Clinical Scenario Classification for Characterization and Outcome Prediction of Acute Decompensated Heart Failure Under Contemporary Phenotyping

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Background: The concept of Clinical Scenario (CS) classification has been widely utilized to aid in choosing appropriate management strategies for acute decompensated heart failure (ADHF).

Methods and Results: The West Tokyo-Heart Failure (WET-HF) Registry is a multicenter, prospective cohort registry enrolling consecutive hospitalized ADHF patients. Based on systolic blood pressure (SBP) at admission, 4,000 patients enrolled between 2006 and 2017 were classified into 3 groups: CS1, SBP ≥140 mmHg; CS2, 100 ≤ SBP <140 mmHg; and CS3, SBP <100 mmHg. The CS1 group had a high rate of fluid retention such as leg edema, and the largest reduction in body weight at discharge. In-hospital diuretics use was the most frequent in CS1. Although the primary endpoint of long-term all-cause death and/or ADHF re-hospitalization was more common in more advanced CS, there was no significant difference between the 3 CS groups in patients with HF with preserved ejection fraction (HFpEF; P=0.10). Although more advanced CS was associated with larger left ventricular (LV) chamber size in HF with reduced EF (HFrEF), it was associated with smaller LV size in HFpEF.

Conclusions: The long-term prognostic value of CS classification was limited in HFpEF. Whereas CS was closely associated with degree of LV remodeling in HFrEF, a smaller LV chamber might be associated with a lower cardiovascular functional reserve in HFpEF.

Key Words: Clinical Scenario; Heart failure; Systolic blood pressure

Heart failure (HF) is a clinical syndrome characterized by typical symptoms that may be accompanied by signs resulting from a structural and/or functional cardiac abnormality that lead to a reduced cardiac output and/or elevated intracardiac pressure. Choosing the appropriate initial treatment strategy is important in achieving the optimal outcome of acute decompensated HF (ADHF). A decade ago, Mebazaa et al proposed the Clinical Scenario (CS) classification as a tool to manage patients with ADHF in the prehospital and early in-hospital phase, given the lack of large randomized, controlled, clinical trials in this area. CS is a unique system that is based on the initial systolic blood pressure (SBP) and other symptoms, as follows: CS1, SBP ≥140 mmHg; CS2, 100 ≤ SBP <140 mmHg; CS3, SBP <100 mmHg; CS4, ADHF with signs of acute coronary syndrome (ACS); and CS5, isolated right ventricular failure. Although the concept of CS has been widely accepted, the characteristics, details of in-hospital management, and subsequent outcome of ADHF patients, by CS class, have not been reported widely. Accumulating evidence suggests that the pathology of HF differs vastly according to phenotype. In particular, HF with preserved ejection fraction (HFpEF) presents a substantial public health and socioeconomic burden due to its explosively increasing prevalence and limited evidence of effective treatment. HFpEF is a clinical entity that has a distinct pathophysiology from HF with reduced ejection fraction (HFrEF). This might lead to variation in the significance of CS, given the differing impact of SBP in HFpEF vs. HFrEF for patients with compensated status.
Clinical Scenario for ADHF

Methods

Study Design
The WET-HF Registry is an ongoing, prospective, multicenter cohort registry designed to collect data on the clinical background and outcome of patients hospitalized for ADHF. A total of 4,000 consecutive patients who were
Outcomes

We collected the data on in-hospital mortality as a short-term outcome measure. The subjects were also followed up after discharge for the primary endpoint, defined as all-cause death or re-hospitalization for ADHF in ≤1,000 days as a long-term outcome measure.

Statistical Analysis

In this study, we defined HFpEF as HF with left ventricular ejection fraction (LVEF) ≥50%, HFrEF as HF with LVEF <40%, and HF with mid-range ejection fraction (HFmrEF) as HF with LVEF 40–49%. Patients presenting with ACS or isolated right-sided HF were excluded. The clinical diagnosis of ADHF was made by the individual cardiologists at each institution. Exclusive on-site auditing by the investigators (Y. Shiraishi and S.K.) ensured proper registration of each patient. Before the launch of the WET-HF registry, information on the objective of the present study and its social significance and an abstract were provided for clinical trial registration with the University Hospital Medical Information Network (UMIN000001171). The study protocol was approved by the institutional review boards at each site, and research was conducted in accordance with the Declaration of Helsinki. Written and/or oral informed consent were obtained from each subject before the study.

