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ORIGINAL ARTICLE

Clinical and Economic Evaluation of Impella Treatment for Fulminant Myocarditis

— A Preliminary Retrospective Cohort Study in Japan —

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Background: Fulminant myocarditis (FM) is rare but has an extremely poor prognosis. Impella, a catheter-based heart pump, is a new therapeutic strategy, but reports regarding its health economics are lacking.

Methods and Results: This retrospective cohort study compared Impella treatment (Group I) with existing treatments (Group E) using medical data collected from October 2017 to September 2021, with a 1-year analysis period. Cost-effectiveness indices were life-years (LY; effect index) and medical fee amount (cost index). Results were validated using probabilistic sensitivity analysis. The incremental cost-effectiveness ratio (ICER) was calculated using quality-adjusted LY (QALY) and medical costs. Each group included 7 patients, and more than half (57.1%) received combined Impella plus extracorporeal membrane oxygenation. There was no significant difference between Groups I and E in 1-year mortality rates (28.6% vs. 57.1%, respectively) or LY (mean [±SD] 163.1±128.3 vs. 107.8±127.3 days, respectively), but mortality risk was significantly lower in Group I than Group E (95% confidence interval 0.02–0.96; P<0.05). Compared with Group E, Group I had higher total costs (9,270,597±4,121,875 vs. 6,397,466±3,801,364 JPY/year; P=0.20) and higher cost-effectiveness (32,443,987±14,742,966 vs. 92,637,756±98,225,604 JPY/LY; P=0.74), which was confirmed in the sensitivity analysis. ICER probability distribution showed 23.2% and 51.5% reductions below 5 million and 10 million JPY/QALY, respectively.

Conclusions: Impella treatment is more cost-effective than conventional FM treatments. Large-scale studies are needed to validate the added effects and increasing costs.

Key Words: Assisted circulation; Data science; Fulminant myocarditis; Health economics

Acute myocarditis has diverse etiology, most commonly viral infections and drugs. Fulminant myocarditis (FM), a rapidly progressing acute myocarditis leading to cardiogenic shock due to left ventricular dysfunction or cardiac arrest due to fatal arrhythmia, is rare but has an extremely poor prognosis.[1] Treatment of FM often involves the use of artificial cardiopulmonary devices, such as extracorporeal membrane oxygenation (ECMO) or intra-aortic balloon pump (IABP). If recovery with these treatments fails, a ventricular assist device (VAD) is often implanted to enable long-term heart recovery or to act as a bridge to heart transplantation. In Japan, FM was reported to have an annual mortality rate of 42% among patients requiring venoarterial ECMO.[2]

Despite their usefulness for cardiopulmonary support, IABP and ECMO also have disadvantages, such as providing insufficient assistance and increasing ventricular afterload, respectively. Under such circumstances, a catheter-based heart pump for circulatory support with intracardiac placement (Impella®) was approved for use in Japan from September 2016. This innovative device-based treatment enables rapid reductions in left ventricular load after insertion of the Impella percutaneously (if it is of small size), although generally for a limited period of several days. Impella treatment was also reported to be useful in patients with FM, as a bridge to recovery.[3]

In Japan, Impella treatment was set for reimbursement by the public medical insurance system for approximately

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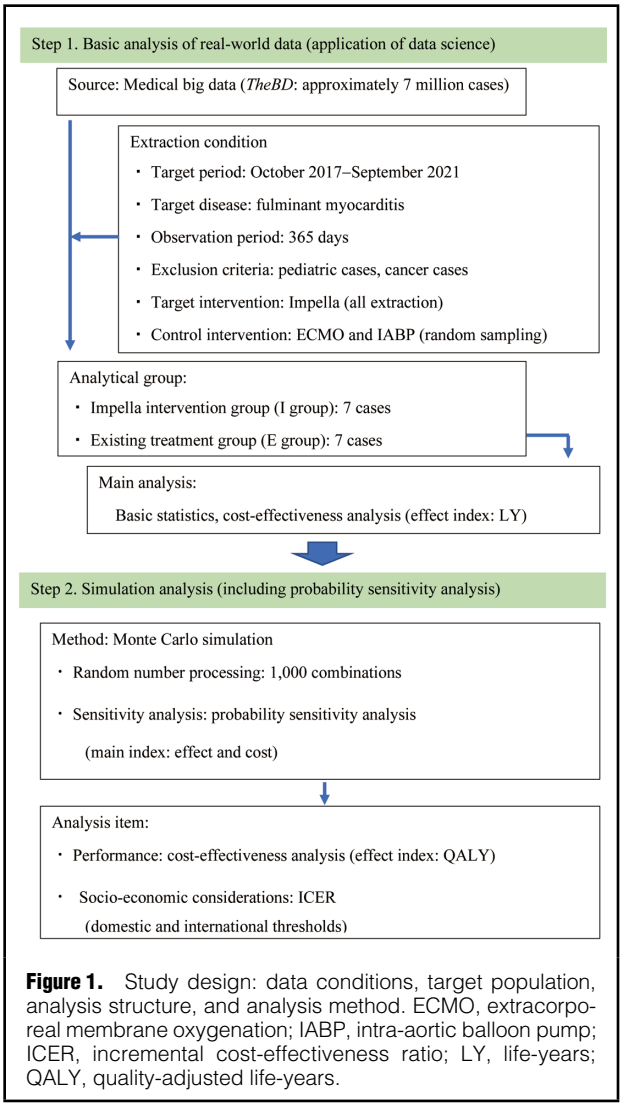

Figure 1. Study design: data conditions, target population, analysis structure, and analysis method. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICER, incremental cost-effectiveness ratio; LY, life-years; QALY, quality-adjusted life-years.

JPY 2.59 million in September 2017. This cost is higher than that of conventional ECMO or IABP, resulting in increasing interest in verifying the clinical effectiveness and economic efficiency of Impella treatment (either alone or in combination with ECMO or IABP) compared with conventional interventions centered on ECMO and IABP. Worldwide, only few studies on clinical and economic analyses in the field of FM have been published, and no such studies exist in Japan. These studies would provide health economics-based evidence essential for promoting medical progress, developing a sustainable medical system, and reducing patients' disease and economic burdens. Therefore, we conducted a preliminary cost-effectiveness analysis of Impella treatment in patients with FM in a small real-world sample to clarify the clinical and economic aspects of this treatment in the Japanese medical system.

Methods

Study Design

This was a multicenter retrospective longitudinal cohort study using medical big data while keeping in mind real-world evaluations (data science). We followed the STROBE guidelines for cohort studies.[4] The data collection period was set from October 2017, when Impella treatment was granted insurance coverage in Japan, to September 2021. The analysis period was 365 days. Patients who underwent Impella treatment, alone or in combination with ECMO or IABP, comprised the Impella group (Group I), whereas those who received combined ECMO and IABP treatment comprised the existing treatment group (Group E). Pediatric and cancer cases were excluded.

The selected analysis method was cost-effectiveness analysis, with life-years (LY) as the effect index and medical fee amount as the cost index. The target disease was FM, identified based on the International Classification of Diseases, 10th revision (ICD-10) code I40.8, insurance code 20088416, and the disease name. The position of evaluation was set to society (public insurer).

In creating the study design, we considered the following constraints specific to the disease studied and the evaluation technique. The number of FM cases in Japan is extremely small, which was speculated to pose restrictions on statistical processing. Thus, when selecting the test method (test of difference in population mean, test of difference in population ratio), although there were no existing reference data (mean or standard deviation), we confirmed the minimum sample size. Non-parametric methods can be applied regardless of the form of distribution or variance, but it was thought that the performance would deteriorate if the sample size was ≤6.[5] Therefore, the sample size was set to 7 patients in each group, for a total of 14 patients.

Given the above sample size constraints, to verify the robustness of the analysis results, we conducted probabilistic sensitivity analysis (PSA) based on the results of real-world data analysis using the Monte Carlo method. PSA is an uncertainty evaluation method that is stipulated in international guidelines and is frequently used in health economics experiments.[6] We also converted the effect index LY into quality-adjusted LY (QALY) and calculated the incremental cost-effectiveness ratio (ICER) by using the obtained QALY and medical costs. The ICER based on QALY has been introduced in the Japanese medical insurance system since financial year (FY) 2019 and has a clear criterion for judging cost-effectiveness: JPY 5–7.5 million per QALY acquisition. For comparison, in other countries, this criterion is set at approximately JPY 10 million.[7,8] The study design, roughly divided into analysis using real-world data and simulations that used those results, is shown in **Figure 1**.

This study was conducted in accordance with the Declaration of Helsinki and was approved in March 2019 by the Institutional Review Board of the University of Tokyo Hospital (Approval no. 2018167NI). Because we used database records for analysis, the need for informed consent was waived.

Data Source

Data were obtained from a large database that includes medical service data examined by a specialized public organization (Social Insurance Medical Fee Payment Fund), in accordance with the format stipulated by the Ministry of Health, Labour, and Welfare of Japan (MHLW Notification: Vol. 831, No. 1). We selected the medical economic big data (TheBD: The Tokyo University Health Economy Big Data; **Supplementary Table 1**),[9,10] which included medical

Table 1. Patient Characteristics

Characteristic	Impella intervention group	Existing treatment group	P value
Sample			
No. patients	7	7	–
Age (years)	35.9±12.8	43.1±13.0	0.35
% Male	85.7	71.4	0.51
Disease (comorbidity: based on ICD-10)			
Atrioventricular block	28.6	42.9	0.57
Ventricular beats	28.6	14.3	0.51
Sinus arrhythmia	0.0	28.6	0.12
HF (pump dysfunction or CS)	100.0	71.4	0.12
Renal failure	14.3	28.6	0.51
Liver dysfunction	28.6	0.0	0.12
Hypertension[A]	28.6	14.3	0.51
Diabetes[A]	14.3	0.0	0.29
Cardiac resynchronization therapy			
Temporary pacemaker	28.6	42.9	0.57
Drug therapy			
Cardiac stimulant	71.4	85.7	0.51
Arrhythmia agent	28.6	57.1	0.24
Diuretic	57.1	28.6	0.24
Antihypertensive drug	57.1	28.6	0.24
Vasoconstrictor	28.6	0.0	0.12
Vasodilator	42.9	42.9	1.00
Other cardiovascular drugs	28.6	28.6	1.00
Steroid	28.6	0.0	0.12
Surgical therapy			
Impella	100.0	0.0	<0.01
2.5	57.1	–	–
CP	28.6	–	–
5.0	14.3	–	–
ECMO	57.1	100.0	0.05
IABP	28.6	100.0	<0.01
PCI	0.0	0.0	1.00
CABG	14.3	0.0	0.29

Unless indicated otherwise, data are given as the mean±SD or percentages. Tests: Mann-Whitney U test, Fisher's exact test. [A]Some cases include the preexisting diseases. CABG, coronary artery bypass grafting; CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; HF, heart failure; IABP, intra-aortic balloon pump; ICD-10, International Classification of Diseases, 10th Revision; PCI, percutaneous coronary intervention.

service bills gathered from public insurers (including the health insurance societies of companies) throughout Japan between April 2012 and March 2021, representing coverage for 7 million insured patients. As for the sample composition by year, 2016 accounted for the largest proportion (22.1% of the total). Medical information accounted for 6.18 million results, whereas dispensing information accounted for 6.20 million results (including duplications). The patient-based hospitalization rate was 13.5% (including duplications), and the average percentage of male patients for all years was 46.8%. This database is updated every 6 months. All data on disease name, testing, medication, surgery, and any other medical interventions with dates of initiation and related costs are linked in chronological order using unique IDs for each patient. During each biannual update, the transfer of data for insured people is managed, and adjustments are made according to the relocation of medical facilities. TheBD has been used in several studies evaluating the economic aspects of medical interventions (**Supplementary Table 2**).

Evaluation Method

Evaluated Treatment Impella is a circulatory assist device, a catheter-mounted axial flow pump that is inserted retrogradely into the left ventricle through the aortic valve and pumps blood from the left ventricle to the ascending aorta by the lifting force of rotation, thereby reducing left ventricular load. It is indicated for drug therapy-resistant acute heart failure, such as cardiogenic shock. There are 3 types of Impella, namely Impella® 2.5, CP, and 5.0, that differ in the maximum auxiliary flow possible (2.5, 3.5, and 5.0 L/min, respectively). Impella® 2.5 and CP can be inserted through the femoral artery with a sheath, whereas the 5.0 requires insertion through blood vessel cutdown. Data were organized according to device type. We also extracted data on comorbidities (classification by ICD-10 code) and drug therapy (organized by drug efficacy classification code) and evaluated treatments (medical practice code).

Table 2. Key Clinical and Economic Outcomes

Index	Impella intervention group	Existing treatment group	P value
Vital prognosis[A]			
Mortality			
30 days	14.3	28.6	0.51
12 months	28.6	57.1	0.24
LY[B] (days)	163.1±128.3	107.8±127.3	0.30
Adverse event (based on ICD-10)			
Cardiopulmonary arrest	14.3	71.4	<0.05
Thrombocytopenia	57.1	42.9	0.59
Anemia	71.4	57.1	0.57
AMI	28.6	14.3	0.51
Cerebral dysfunction	0.0	28.6	0.12
Venous thrombosis	14.3	14.3	1.00
Pulmonary hypertension	14.3	0.0	0.29
Surgical therapy			
VAD	14.3	0.0	0.29
Heart transplantation	0.0	0.0	1.00
Therapy duration			
Hospital stay (days/year)	31.0±16.8	22.1±12.4	0.40
Outpatient visit (days/year)	8.7±4.1	5.6±8.9	0.08
Medical costs			
Total cost (JPY/year)	9,270,597±4,121,875	6,397,466±3,801,364	0.20
Total cost+VAD (JPY/year)	12,238,664±8,588,876		0.11
Material costs[C] (JPY/year)	3,888,291±1,597,517	2,563,206±1,515,738	0.07

Unless indicated otherwise, data are given as the mean±SD or percentages. Tests: Mann-Whitney U test, Fisher's exact test. [A]This ratio calculation is based on the start of mechanical circulatory support, which is different from the start date of hospitalization. [B]Observation period 12 months. [C]Material costs are those for drugs and devices. AMI, acute myocardial infarction; ICD-10, International Classification of Diseases, 10th Revision; LY, life-years; VAD, ventricular assist device.

Clinical Index For the clinical endpoint of LY, the time of intervention (mechanical circulatory support) was considered the index day, and 30-day and 1-year mortality rates were calculated. Survival analysis was based on the date of admission in consideration of consistency with medical costs. The quality-of-life outcome, QALY, was calculated by integrating the utility values obtained from previous studies[11–21] into LY (extrapolated by the Monte Carlo method) for each disease in which onset was observed. The utility value search was conducted from 2010 to 2021 in the PubMed and MEDLINE databases using the following search terms: "disease OR treatment technique" AND "utility OR QALY". Only original articles were selected (clinical trials). We did not focus on the level of evidence of the searched papers, but we prioritized Japanese reports.

Economic Index For medical costs, the amount charged by medical facilities to public insurers was cumulatively calculated. The calculation period included medical costs incurred over 12 months from the month of hospitalization when FM was diagnosed and the treatment intervention was conducted. The cost also included outpatient visit costs. The scope of medical costs was direct medical expenses and covered all medical examinations, evaluations/diagnostics, procedures/operations, guidance/rehabilitation, and other treatment-related procedures. For analysis, medical materials were divided into medical equipment and drugs. Costs that were incurred across multiple facilities were linked via a subject ID. We also included the applicable length of hospital stay and the number of hospital visits. It should be noted that this is different from the index day of the evaluated treatment because it is based on the first day of hospitalization.

Statistical Analysis

We selected non-parametric methods for testing differences in the population mean and population ratio, and set the level of statistical significance to 5%. Survival analysis was performed using Kaplan-Meier curves. The clinical usefulness of Impella treatment was evaluated in a multifaceted manner using the Cox proportional hazard model, where a mortality event was the objective variable and patient background and treatment intervention were explanatory variables. PSA was conducted using the Monte Carlo method; the measured (LY and medical cost) or extrapolated (utility) value was randomly changed within a range of 50% up and down for the LY, utility, and cost (by breakdown) of each sample. The random number processing combination (joint distribution of each index) was set to 1,000 times. The ICER was calculated as follows:

$$\mathrm{ICER} = (\mathrm{Cost\ [Group\ I]} - \mathrm{Cost\ [Group\ E]}) \div (\mathrm{QALY\ [Group\ I]} - \mathrm{QALY\ [Group\ E]})$$

EZR version 4.0.0 (open source; R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) were used for statistical analysis. Unless indicated otherwise, data are presented as the mean±SD.

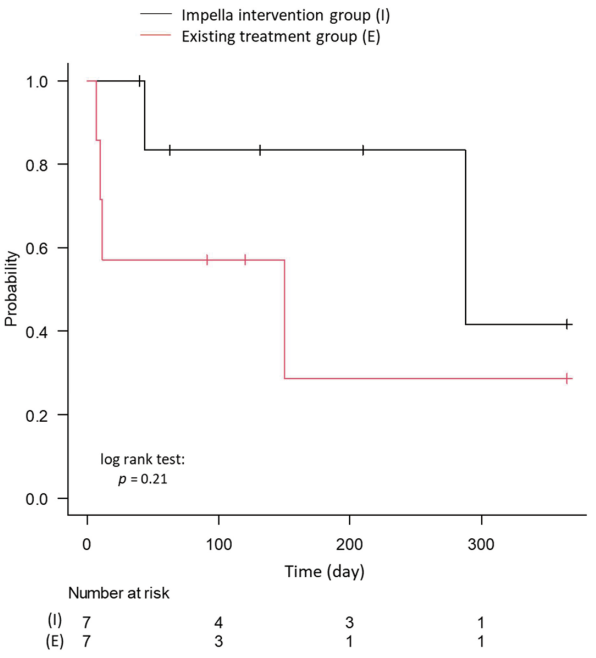

Figure 2. Survival curve analysis. Comparison of survival outcomes between Impella treatment (Group I) and existing treatments (Group E).

Table 3. Factors Related to Mortality According to Cox Proportional Hazard Model Analysis

Index	HR	95% CI	P value
Impella	0.34	0.02–0.96	<0.05
Sex[A]	0.21	0.01–3.43	0.29
Age	1.38	1.12–1.71	<0.05
Arrhythmia	4.43	0.39–150.39	0.23
VAD	6.10	0.96–179.89	0.05
Cardiac stimulant	0.29	0.02–13.28	0.78

Model: P<0.05 (likelihood ratio test), n=14. [A]Sex was dummy coded (male: 1; female: 2). CI, confidence interval; HR, hazard ratio; VAD, ventricular assist device.

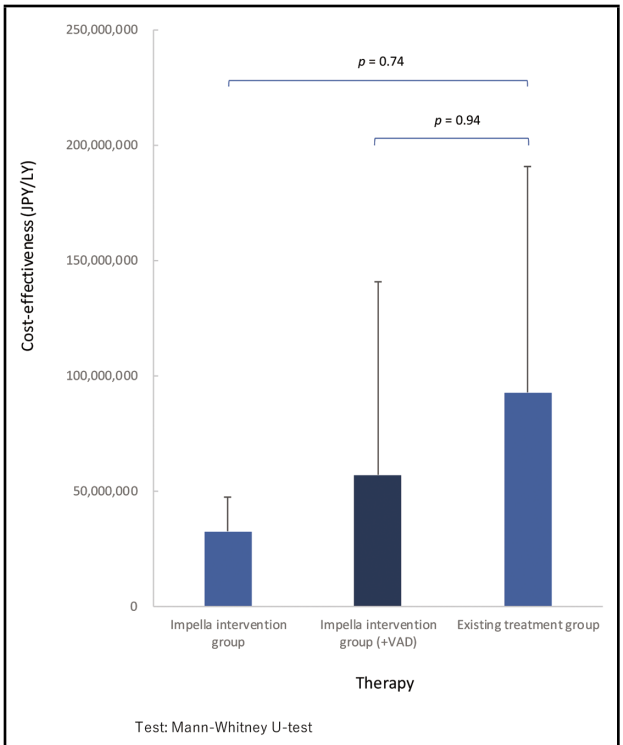

Figure 3. Cost-effectiveness analysis by life-year (LY; analysis of real-world data). Data are the mean±SD. VAD, ventricular assist device.

Results

Patient Characteristics

There were 7 patients in each group, for a total of 14 patients (**Table 1**). Mean age in Groups I and E was 35.9±12.8 and 43.1±13.0 years, respectively (P=0.35). Although both groups had a higher proportion of male patients (85.7% in Group I, 71.4% in Group E), the difference in male proportion between groups I and E was not statistically significant.

All patients presented with cardiogenic shock with lethal arrhythmia or pump dysfunction. The comorbidity rates at the index day were similar, with heart failure (cardiogenic shock associated with pump dysfunction) being the most prevalent (100.0% in Group I, 71.4% in Group E). In addition, temporary pacemaker use was equally common in the 2 groups (28.6% in Group I, 42.9% in Group E). Regarding drug therapy, most patients received cardiac stimulants (**Table 1**). One patient in Group E had COVID-19.

Impella 2.5 was the most commonly used device in Group I (57.1%), whereas the most common concurrent treatment was ECMO (ECPELLA; 57.1%). In terms of treatment distribution, ECMO and IABP (both used in all Group E patients) were implemented in 57.1% (P=0.05 vs. Group E) and 28.6% (P<0.01 vs. Group E) of patients in Group I, respectively. In Group I, 1 patient required VAD transition (as for the related part, 2 patterns of exclusion case as the standard and an inclusion case were shown in the cost calculation; **Table 2**).

Basic Real-World Data Analysis

The key clinical and economic outcomes in the 2 groups are presented in **Table 2**. Although Group I had lower 30-day (14.3% vs. 28.6%) and 1-year mortality rates (28.6% vs. 57.1%) and a higher LY index (163.1±128.3 vs. 107.8±127.3 days) than Group E, the between-group differences were not statistically significant.

In terms of adverse events, cardiopulmonary arrest was significantly more prevalent in Group E than in Group I (71.4% vs. 14.3%, respectively; P<0.05). Thrombocytopenia and anemia were more prevalent in Group I, whereas cerebral dysfunction was more prevalent in Group E; however, the between-group differences were not statistically significant.

Regarding therapy duration, compared with Group E patients, those in Group I had longer hospital stays (31.0±16.8 vs. 22.1±12.4 days/year) and more outpatient visits (8.7±4.1 vs. 5.6±8.9 days/year), although the differences did not reach statistical significance. Similarly, there were no significant between-group differences in terms of

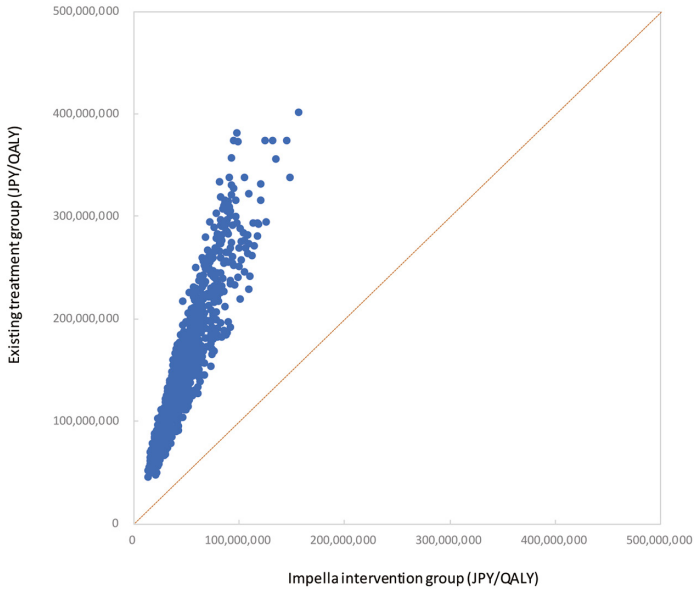

Figure 4. Probabilistic sensitivity analysis. The performance of both groups was compared by quality-adjusted life-years (QALYs) and medical cost using Monte Carlo simulation of 1,000 combinations by random number processing.

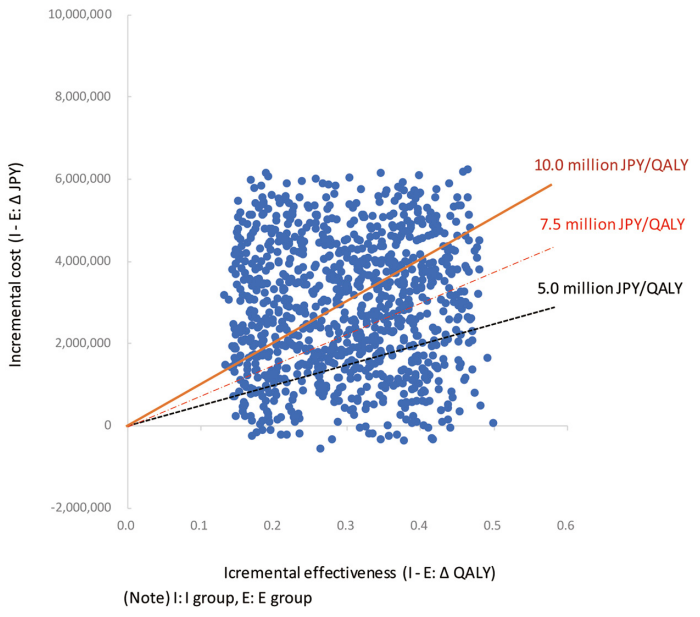

Figure 5. Incremental cost-effectiveness ratio analysis (increased effect and variance of incremental cost: Monte Carlo simulation). QALY, quality-adjusted life-years.

medical costs, although the total (9,270,597±4,121,875 vs. 6,397,466±3,801,364 JPY/year) and material (drugs and equipment; 3,888,291±1,597,517 vs. 2,563,206±1,515,738 JPY/year) costs were higher in Group I than in Group E (P=0.07).

In the Kaplan-Meier analysis, Group I had more favorable outcomes than Group E, although the difference was not statistically significant (log-rank, P=0.21; **Figure 2**). However, Cox proportional hazards regression analysis showed that Impella treatment significantly reduced mortality, with a hazard ratio of 0.34 (95% confidence interval 0.02–0.96; P<0.05; **Table 3**).

In the cost-effectiveness analysis, Group I was superior to Group E, with an approximately 66% lower value, although the difference was not statistically significant (32,443,987±14,742,966 vs. 92,637,756±98,225,604 JPY/LY; P=0.74; **Figure 3**). The cost-effectiveness of Group I, including VAD treatment cost, was 57,065,453±83,478,140 JPY/LY.

Simulation Analysis

Based on the utility value search, we organized the utility value levels from previous studies for 6 pathological conditions (treatment status) excluding the base level

(**Supplementary Table 3**).[11–21] No study directly measured FM-related utility. The obtained utility values were extrapolated to the Monte Carlo simulations, and QALY was calculated for each disease occurrence or treatment in each sample, which was also a measure against selection and uncertainty level.

By using QALY as an effect index in the PSA, the cost-effectiveness of Group I was superior to that of Group E in all combinations (**Figure 4**). Furthermore, Group E exhibited more variability than Group I.

ICER calculation using the obtained QALY showed that, for the distribution of each index by random number processing, the difference in the effect index (ΔQALY) changed from 0.1 QALY to 0.5 QALY, and the difference in the cost index (ΔJPY) changed from JPY –550,000 to JPY 6.25 million (**Figure 5**). ICER probability distribution showed a 23.2% reduction probability below JPY 5 million/QALY, a 38.0% reduction probability below JPY 7.5 million/QALY, and a 51.5% reduction probability below JPY 10 million/QALY.

For reference, we organized the effects of each element of ICER in a tornado diagram (**Supplementary Figure**). The results showed that the medical cost factor of Group I had the largest influence. Furthermore, the utility factor (quality of life) had a relatively large effect in both groups. The utility factor was thought to act in the direction of becoming less cost-effective due to the ceiling effect against the background of the characteristics of the scale (maximum of 1.0) and set utility level (around 0.8).

Discussion

This study attempted a clinical and economic evaluation of Impella treatment for FM in Japan. Compared with conventional treatments, Impella treatment increased medical costs, particularly those related to medical materials, but also improved the long-term clinical prognosis of patients. The cost-effectiveness analysis showed that Impella treatment was generally superior to conventional treatments. However, because the sample size of this study was very small, PSA was used to supplement robustness. Nonetheless, uncertainty in the results should still be considered.

The study design was roughly divided into basic analysis using real-world data and simulations that used those results. In the basic real-world data analysis, Group I had more favorable mortality rates and LY at 30 days and 1 year after treatment than Group E. However, statistically significant differences were not observed, which is considered to be due to the small sample size and the variations in patient background and treatment interventions. Hence, we conducted a multivariate analysis (Cox proportional hazard model), which showed that Impella treatment was significantly superior in terms of the hazard ratio. Interpretation of this result is difficult given the confidence intervals and proportional hazard uncertainties, but, in light of the other results and suggestions obtained, it was inferred that there was some clinical usefulness associated with Impella treatment.

Various therapeutic interventions are implemented in patients with FM, such as the use of cardiac stimulants and mechanical circulatory support, to prevent and improve multiple organ failure due to decreased cardiac function and maintain hemodynamics.[22–27] This study also showed that many combined therapies were used. Accordingly, when evaluating therapeutic interventions for FM, it is desirable to evaluate combination therapy rather than single medical techniques. To that end, adjusting the patient background and treatment technique is essential, and this requires not only devising new research designs, but also selecting a sample size of a particular scale and detailed clinical information. The database used in the present study did not include test values, and patient conditions were treated using diagnostic classifications and interventions as surrogates. Our study had major restrictions in this regard.

Initial management of patients with FM involves the use of diverse mechanical circulatory support techniques to maintain stable hemodynamics, and strategic changes are needed if cardiac dysfunction progresses or requires longer-term management.[28,29] In the present longitudinal study, we organized the history of various treatment interventions daily according to the progression of the pathological condition. Nonetheless, sufficient accuracy could not be ensured due to inconsistency in records and the absence of inspection values. The relationship between the occurrence of each event and intervention timing needs to be investigated further. In particular, there is a need to investigate the process from FM onset to Impella intervention while considering cardiogenic shock status, which was observed in this study.

The prognosis and long-term cardiac function of patients with FM have not been fully elucidated, but the long-term prognosis after the acute phase is thought to be favorable.[30] However, studies have also indicated disease recurrence and long-term cardiac dysfunction.[2,26,31–33] A recent Japanese study reported that patients with FM who underwent IABP had a poor prognosis.[34] Furthermore, patients with eosinophilic myocarditis were reported to have long-term cardiac dysfunction.[34] We also found between-group variability in the treatment process during hospitalization and the prognosis after hospital discharge; however, further investigations of treatment interventions and patient characteristics are needed to interpret the cause. It is particularly important to discuss the risk of bleeding, a phenomenon unique to Impella that also had a tendency to occur in the present study.[35]

Patients with cardiogenic shock have a wide variety of pathologies, and prognosis varies greatly. Therefore, patient background (severity) is important in the evaluation of medical technologies. Many studies have attempted to classify patients based on the risk of cardiogenic shock using scoring, but the challenge of generalization was great.[36,37] Under these circumstances, the SCAI expert consensus classification of the severity of cardiogenic shock can help by stratifying patient risk simply and practically, ensuring prompt treatment.[38] Although we did not have sufficient information for such classification, it was presumed to be Class C or higher because both groups required cardiac stimulants and mechanical circulatory support, including ECMO. Class C is the classic cardiogenic shock phenotype. From the above, it was inferred that the severity in both groups was generally equivalent.

Cost-effectiveness analysis for FM is rarely reported worldwide, and this is one of the significant interdisciplinary aspects of the present study. The total medical cost over 12 months was approximately 1.5-fold higher in Group I than in Group E, and the cost of medical materials accounted for half of this. Furthermore, Group I patients had longer hospital stays and more hospital visits than Group E patients, factors that are closely related to

medical costs. The relatively long hospital stays in Group I may be interpreted as an increase in treatment opportunities with the decrease in in-hospital deaths. Similarly, the higher number of hospital visits may be due to the higher proportion of patients being discharged from hospital.

In the present study, we excluded the part related to VAD treatment in the basic cost calculation for 2 reasons. First, in insurance medical treatment, VAD is mainly used to serve as a bridge to transplantation and destination therapy, although it may also be used as a bridge to recovery. Against this background, it was possible that the handling may exceed that set for this study because the cost level and facility standards were somewhat special. Second, in the intervention procedure for FM, VAD is generally positioned as the next intervention after Impella or ECMO/IABP, which were the targets of this study.[2,28,39–41] Therefore, to reduce analysis bias, VAD should be distinguished. Conversely, if the patient is alive but Impella has not sufficiently restored cardiac function, VAD is required as an additional treatment. Considering continuity of treatment, in the present study we performed a cost-effectiveness analysis that added VAD treatment-related costs. In addition, in the effect index calculation, we considered the significance of providing the next treatment opportunity that affects life prognosis.

Although there were no statistically significant differences in the cost-effectiveness analysis by LY and medical costs, Group I tended to show major improvements relative to Group E. Aside from the sample size, the standard deviation of Group E was thought to have affected statistical processing. The diversity of the prognosis (i.e., number of events) was considered another reason. This suggests that Impella treatment has a favorable prognosis and that there may be progress in standardizing procedures for this treatment compared with conventional treatments. There are several concepts of cost-effectiveness, and the above result was a comparison of performance between groups. This approach evaluates performance superiority or inferiority, but a judgment of the socioeconomic aspects of Impella treatment requires a QALY-based approach, such as the ICER.

We also developed random number processing simulations as a measure against the above-mentioned statistical restrictions. The cost–utility analysis using QALY that was estimated from LY showed that Group I was superior to Group E in all random combinations. This suggested that Impella treatment may be more cost-effective than conventional treatments. However, whether the extent of improvement satisfies the medical and economic criteria needs to be verified. Therefore, we used the ICER to evaluate the balance between the added clinical benefits and increased economic burden. When the thresholds of the medical insurance system in Japan and overseas were applied, the reduction probability below JPY 5 million/QALY was 23.2%, and that below JPY 10 million/QALY was 51.5%. The above-mentioned study characteristics need to be considered to interpret this result, but it is inferred that the current applicable pathological conditions and intervention methods should be investigated further. In the future, it is expected that the clinical and economic performance of Impella treatment will improve further, not only with regard to medical developments, but also in terms of reducing various burdens on patients with FM.

The results of the present study, as the first report on this subject, will serve as baseline data for clinical and economic evaluation methods in the FM field and are expected to help design prospective clinical trials in the future. Several directions can be considered in view of the contribution of our results towards the improvement of clinical and economic performance. Among them is the combined use of various therapies with optimized intervention timing. In the present study, Impella was combined with IABP and ECMO in a number of patients, and a time lag between hospital admission and intervention is suggested. Accordingly, investigations can be conducted with the aim of further improving clinical and economic aspects while considering the technical characteristics of Impella and the pathological mechanisms of FM. Although it has several limitations, the present study revealed the clinical and economic significance of Impella treatment, including its potential usefulness, which is difficult to verify.

In conclusion, compared with conventional treatments, Impella treatment increased medical costs, particularly medical material costs, but also improved the long-term clinical prognosis of patients with FM. The cost-effectiveness analysis showed that Impella treatment was generally superior to conventional treatments. However, the balance between the added effects and increased costs needs to be investigated from multiple perspectives based on socioeconomic value judgments. With this, we hope that large-scale, long-term clinical studies will be developed in the future based on a high-quality research design that considers the results of the present study.

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IRB Information

This study was approved by the Institutional Review Board of the University of Tokyo Hospital (Approval no.: 2018167NI).

Data Availability

The deidentified participant data will not be shared because it targets special interventions for rare diseases and there are concerns that anonymization cannot be guaranteed.

References

1. Adachi Y, Kinoshita O, Hatano M, Shintani Y, Naito N, Kimura M, et al. Successful bridge to recovery in fulminant myocarditis using a biventricular assist device: A case report. *J Med Case Rep* 2017; **11:** 295.
2. Aoyama N, Izumi T, Hiramori K, Isobe M, Kawana M, Hiroe M, et al. National survey of fulminant myocarditis in Japan: Therapeutic guidelines and long-term prognosis of using percutaneous cardiopulmonary support for fulminant myocarditis (special report from a scientific committee). *Circ J* 2002; **66:** 133–144.
3. Tominaga Y, Toda K, Miyagawa S, Yoshioka D, Kainuma S, Kawamura T, et al. Total percutaneous biventricular assist device implantation for fulminant myocarditis. *J Artif Organs* 2021; **24:** 254–257.

4. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. *Epidemiology* 2007; **18:** 805–835.
5. Hamada C. Concept of nonparametric test: Educational commentary. *Adv Ther* 2015; **6:** 63–69.
6. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. Probabilistic sensitivity analysis for NICE technology assessment: Not an optional extra. *Health Econ* 2005; **14:** 339–347, doi:10.1002/hec.985.
7. Ministry of Health, Labour, and Welfare of Japan. About the immediate operation of the cost-effectiveness evaluation system (Central Social Insurance Medical Council-9: 3.2.10) [in Japanese]. 2020. https://www.mhlw.go.jp/content/12404000/000736552.pdf (accessed May 27, 2022).
8. National Health Care Institute of the Netherlands. Cost-effectiveness in practice. 2015. https://english.zorginstituutnederland.nl/publications/reports/2015/06/16/cost-effectiveness-in-practice (accessed May 27, 2022).
9. Takura T, Yokoi H, Tanaka N, Matsumoto N, Yoshida E, Nakata T, et al. Health economics-based verification of functional myocardial ischemia evaluation of stable coronary artery disease in Japan: A long-term longitudinal study using propensity score matching. *J Nucl Cardiol* 2022; **29:** 1356–1369.
10. University of Tokyo. TheBD (The Tokyo University Health Economy Big Data) [in Japanese]. 2019. http://plaza.umin.ac.jp/hehp/pdf/thebd.pdf (accessed May 27, 2022).
11. Takura T, Tachibana K, Isshiki T, Sumitsuji S, Kuroda T, Mizote I, et al. Preliminary report on a cost-utility analysis of revascularization by percutaneous coronary intervention for ischemic heart disease. *Cardiovasc Interv Ther* 2017; **32:** 127–136.
12. Joundi RA, Rebchuk AD, Field TS, Smith EE, Goyal M, Demchuk AM, et al. Health-related quality of life among patients with acute ischemic stroke and large vessel occlusion in the ESCAPE trial. *Stroke* 2021; **52:** 1636–1642.
13. Takura T, Kyo S, Ono M, Tominaga R, Miyagawa S, Tanoue Y, et al. Preliminary report on the cost effectiveness of ventricular assist devices. *J Artif Organs* 2016; **19:** 37–43.
14. Behar JM, Chin HMS, Fearn S, Ormerod JOM, Gamble J, Foley PWX, et al. Cost-effectiveness analysis of quadripolar versus bipolar left ventricular leads for cardiac resynchronization defibrillator therapy in a large, multicenter UK registry. *JACC Clin Electrophysiol* 2017; **3:** 107–116.
15. Israelsson J. Health-related quality of life after cardiac arrest. Linköping, Sweden: Linköping University, 2020.
16. Takura T, Nakanishi T, Kawanishi H, Nitta K, Akizawa T, Hiramatsu M, et al. Cost-effectiveness of maintenance hemodialysis in Japan. *Ther Apher Dial* 2015; **19:** 441–449.
17. Takura T, Hiramatsu M, Nakamoto H, Kuragano T, Minakuchi J, Ishida H, et al. Health economic evaluation of peritoneal dialysis based on cost-effectiveness in Japan: A preliminary study. *Clinicoecon Outcomes Res* 2019; **11:** 579–590.
18. Gaziano TA, Fonarow GC, Velazquez EJ, Morrow DA, Braunwald E, Solomon SD. Cost-effectiveness of sacubitril-valsartan in hospitalized patients who have heart failure with reduced ejection fraction. *JAMA Cardiol* 2020; **5:** 1236–1244.
19. Alsumali A, Djatche LM, Briggs A, Liu R, Diakite I, Patel D, et al. Cost effectiveness of vericiguat for the treatment of chronic heart failure with reduced ejection fraction following a worsening heart failure event from a US Medicare perspective. *Pharmacoeconomics* 2021; **39:** 1343–1354.
20. Turk E, Rupel VP, Tapajner A, Isola A. Reliability and validity of the Audit on Diabetes-Dependent Quality of Life (ADDQoL) and EQ-5D in elderly Slovenian diabetes mellitus type 2 patients. *Health* 2014; **6:** 699–711.
21. Berg J, Lindgren P, Nieuwlaat R, Bouin O, Crijns H. Factors determining utility measured with the EQ-5D in patients with atrial fibrillation. *Qual Life Res* 2010; **19:** 381–390.
22. Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, et al. Recognition and initial management of fulminant myocarditis: A scientific statement from the American Heart Association. *Circulation* 2020; **141:** e69–e92.
23. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: An expert consensus document. *Circ Heart Fail* 2020; **13:** e007405.
24. Sharma AN, Stultz JR, Bellamkonda N, Amsterdam EA. Fulminant myocarditis: Epidemiology, pathogenesis, diagnosis, and management. *Am J Cardiol* 2019; **124:** 1954–1960.
25. Gustafsson F. Management of patients with cardiogenic shock on temporary mechanical circulatory support: Urgent transplantation or on to the next pump? *Eur J Heart Fail* 2018; **20:** 187–189.
26. Veronese G, Cipriani M, Petrella D, Pedrotti P, Giannattasio C, Garascia A, et al. Not every fulminant lymphocytic myocarditis fully recovers. *J Cardiovasc Med (Hagerstown)* 2018; **19:** 453–454.
27. Atluri P, Ullery BW, MacArthur JW, Goldstone AB, Fairman AS, Hiesinger W, et al. Rapid onset of fulminant myocarditis portends a favourable prognosis and the ability to bridge mechanical circulatory support to recovery. *Eur J Cardiothorac Surg* 2013; **43:** 379–382.
28. Saito S, Toda K, Miyagawa S, Yoshikawa Y, Hata H, Yoshioka D, et al. Diagnosis, medical treatment, and stepwise mechanical circulatory support for fulminant myocarditis. *J Artif Organs* 2018; **21:** 172–179.
29. Matsumoto M, Asaumi Y, Nakamura Y, Nakatani T, Nagai T, Kanaya T, et al. Clinical determinants of successful weaning from extracorporeal membrane oxygenation in patients with fulminant myocarditis. *ESC Hear Fail* 2018; **5:** 675–684.
30. McCarthy RE 3rd, Boehmer JP, Hruban RH, Hutchins GM, Kasper EK, Hare JM, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. *N Engl J Med* 2000; **342:** 690–695.
31. Ammirati E, Cipriani M, Lilliu M, Sormani P, Varrenti M, Raineri C, et al. Survival and left ventricular function changes in fulminant versus nonfulminant acute myocarditis. *Circulation* 2017; **136:** 529–545.
32. Cooper LT Jr, Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, et al. Usefulness of immunosuppression for giant cell myocarditis. *Am J Cardiol* 2008; **102:** 1535–1539.
33. Moloney ED, Egan JJ, Kelly P, Wood AE, Cooper LT Jr. Transplantation for myocarditis: A controversy revisited. *J Hear Lung Transplant* 2005; **24:** 1103–1110.
34. Kondo T, Okumura T, Shibata N, Imaizumi T, Dohi K, Izawa H, et al. Differences in prognosis and cardiac function according to required percutaneous mechanical circulatory support and histological findings in patients with fulminant myocarditis: Insights from the CHANGE PUMP 2 study. *J Am Heart Assoc* 2022; **11:** e023719.
35. Hassett CE, Cho SM, Hasan S, Rice CJ, Migdady I, Starling RC, et al. Ischemic stroke and intracranial hemorrhages during Impella cardiac support. *ASAIO J* 2020; **66:** e105–e109.
36. Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, et al. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur J Heart Fail* 2015; **17:** 501–509.
37. Pöss J, Köster J, Fuernau G, Eitel I, de Waha S, Ouarrak T, et al. Risk stratification for patients in cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol* 2017; **69:** 1913–1920.
38. Baran DA, Grines CL, Bailey S, Burkhoff D, Hall SA, Henry TD, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. *Catheter Cardiovasc Interv* 2019; **94:** 29–37.
39. Acker MA. Mechanical circulatory support for patients with acute-fulminant myocarditis. *Ann Thorac Surg* 2001; **71**(Suppl)**:** S73–S76.
40. Leprince P, Combes A, Bonnet N, Ouattara A, Luyt CE, Theodore P, et al. Circulatory support for fulminant myocarditis: Consideration for implantation, weaning and explantation. *Eur J Cardiothorac Surg* 2003; **24:** 399–403.
41. Tadokoro N, Fukushima S, Minami K, Taguchi T, Saito T, Kawamoto N, et al. Efficacy of central extracorporeal life support for patients with fulminant myocarditis and cardiogenic shock. *Eur J Cardiothorac Surg* 2021; **60:** 1184–1192.

Supplementary Files

Please find supplementary file(s);
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