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Methods and Results: We examined the association between LOS and baseline characteristics, 10-day post-discharge HF readmission, and 90-day post-discharge mortality in 1,347 patients with AHF enrolled in the VERITAS program. Longer LOS was associated with greater HF severity and disease burden at baseline; however, most of the variability of LOS could not be explained by these factors. LOS was not associated with readmissions during the first days after discharge. However, LOS was a significant predictor of 90-day mortality (Hazard ratio for 1 day increase: 1.05; 95% C.I. 1.02, 1.07, p=0.00004), although the association is partially explained by concurrent end organ damage and worsening heart failure (WHF) during the first days of admission.
Conclusions: In patients who have been admitted for Acute HF; longer length of hospital stay is associated with a higher rate of short-term mortality.
Clinical Trial Registration: VERITAS-1 and -2:Clinicaltrials.gov identifiers NCT00525707 and NCT00524433.
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Predictors and associations with outcomes of length of hospital stay in patients with acute heart failure: Results from VERITAS

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Abstract

Background: The length of hospital stay (LOS) is important in patients admitted for acute heart failure (AHF) as it prolongs an unpleasant experience for the patients and adds substantially to health care costs.

Methods and Results: We examined the association between LOS and baseline characteristics, 10-day post-discharge HF readmission, and 90-day post-discharge mortality in 1,347 patients with AHF enrolled in the VERITAS program. Longer LOS was associated with greater HF severity and disease burden at baseline; however, most of the variability of LOS could not be explained by these factors. LOS was not associated with readmissions during the first days after discharge. However, LOS was a significant predictor of 90-day mortality (Hazard ratio for 1 day increase: 1.05; 95% C.I. 1.02, 1.07, p=0.00004), although the association is partially explained by concurrent end organ damage and worsening heart failure (WHF) during the first days of admission.

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Keywords: heart failure, length of stay, prognosis

Hospitalization for acute heart failure (AHF) is a major cause of morbidity and mortality and a significant burden on healthcare systems worldwide (1.2). A hospitalization for AHF represents an important clinical event with significant consequences for the patient, including disruption of the patient's normal home life, a relatively high risk of in-hospital mortality and a post-discharge period of increased re-admission and death. The relationship between hospital length-of-stay (LOS) and post-discharge outcomes is of considerable interest. Although LOS has recently been suggested as a surrogate measure of hospital performance (3), LOS varies widely between countries and geographic regions (4-7), and neither studies nor guidelines provide criteria for determining the optimal LOS for patients. This absence of recommendation is driven by the paucity of data examining determinants of LOS and its relationship with outcomes after discharge. Indeed, the few studies that have examined LOS as a marker of disease severity reported conflicting results; on the one hand, some studies showed that longer LOS is associated with higher readmission rates and mortality (8), while on the other hand, regions with longer LOS have lower rates of short-term readmission up to day 30 (9), claimed to be mostly due to very early "rebound" admissions with days of discharge. Importantly, local medical practice and health system operation is also relevant. In some regions, a stringent system-based strategy to shorten LOS operates, while in others, extended hospital stays are widely accepted. These cultural disparities may have implications for developing strategies to prevent readmission, defining quality measures, and designing clinical trials in AHF. To better understand the implications of differences in LOS across different countries, we studied patient outcomes in hospital and up to 90 days after admission, adjusted for regional LOS disparities, among the 1347 patients with AHF enrolled within 24h of admission into the Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies (VERITAS; 10,11).

Methods:

This study is a post-hoc analysis of the VERITAS program, the design and results of which have been published (10). Briefly, VERITAS-1 and -2 (Clinicaltrials.gov identifiers NCT00525707 and NCT00524433) were concurrent, identical, double-blind, randomized, placebo-controlled, parallel-group studies designed to evaluate tezosentan in the treatment of acute heart failure (AHF). Patients > 18 years old who had been admitted for AHF within the previous 24 hours, with persistent dyspnea at rest and respiratory rate of > 24 breaths per minute, and who had received at least one dose of intravenous diuretic 2-24 hours prior to study drug initiation were potentially eligible for enrollment. Eligible patients had to meet at least two of the following four additional criteria: 1) elevated B-type natriuretic peptide (BNP) or NT-pro BNP, 2) pulmonary edema on physical examination, 3) radiologic pulmonary congestion or edema, and 4) either left ventricular ejection fraction [LVEF] < 0.40 or wall motion index ≤ 1.2. For patients monitored with a pulmonary artery catheter, a cardiac index ≤ 2.5 L/min/m^2 and pulmonary capillary wedge pressure ≥ 20 mmHg were required. Patients were excluded if they had cardiogenic shock, ST segment elevation myocardial infarction, administration of a thrombolytic agent or ongoing ischemia, systolic blood pressure < 100 mg if not receiving a vasodilator or < 120 mmHg if receiving a vasodilator, hemoglobin < 10 g/dL or hematocrit < 30%, or creatinine > 2.5 mg/dL.

After obtaining informed consent, patients were randomized to receive an intravenous infusion of either placebo or tezosentan, in addition to conventional care. A total of 1435 patients were enrolled and treated between April 2003 and November 2005. Medical history was taken and routine clinical laboratory measures assayed locally at baseline. Plasma samples were obtained immediately prior to study drug initiation (baseline) and stored at -20^{o}C locally and shipped to a core laboratory for analysis (BioProof AG, Munich, Germany) (12). BNP and troponin I were measured using commercially-available ELISA kits: Peninsula Laboratories, San Carlos, USA for BNP and Labmaster, Turku, Finland for troponin I.

Troponin T was measured using an electrochemiluminescence immunoassay (Roche, Germany). The lower limit of quantification (LLOQ) was 0.041 ng/mL for BNP, 0.01 ng/mL for troponin T and reported by the laboratory as not applicable for troponin I. Because troponin I and T were highly correlated ($r=0.87$, $p<0.0001$) and troponin T was more often missing; only troponin I was considered. Non-detectable values were set to 0.5 times the LLOQ for BNP and to 0.5 times the minimum reported value for troponin I prior to log transformation. In-hospital WHF, which was reported through day 7, was defined as either the development of pulmonary edema, cardiogenic shock or other evidence of WHF, or failure of the patient's HF condition to improve with treatment, which required the initiation, reinstitution, or increase in intravenous therapy for HF or use of mechanical circulatory or ventilatory support or the use of hemodialysis, hemofiltration or ultrafiltration.