Subjects

After excluding 8 cases of missing SBP data at admission (1.0%), a total of 3,992 subjects were available for analysis. Based on SBP at admission, the subjects were classified into 3 groups: CS1, SBP ≥140 mmHg, n=1,862 (46.6%); CS2, 100≤SBP<140 mmHg, n=1,779 (44.6%); and CS3, SBP <100 mmHg, n=351 (8.8%).

In-hospital treatment for ADHF such as i.v. agents and non-pharmacological therapy was recorded. Carperitide is an i.v. recombinant atrial natriuretic peptide approved only in Japan for ADHF, whereas nesiritide (a recombinant B-type natriuretic peptide) is available in USA, Argentina, Columbia, Switzerland, and Israel. The expected cardiovascular effects of carperitide are vasodilatation and sympathetic tone reduction in the peripheral vasculature.

![Figure 1](image-url). In-hospital treatment in acute decompensated heart failure patients according to Clinical Scenario (CS) group. IABP, intra-aortic balloon pump; NIPPV, non-invasive positive pressure ventilation; PDEI, phosphodiesterase-III inhibitor. *P<0.05, **P<0.001 between CS1–3.
Clinical Scenario for ADHF

and LVDd and LV end-systolic diameter (LVDs) were larger in more advanced CS.

The in-hospital treatment in each CS group is shown in Figure 1. The use of loop diuretics, nitrates, carperitide, and respirator including non-invasive positive pressure ventilation were more common, and the use of inotropes/vasopressors and intra-aortic balloon pump (IABP) was less common in CS1 (CS1/2/3: furosemide, 69/67/62%, P=0.0305; nitrates, 44/13/9%, P<0.001; carperitide, 54/46/30%, P<0.001; respirator, 27/13/15%, P<0.001; phosphodiesterase-III inhibitor (PDEI), 2/3/8%, P<0.001; catecholamine, 11/16/34%, P<0.001; IABP, 2/2/4%, P=0.02,

Results

CS: Baseline Characteristics and In-Hospital Treatment

The subject baseline characteristics are listed in Table 1. At baseline, age was younger, although de novo ADHF was less common, in more advanced CS. Heart rate (HR) at admission was lower in more advanced CS. The findings related to pulmonary congestion, such as paroxysmal nocturnal dyspnea, orthopnea, and crackles, and that related to fluid retention such as leg edema were less common in more advanced CS. Conversely, cold extremities were more common in more advanced CS. LVEF was lower,
Figure 4. Kaplan-Meier curves for (A) primary endpoint (composite of all-cause death or re-hospitalization due to acute decompensated heart failure [ADHF]), (B) all-cause death, and (C) re-hospitalization for ADHF according to Clinical Scenario (CS) group.

Figure 5. Kaplan-Meier curves for (A–C) primary endpoint (all cause death and re-hospitalization due to ADHF), (D–F) all-cause death, and (G–I) re-hospitalization for ADHF, in patients with (A,D,G) heart failure with reduced ejection fraction (HFrEF; LVEF <40%); (B,E,H) heart failure with mid-range ejection fraction (HFmrEF; LVEF 40–49%); and (C,F,I) heart failure with preserved ejection fraction (HFpEF; LVEF ≥50%), according to CS group. Abbreviations as in Figure 4.
Figure 1). The use of percutaneous cardiopulmonary support was similar between the 3 CS groups (CS1/2/3: 0.5/0.5/0.3%, P=0.864).

CS and In-Hospital/Long-Term Outcome
Crude in-hospital mortality was higher in more advanced CS (Table 1). On logistic regression analysis CS3 was independently associated with higher in-hospital mortality after adjustment for covariates, including in-hospital treatment strategies (CS3–1: OR, 2.98; 95% CI: 1.62–5.69, P<0.001; CS3–2: OR, 1.83; 95% CI: 1.07–3.11, P=0.03; Figure 2). Although catecholamine use was associated with higher in-hospital mortality in all CS groups, i.e. loop diuretics were associated with in-hospital death only in CS3. (Figure 3). The reduction of body weight (ΔBW) at discharge was the largest in CS1 (Table 1). After discharge, the primary endpoint of all-cause death or re-hospitalization for ADHF was more common in CS3 compared with CS1 and CS2 (P<0.001, log-rank test, Figure 4A). Both all-cause death and HF re-hospitalization were also more common in CS3 (all-cause death, P<0.001, Figure 4B; HF re-hospitalization, P<0.001, Figure 4C).

CS in HF According to EF Status
Although the occurrence of the primary endpoint was more common in more advanced CS in the HFrEF and HFmrEF subgroups, there was no significant difference between the CS groups in HFpEF (HFrEF, P=0.018; HFpEF, P=0.02). All-cause death was more common in more advanced CS in all of the 3 subgroups (Figure 5D–F). Although re-hospitalization for ADHF was also more common in more advanced CS in HFpEF, CS3 was characterized by more advanced CS in HFrEF, this was not significantly different in HFmrEF or HFpEF (HFrEF, P<0.001; HFmrEF, P=0.085; HFpEF, P=0.20, Figure 5G–I). On Cox proportional hazard model analysis, CS was an independent predictor of primary endpoint, even after adjusting for covariates, including in-hospital treatment (Table 2). CS was an independent predictor of primary endpoint in HFrEF (P=0.037) and HFmrEF (P=0.033), but it was not significant in HFpEF (P=0.074, Supplementary Table).

Factors Related to CS
Although CS aids in navigating the initial treatment strategies, the mechanisms underlying the differentiation of the CS categories remain unknown. Therefore, we sought to determine the factors associated with CS. On multivariate analysis age, BMI, TB, and LVEF were associated with CS (Figure 6A). Lower LVEF was associated with more advanced CS in HFrEF, but not in HFmrEF or HFpEF (Figure 6B–D). Larger LVDd was associated with more advanced CS in HFrEF. Conversely, however, smaller LVDd was associated with more advanced CS in HFpEF (Figure 6B,D). Neither LVEF nor LVDd was associated with CS in HFmrEF (Figure 6C).

Discussion
Since Mebazaa et al proposed the CS classification a decade ago, this system has been widely utilized in actual clinical settings such as emergency rooms and intensive care units. Despite this, to date there have been no studies that have validated its clinical use in the real world. In the present study, we reported 4 main findings. First, the ADHF patients in the 3 CS groups had substantially different clinical presentations, including baseline characteristics and in-hospital treatment strategies. For example, whereas CS1 was characterized by reduced HF severity (e.g., higher LVEF), and the physical findings related to pulmonary congestion, CS3 was characterized by more severe disease and frequent cold extremities representing low output, in line with previous reports.14 This suggests that CS is likely to be associated with the HF phenotype and cardiovascular reserve and to represent the primary pathophysiologic problems of each patient. Of note, unlike the initial proposal by Mebazaa et al.3 CS1 was the most closely associated with fluid retention such as leg edema and ABW, assuming fluid excretion after ADHF treatment. Second, CS predicted both in-hospital outcome and future clinical adverse events, even after adjustment for

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Table 2. Multivariate Indicators of Primary Endpoint† in ADHF Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall</th>
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<tr>
<td></td>
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<tr>
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<tr>
<td>NIPPV/Respirator</td>
<td>1.098</td>
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†Composite of all-cause death or re-hospitalization due to ADHF. NIPPV, non-invasive positive pressure ventilation; PDEI, phosphodiesterase-III inhibitor. Other abbreviations as in Table 1.
CS-guided in-hospital treatment strategies that can potentially affect them.8,15,16 Third, the prognostic importance of CS was less significant in HFrEF. Fourth, CS was related to various factors, including age, BMI, and LVEF. In HFrEF, CS was associated with measures of LV remodeling, such as LVEF and LV chamber size. On the basis of these findings, we concluded that CS was both a helpful measure to guide the early in-hospital management strategy and also a predictor of short-term and long-term clinical outcome. Although some HF risk scores such as the Seattle Heart Failure Model17 have been developed and are helpful to predict long-term outcome, CS is a simpler predictor suitable for prompt evaluation of patients with ADHF. To the best of our knowledge, this is the first study to validate the clinical use of CS in the real world and its value for the characterization of patients with ADHF.

**Fluid Retention and Diuretic Use in CS1**

The practical recommendations by Mebazaa et al stated that minimal systemic edema is present in CS1 based on the data from the OPTIMIZE-HF registry,11 and they designated it as “vascular failure”, representing inappropriate vascular constriction. In the present study, however, the higher percentage of leg edema and diuretic use was noted in CS1; and ∆BW, assuming fluid excretion after ADHF treatment, was also the largest in CS1 (Table 1). CS1 includes older patients (Table 1; Figure 1), in line with the findings in another Japanese HF cohort.18 It might be, at least partly, explained by the distinct dietary pattern of high salt intake in Japanese people, especially in the elderly,19 leading to retention of sodium and volume overload.20 Given that increased LV wall stiffness inevitably accompanies arterial stiffening according to LV-arterial coupling,21 in such cases volume overload can easily lead to elevated blood pressure via elevated LV end-diastolic pressure. From these findings, CS1 might be more associated with fluid retention representing increased preload and elevated LV end-diastolic pressure than initially proposed. Of note, the impact of diuretic use on in-hospital death was not significant in CS1, although it was in CS3 (Figure 3). Therefore, for patients in CS1, diuretics, which have no negative impact on in-hospital outcome (Figure 3A), should be used appropriately according to the degree of volume retention, contrary to the recommendation by Mebazaa et al. Diuretics, however, might have a low priority as initial treatment because a nitrate-predominant strategy was shown to be superior to a diuretic-predominant one in terms of improvement of oxygen desaturation and subsequent need for mechanical ventilation.22

