmias.[3] The mortality in patients with sarcoidosis with cardiac manifestation is as high as 25% in Western countries[4] and is even higher in the Japanese population,[5] indicating the need for therapeutic intervention.

Cardiac sarcoidosis is characterized by the presence of cardiac symptoms, particularly impaired systolic left ventricular function, or ECG changes. Frequently, however, the only indicators of cardiac sarcoidosis are minor ECG abnormalities and atypical cardiac symptoms, such as bundle branch and atrioventricular block, and ventricular arrhythmia. Furthermore, cardiac involvement in sarcoidosis is difficult to detect because the infiltration of granulomas into cardiac tissue is often not associated with clinical symptoms.[6,7] Thus, early detection of cardiac involvement in patients with sarcoidosis may improve treatment strategies and mortality.

Noninvasive imaging approaches, such as late gadolinium enhancement (LGE) with cardiovascular MRI (CMR) (LGE-CMR), have enabled detection of cardiac infiltration of sarcoidosis at much earlier phases of the disease.[8,9] LGE distribution varies according to the type of myocardial disease. For example, gadolinium is predominantly distributed in the endocardium of patients with ischemic cardiomyopathy, in the myocardial wall of patients with dilated cardiomyopathy, and in the epicardium of patients with myocarditis.[10,11] Several studies have demonstrated that CMR is able to detect characteristic fibrosis patterns of cardiac sarcoidosis, such as septal thinning, ventricular dilation, and systolic dysfunction.[12,13] LGE-CMR is reported to have high sensitivity and specificity for the detection of cardiac involvement in patients with sarcoidosis, who typically exhibit a nonischemic pattern of LGE.[14,15]

Patel et al[9] reported a retrospective analysis of patients with systemic sarcoidosis. In their study, 19% of patients with systemic sarcoidosis with preserved ejection fraction (left ventricular ejection fraction [LVEF] $>50\%$) showed LGE; some of these patients had cardiac symptoms or an ECG abnormality (37%), and one-quarter (25%) satisfied the Japanese Ministry of Health and Welfare (JMHW) criteria. This study was limited to investigating the characteristics of the LGE-positive and LGE-negative groups and did not include outcome. Patel et al[8] also demonstrated that the prevalence of myocardial damage detected by LGE-CMR in patients with extracardiac sarcoidosis was 26%, and the presence of LGE predicted future adverse events. Their prospective cohort specifically included patients with left ventricular dysfunction, cardiac manifestation (21%), and those who already satisfied the JMHW criteria (10%). Notably, their LGE-positive group had significantly lower LVEF compared with the LGE-negative group; thus, the results were easily understandable.

Therefore, based on these studies, the role of LGE-CMR in less symptomatic patients is still unclear. Detection of myocardial damage by LGE-CMR in patients with extracardiac sarcoidosis without cardiac manifestation is becoming common in daily practice, and the aim of the current study is to clarify the usefulness of LGE-CMR for detecting myocardial damage and future risk stratification in such patients with sarcoidosis.

Materials and Methods

Patient Population

A total of 61 consecutive patients who were histologically and/or clinically diagnosed with extracardiac sarcoidosis, including lung, eye, and skin involvement, were prospectively assessed. Inclusion criteria were the absence of cardiac symptoms suggestive of ischemic or other heart disease; LVEF $\geq 50\%$; no contraindication for LGE-CMR, such as renal impairment or implanted metallic device; and not meeting the diagnostic criteria for cardiac sarcoidosis by tests other than LGE-CMR, as described in the 2006 revised version of the JMHW guidelines.[16,17]

Patients were divided into LGE-CMR-positive and LGE-CMR-negative groups based on the results of CMR imaging performed during an initial evaluation. All subjects provided written informed consent prior to participation in the study. The study was approved by the ethics committee of Keio University Hospital (20-77) and registered under the Japanese UMIN Clinical Trials Registry (UMIN000001549).

Blood Sampling and Testing

Prior to CMR, venous blood samples were collected, and the serum C-reactive protein (CRP) level was then measured by latex photometric immunoassay (Mitsubishi Chemical, Inc). Serum creatinine level was measured enzymatically using the creatinase-sarcosine oxidase-peroxidase method. Angiotensin-converting enzyme (ACE) activity was measured by the Kasahara method.[18]

Echocardiography

Echocardiography was performed prior to CMR. Left ventricular wall-motion abnormality and thinning of the interventricular septum (IVS) were interpreted by two experienced clinicians without knowledge of the patients' background.