Rehospitalizations through 30 days and vital status through 180 days from baseline were collected. Given that the time at risk for rehospitalization in patients with longer LOS is reduced, creating possible bias - they spend more of the first 30 days in the hospital and hence they have no time to be readmitted up to day 30 when the collection of information was truncated, we examined the association between LOS and the risk of HF readmission during the first 10 days post-discharge in patients discharged before day 20. For the same considerations, 90 days post-discharge mortality was assessed and modeled (see below).

Statistical Methods

Patients were excluded if they were enrolled more than 24 hours after admission, or if missing the discharge date such that the LOS could not be calculated. Each patient's LOS was categorized as short, medium, or long based on the first and third tertiles within geographic region, which were 5 and 8 days in North America/Australia, 4 and 7 days in Israel, 8 and 14 days in Western Europe, and 8 and 11 days in Eastern Europe. Baseline characteristics are presented by short, medium and long LOS. Means and

standard deviations, medians and first and third quartile, or geometric means for log-transformed variables are presented for continuous variables; groups were compared using ANOVA F-tests. Absolute and relative frequencies are presented for discrete variables, and were compared between groups using chi-square tests.

Associations between baseline characteristics and LOS and between LOS and i) 90-day post-discharge mortality and ii) 10-day post-discharge HF readmission were examined using linear regression, Cox proportional hazards, and logistic regression models, respectively. Because rehospitalizations were captured only through day 30 from baseline in VERITAS, analyses of 10-day post-discharge readmissions were limited to patients discharged by day 20. Multivariable models were developed for length of stay (LOS), 10-day post-discharge HF readmission, and 90-day post-discharge mortality using a common approach. Non-linearity of the association between each continuous predictor and the outcome was assessed through testing the significance of non-linear components of a restricted cubic spline transformation. Plots of the predicted outcome against the value of the predictor and values of Akaike's Information Criterion (AIC) and adjusted R^2 were used to select transformations where needed. Multiple imputation assuming multivariate normality was used for missing predictors; the proportion missing each covariate is given in Table 2. The final multivariable model included the predictors selected in the majority of the 10 imputation datasets using backwards selection at a 0.05 significance level for linear regression and a 0.10 significance level for Cox and logistic regression models. Estimated effect sizes, confidence intervals and p-values were obtained by averaging across the imputation datasets using Rubin's algorithm (13). C-statistics were computed using Harrell's method (14, 15). A multivariable-adjusted estimate of the association between LOS and the outcome of interest was obtained by adding the LOS as a predictor in the multivariable model. The occurrence of in-hospital WHF was then added to evaluate whether any association between LOS and the outcome might be explained by in-hospital WHF. Days in the intensive care unit (ICU) up to day 30 were collected. Unadjusted and multivariable-

adjusted associations between days in the ICU and 90-day post-discharge mortality were also examined. All models were either adjusted or stratified by geographic region. SAS® version 9.3 (SAS Institute, Cary, NC, USA) software was used for all analyses.

Results:

Of the 1449 patients eligible for analysis, 102 (7.0%) were excluded because they were enrolled more than 24 hours after admission and 10 patients because of missing LOS data. Of the remaining 1337 patients, 55 (4.1%) died during the initial hospitalization. The LOS by region in patients who survived to discharge and those who did not are presented in Table 1, and the distributions by geographic region in those who survived are presented in Figure 1. Patient characteristics by short, medium and long LOS within region are presented in Table 2. Univariable and multivariable models for LOS are presented in Table 3. After multivariable adjustment, more severe dyspnea at randomization, history of diabetes mellitus or valvular heart disease, higher creatinine or troponin I, and lower hemoglobin (up to 14.5 g/dL) or sodium (up to 140 mmol/L) were associated with longer LOS. Higher systolic BP (up to 145 mmHg) was associated with shorter LOS.

With adjustment for region, longer LOS was not associated with the risk of HF readmission from randomization to day 30 (OR 1.01, 95% CI 0.97-1.06, p=0.5768) in patients who were alive and discharged before day 30. As described above, to further examine the associations of LOS with early readmissions, taking into account that during the 30 days after randomization patients with longer LOS had less days at risk for readmission, we examined the association between LOS and the risk of HF readmission during the first 10 days post discharge (early "rebound" re-admissions) in the 1199 patients discharged before day 20. Univariable associations between baseline characteristics and 10-day post-discharge HF readmission are presented in supplemental Table 1. Each additional day of LOS was associated with an OR for 10-day readmission of 1.08 (95% CI 1.01-1.16); p=0.0189. However, after

multivariable adjustment for baseline characteristics, the association became non-significant [Table 4; OR 1.06 (0.99 -1.14); p=0.0961]. Introducing both LOS and WHF into the model diminished the association further [OR = 1.05 (0.97 – 1.13); p = 0.2336].

Univariable associations with 90-day post-discharge mortality are presented in supplemental Table 2, and the cumulative risk by LOS category is presented in Figure 2. With adjustment only for region, longer LOS was associated with a higher rate of 90-day post-discharge mortality (HR for 1-day increase 1.05, 95% CI 1.02-1.07, p=0.0004). After multivariable adjustment for baseline characteristics (Table 4), the HR for each additional day of LOS was reduced to 1.04 (1.01-1.07), p=0.0166. After further adjustment for the occurrence of in-hospital worsening heart failure (WHF), the association between LOS and 90-day post-discharge mortality was further reduced and became non-significant: 1.03 (1.00-1.06), p=0.0629, while the association between WHF and 90-day post-discharge mortality remained highly significant [HR 1.59 (1.02-2.48), p= 0.0396]. Further adjustment for changes from baseline to 24 hours in albumin, creatinine, BUN, and ALT did not change the estimated HR for LOS, although further reduced statistical significance (1.03, 95% CI 0.99-1.06, p=0.0997). There was no interaction between LOS and tezosentan treatment (p=0.5482).

Adjusted only for geographic region, days in the ICU were not significantly associated with 90-day post-discharge mortality (HR 1.04, 95% CI 0.99-1.09, p=0.0823). After multivariable adjustment for baseline characteristics, the association was nearly statistically significant (HR 1.05, 95% CI 1.00-1.11, p=0.0577); however, after adjustment for overall hospital LOS, association with ICU days was significantly reduced and became non-significant (HR 1.03, 95% CI 0.98-1.09, p=0.2717).

