Prognostic Implication of Physical Signs of Congestion in Acute Heart Failure Patients and Its Association with Steady-State Biomarker Levels

Sayoko Negi, Mitsuaki Sawano, Shun Kohsaka, Taku Inohara, Yasuyuki Shiraiishi, Takashi Kohno, Yuichiro Maekawa, Motoaki Sano, Tsutomu Yoshikawa, Keiichi Fukuda

Abstract

Background: Congestive physical findings such as pulmonary rales and third heart sound (S3) are hallmarks of acute heart failure (AHF). However, their role in outcome prediction remains unclear. We sought to investigate the association between congestive physical findings upon admission, steady-state biomarkers at the time of discharge, and long-term outcomes in AHF patients.

Methods: We analyzed the data of 133 consecutive AHF patients with an established diagnosis of ischemic or non-ischemic (dilated or hypertrophic) cardiomyopathy, admitted to a single-center university hospital between 2006 and 2010. The treating physician prospectively recorded major symptoms and congestive physical findings of AHF: paroxysmal nocturnal dyspnea, orthopnea, pulmonary rales, jugular venous distention (JVD), S3, and edema. The primary endpoint was defined as rehospitalization for HF.

Results: Majority (63.9%) of the patients had non-ischemic etiology and, at the time of admission, S3 was seen in 69.9% of the patients, JVD in 54.1%, and pulmonary rales in 43.6%. The mean follow-up period was 726 ± 31 days. Patients with pulmonary rales (p = 0.001) and S3 (p = 0.011) had worse readmission rates than those without these findings; the presence of these findings was also associated with elevated troponin T (TnT) levels at the time of discharge (odds ratio [OR] 2.8; p = 0.02 and OR 2.6; p = 0.05, respectively).

Conclusion: Pulmonary rales and S3 were associated with inferior readmission rates and elevated TnT levels on discharge. The worsening of the readmission rate owing to congestive physical findings may be a consequence of on-going myocardial injury.

Introduction

The evaluation of acute heart failure (AHF) patients starts with careful history taking and physical examination. Signs of congestion and findings related to pulmonary rales, third heart sound (S3), and jugular venous distention (JVD) are known to have important diagnostic importance for AHF patients. However, the association between congestive physical findings in AHF patients and their clinical outcomes has not been well established [1]. In addition, the exact reason why these congestive physical findings are related to adverse clinical outcomes is still unclear.

In the modern management of AHF, biomarkers are used because they are thought to reflect common pathological abnormalities such as acute myocardial injury [2–6] or volume overload in the left ventricle [7–9]. The levels of these biomarkers are measured to obtain “subclinical” pathological and additional prognostic information. Therefore, we sought to examine the association between congestive physical findings upon admission, steady-state biomarker levels at the time of discharge, and long-term outcomes in AHF patients. Clarification of the role of congestive physical findings will aid in risk stratification of AHF patients in a cost-effective manner.

Methods

Study Subjects

This study registered AHF patients admitted to a single-center tertiary hospital between 2006 and 2010, for treatment of AHF, which was diagnosed according to the Framingham criteria. From a total of 339 patients, 110 patients (32.4%) were excluded from the final analysis because of incomplete data about physical findings on admission, biomarker levels on discharge, dates of admission and discharge, outcomes, or underlying conditions; and 96 patients (28.3%) were excluded because of diagnoses other than ischemic cardiomyopathy (ICM) or non-ischemic cardiomyopathy such as dilated cardiomyopathy (DCM) or hypertrophic cardio-
myopathy (HCM). The final study population consisted of 133 patients. Informed consent was obtained from each patient, and written consent was also obtained from all of the participants in the study.

DCM was defined as echocardiographic demonstration of unexplained left ventricular (LV) dilatation (i.e., LV diastolic dimension ≥55 mm) and impaired contraction (i.e., LV ejection fraction <45%) without the presence of obstruction coronary disease. ICM was defined as LV ejection fraction <40% with previously known myocardial infarction or evidence of severe coronary disease on coronary angiography. HCM was defined as presence of increased LV wall thickening ≥15 mm in the absence of identifiable cause for LVH such as hypertension or valvular heart disease. All patients with non-ischemic cardiomyopathy underwent coronary angiography and cardiac biopsy to rule out obstructive coronary disease and infiltrative heart disease. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and the study was approved by Institutional Review Board of Keio University School of Medicine.