**Inotropes in CS**

CS3 was characterized by more severe disease and frequent cold extremities representing low output. Further, the negative impact of catecholamines and PDEI on short-term...
outcome was less significant in more advanced CS (Figure 3). In particular, PDEI did not lead to increased mortality in CS3 (Figure 3C). These findings might support the recommendation from Mebazaa et al that inotropes can be used in some patients mainly in CS3, although we could not precisely examine the appropriateness of each treatment strategy because of the observational nature of the study.

LV Chamber Size as a CS-Related Factor in HFrEF and HfP EF
Given that CS was found to predict the future clinical outcome in subjects with ADHF, it is intriguing to explore what factors are related to CS. In the present study, multiple regression analysis indicated that various factors, including age, BMI, and LV mass, were related to CS. In HFrEF patients, lower LV EF and larger LV dimension, which precisely represent the disease process of LV remodeling in HFrEF,23 were associated with advanced CS. Conversely, in HfP EF patients, smaller LV size was associated with advanced CS. In HfP EF, unlike HFrEF, the time course change and the significance of LV chamber size in the disease process are controversial and not well established.24,25 A smaller LV chamber might be associated with a lower cardiovascular functional reserve in HfP EF possibly through impaired LV diastolic function, given that a smaller LV chamber might be associated with lower stroke volume26 or exercise intolerance27 in patients with HfP EF.

Significance of CS in HFrEF and HfP EF
LV remodeling in HFrEF is characterized by depressed LV systolic function and LV chamber dilatation.23–29 A more remodeled LV generally represents an advanced disease process. In the present study, in HFrEF patients, the LV diameter was larger and LV mass was lower in more advanced CS, which suggests that CS might be correlated with advanced LV remodeling in other words, with the severity of HF. Moreover, CS was an independent predictor of primary endpoint in this subgroup. CS did, however, fail to predict outcome in HfP EF. The mechanism underlying the differing prognostic impact of CS remains unknown. We initially speculated that it might be derived from the higher proportion of valvular heart disease (VHD) in HfP EF. Although the analysis was conducted after excluding patients with VHD, again CS failed to predict the primary endpoint in HfP EF (data not shown). As noted, the cardiac remodeling process in HfP EF is still obscure.24–26 Also, it has been proven that extra-cardiac burden is more significant in HfP EF than HFrEF.30,31 Given that the patients were older, and that comorbidities such as atrial fibrillation (AF) and anemia were more common in patients with HfP EF in line with previous studies,30,31 these additional factors might also substantially affect the long-term clinical outcome. These issues might lead to the less significant prognostic value of CS in HfP EF.

Study Limitations
There are several limitations in this study. First, although we saw a difference in the in-hospital treatment strategies between the 3 CS categories, we could not examine their appropriateness for each patient because it was an observational study. Second, although CS was originally intended to create a guide for early management strategy for ADHF, we do not have data related to the time course of in-hospital treatment (e.g., first- and second-line therapy). Third, in the subgroup analysis, the number of patients was relatively small for comparison of the 3 CS groups, especially in the HfPfEF group. Fourth, most participants in the present study were Japanese. Caution is thus needed when applying these results to ADHF patients in other regions. Fifth, although we sought to characterize ADHF patients by CS, patients with ACS (CS4) or isolated right-sided HF (CS5) were excluded. Sixth, given that this registry was organized to elucidate the characteristics and prognosis of ADHF patients from a different point of view and it does not solely focus on the blood pressure, the method of blood pressure measurement was not unified in this study.

Conclusions
CS was simple and useful to predict short-term and long-term clinical outcome in patients with ADHF. In HFrEF, CS was closely associated with LV remodeling, and it predicted in-hospital mortality and future clinical adverse events. Although, in HfP EF, its prognostic value was limited in contemporary clinical practice, those patients with a small LV chamber might need to be managed carefully. Further investigation is needed to elucidate the mechanism of the differing prognostic impact of CS on clinical outcome between HFrEF and HfP EF.

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Disclosures
The authors declare no conflicts of interest.

References


**Supplementary Files**

Please find supplementary file(s):