Discussion

Hospital length of stay is increasingly used as a measure of quality of care in patients admitted for acute heart failure (2) both from the perspective of the patients, who perceive time in the hospital as an unpleasant experience and would in some cases trade years of life for less time in the hospital (16) and health systems for which HF admissions represent an ever-growing financial burden (17). We examined the predictors and associations between LOS and outcomes in the VERITAS study. First, as noted previously (3-6), we found that LOS varied substantially by geographical region and hence all analysis performed here were adjusted for geographical region. Adjusted for region, longer LOS was associated with some measures of more severe HF, including worse dyspnea and greater end organ dysfunction/ damage (elevated troponin, creatinine/ BUN), as well as co-morbidities (age, diabetes, chronic kidney disease, anemia)(Table 2). However, BNP was not a predictor of LOS, in either the univariable or multivariable analyses. The adjusted r-square (0.19) from a multivariable model suggests that most of the variability of LOS is not explained by heart failure severity or co-morbidities, even after adjustment for region. Conceivably some of this variability may be related to other factors such as hospital bed availability and patients' socioeconomic status and availability of social support (18), factors that were not captured in the VERITAS program.

Data on the association of LOS and outcomes is scarce. From the one hand it was suggested (4) that longer LOS is associated with lower short-term (up to day 30) readmissions rates, mostly due to quick post discharge readmissions in the days after discharge while on the other hand a recent US based health care provider analysis suggested that longer LOS is associated with more early ("rebound") and late readmissions and death (8)In both analysis, readmission and death were measured from presentation, hence patients with shorter LOS have "more time" to be readmitted since they are discharged earlier and have therefore "more days" at risk given the fixed follow-up period from

randomization and admission, potentially biasing the analysis of the association between LOS and short-term readmission. To clarify this issue we have undertaken an analysis in which a fixed period of days post discharge was examined. As the vast majority of patients had a LOS < 20 days and readmission information was available in VERITAS for only 30 days, we examined the rate of HF readmissions during the vulnerable period of the first 10 days post-discharge. This approach towards analyzing readmissions in early vulnerable period after discharge and their association with LOS was also supported by a recent analysis suggesting that post-discharge readmissions during the first few days after discharge are common and potentially associated with LOS, while readmissions occurring later during the post-discharge period are not (18). In VERITAS, longer LOS was associated with a higher (and not lower) rate of short-term readmission, although this association was diminished by adjustment for severity of heart failure at baseline, and further diminished when adjusted for the occurrence of in-hospital WHF (Table 4).

The univariable and multivariable associations of post discharge 90-day mortality are presented in supplemental table 2 and table 5. Overall baseline characteristics alone were moderately predictive of post discharge 90-day mortality (c-index = 0.7421). Longer LOS was associated with greater risk of 90-day mortality. This association remained significant even after adjustment for baseline characteristics (Table 4). The significance of the association of LOS and 90-day post discharge mortality was reduced after further adjustment for changes from baseline to 24 hours in albumin, creatinine, BUN, and ALT, suggesting that changes in end organ function during the first day of admission may herald the adverse outcomes associated with longer LOS. Similarly, the association of LOS with 90-day post discharge mortality was significantly reduced after adjustment for in-hospital worsening heart failure (WHF). The association between in-patient WHF, longer LOS and adverse outcomes in VERITAS has been previously described (19). Indeed, in the current analysis the introduction of both in-patient WHF and LOS into the multivariable model diminished the association between LOS and 90-day mortality but not that of WHF

and 90 day mortality. This suggests that some of the risk of mortality associated with longer LOS is attributable to the occurrence of in-hospital WHF.

We observed a trend towards association between ICU days and 90-days post discharge mortality, however this trend did not reach statistical significance, and was further reduced by adjustment for total in hospital LOS. As ICU days were captured in the VERITAS database only in full days it did not allow for granular determination of the time spent in the ICU and hence, full analysis of the contribution of ICU to the associations of LOS and outcomes will require further analysis in larger studies where LOS and ICU days are captured in more detail.

Therefore, the analysis of the associations between LOS and 90-day mortality and LOS and 10-day readmission rates demonstrates concordance, i.e., longer LOS is associated with higher risk of short-term mortality and HF readmission.

Limitations

This analysis is a retrospective analysis of the VERITAS program and is hence limited by the data collected in the study, the relatively small sample size, and especially with regard to post-discharge readmissions which were only collected during the first 30 days after randomization regardless of the discharge date.

Conclusions:

Longer LOS is an important outcome in AHF both from the perspective of the patient experience and healthcare systems. Longer LOS is only partially explained by severity of HF and co-morbidities at baseline. Longer LOS is associated with a higher risk of adverse outcomes post-discharge; both 10-day HF readmission and 90-day death, although the association with readmission was significantly reduced after adjustment for baseline characteristics. The association between longer LOS and mortality may be

heralded by worsening end organ function in the first day of admission and importantly, mediated by in-hospital WHF. The finding that WHF is associated with longer LOS and higher mortality raises the possibility that therapies that prevent in-hospital WHF could improve outcomes.

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Figure 1: ***Distribution of length of stay (excluding in-hospital deaths) by geographic region.*** Lines on the box represent the 25th, 50th, and 75th percentiles, whiskers the 10th and 90th percentiles, and dots the 5th and 95th percentiles of the distributions.

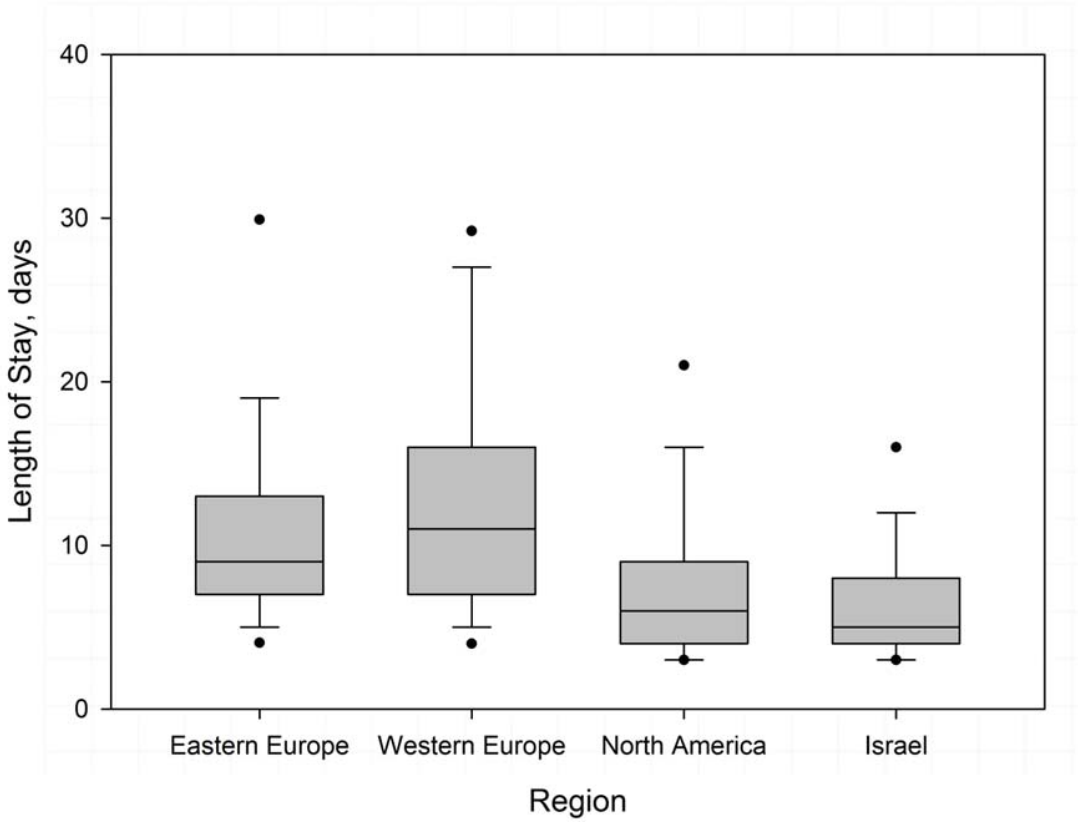

Figure 2: ***Association of length of stay (excluding in-hospital deaths) with 90-day post-discharge mortality.*** Classification of LOS as short, medium, or long is based on tertiles of the distributions within geographic region.

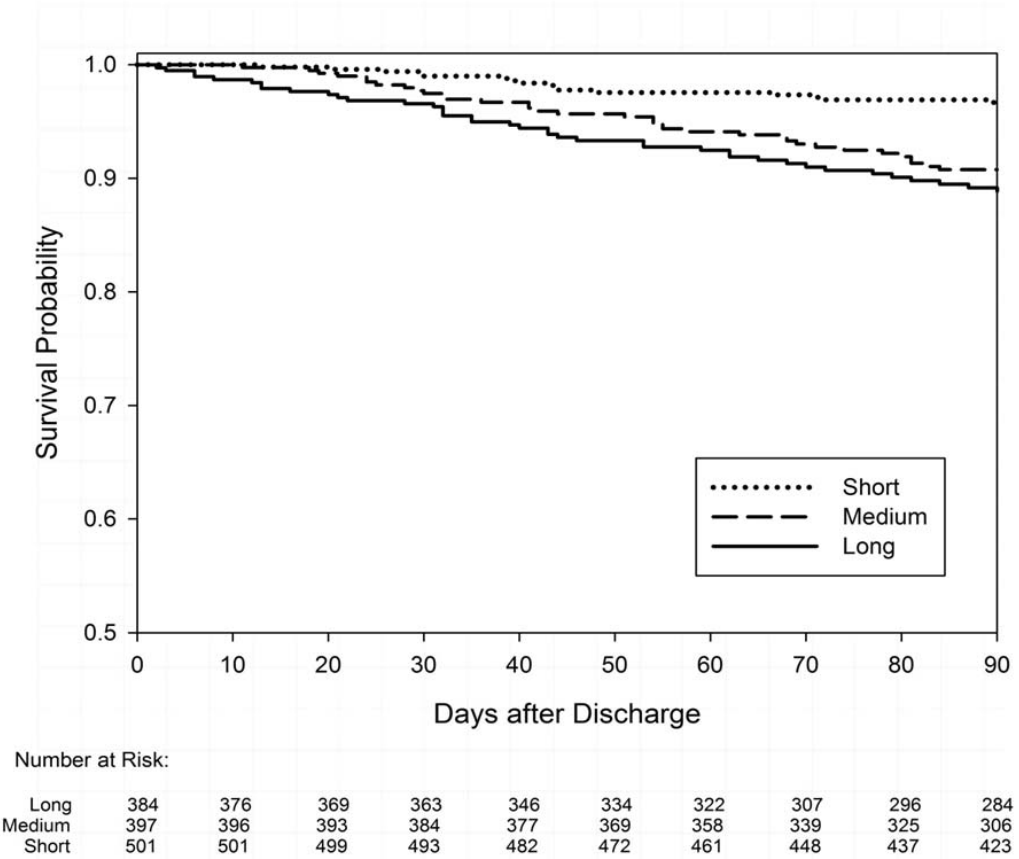
1.0
0.9
0.8
0.7
0.6
0.5
Survival Probability
0
10
20
30
40
50
60
70
80
90
Days after Discharge
Short
Medium
Long
Number at Risk:
Long 384 376 369 363 346 334 322 307 296 284
Medium 397 396 393 384 377 369 358 339 325 306
Short 501 501 499 493 482 472 461 448 437 423

Table 1: ***Length of stay by patient status and region***

	---- Subjects who survived to discharge ---- (N = 1282)		Subjects who died during initial hospital stay (N = 55)		---------- Total ---------- (N = 1337)	
Region	***Number of subjects***	***Length of stay [1]***	***Number of subjects***	***Length of stay [1]***	***Number of subjects***	***Length of stay [1]***
North America and Australia	346 (27.0%)	7.8 (5.90), 6.0 (4.0 - 9.0)	8 (14.5%)	17.6 (13.88), 14.5 (6.0 - 26.0)	354 (26.5%)	8.0 (6.33), 6.0 (4.0 - 9.0)
Israel	454 (35.4%)	6.7 (4.39), 5.0 (4.0 - 8.0)	12 (21.8%)	24.1 (30.10), 11.5 (7.5 - 31.0)	466 (34.9%)	7.2 (6.91), 5.0 (4.0 - 8.0)
Western Europe	294 (22.9%)	12.8 (7.39), 11.0 (7.0 - 16.0)	23 (41.8%)	29.8 (43.35), 9.0 (7.0 - 31.0)	317 (23.7%)	14.0 (14.18), 11.0 (7.0 - 16.0)
Eastern Europe	188 (14.7%)	10.9 (6.05), 9.0 (7.0 - 13.0)	12 (21.8%)	35.8 (49.20), 10.0 (5.0 - 52.0)	200 (15.0%)	12.4 (14.26), 9.0 (7.0 - 13.0)
Overall	1282 (100%)	9.0 (6.33), 7.0 (5.0 - 11.0)	55 (100%)	28.1 (38.76), 10.0 (6.0 - 31.0)	1337 (100%)	9.8 (10.66), 7.0 (5.0 - 11.0)

Notes:
[1] Results shown are mean (standard deviation), median (25th - 75th percentile).

Table 2: ***Baseline characteristics by length of stay categories (excluding in-hospital deaths)***

		---------- *Length of stay [1]* ----------			
Parameter	***n (% missing)***	***Short (N = 501)***	***Medium (N = 397)***	***Long (N = 384)***	***P-value [2]***
Age (years)	1282 (0.0%)	68.3 (12.67), 70.0 (60.0 - 78.0)	71.4 (12.06), 74.0 (65.0 - 81.0)	70.7 (11.93), 73.0 (64.0 - 79.0)	0.0004
Gender: Male	1282 (0.0%)	303 (60.5%)	226 (56.9%)	228 (59.4%)	0.5544
Race: White	1282 (0.0%)	409 (81.6%)	353 (88.9%)	343 (89.3%)	0.0008
Time to randomization (hours)	1282 (0.0%)	10.8 (6.88), 9.3 (4.5 - 16.9)	10.8 (6.69), 8.9 (4.7 - 15.8)	11.1 (7.01), 9.3 (4.7 - 17.1)	0.6996
BMI (kg/m2)	1215 (5.2%)	29.2 (6.45), 28.0 (24.5 - 32.5)	28.7 (5.78), 27.7 (24.9 - 31.8)	28.7 (6.48), 27.4 (24.5 - 31.2)	0.4866
Atrial fibrillation on admission	1272 (0.8%)	124 (24.9%)	103 (26.1%)	110 (28.9%)	0.4191
History of CHF	1272 (0.8%)	376 (75.4%)	286 (73.1%)	272 (71.2%)	0.3811
History of COPD	1281 (0.1%)	89 (17.8%)	74 (18.6%)	82 (21.4%)	0.3767
History of diabetes	1281 (0.1%)	218 (43.5%)	190 (47.9%)	205 (53.5%)	0.0128
History of hyperlipidemia	1281 (0.1%)	186 (37.1%)	146 (36.8%)	125 (32.6%)	0.3313
History of hypertension	1281 (0.1%)	393 (78.4%)	316 (79.6%)	309 (80.7%)	0.7151
History of smoking	1281 (0.1%)	45 (9.0%)	31 (7.8%)	23 (6.0%)	0.2589
History of IHD, PVD, stroke	1281 (0.1%)	333 (66.5%)	282 (71.0%)	275 (71.8%)	0.1679
History of mitral/aortic valve disease	1281 (0.1%)	69 (13.8%)	64 (16.1%)	73 (19.1%)	0.1055
History of renal impairment	1272 (0.8%)	157 (31.6%)	158 (40.1%)	155 (40.7%)	0.0064
History of liver disease	1272 (0.8%)	35 (7.0%)	30 (7.6%)	36 (9.4%)	0.4082
Previous PCI or CABG	1281 (0.1%)	186 (37.1%)	137 (34.5%)	129 (33.7%)	0.5274

		Length of stay [1]			
Parameter	***n (% missing)***	***Short (N = 501)***	***Medium (N = 397)***	***Long (N = 384)***	***P-value [2]***
Systolic blood pressure (mmHg)	1268 (1.1%)	130.3 (20.98), 126.5 (115.0 - 143.0)	133.0 (23.75), 129.0 (115.0 - 147.0)	131.9 (22.78), 128.0 (115.0 - 145.0)	0.1838
Respiratory rate (breaths/min)	1266 (1.2%)	25.8 (3.79), 25.5 (24.0 - 28.0)	26.3 (4.39), 26.0 (24.0 - 28.0)	26.4 (3.93), 26.0 (24.0 - 28.0)	0.0861
Heart rate (bpm)	1281 (0.1%)	82.9 (17.10), 81.5 (70.5 - 93.5)	83.9 (17.73), 82.5 (71.0 - 94.5)	84.1 (17.63), 82.0 (71.0 - 95.5)	0.5363
ECG QRS interval (ms)	1273 (0.7%)	111.7 (34.88), 102.0 (80.0 - 130.0)	114.5 (34.56), 105.5 (82.0 - 139.0)	113.4 (35.29), 102.0 (86.0 - 134.0)	0.4743
Baseline dyspnea VAS (mm)	1266 (1.2%)	60.5 (22.69), 62.0 (50.0 - 75.0)	63.4 (23.59), 68.0 (50.0 - 80.0)	64.1 (23.76), 70.0 (50.0 - 81.0)	0.0495
Albumin (g/L)	992 (22.6%)	38.41 (5.137), 38.50 (35.00 - 42.00)	37.69 (5.138), 38.00 (34.00 - 41.00)	37.18 (5.081), 37.00 (34.00 - 40.90)	0.0067
ALT (U/L) [3]	1113 (13.2%)	18.87, 18.39 (12.44 - 27.33)	20.50, 19.06 (12.91 - 29.20)	19.44, 18.00 (11.71 - 30.91)	0.2564
BUN (mmol/L) [3]	1241 (3.2%)	7.80, 7.69 (5.84 - 10.00)	8.49, 8.03 (6.16 - 10.99)	8.99, 8.92 (6.48 - 12.23)	<.0001
Creatinine (umol/L)	1279 (0.2%)	110.64 (34.847), 104.31 (88.40 - 129.06)	117.75 (39.304), 112.13 (88.40 - 138.34)	121.85 (40.590), 114.92 (90.00 - 147.31)	<.0001
Hemoglobin (g/dL)	1281 (0.1%)	13.55 (1.784), 13.60 (12.38 - 14.80)	13.34 (1.885), 13.30 (11.90 - 14.60)	13.08 (1.935), 12.90 (11.50 - 14.50)	0.0009
Sodium (mmol/L)	1264 (1.4%)	138.96 (3.669), 139.00 (137.00 - 141.00)	138.75 (3.839), 139.00 (137.00 - 141.00)	138.52 (4.218), 139.00 (136.00 - 141.00)	0.2426
WBC (10**9/L)	1275 (0.5%)	9.48 (3.677), 8.80 (7.00 - 11.15)	9.84 (3.657), 9.20 (7.50 - 11.40)	9.80 (3.915), 8.90 (7.20 - 11.40)	0.2780
BNP (pg/mL) [3]	1196 (6.7%)	326.6, 378.0 (130.0 - 814.0)	389.4, 442.0 (169.0 - 990.0)	400.1, 455.0 (180.0 - 996.0)	0.0584
Troponin I (ng/mL) [3]	1195 (6.8%)	0.0110, 0.0200 (0.0005 - 0.0780)	0.0225, 0.0420 (0.0005 - 0.1620)	0.0276, 0.0380 (0.0005 - 0.1600)	<.0001

Notes:
ALT, alanine aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; VAS, visual analogue scale; WBC, white blood cells.
[1] Results shown are mean (standard deviation), median (25th - 75th percentile) for continuous variables, or prevalence (%) for dichotomous variables, unless otherwise noted. Numbers may vary due to missing values.
[2] P-values from ANOVA (F-test) for continuous variables, or from Chi-squared test for dichotomous variables, unless otherwise noted.
[3] Results shown are geometric mean, median (25th - 75th percentile). P-value from ANOVA (F-test) based on log2 transformed values.

Table 3: ***Univariable and multivariable associations of baseline characteristics with length of stay (excluding in-hospital deaths)***

		------- Univariable model [1] -------		------ Multivariable model [1] ------	
Parameter	***Mean difference for a change of***	***Mean difference (95% CI)***	***P-value***	***Mean difference (95% CI)***	***P-value***
Age (years)	10	0.05 (-0.23, 0.33)	0.7376		
Gender: Male	Yes vs. No	0.07 (-0.58, 0.73)	0.8291		
Race: White	Yes vs. No	1.44 (0.29, 2.59)	0.0141		
Time to randomization (hours)	1	0.02 (-0.02, 0.07)	0.3315		
BMI (kg/m2)	5	0.06 (-0.21, 0.34)	0.6468		
Atrial fibrillation on admission	Yes vs. No	0.39 (-0.34, 1.13)	0.2927		
History of CHF	Yes vs. No	-0.07 (-0.81, 0.67)	0.8522		
History of COPD	Yes vs. No	0.68 (-0.14, 1.50)	0.1025		
History of diabetes	Yes vs. No	1.11 (0.47, 1.75)	0.0007	0.96 (0.32, 1.60)	0.0033

		------- Univariable model [1] -------		------ Multivariable model [1] ------	
Parameter	***Mean difference for a change of***	***Mean difference (95% CI)***	***P-value***	***Mean difference (95% CI)***	***P-value***
History of hyperlipidemia	Yes vs. No	-0.42 (-1.13, 0.28)	0.2419		
History of hypertension	Yes vs. No	-0.11 (-0.91, 0.69)	0.7886		
History of smoking	Yes vs. No	-1.00 (-2.24, 0.25)	0.1159		
History of IHD, PVD, stroke	Yes vs. No	0.62 (-0.09, 1.33)	0.0868		
History of mitral/aortic valve disease	Yes vs. No	1.12 (0.24, 1.99)	0.0124	0.94 (0.08, 1.80)	0.0319
History of renal impairment	Yes vs. No	1.16 (0.49, 1.83)	0.0007		
History of liver disease	Yes vs. No	0.96 (-0.24, 2.16)	0.1156		
Previous PCI or CABG	Yes vs. No	-0.04 (-0.73, 0.64)	0.8980		
Systolic blood pressure <=145 mmHg [2]	10	-0.25 (-0.49, -0.01)	0.0067	-0.25 (-0.49, -0.01)	0.0104
Systolic blood pressure >145 mmHg [2]	10	0.54 (0.20, 0.88)		0.50 (0.16, 0.83)	
Respiratory rate (breaths/min)	5	0.36 (-0.04, 0.76)	0.0782		
Heart rate (bpm)	5	0.03 (-0.07, 0.12)	0.5978		
ECG QRS interval (ms)	10	0.04 (-0.06, 0.13)	0.4396		
Baseline dyspnea VAS (mm)	10	0.20 (0.06, 0.34)	0.0054	0.18 (0.05, 0.32)	0.0084
Albumin (g/L)	5	-0.53 (-0.89, -0.17)	0.0041		
ALT (U/L), log2 <=4.2 [2]	Doubling	-0.79 (-1.54, -0.03)	0.0875		
ALT (U/L), log2 >4.2 [2]	Doubling	0.44 (-0.12, 0.99)			
BUN (mmol/L), log2 <=3 [2]	Doubling	-0.13 (-1.12, 0.86)	0.0002		
BUN (mmol/L), log2 >3 [2]	Doubling	1.53 (0.74, 2.32)			
Creatinine (umol/L)	10	0.18 (0.09, 0.26)	<.0001	0.10 (0.02, 0.19)	0.0202

		------- Univariable model [1] -------		------ Multivariable model [1] ------	
Parameter	***Mean difference for a change of***	***Mean difference (95% CI)***	***P-value***	***Mean difference (95% CI)***	***P-value***
Hemoglobin <=14.5 g/dL [2]	1	-0.55 (-0.80, -0.30)	<.0001	-0.41 (-0.67, -0.16)	0.0063
Hemoglobin >14.5 g/dL [2]	1	0.22 (-0.27, 0.70)		0.24 (-0.23, 0.72)	
Sodium <=140 mmol/L [2]	3	-0.59 (-0.95, -0.24)	0.0046	-0.57 (-0.92, -0.22)	0.0048
Sodium >140 mmol/L [2]	3	0.45 (-0.19, 1.10)		0.61 (-0.03, 1.24)	
WBC (10**9/L)	5	0.25 (-0.18, 0.69)	0.2542		
BNP (ng/mL), log2	Doubling	0.15 (-0.02, 0.33)	0.0927		
Troponin I (ng/mL), log2	Doubling	0.14 (0.06, 0.22)	0.0005	0.12 (0.05, 0.20)	0.0019
Observed adjusted R-squared				0.1935	
Bias-corrected adjusted R-squared (95% CI) [3]				0.1830 (0.1433, 0.2228)	

Notes:
ALT, alanine aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CHF, chronic heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HR, hazard ratio; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; VAS, visual analogue scale; WBC, white blood cells; WHF, worsening heart failure.
[1] Results from linear regression model adjusted for region.
[2] Non-linear association modeled as a linear spline.
[3] Bootstrap estimate with 1000 resampling steps.

Table 4: ***Association of length of stay (excluding in-hospital deaths) with 10-day post-discharge HF readmission***

		Multivariable model [1]		*Multivariable model incl. length of stay [1]*		*Multivariable model incl. length of stay and in-hospital WHF by day 7 [1]*	
Parameter	***RR for a change of***	***OR (95% CI)***	***P-value***	***OR (95% CI)***	***P-value***	***OR (95% CI)***	***P-value***
Age (years)	1	1.03 (1.00, 1.06)	0.0306	1.03 (1.00, 1.06)	0.0369	1.03 (1.00, 1.06)	0.0401
Systolic Blood Pressure (mmHg)	1	0.99 (0.97, 1.00)	0.0613	0.99 (0.97, 1.00)	0.0578	0.99 (0.97, 1.00)	0.0672
Creatinine (umol/L)	1	1.01 (1.00, 1.02)	0.0049	1.01 (1.00, 1.02)	0.0095	1.01 (1.00, 1.02)	0.0145
Sodium (mmol/L)	1	0.93 (0.87, 1.00)	0.0356	0.93 (0.87, 1.00)	0.0379	0.93 (0.87, 1.00)	0.0456
History of Diabetes	Yes vs. No	1.78 (0.99, 3.20)	0.0533	1.76 (0.98, 3.16)	0.0584	1.75 (0.98, 3.16)	0.0608
Length of stay (days)	1			1.06 (0.99, 1.14)	0.0961	1.05 (0.97, 1.13)	0.2336
In-hospital WHF by day 7	Yes vs. No					1.43 (0.77, 2.67)	0.2544
Observed C-statistic		0.7053		0.7137		0.7202	
Interaction test of length of stay with region					0.5830		0.5971

Notes:
CI, confidence interval; OR, odds ratio; WHF, worsening heart failure.
[1] Results from logistic regression model stratified by region.

Table 5: ***Association of length of stay (excluding in-hospital deaths) with 90-day post-discharge mortality***

		Multivariable model [1]		*Multivariable model incl. length of stay [1]*		*Multivariable model incl. length of stay and in-hospital WHF by day 7 [1]*	
Parameter	***HR for a change of***	***HR (95% CI)***	***P-value***	***HR (95% CI)***	***P-value***	***HR (95% CI)***	***P-value***
Age (years) [2]	79.00 vs. 62.00	2.88 (1.62, 5.13)	0.0005	2.89 (1.63, 5.11)	0.0014	2.87 (1.63, 5.07)	0.0011
BMI <=30 kg/m2 [3]	5	0.69 (0.50, 0.97)	0.0971	0.69 (0.49, 0.96)	0.0920	0.69 (0.50, 0.97)	0.0950
BMI >30 kg/m2 [3]	5	1.16 (0.77, 1.75)		1.16 (0.77, 1.74)		1.17 (0.77, 1.75)	
History of IHD, PVD, stroke	Yes vs. No	1.68 (0.94, 2.98)	0.0785	1.60 (0.90, 2.86)	0.1112	1.59 (0.89, 2.84)	0.1180
History of renal impairment	Yes vs. No	1.73 (1.12, 2.66)	0.0128	1.66 (1.07, 2.55)	0.0223	1.61 (1.04, 2.48)	0.0324
Systolic blood pressure (mmHg)	10	0.89 (0.80, 0.99)	0.0346	0.89 (0.80, 0.99)	0.0381	0.89 (0.80, 1.00)	0.0427
Albumin (g/L) [4]	41.27 vs. 34.31	0.57 (0.39, 0.83)	0.0270	0.59 (0.40, 0.86)	0.0441	0.61 (0.42, 0.88)	0.0571
Troponin I (ng/mL), log2	Doubling	1.04 (0.99, 1.10)	0.1149	1.04 (0.98, 1.09)	0.1780	1.03 (0.98, 1.09)	0.2270
Length of stay (days)	1			1.04 (1.01, 1.07)	0.0166	1.03 (1.00, 1.06)	0.0629
In-hospital WHF by day 7	Yes vs. No					1.59 (1.02, 2.48)	0.0396
Observed C-index		0.7421		0.7527		0.7559	

		Multivariable model [1]		Multivariable model incl. length of stay [1]		Multivariable model incl. length of stay and in-hospital WHF by day 7 [1]	
Parameter	*HR for a change of*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Interaction test of length of stay with region					0.1246		0.1292

Notes:
BMI, body mass index; CI, confidence interval; HR, hazard ratio; IHD, ischaemic heart disease; PVD, peripheral vascular disease; WHF, worsening heart failure.
[1] Results from Cox proportional hazards model stratified by region.
[2] Non-linear association modeled as a cubic polynomial. HR for the 75th vs. the 25th percentile is presented.
[3] Non-linear association modeled as a linear spline.
[4] Non-linear association modeled as a quadratic polynomial. HR for the 75th vs. the 25th percentile is presented.
[5] Bootstrap estimate with 1000 resampling steps.

Table

Supplemental Material

Supplemental table 1: ***Univariable associations between length of stay (excluding in-hospital deaths) with 10-day post-discharge HF readmission***

		------- *Univariable model [1]* -------	
Parameter	***OR for a change of***	***OR (95% CI)***	***P-value***
Age (years)	1	1.03 (1.00, 1.06)	0.0298
Male Sex	Yes vs. No	0.79 (0.46, 1.38)	0.4107
White Race	Yes vs. No	1.17 (0.40, 3.39)	0.7728
Time from randomization (hours)	1	0.99 (0.95, 1.03)	0.7051
BMI (kg/m2)	1	0.97 (0.92, 1.02)	0.2384
Atrial Fibrillation on Admission	Yes vs. No	1.13 (0.60, 2.12)	0.7113
History of CHF	Yes vs. No	2.32 (1.02, 5.26)	0.0439
History of COPD	Yes vs. No	1.25 (0.64, 2.42)	0.5117
History of Diabetes	Yes vs. No	1.63 (0.93, 2.87)	0.0882
History of Hyperlipidemia	Yes vs. No	0.71 (0.39, 1.29)	0.2657
History of Hypertension	Yes vs. No	1.52 (0.67, 3.44)	0.3119
History of Smoking	Yes vs. No	0.45 (0.14, 1.51)	0.1959
History of mitral/aortic Valve Disease	Yes vs. No	1.27 (0.64, 2.53)	0.4910
History of IHD, PVD, Stroke	Yes vs. No	1.12 (0.59, 2.12)	0.7289
History of Renal Impairment	Yes vs. No	1.88 (1.08, 3.28)	0.0255
History of Liver Disease	Yes vs. No	0.94 (0.33, 2.71)	0.9087
Previous PCI or CABG	Yes vs. No	1.25 (0.71, 2.20)	0.4364
Dyspnea VAS (mm) [2]	75th vs 25th (77 vs. 50)	0.82 (0.46, 1.46)	0.1021
Systolic Blood Pressure (mmHg)	1	0.99 (0.98, 1.00)	0.0990
Respiratory Rate (breaths/min)	1	1.03 (0.96, 1.10)	0.3785
Heart Rate (bmp)	1	1.01 (0.99, 1.02)	0.5730
ECG QRS Interval (ms)	1	1.00 (0.99, 1.01)	0.6921
Albumin (g/L)	1	0.95 (0.89, 1.01)	0.0921

		------- Univariable model [1] -------	
Parameter	***OR for a change of***	***OR (95% CI)***	***P-value***
ALT (U/L)	1	0.99 (0.97, 1.01)	0.3172
BUN (mmol/L), log2	Doubling	1.90 (1.32, 2.74)	0.0005
Creatinine (umol/L)	1	1.01 (1.00, 1.02)	0.0010
Hemoglobin (g/dL)	1	0.83 (0.71, 0.97)	0.0206
Sodium (mmol/L)	1	0.92 (0.86, 0.98)	0.0127
Leucocytes (10^9/L)	1	0.99 (0.91, 1.07)	0.7364
BNP (ng/mL), log2	Doubling	1.10 (0.94, 1.28)	0.2260
Troponin I (ng/mL), log2	Doubling	1.01 (0.94, 1.08)	0.8799
Length of Stay (Days)	1	1.08 (1.01, 1.16)	0.0189
WHF by Day 7	Yes vs. No	2.13 (1.21, 3.75)	0.0091

Notes:
ALT, alanine aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CHF, chronic heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; IHD, ischaemic heart disease; OR, odds ratio; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; VAS, visual analogue scale; WBC, white blood cells; WHF, worsening heart failure.
[1] Results from logistic regression model stratified by region.
[2] Non-linear association modeled as a cubic polynomial. IR for the 75th vs. the 25th percentile is presented.

Supplemental table 2: ***Univariable associations between length of stay (excluding in-hospital deaths) and 90-day post-discharge mortality***

		------- Univariable model [1] -------	
Parameter	***HR for a change of***	***HR (95% CI)***	***P-value***
Age (years) [2]	79.00 vs. 62.00	3.81 (2.30, 6.33)	0.0186
Gender: Male	Yes vs. No	1.00 (0.66, 1.52)	0.9956
Race: White	Yes vs. No	1.46 (0.65, 3.28)	0.3606
Time to randomization (hours)	1	1.00 (0.97, 1.03)	0.8515
BMI <=30 kg/m2 [3]	5	0.58 (0.42, 0.79)	0.0003
BMI >30 kg/m2 [3]	5	0.90 (0.60, 1.34)	

		------- Univariable model [1] -------	
Parameter	***HR for a change of***	***HR (95% CI)***	***P-value***
Atrial fibrillation on admission	Yes vs. No	1.01 (0.63, 1.61)	0.9703
History of CHF	Yes vs. No	1.32 (0.80, 2.17)	0.2759
History of COPD	Yes vs. No	1.62 (1.02, 2.57)	0.0417
History of diabetes	Yes vs. No	1.11 (0.74, 1.68)	0.6162
History of hyperlipidemia	Yes vs. No	1.02 (0.65, 1.62)	0.9212
History of hypertension	Yes vs. No	0.96 (0.58, 1.59)	0.8821
History of smoking	Yes vs. No	0.55 (0.20, 1.54)	0.2573
History of IHD, PVD, stroke	Yes vs. No	2.37 (1.36, 4.16)	0.0026
History of mitral/aortic valve disease	Yes vs. No	1.59 (0.97, 2.60)	0.0636
History of renal impairment	Yes vs. No	2.22 (1.47, 3.37)	0.0002
History of liver disease	Yes vs. No	0.66 (0.26, 1.66)	0.3773
Previous PCI or CABG	Yes vs. No	1.28 (0.83, 1.96)	0.2609
Systolic blood pressure (mmHg)	10	0.88 (0.79, 0.98)	0.0164
Respiratory rate (breaths/min)	5	1.04 (0.82, 1.33)	0.7373
Heart rate (bpm)	5	1.01 (0.95, 1.07)	0.7009
ECG QRS interval (ms)	10	1.03 (0.97, 1.09)	0.3730
Baseline dyspnea VAS (mm)	10	1.03 (0.94, 1.12)	0.5584
Albumin (g/L) [4]	41.27 vs. 34.31	0.53 (0.36, 0.80)	0.0093
ALT (U/L), log2	Doubling	0.93 (0.76, 1.16)	0.5325
BUN (mmol/L), log2	Doubling	1.57 (1.20, 2.06)	0.0011
Creatinine (umol/L)	10	1.09 (1.04, 1.14)	0.0005
Hemoglobin (g/dL)	1	0.84 (0.75, 0.94)	0.0033
Sodium (mmol/L)	3	0.92 (0.79, 1.07)	0.2596
WBC (10**9/L)	5	1.21 (0.94, 1.55)	0.1417
BNP (ng/mL), log2	Doubling	1.17 (1.03, 1.32)	0.0128
Troponin I (ng/mL), log2	Doubling	1.08 (1.02, 1.14)	0.0053
Length of stay (days)	1	1.05 (1.02, 1.07)	0.0004
WHF by day 7	Yes vs. No	2.31 (1.52, 3.50)	<.0001

		------- Univariable model [1] -------	
Parameter	***HR for a change of***	***HR (95% CI)***	***P-value***
In-hospital WHF by day 7	Yes vs. No	2.27 (1.49, 3.45)	0.0001

Notes:
ALT, alanine aminotransferase; BMI, body mass index; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; CHF, chronic heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HR, hazard ratio; IHD, ischaemic heart disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; VAS, visual analogue scale; WBC, white blood cells; WHF, worsening heart failure.
[1] Results from Cox proportional hazards model stratified by region.
[2] Non-linear association modeled as a cubic polynomial. HR for the 75th vs. the 25th percentile is presented.
[3] Non-linear association modeled as a linear spline.
[4] Non-linear association modeled as a quadratic polynomial. HR for the 75th vs. the 25th percentile is presented.