Cardiovascular shock is a clinical manifestation of circulatory failure related to insufficient blood flow to tissues. Despite advances in emergency care systems and treatments, including early revascularization and mechanical circulatory assist, the mortality rate in patients with cardiovascular shock remains high, approaching 30–50%. Shock is diagnosed by detecting the presence of systemic arterial hypotension, hyperlactatemia, and tissue hypoperfusion. Although arterial hypotension is usually observed in cardiovascular shock patients, its clinical sig-

Background: Consciousness disturbance is one of the major clinical signs associated with shock state, but its prognostic value has not been previously evaluated in cardiovascular shock patients. We aimed to evaluate the prognostic value of neurological status for 30-day mortality in cardiovascular shock patients without out-of-hospital cardiac arrest (OHCA).

Methods and Results: Patients with out-of-hospital onset cardiovascular shock were recruited from the Japanese Circulation Society Shock Registry. Neurological status upon hospital arrival was evaluated using the Japan Coma Scale (JCS). Patients were divided into 4 groups according to the JCS: alert, JCS 0; awake, JCS 1–3 (not fully alert but awake without any stimuli); arousable, JCS 10–30 (arousable with stimulation); and coma JCS 100–300 (unarousable). The primary endpoint was 30-day all-cause death. In total, 700 cardiovascular shock patients without OHCA were assessed. The coma group was associated with a higher incidence of 30-day all-cause death compared with other groups (alert, 15.3%; awake, 24.4%; arousable, 36.8%; coma, 48.5%, P<0.001). Similar trends were observed in etiologically divergent subgroups (acute coronary syndrome, non-ischemic arrhythmia, and aortic disease). On multivariate Cox regression analysis, arousable (hazard ratio [HR], 1.82; 95% CI: 1.16–2.85, P=0.009) and coma (HR, 2.72; 95% CI: 1.76–4.22, P<0.001) (reference: alert) independently predicted 30-day mortality.

Conclusions: Neurological status upon hospital arrival was useful to predict 30-day mortality in cardiovascular shock patients without OHCA.

Key Words: Cardiovascular shock; Mortality; Neurological status
There are clinical signs of tissue hypoperfusion, apparent significance varies depending on baseline blood pressure. An altered mental state, including obtundation, disorientation, and confusion, might facilitate early recognition of cardiovascular shock and can be assessed quantitatively using several coma scales. Although the consciousness disturbance in patients with out-of-hospital cardiac arrest (OHCA) has been acknowledged as a well-known predictor for in-hospital death, data are scarce regarding its prognostic value in cardiovascular shock patients without OHCA. Therefore, we hypothesized that the quantitative assessment of shock severity using neurological status would enable prediction of outcome in cardiovascular shock patients without OHCA. In the present study, we aimed to evaluate the predictive value of neurological status for 30-day mortality in cardiovascular shock patients without OHCA.

### Methods

Patients diagnosed with cardiovascular shock between May 2012 and June 2014 were recruited from 82 centers of the Japanese Circulation Society Cardiovascular Shock Registry, a prospective, observational, multicenter, cohort study in Japan (University Hospital Medical Information Network Clinical Trials Registry, no.: UMIN000008441; http://www.umin.ac.jp/ctr/index.htm). This registry was approved by the ethics committee of each hospital, and the study was performed in accordance with the Declaration of Helsinki. Cardiovascular shock included acute coronary syndrome (ACS), non-ischemic arrhythmia, aortic disease, myocarditis, cardiomyopathy, pulmonary thromboembolism, valvular heart disease, infective endocarditis, and cardiac tamponade. Eligible patients for the Japanese Circulation Society Cardiovascular Shock Registry had out-of-hospital onset of cardiovascular shock and had to meet 1 major criterion and ≥1 minor criteria. Major criteria were:

#### Table. Patient Characteristics According to Neurological Status at Admission

| Variables                          | Overall (n=700) | Alert (n=288) | Awake (n=201) | Arousable (n=114) | Coma (n=97) | P-value |
|------------------------------------|----------------|--------------|---------------|-------------------|-------------|---------|
| Age (years)                        | 74 (65–82)     | 72.0 (63–80) | 75.0 (67–83)  | 75.0 (65–83)      | 75.0 (64–83) | 0.012   |
| Male                               | 446 (63.7)     | 203 (70.5)   | 121 (60.2)    | 67 (58.8)         | 55 (56.7)   | 0.018   |
| Onset to hospital arrival time (min) (n=561) | 110 (47–363)  | 146 (51–465) | 81 (48–282)   | 80 (44–429)       | 91 (40–291) | 0.043   |
| SBP (mmHg) (n=695)                 | 80 (70–90)     | 82 (73–91)   | 79 (70–88)    | 76 (67–85)        | 76 (60–86)  | <0.001  |
| Heart rate (beats/min) (n=693)     | 82 (50–110)    | 80 (54–107)  | 81 (50–108)   | 80 (46–106)       | 94 (56–120) | 0.398   |
| CHF (n=699)                        | 419 (59.9)     | 162 (56.4)   | 121 (60.2)    | 70 (61.4)         | 66 (68.0)   | 0.239   |
| LVEF (%) (n=423)                   | 45.0 (30.0–60.0) | 49.0 (34.0–60.0) | 47.0 (34.0–60.0) | 42.0 (30.0–60.0) | 33.0 (20.0–54.0) | 0.011   |
| Laboratory data                    |               |              |               |                   |             |         |
| pH (n=517)                         | 7.35 (7.24–7.41) | 7.38 (7.32–7.43) | 7.35 (7.26–7.41) | 7.30 (7.21–7.38) | 7.23 (7.04–7.33) | <0.001  |
| PO2 (mmHg) (n=516)                 | 117 (67.5–198.5) | 112.0 (51.9–170.0) | 115.7 (74.2–215.5) | 121.3 (72.5–223.0) | 124.0 (68.6–235.6) | 0.275   |
| PCO2 (mmHg) (n=518)                | 27.8 (34.3–42.8) | 33.7 (26.5–40.2) | 34.0 (27.6–42.5) | 33.2 (26.3–41.3) | 39.6 (30.7–63.0) | <0.001  |
| HCO3 (mmHg) (n=510)                | 18.3 (14.3–21.9) | 19.6 (15.7–22.9) | 18.8 (13.8–22.1) | 16.5 (13.0–20.0) | 16.7 (12.9–19.7) | <0.001  |
| Lactate (mg/dL) (n=391)            | 28.0 (12.6–60.4) | 21.0 (11.7–40.0) | 26.0 (10.4–57.0) | 42.3 (15.6–76.8) | 55.0 (17.0–99.8) | <0.001  |
| eGFR (mL/min/1.73m2) (n=687)       | 43.2 (29.3–56.6) | 46.1 (32.9–60.3) | 42.8 (28.3–56.0) | 37.1 (22.5–53.8) | 39.3 (29.0–52.5) | 0.001   |

Data given as median (IQR) or n (%). Continuous variables were compared with the Kruskal-Wallis test, and binary and categorical variables were compared with the chi-squared test or Fisher’s exact test. CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SPB, systolic blood pressure.
Neurological Status and Cardiovascular Shock Outcome and were compared using the Kruskal-Wallis test. Binary and categorical variables are given as n (%), and were compared with the chi-squared test or Fisher’s exact test. Survival curves were constructed for time-to-event variables using the Kaplan-Meier method, and compared using the log-rank test. Multivariate Cox regression analysis was performed for 30-day mortality and CPC 3–5 at hospital discharge. Clinically important variables, such as age, sex, SBP, heart rate, neurological status, congestive heart failure, renal function, and causes of shock, were entered as confounders into a multivariate model.

If the variables were missing in >5% of patients, they were excluded from the multivariate analysis. Two-tailed P-values were used, and P<0.05 was considered statistically significant in all analyses. Data were analyzed using SPSS version 23.0 (SPSS, Chicago, IL, USA).

Results

Of the 1,004 patients enrolled in the Japanese Circulation Society Shock Registry between May 2012 and June 2014, 304 were excluded because they had OHCA (n=298), did not have cardiovascular shock (n=2), or were missing JCS upon hospital arrival (n=4). Finally, 700 patients were assessed in the present study. The patients were divided into 4 groups according to neurological status on hospital arrival (alert, n=288; awake, n=201; arousable, n=114; coma, n=97).

Patient characteristics are listed in Table. The percentage of male patients, and levels of SBP, estimated glomerular filtration rate, and left ventricular ejection fraction (LVEF) were lower, while lactate level and the incidence of congestive heart failure were higher in coma patients than in others.

The incidence of 30-day mortality is shown in Figure 1. The 30-day mortality increased with worsening neurological status: alert, 15.3% (n=44/288); awake, 24.4% (n=49/201); arousable, 36.8% (n=42/114); coma, 48.5% (n=47/97); and were compared using the Kruskal-Wallis test. Binary and categorical variables are given as n (%), and were compared with the chi-squared test or Fisher’s exact test. Survival curves were constructed for time-to-event variables using the Kaplan-Meier method, and compared using the log-rank test. Multivariate Cox regression analysis was performed for 30-day mortality and CPC 3–5 at hospital discharge. Clinically important variables, such as age, sex, SBP, heart rate, neurological status, congestive heart failure, renal function, and causes of shock, were entered as confounders into a multivariate model.13–17 If the variables were missing in >5% of patients, they were excluded from the multivariate analysis. Two-tailed P-values were used, and P<0.05 was considered statistically significant in all analyses. Data were analyzed using SPSS version 23.0 (SPSS, Chicago, IL, USA).

Figure 1. Kaplan-Meyer curve for 30-day mortality overall according to neurological status in patients with cardiovascular shock without out-of-hospital cardiac arrest. SE, standard error.
Similar trends were observed in patients with ACS (alert, 15%, n=23/153; awake, 23.3%, n=24/103; arousable, 42.6%, n=23/54; coma, 53.3%, n=24/45), non-ischemic arrhythmia (alert, 2.1%, n=1/47; awake, 4.2%, n=1/24; arousable, 6.7%, n=1/15; coma, 30%, n=3/10), and aortic disease (alert, 21.6%, n=8/37; awake, 42.9%, n=15/35; arousable, 50%, n=14/28; coma, 57.9%, n=11/19; Figure 2). CPC scale at hospital discharge was available for 698 patients. Prevalence of CPC 3–5 at discharge in the alert group was lower than in the other groups (alert, 29.2%, n=84/288; awake, 53.8%, n=107/199; arousable, 58.8%, n=67/114; coma, 64.9%, n=63/97; Figure 3). The 30-day mortality stratified by neurological status (alert or non-alert) and SBP (SBP ≥80 or SBP <80 mmHg, based on the median: 79 mmHg; IQR, 64–89 mmHg) is shown in Figure 4. The 30-day mortality in each group gradually increased as SBP decreased and neurological status worsened (alert and SBP ≥80 mmHg, 11.5%; alert and SBP <80 mmHg, 21.1%; non-alert and SBP ≥80 mmHg, 26.9%; non-alert and SBP <80 mmHg, 37%).
Neurological Status and Cardiovascular Shock Outcome

Neurological Status and Cardiovascular Shock Outcome were independent predictors of 30-day mortality. Moreover, neurological status was also an independent predictor of CPC 3–5 at hospital discharge (awake: HR, 1.36; 95% CI: 1.01–1.84, P=0.041; arousable: HR, 1.78; 95% CI: 1.26–2.52, P=0.001; coma: HR, 2.37; 95% CI: 1.63–3.39, P<0.001).

Cox regression analysis of 30-day mortality and of CPC 3–5 at hospital discharge are shown in Figure 5 and Supplementary Figure, respectively. On multivariate analysis, arousable (hazard ratio [HR], 1.82; 95% CI: 1.16–2.85, P=0.009) and coma (HR, 2.72; 95% CI: 1.76–4.22, P<0.001) (reference: alert) were independent predictors of 30-day mortality. Moreover, neurological status was also an independent predictor of CPC 3–5 at hospital discharge (awake: HR, 1.36; 95% CI: 1.01–1.84, P=0.041; arousable: HR, 1.78; 95% CI: 1.26–2.52, P=0.001; coma: HR, 2.37; 95% CI: 1.63–3.39, P<0.001).

**Table 1.**

| Variable                              | Unadjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value |
|---------------------------------------|------------------------|---------|----------------------|---------|
| Age (per 10-year increase)            | 1.28 (1.13–1.45)       | <0.001  | 1.22 (1.05–1.41)     | 0.008   |
| Male sex                              | 0.86 (0.64–1.16)       | 0.324   | 1.10 (0.80–1.53)     | 0.550   |
| Systolic blood pressure (per 10-mmHg decrease) | 1.11 (1.05–1.17)       | <0.001  | 1.10 (1.03–1.18)     | 0.004   |
| Heart rate (per 10-beats/min decrease) | 0.99 (0.95–1.03)       | 0.495   | 0.97 (0.92–1.02)     | 0.185   |
| Neurologic status (reference: alert)  |                        |         |                      |         |
| Awake                                 | 1.67 (1.11–2.51)       | 0.013   | 1.26 (0.83–1.92)     | 0.275   |
| Arousable                             | 2.68 (1.76–4.10)       | <0.001  | 1.82 (1.16–2.85)     | 0.009   |
| Coma                                  | 3.96 (2.62–5.97)       | <0.001  | 2.72 (1.76–4.22)     | <0.001  |
| Congestive heart failure              | 1.73 (1.26–2.39)       | 0.001   | 2.54 (1.63–3.95)     | <0.001  |
| eGFR (per 10-mL/min/1.73m² decrease)  | 1.20 (1.12–1.29)       | <0.001  | 1.19 (1.09–1.29)     | <0.001  |

**Figure 5.** Cox regression analysis of 30-day mortality in patients with cardiovascular shock without out-of-hospital cardiac arrest. Of the study patients, 97.4% (682/700) were entered into the multivariate model. ACS, acute coronary syndrome; CI, confidence interval; CPC, cerebral performance categories; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IE, infective endocarditis; ACS, acute coronary syndrome; PE, pulmonary thromboembolism; VHD, valvular heart disease.

**Figure 6.** Kaplan-Meyer curve for 30-day mortality stratified by temporal change in neurological status from emergency medical service contact to hospital arrival, in patients with cardiovascular shock without out-of-hospital cardiac arrest.
Disturbance of consciousness level reflects systemic hypoperfusion leading to insufficient cerebral blood flow and hypoxia due to lung congestion. In the initial stage of shock, the cerebral circulation is protected by autoregulatory mechanisms. A previous animal study reported that cerebral blood flow in rats was maintained within a mean arterial pressure of 60–140 mmHg. Microcirculatory alterations increase peripheral resistance in order to maintain blood pressure and redistribute blood volume from the peripheral to the vital organs (heart and brain). Once the autoregulation system fails, shock progresses to the decompen-satory and refractory stage, resulting in irreversible organ failure. Neurological status could enable the detection of such dynamic changes of shock state, which are difficult to be evaluated by other “windows” (i.e., cutaneous and renal), as well as by blood pressure. In the present study, patients with preserved (≥80 mmHg) SBP, those with poor neurological status (non-alert) had higher 30-day mortality compared with those without (26.9% vs. 11.5%). Moreover, the failure of neurohumoral mechanisms following cerebral hypoperfusion, which preserve the viability of vital organs by maintaining perfusion pressure and microcirculation, might take part in the vicious cycle of shock.

In the present study, neurological status upon hospital arrival was also useful in patients with ACS, non-ischemic arrhythmia, or aortic disease. In particular, patients with non-ischemic arrhythmia, especially those who were alert, awake, and arousable, had an outstandingly better prognosis compared with those with ACS and aortic disease, most likely because of a rapid recovery from the shock state by means of anti-arrhythmic drugs, defibrillation, or temporary pacing.

The present study also demonstrated that temporal change in neurological status was useful to stratify short-term prognosis in cardiovascular shock patients. Interestingly, even patients with a poor initial neurological status had a relatively better outcome ( arousable, 15.8%; coma, 18.2%) if neurological status improved over time, compared with those who had a good initial neurological status, but who had worsened over time (alert, 33.9%; awake, 44.1%). The etiology of cardiovascular shock and reactivity to the initial treatment during transportation are plausible explanations for these findings. Temporal change in neurological status should also be acknowledged when evaluating the severity of cardiovascular shock.

**Study Limitations**

The present study has several limitations. First, we used only the JCS to evaluate consciousness level. The GCS, which is more widely used than the JCS, was not available in the present study. Second, some variables, including onset to hospital arrival time, vital signs, blood lactate level, and LVEF, could be determinant variables of short-term mortality in patients with cardiovascular shock, but such variables were not available for all patients. Moreover, we could not incorporate these variables in the multivariate Cox regression analysis because of the lack of data, thus whether these clinically important variables are associated with 30-day mortality remains unknown. Third, the differences in medical staff organization and emergency service capacity between participating centers were not taken into account in the present study. Finally, we cannot address whether the change in neurological status after hospital arrival had an impact on prognosis. Future studies are...
required to determine whether or not neurological status can be a therapeutic target in cardiovascular shock patients.

Conclusions
Neurological status upon hospital arrival is useful to predict short-term mortality in cardiovascular shock patients without OHCA. Physicians should recognize consciousness level upon hospital arrival as an important predictor in cardiovascular shock patients.

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Conflict of Interest
None.

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Supplementary Files
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