CMR Protocol

CMR was performed using a standardized clinical protocol on a 1.5-T magnetic resonance system (Signa TwinSpeed; General Electric Co). All CMR images were ECG-gated and obtained during repeated

breath holds. Cine images were acquired with a steady-state free precession (SSFP) pulse sequence with the following parameters: repetition time, 4.8 milliseconds; echo time, 1.2 milliseconds; flip angle, 55°; matrix, 256 × 128; field of view, 350 mm; section thickness, 10 mm; section interval, 10 mm; and sensitivity encoding factor, ECG-gated inversion-recovery true fast imaging with SSFP performed in the mid-diastolic phase using an inversion time of 300 milliseconds. After localization of the heart, nine to 12 contiguous short-axis sections encompassing the entire left ventricle and two-, three-, and four-chamber, long-axis projections were collected. Gadopentetate meglumine (0.15 mmol/kg; Magnevist; Schering AG) was administered at a rate of 3 to 4 mL/s using a power injector, and delayed-enhancement images were acquired 10 min after the injection of gadopentetate meglumine, using an inversion-recovery SSFP pulse sequence. Seven short axial sections were obtained at each time point. Inversion time was fixed at 300 milliseconds after the R wave.

Study End Point and Clinical Follow-up

The study end point was a composite of all-cause death, heart failure necessitating admission, and symptomatic arrhythmia, which was defined as ventricular arrhythmia with clinical symptoms and necessitating admission, or bradyarrhythmia leading to pacemaker implantation. Follow-up data, including the results of additional LGE-CMR imaging performed after 6 months with patient permission, were obtained from hospital records; by direct contact with patients or patients' physicians at hospital or outpatient clinic; telephone interview of patients or, if deceased, of family members; and mail, by dedicated coordinators and investigators.

Statistical Analysis

Continuous data are expressed as mean ± SD. LGE-CMR-positive and LGE-CMR-negative groups were compared using an unpaired *t* test or nonparametric means test for continuous variables. Categorical variables were reported as frequencies with percentages and compared between the two groups using the χ^2 test and Fisher exact test. Long-term outcome was estimated using Kaplan-Meier curves and the log-rank (Mantel-Cox) test to assess the significance of differences according to the presence or absence of LGE. Multiple logistic regression analysis, including determinants with a *P* value < .10 in univariate analysis, was used to assess the effects of various factors on positive LGE. All statistical analyses were performed using SPSS 13.0 for Windows (IBM). Statistical significance was defined as $P < .05$.

Results

Baseline and Clinical Characteristics

Patients were predominantly middle aged (57 ± 15 years) and female (66%) and had a relatively prolonged course of stable sarcoidosis (median, 38 months). Most patients (89%) had pulmonary involvement and were not treated with immunosuppressants (Table 1).

Delayed Enhancement Imaging

Eight of the 61 patients (13%) had positive LGE findings, including perimyocardial involvement in two patients (Fig 1A), transmyocardial involvement in two patients (Fig 1B), and intramyocardial involvement in four patients (Figs 1C, 1D).

Differences Between LGE-Positive and LGE-Negative Groups

Although no significant differences were detected between the LGE-positive and LGE-negative groups with respect to baseline characteristics, extracardiac organ involvement, disease duration, and steroid use, the LGE-positive group tended to have a higher incidence of baseline steroid therapy and more organ involvement than the LGE-negative group (Table 1). Echocardiographic analysis revealed that the prevalence of IVS thinning was significantly higher in the LGE-positive group (38% vs 4%, $P < .05$). No difference in the prevalence of left ventricular wall-motion abnormality or positive gallium-scintigram findings was seen between the two groups (Table 2).

Blood tests revealed that serum ACE activity was significantly lower in the LGE-positive group, but no significant difference was detected for other laboratory test results, including CRP and hemoglobin levels, or lung volume capacity (Table 1).

In both groups, no patient had any signs suggestive of coronary artery disease (CAD). This included ischemic ST-T change and/or abnormal Q-wave in the ECG or local left ventricular wall-motion abnormality corresponding to coronary territory in the echocardiogram.

Determinants of Positive LGE

Univariate logistic regression analysis identified multiple organ involvement and IVS thinning as possible independent factors for positive LGE ($P = .09$ and $P = .01$, respectively) (Table 3). These two variables were included in a multivariate logistic regression analysis model, which revealed that IVS thinning shown by echocardiography was an independent determinant of positive LGE (OR, 11.7; 95% CI, 1.49-92.0; $P = .019$) (Table 3).