Verification of Physical Findings and Measurement of Cardiac Biomarkers

Internal medicine residents obtained all physical findings of patients upon admission and coded the findings in pre-specified case report form. The physical findings were consisted with paroxysmal nocturnal dyspnea, orthopnea, pulmonary rales, JVD, and S3. Cardiology physicians verified these findings subsequently when the patients were transferred to in-patient service.

Plasma brain natriuretic peptide (BNP) levels were measured at the time of admission as well as discharge, using a commercially available assay kit (Shionogi, Tokyo, Japan). Cardiac troponin T (cTnT) level was measured at the time of discharge (Roche Diagnostics, Tokyo, Japan). The lower limit for detection of cTnT was 0.01 ng/mL. Serum creatinine levels were determined by standard laboratory methods. Clinical data were obtained by interviewing patients and from hospital medical records.

Follow-up and Endpoints

The study endpoint was rehospitalization for AHF. The treating physicians made decisions under the usual standard of care. In most cases, patients were readmitted when clinical signs of decompensation such as orthopnea or lower extremity edema were present. The mean length of stay for the index hospitalization was 19 ± 13 days. The mean delay for the initial outpatient follow-up visit upon discharge was 14 ± 10 days (16 patients were transferred to a different hospital, one patient died during hospitalization, one patient was transferred to a different department, and 13 were unknown). The data regarding endpoints were available for all the patients and the mean follow-up period was 726 ± 31 days. Follow-up data were obtained from either the medical records or direct inquiry with the patients or patients’ family by mail or phone.

Statistical Analysis

The study population was divided into two groups: readmission group and non-readmission group. Low ejection fraction (EF) was defined as EF <40% and elevated TnT level was defined as a serum TnT concentration of >0.1 ng/mL. Chi-square tests were used to compare categorical variables and student t-tests were used for continuous variables. Categorical variables were expressed as numbers (percentages) and continuous variables were expressed as the mean standard deviation.
related to high TnT levels (>0.10 ng/mL). Pulmonary rales (OR 2.874, p = 0.017) and S3 (OR 2.614, p = 0.050) were significantly associated with high TnT levels after adjustment for age, sex, sBP, and BNP on admission.

Discussion

In our single-institution based HF registry, the presence of pulmonary rales and S3 on admission was associated with HF readmission rate and high TnT levels on discharge. These physical findings are harbingers for difficulty achieving adequate decongestion during AHF treatment, suggesting the involvement of underlying complex mechanisms such as on-going inflammation during the acute phase of AHF.

The prognostic implications of signs and symptoms for HF patients have been previously reported. Devroey et al reported that the presence of pulmonary rales was significantly associated with HF (p < 0.001) [10]. Drazner et al reported that the presence of S3 was associated with increased risk of rehospitalization in the Studies of Left Ventricular Dysfunction (SOLVD) trial [1]. These results implying that the left-sided signs of HF are associated with rehospitalization, are consistent with the results of our current study. On the other hand, right-sided HF physical findings such as JVD or edema did not show any statistical significant association with adverse outcomes, and this finding is in contrast with those of previous studies such as the SOLVD or ESCAPE trial [11], probably because of the difference in patient characteristics between the studies; the SOLVD and the ESCAPE trials examined chronic HF patients in the outpatient setting, whereas this study examined AHF patients at the time of admission. Patients with chronic HF who present with JVD have either residual secondary pulmonary hypertension or isolated pulmonary hypertension.

Table 1. Characteristics of the study subjects.

|                       | Readmission for ADHF (± (n = 47) | Readmission for ADHF (–) (n = 86) | P value |
|-----------------------|----------------------------------|-----------------------------------|---------|
| Age, yrs              | 70.21 ± 1.76                     | 62.78 ± 1.73                      | 0.001   |
| Women, %              | 21.3 (n = 10)                    | 23.3 (n = 20)                     | 0.366   |
| Comorbidities         |                                  |                                   |         |
| Ischemic heart disease, % | 36.2 (n = 17)                    | 36.0 (n = 31)                     | 0.931   |
| Dilated cardiomyopathy, % | 57.4 (n = 27)                    | 57.0 (n = 49)                     | 0.958   |
| Hypertrophic cardiomyopathy, % | 6.4 (n = 3)                     | 7.0 (n = 6)                       | 0.892   |
| AF, %                 | 36.2 (n = 17)                    | 27.1 (n = 23)                     | 0.655   |
| Systolic Blood Pressure, mmHg | 132.80 ± 4.98                   | 131.27 ± 3.16                     | 0.530   |
| NYHA functional class | on admission 3.07 ± 0.11         | 3.02 ± 0.08                       | 0.705   |
|                       | on discharge 2.07 ± 0.04         | 1.98 ± 0.02                       | 0.031   |
| BNP, pg/mL            | on admission 770.36 ± 98.26      | 682.62 ± 79.61                    | 0.030   |
|                       | on discharge 395.51 ± 49.90      | 331.59 ± 60.96                    | 0.055   |
| BUN, mg/dL            | on admission 24.59 ± 10.42       | 20.75 ± 9.30                      | 0.041   |
|                       | on discharge 28.80 ± 14.09       | 23.35 ± 12.02                     | 0.031   |
| Left ventricular ejection fraction ≤40%, % | 48.9 (n = 23)                  | 41.9 (n = 36)                     | 0.541   |
| Tropion T level on discharge >0.10 ng/mL, % | 37.2 (n = 16)                | 22.1 (n = 17)                     | 0.004   |
| Death, %              | 18.2 (n = 8)                     | 4.7 (n = 4)                       | 0.001   |
| Physical signs on admission | PND, % | 40.4 (n = 19)                  | 30.2 (n = 26)                     | 0.488   |
|                       | Orthopnea, %                     | 34.0 (n = 16)                     | 35.3 (n = 30)                     | 0.624   |
| JVD, %                | 61.7 (n = 29)                    | 50.6 (n = 43)                     | 0.088   |
| Edema, %              | 53.2 (n = 25)                    | 58.1 (n = 50)                     | 0.982   |
| Rales, %              | 56.5 (n = 26)                    | 37.6 (n = 32)                     | 0.003   |
| S3, %                 | 80.9 (n = 38)                    | 64.0 (n = 55)                     | 0.054   |
| Physical signs on discharge | Edema, % | 4.3 (n = 2)                   | 4.7 (n = 4)                       | 0.989   |
|                       | Rales, %                         | 0.0 (n = 0)                       | 2.3 (n = 2)                       | 0.316   |
| S3, %                 | 21.3 (n = 10)                    | 25.6 (n = 22)                     | 0.800   |
| Medicine on admission | Spironolactone, %                | 34.0 (n = 16)                     | 36.0 (n = 31)                     | 0.862   |
|                       | ACE inhibitor, %                 | 29.8 (n = 14)                     | 23.3 (n = 20)                     | 0.245   |
|                       | ARB inhibitor, %                 | 25.5 (n = 12)                     | 32.6 (n = 28)                     | 0.620   |
|                       | β-blocker, %                     | 57.4 (n = 27)                     | 50.0 (n = 43)                     | 0.156   |

Patients readmitted for ADHF were significantly younger and had higher NYHA class on discharge, BNP levels on admission, BUN levels on admission and discharge, TnT levels on discharge, and death rates than those not readmitted for ADHF (p = 0.001, 0.031, 0.030, 0.041, 0.031, 0.004 and 0.001, respectively). The proportion of patients with rales was significantly higher in the readmission group than in the non-readmission group (p = 0.003). Missing values were considered to be negative about physical signs on discharge (missing values of patients with rales were 21, S3 were 13, edema were 36).

ADHF = acute decompensated heart failure, AF = atrial fibrillation, NYHA = New York Heart Association, BNP = brain natriuretic peptide, BUN = blood urea nitrogen, PND = paroxysmal nocturnal dyspnea, JVD = jugular venous distention, S3 = the third heart sound, ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blockers.

doi:10.1371/journal.pone.0096325.t001
hypertension, both being signs of inadequate compensation. These signs may be of low significance when predicting adverse outcomes in AHF patients.

In our study, the left-sided physical signs of AHF were also related to elevated biomarker levels at the time of discharge. TnT is a sensitive and specific marker for myocyte injury [12] and has been studied in acute and chronic HF patients previously. Missov et al [13] found increased levels of circulating cTnT in patients with HF but no clinically significant signs of ischemia. This phenomenon is thought to be caused by coronary microvascular dysfunction [14]. The findings of previous studies highlight that increased TnT levels are independent markers of mortality in HF patients [4]. In the ADHERE trial, AHF patients who tested positive for elevated troponin levels had lower systolic blood pressure on admission, lower ejection fraction, and higher in-hospital mortality rates than those who tested negative [15]. BNP is another well-known and frequently used biomarker for HF diagnosis and treatment. It is a neurohormone specifically secreted from the cardiac chambers in response to hemodynamic stress. The BNP level is elevated in situations where the ventricles are dilated, hypertrophic, or subject to increased wall tension [16,17]. The clinical validity of brain natriuretic peptide (BNP) measurements has been previously reported. Nishii M et al. reported that a high BNP level was a predictor of long-term risk in patients with non-ischemic dilated cardiomyopathy who were asymptomatic for more than six months after admission for AHF [18]. Januzzi and Troughton reported that BNP-guided therapy resulted in superior medical management compared to traditional care, mostly because of frequent and sophisticated drug adjustment [19]. In addition, BNP-guided therapy might be particularly attractive in older patients who are less physically active and in those whom symptoms are less reliable [20]. In our study, there were few patients with high BNP levels without significant physical findings before discharge. As the reviewer commented, these patients may benefit from BNP measurement to predict their long-term outcome such as readmission or death. However, caution is needed since other studies have suggested that BNP-guided HF management may have little or even a negative impact on elderly patients because of increased risk of drug-drug interactions and worsening organ failure secondary to polypharmacy [21]. Obviously, treatment strategies should be based on both physical signs and biomarkers. Physical signs are safe, cost-efficient non-invasive methods to assess the state of patients with HF. At times, physical signs may serve as unclear indices because of interobserver variation. In such situations, biomarkers could prove to be strong prognostic indices. The precise relationship between physical signs and biomarkers should be studied further.

In our cohort, higher readmission rates were seen in AHF patients with increased TnT levels but not in those with elevated BNP levels. This may be related to relatively high number of DCM patients included in our study. These patients are known to have high BNP levels even after they reach compensated state.

In our study, the left-sided physical signs of AHF were also related to elevated biomarker levels at the time of discharge. TnT is a sensitive and specific marker for myocyte injury [12] and has been studied in acute and chronic HF patients previously. Missov et al [13] found increased levels of circulating cTnT in patients with HF but no clinically significant signs of ischemia. This phenomenon is thought to be caused by coronary microvascular dysfunction [14]. The findings of previous studies highlight that increased TnT levels are independent markers of mortality in HF patients [4]. In the ADHERE trial, AHF patients who tested positive for elevated troponin levels had lower systolic blood pressure on admission, lower ejection fraction, and higher in-hospital mortality rates than those who tested negative [15]. BNP is another well-known and frequently used biomarker for HF diagnosis and treatment. It is a neurohormone specifically secreted from the cardiac chambers in response to hemodynamic stress. The BNP level is elevated in situations where the ventricles are dilated, hypertrophic, or subject to increased wall tension [16,17]. The clinical validity of brain natriuretic peptide (BNP) measurements has been previously reported. Nishii M et al. reported that a high BNP level was a predictor of long-term risk in patients with non-ischemic dilated cardiomyopathy who were asymptomatic for more than six months after admission for AHF [18]. Januzzi and Troughton reported that BNP-guided therapy resulted in superior medical management compared to traditional care, mostly because of frequent and sophisticated drug adjustment [19]. In addition, BNP-guided therapy might be particularly attractive in older patients who are less physically active and in those whom symptoms are less reliable [20]. In our study, there were few patients with high BNP levels without significant physical findings before discharge. As the reviewer commented, these patients may benefit from BNP measurement to predict their long-term outcome such as readmission or death. However, caution is needed since other studies have suggested that BNP-guided HF management may have little or even a negative impact on elderly patients because of increased risk of drug-drug interactions and worsening organ failure secondary to polypharmacy [21]. Obviously, treatment strategies should be based on both physical signs and biomarkers. Physical signs are safe, cost-efficient non-invasive methods to assess the state of patients with HF. At times, physical signs may serve as unclear indices because of interobserver variation. In such situations, biomarkers could prove to be strong prognostic indices. The precise relationship between physical signs and biomarkers should be studied further.

In our cohort, higher readmission rates were seen in AHF patients with increased TnT levels but not in those with elevated BNP levels. This may be related to relatively high number of DCM patients included in our study. These patients are known to have high BNP levels even after they reach compensated state.

Figure 1. Kaplan Meier analysis of event-free survival according to the presence or absence of physical findings. Jugular venous distension (JVD) (A), rales (B), third heart sound (S3) (C), paroxysmal nocturnal dyspnea (D), orthopnea (E), and edema (F). Patients with JVD, pulmonary rales, or S3 had worse readmission rates that those without these findings (log-rank p = 0.024, p < 0.001, p = 0.001, respectively).

doi:10.1371/journal.pone.0096325.g001
Table 2. Predictors associated with readmission rate.

| Predictors                                      | HR (95% CI)       | P value | HR Adjusted for Age and Sex (95% CI) | P value | HR Adjusted for Age, BNP level, and sBP on admission (95% CI) | P value |
|-------------------------------------------------|-------------------|---------|-------------------------------------|---------|---------------------------------------------------------------|---------|
| Age                                             | 1.026 (1.010–1.043) | 0.002   | –                                   | –       | –                                                             | –       |
| Women, %                                        | 1.348 (0.795–2.287) | 0.268   | –                                   | –       | –                                                             | –       |
| Comorbidities                                   |                   |         |                                     |         |                                                                |         |
| Ischemic heart disease, %                       | 0.982 (0.604–1.596) | 0.982   | –                                   | –       | –                                                             | –       |
| Dilated cardiomyopathy, %                       | 1.002 (0.792–1.268) | 0.986   | –                                   | –       | –                                                             | –       |
| Hypertrophic heart disease, %                   | 1.021 (0.729–1.430) | 0.905   | –                                   | –       | –                                                             | –       |
| AF, %                                           | 1.191 (0.714–1.987) | 0.502   | –                                   | –       | –                                                             | –       |
| Systolic Blood Pressure, mmHg                   | 0.997 (0.989–1.006) | 0.503   | –                                   | –       | –                                                             | –       |
| NYHA functional class on admission              | 1.113 (0.816–1.518) | 0.499   | –                                   | –       | –                                                             | –       |
| on discharge                                    | 3.064 (1.141–8.232) | 0.026   | –                                   | –       | –                                                             | –       |
| BNP, pg/mL                                      | 1.001 (1.000–1.001) | <0.001  | –                                   | –       | –                                                             | –       |
| on admission ≥150                               | 8.936 (2.185–36.555) | 0.002   | –                                   | –       | –                                                             | –       |
| on discharge                                    | 1.001 (1.001–1.001) | <0.001  | –                                   | –       | –                                                             | –       |
| on discharge ≥150                               | 2.610 (1.440–4.731) | 0.002   | –                                   | –       | –                                                             | –       |
| Left ventricular ejection fraction ≤40%, %      | 1.166 (0.729–1.866) | 0.322   | –                                   | –       | –                                                             | –       |
| Troponin T on discharge >0.10 ng/mL, %          | 2.404 (1.44–3.986)  | 0.001   | –                                   | –       | –                                                             | –       |
| PND                                             | 1.351 (0.819–2.228) | 0.239   | 1.174 (0.706–1.952) | 0.535   | 1.167 (0.668–2.037) | 0.587 |
| Orthopnea                                       | 0.867 (0.496–1.517) | 0.618   | 0.727 (0.408–1.294) | 0.278   | 0.690 (0.378–1.260) | 0.227 |
| JVD                                             | 1.819 (1.074–3.078)  | 0.026  | 1.513 (0.869–2.632) | 0.143   | 1.396 (0.783–2.488) | 0.258 |
| Edema                                           | 1.246 (0.750–2.069)  | 0.396  | 1.077 (0.634–1.830) | 0.783   | 1.055 (0.597–1.863) | 0.855 |
| Rales                                           | 2.489 (1.479–4.191)  | 0.001  | 1.951 (1.096–3.474) | 0.023   | 2.034 (1.090–3.794) | 0.026 |
| S3                                              | 2.077 (1.165–3.700)  | 0.013  | 1.908 (1.064–3.419) | 0.030   | 2.056 (1.126–3.754) | 0.019 |

Predictors associated with readmission rate according to multivariable Cox proportional hazards models. Even after adjusting for age, sex, BNP level, and sBP on admission, the presence of rales and S3 were significantly related to the readmission rate (p = 0.026 and 0.019, respectively).

HR = hazard ratio, sBP = systolic blood pressure, AF = atrial fibrillation, NYHA = New York Heart Association, BNP = brain natriuretic peptide, PND = paroxysmal nocturnal dyspnea, JVD = jugular venous distention, S3 = the third heart sound.

doi:10.1371/journal.pone.0096325.t002
The lack of statistical differences could have resulted from this unique cohort. On the contrary, AHF patients with elevated TnT level at discharge were those that required early readmission. Elevated TnT may be a more sensitive biomarker compared to BNP in identifying vulnerable AHF patients who require close monitoring post discharge.

Our study has several limitations. First, this study was conducted in a single-center tertiary university hospital. Therefore, a multicenter study with a large study population is needed to determine the correlation between physical findings and biomarker levels. Second, despite adjusting for known risk factors, according to the results of the Cox hazards models, residual confounding may have been caused by unmeasured and measured variables. Third, there were no standardized instructions for obtaining physical findings and this may have led to some degree of misclassification depending on the physicians. The physical examination results could have been inaccurate to some extent, and no confirmatory tests such as phonocardiography for S3 were performed during this study.

The significance of physical examination cannot be underestimated. A strong relationship has been shown between left-sided HF symptoms and elevated TnT levels. Therefore, focused bedside assessment is vital and our findings add to the prognostic importance of physical findings in AHF patients.

### Supporting Information

#### Tables S1

This file includes Table S1 and S2. Table S1. Presence of physical signs by the use of guideline-based heart failure medications on admission. All the data in the table are percentages. There was no significant difference in the readmission rate between patients receiving each of the optimal guideline-based medications before and after admission. Individually, patients on beta-blockers had a lower percentage of jugular venous distention, edema, and S3 (P = 0.042, 0.010, and 0.028, respectively). Patients receiving spironolactone before admission had a lower percentage of paroxysmal nocturnal dyspnea, edema, and rales (P = 0.023, 0.010, and 0.028, respectively). Table S2. Readmission rate according to the use of guideline-based heart failure medication at the time of admission.

#### Acknowledgments

The 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: SN SK TI. Analyzed the data: SN MS SK. Contributed reagents/materials/analysis tools: YS TK YM. Wrote the paper: SN MS SK. Contributed reagents/materials/analysis tools: YS TK YM. Wrote the paper: SN MS SK.

### References

1. Drazner MH, Rame JE, Stevenson LW, Dries DL (2001) Prognostic importance of elevated jugular venous pressure and a third heart sound in patients with heart failure. N Engl J Med 345: 574–581.

2. Miller WL, Hartman KA, Burritt MF, Grill DE, Rodeheffer RJ, et al. (2007) Serial biomarker measurements in ambulatory patients with chronic heart failure: the importance of change over time. Circulation 116: 249–257.

---

### Table 3. Logistic regression analysis.

#### A. Predictors of BNP level on discharge ≥150 pg/mL

| Variables | OR (95% CI) | P value | OR Adjusted for Age and Sex (95% CI) | P value | OR Adjusted for Age, Sex, BNP level, and sBP on admission (95% CI) | P value |
|-----------|-------------|---------|--------------------------------------|---------|---------------------------------------------------------------|---------|
| PND       | 0.901 (0.448–1.811) | 0.770 | 0.732 (0.352–1.521) | 0.403 | 0.545 (0.237–1.252) | 0.153 |
| Orthopnea | 1.023 (0.492–2.125) | 0.952 | 0.963 (0.456–2.036) | 0.922 | 0.757 (0.330–1.735) | 0.511 |
| JVD       | 1.488 (0.767–2.889) | 0.240 | 1.237 (0.617–2.479) | 0.548 | 0.559 (0.242–1.288) | 0.172 |
| Edema     | 1.397 (0.717–2.725) | 0.326 | 1.235 (0.622–2.454) | 0.546 | 0.841 (0.379–1.870) | 0.671 |
| Rales     | 2.208 (1.077–4.525) | 0.031 | 1.689 (0.790–3.609) | 0.176 | 1.473 (0.625–3.473) | 0.376 |
| S3        | 1.852 (0.940–3.650) | 0.075 | 1.677 (0.836–3.364) | 0.146 | 1.656 (0.741–3.702) | 0.219 |

#### B. Predictors of troponin T on discharge >0.10 ng/mL

| Variables | OR (95% CI) | P value | OR Adjusted for Age and Sex (95% CI) | P value | OR Adjusted for Age, Sex, BNP level, and sBP on admission (95% CI) | P value |
|-----------|-------------|---------|--------------------------------------|---------|---------------------------------------------------------------|---------|
| PND       | 1.368 (0.663–2.822) | 0.397 | 1.119 (0.521–2.406) | 0.773 | 1.054 (0.475–2.337) | 0.897 |
| Orthopnea | 0.870 (0.394–1.919) | 0.730 | 0.750 (0.325–1.729) | 0.499 | 0.654 (0.273–1.567) | 0.340 |
| JVD       | 1.773 (0.854–3.678) | 0.124 | 1.155 (0.522–2.553) | 0.722 | 1.043 (0.449–2.424) | 0.922 |
| Edema     | 3.758 (1.719–8.212) | 0.001 | 3.019 (1.333–6.838) | 0.008 | 3.134 (1.302–7.546) | 0.011 |
| Rales     | 3.990 (1.869–8.516) | <0.001 | 2.548 (1.127–5.760) | 0.025 | 2.583 (1.097–6.082) | 0.030 |
| S3        | 2.939 (1.206–7.159) | 0.018 | 2.547 (1.000–6.490) | 0.050 | 2.459 (0.941–6.421) | 0.066 |
3. Del Carlo CH, O’Connor CM (1999) Cardiac troponins in congestive heart failure. Am Heart J 138: 646–653.
4. Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, et al. (2001) Persistently increased serum concentrations of cardiac troponin I in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. Circulation 103: 369–374.
5. Perna ER, Macin SM, Canella JP, Augier N, Sival JL, et al. (2004) Ongoing myocardial injury in stable severe heart failure: value of cardiac troponin T monitoring for high-risk patient identification. Circulation 110: 2376–2382.
6. Latini R, Masson S, Anand IS, Missov E, Carlou M, et al. (2007) Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 116: 1242–1249.
7. Betencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, et al. (2004) N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. Circulation 110: 2168–2174.
8. Cheng V, Kazanagia R, Garcia A, Lenert L, Krishnasawmy P, et al. (2003) A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol 47: 386–391.
9. Januzzi JL, van Kinnenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, et al. (2006) NT-proBNP testing for diagnosis and short-term prognosis in acute decompensated heart failure: an international pooled analysis of 1236 patients: the International Collaborative of NT-proBNP Study. Eur Heart J 27: 330–337.
10. Devroey D, Van Casteren V (2011) Signs for early diagnosis of heart failure in primary health care. Vasc Health Risk Manag 7: 591–596.
11. Drazer MH, Hellkamp AS, Lierer CV, Shahi MR, Miller LW, et al. (2008) Value of clinician assessment of hemodynamics in advanced heart failure: the ESCAPE trial. Circ Heart Fail 1: 170–177.
12. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M (2007) Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 49: 1943–1950.
13. Missov E, Calzolari C, Pau R (1997) Circulating cardiac troponin I in severe congestive heart failure. Circulation 96: 2953–2958.
14. Takashio S, Yamamura M, Izumiya Y, Sugiyama S, Koijima S, et al. (2013) Coronary microvascular dysfunction and diastolic load correlate with cardiac troponin T release measured by a highly sensitive assay in patients with nonischemic heart failure. J Am Coll Cardiol 62: 632–640.
15. Fonarow GC, Peacock WF, Horwich TB, Phillips CO, Givertz MM, et al. (2008) Usefulness of B-type natriuretic peptide and cardiac troponin levels to predict in-hospital mortality from ADHERE. Am J Cardiol 101: 231–237.
16. Gheorghide M, Follath F, Ponikowski P, Barsuk JH, Blair JE, et al. (2010) Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. Eur J Heart Fail 12: 423–433.
17. Danich LR, Maisel AS (2007) Natriuretic peptides. J Am Coll Cardiol 50: 2357–2368.
18. Nishii M, Inomata T, Takehana H, Naruke T, Yanagisawa T, et al. (2008) Prognostic utility of B-type natriuretic peptide assessment in stable low-risk outpatients with nonischemic cardiomyopathy after decompensated heart failure. J Am Coll Cardiol 51: 2329–2335.
19. Januzzi JL, Troughton R (2013) Are serial BNP measurements useful in heart failure management? Serial natriuretic peptide measurements are useful in heart failure management. Circulation 127: 500–507; discussion 508.
20. Pintoier M, Buser P, Rickli H, Gutmann M, Erne P, et al. (2009) BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 301: 383–392.
21. Gaggin HK, Mohammed AA, Bhardwaj A, Rbman SU, Gregory SA, et al. (2012) Heart failure outcomes and benefits of NT-proBNP-guided management in the elderly: results from the prospective, randomized ProBNP outpatient tailored chronic heart failure therapy (PROTECT) study. J Card Fail 18: 626–634.