Short-term (6-Month) Outcomes of Patients in LGE-Positive Group

The characteristics of patients in the LGE-positive group are summarized in Table 4 and Figure 2. During the initial 6-month follow-up period, one patient (No. 1) underwent pacemaker implantation almost 1 month after CMR for advanced atrioventricular block. However, other patients did not experience any major adverse cardiac events. Four patients refused induction of steroid therapy, but did not show progression of LGE on follow-up CMR performed 6 months after study enrollment. Patient No. 8 was treated with steroids upon patient's request, and LGE was not detected 6 months after initiating treatment.

TABLE 1] Baseline Characteristics of Patients

Characteristic	Overall (N = 61)	LGE Positive (n = 8)	LGE Negative (n = 53)	*P* Value
Age, y	57 ± 15	66 ± 9	56 ± 15	.06
Female patients	40 (66)	6 (75)	34 (64)	.84
Interval after diagnosis of sarcoidosis, mo (Q1, Q3)	38 (6, 155)	25 (8, 60)	42 (5, 156)	.39
Steroid use	7 (11)	3 (38)	4 (8)	.06
Other immunosuppressants	0 (0)	0 (0)	0 (0)	...
Organ involvement				
Pulmonary	54 (89)	7 (88)	47 (89)	.62
Extrapulmonary	31 (51)	6 (75)	25 (47)	.26
Organs involved, No.				
1	31 (54)	3 (38)	28 (57)	.51
≥ 2	27 (44)	5 (63)	22 (42)	.45
Laboratory data				
ACE, mg/dL	25.7 ± 12.7	20.6 ± 5.8	26.5 ± 13.3	.04
CRP, mg/dL	0.24 ± 0.44	0.18 ± 0.24	0.25 ± 0.21	.52
Hemoglobin, g/dL	13.7 ± 1.4	13.3 ± 1.3	13.8 ± 1.4	.40
Creatinine, mg/dL	0.73 ± 0.22	0.74 ± 0.37	0.73 ± 0.20	.97
Spirogram				
% VC	94.5 ± 21.4	85.3 ± 34.9	96.8 ± 16.7	.83

Continuous variables are presented as mean ± SD and categorical variables are presented as No. (%), unless otherwise indicated. ACE = angiotensin-converting enzyme; CRP = C-reactive protein; LGE = late gadolinium enhancement; Q = quarter; VC = volume capacity.

Long-term Patient Outcomes

During the follow-up period of 50 ± 12 months, two patients were lost. One in the LGE-positive group (No. 2) was lost at 46 months after enrollment; the other, in the LGE-negative group, was lost at 37 months after enrollment. No patient in either group experienced cardiac death. In addition, no significant differences in the study end points were detected between the two groups (Fig 3). Three patients in the LGE-CMR-negative group died of noncardiac causes (hepatic cell carcinoma, malignant lymphoma, and pulmonary sarcoidosis).

Discussion

In this prospective study of 61 Japanese patients with extracardiac sarcoidosis, 13% of patients who did not meet the diagnostic criteria for cardiac sarcoidosis based on conventional assessment by ECG, echocardiography, and gallium scintigram nevertheless showed cardiac involvement on LGE-CMR. We also found that thinning of the IVS was an independent determinant of myocardial damage detected by LGE. However, cardiac involvement was not associated with a higher risk for short- or long-term adverse outcomes in this patient population. Together, these findings suggest that LGE-CMR sensitively detects cardiac involvement associated with extracardiac sarcoidosis, even during the clinically silent stages of cardiac involvement, but has limited prognostic implication in the absence of clinical cardiac manifestations, such as heart failure or symptomatic arrhythmias. This study could answer a very relevant clinical issue faced in the management of cardiac sarcoidosis patients: what to do about incidentally discovered CMR abnormalities in the context of systemic sarcoidosis. There are a few articles published on this issue, but no study has prospectively scanned individuals in the absence of cardiac symptoms.

The JMHW has established guidelines for the diagnosis of cardiac sarcoidosis,[16] which include invasive diagnostic tests, such as myocardial biopsy, and noninvasive methods, including nuclear-medicine testing by thallium and gallium scintigraphy. However, these criteria suffer from low sensitivity[12,19] and often fail to detect early signs of cardiac involvement, particularly myocardial infiltration and tissue damage. Therefore, the application of LGE-CMR as a diagnostic imaging approach for cardiac involvement in patients with extracardiac sarcoidosis requires the accurate detection of characteristic myocardial damage. In the present study, the LGE-positive group of patients with extracardiac sarcoidosis showed various types of LGE imaging patterns, including

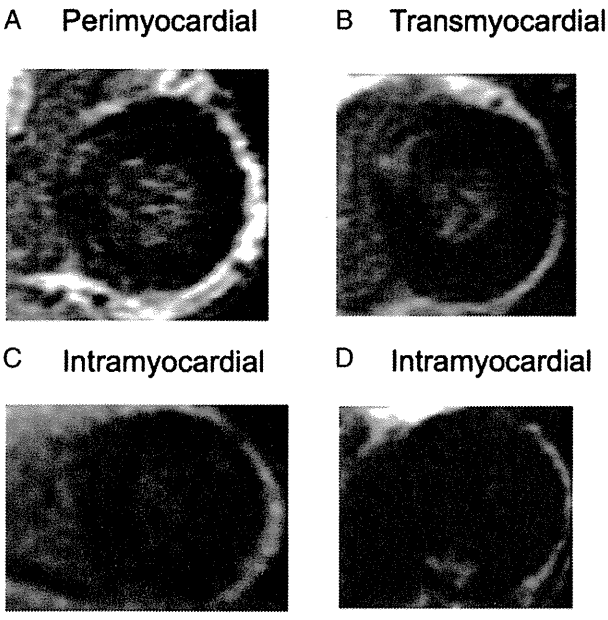

Figure 1 – *Representative findings and enhancement patterns in the late gadolinium enhancement-positive group (n = 8) of patients with extracardiac sarcoidosis patients. A, Perimyocardial pattern (n = 2). B, Transmyocardial pattern (n = 2). C and D, Intramyocardial pattern (n = 4).*

peri-, trans-, and intramyocardial involvement. The observed patterns are comparable to those reported by Watanabe et al,[11] who examined CMR images of patients with cardiac sarcoidosis who were enrolled in a multicenter study and found that LGE was most frequent in the subepicardial layer, where the appearance of LGE staining was band-shaped with distinct margins. In addition, transmural lesions were more common in patients with reduced LVEF (<35%). However, even among patients who showed characteristic LGE images of cardiac sarcoidosis, a number were additionally diagnosed with various types of cardiomyopathy, including dilated and hypertrophic cardiomyopathy, which suggests that the observed patterns may not have been specific for damage caused by sarcoidosis.

Our current studies suggest that patients with extracardiac sarcoidosis with no cardiac symptoms and preserved left ventricular systolic function have better clinical outcomes and fewer events than those with symptomatic and left ventricular systolic dysfunction. Our present findings differ from the results of two similar studies conducted in Western countries, with respect to the detection rates of cardiac involvement and long-term outcomes of patients with LGE-positive sarcoidosis, even though the longer observation periods (from 3 to 4 years) and end points were similar.[8,9] For example, the frequency of patients who were LGE positive in the previous studies ranged from 19% to 26%, which is approximately twofold higher than the detection rate of 13% in the present study. In addition, the rate of cardiac events in patients in the LGE-positive group (12.5%) was markedly lower than that of approximately 29% in one study,[8] suggesting that differences in disease duration, inclusion criteria, or incidence of immunosuppressant use may have influenced the long-term outcome in these patient populations. With

TABLE 2] Baseline Cardiac Characteristics of Patients

Characteristic	Overall (N = 61)	LGE Positive (n = 8)	LGE Negative (n = 53)	*P* Value
ECG				
First-degree AVB	3 (5)	1 (13)	2 (4)	.85
Wenckebach-type AVB	1 (5)	1 (13)	0 (0)	.27
Mobitz-type AVB	0 (0)	0 (0)	0 (0)	...
Left BBB	0 (0)	0 (0)	0 (0)	...
Right BBB	4 (7)	2 (25)	15 (28)	.82
ST-T change	3 (5)	1 (12)	1 (2)	.61
Echocardiogram				
IVS thinning	19 (31)	3 (38)	2 (4)	.01
Wall-motion abnormality	17 (28)	2 (25)	15 (28)	.82
CMR				
LVEDV, mL	104.6 ± 23.9	104.6 ± 8.5	104.6 ± 3.3	.99
LVEF, %	63.1 ± 7.1	59.7 ± 2.5	63.6 ± 0.9	.15
Positive for cardiac Ga-scintigram	2 (3)	1 (13)	1 (2)	.61

Continuous variables are presented as mean ± SD, categorical variables are presented as No. (%). AVB = atrioventricular block; BBB = bundle branch block; CMR = cardiovascular MRI; Ga = gallium; IVS = interventricular septum; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction.