Title: Abnormal liver function tests in acute heart failure: relationship with clinical characteristics and outcome in the PROTECT study

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Abstract

Aims: Episode of acute heart failure (AHF) unfavorably affects multiple organs which may have an adverse impact on the outcomes. We investigated the prevalence and clinical consequences of abnormal liver function tests (LFTs) in AHF patients enrolled in the PROTECT study.

Methods and Results. LFTs comprised serial assessment of AST (Aspartate aminotransferase), ALT (Alanine Aminotransferase) and albumin at baseline and during follow up (daily until discharge, on day 7 and 14). Prevalence of abnormal LFTs (above upper limit of normal for AST and ALT or below lower limit of normal for albumin) was: at baseline AST- 20%, ALT- 12%, albumin- 40% and at Day-14: AST- 15%, ALT- 9%, albumin- 26%, respectively. Abnormal LFTs at baseline were associated with higher risk of in-hospital death with odds ratios (95% confidence interval [CI]) for AST 3.5 (1.7-7.3), for ALT 3.9 (1.8-8.4), and for albumin 2.8 (1.3-5.9) (all $p<0.01$). Abnormal baseline and discharge LFTs unfavorably impacted 180-day mortality with hazard ratios (95%CI) for baseline AST, ALT, albumin: 1.3 (1.0-1.7), 1.1 (1.0-1.2), 1.4 (1.1-1.8) and for discharge AST, ALT, albumin: 1.5 (1.1-2.0), 1.5 (1.0-2.2), 1.6 (1.2-2.1), respectively (all $p<0.05$). Analysis of LFTs trajectories (calculated as changes in LFTs over time) revealed that increasing AST and ALT on day-3 as well as decreasing albumin on day-4 were independent prognosticators of 180-day outcome (all $p<0.05$).

Conclusions: Abnormal LFTs are frequent in AHF at baseline and during hospital stay, and predict worse outcomes. Whether this association is causal, and which are the underlying mechanisms involved, require further study.

Key words: acute heart failure, liver dysfunction, prognosis, liver function tests.

Introduction

Despite advances in modern cardiology, acute heart failure (AHF) remains a challenging problem in everyday clinical practice with growing incidence and unacceptably high morbidity and mortality (1). In the complex pathophysiology of AHF several mechanisms are involved, among which dysfunction or damage of multiple end-organs (ie. heart, kidney, liver) may play an important role with further ominous consequences for long-term outcomes (2). It has been well established that myocardial injury as evidenced by troponin release and deterioration in renal function occurring during an episode of AHF are both independent predictors of poor outcome (3-5). Abnormalities in liver function have been recognized to accompany the natural course of chronic heart failure (6,7). Surprisingly however, the data on the prevalence and clinical significance of abnormalities in liver function tests (LFTs) in patients with AHF remain rather scarce (2,8-10). Only recently, Ambrosy et al (9) have studied a population of AHF patients enrolled in the placebo arm of the EVEREST trial and demonstrated that abnormal LFTs are relatively common and carry important prognostic information. It has been subsequently confirmed by van Deursen et al (10) in AHF patients enrolled in the Pre-RELAX-AHF study. However, due to limited sample size and rather small number of events in this study, the prognostic impact of impaired LFTs needs further confirmation.

This study reports post-hoc analysis of patients enrolled in A **P**lacebo-controlled **R**andomized study of the selective A1 adenosine receptor antagonist KW-3902 for patients hospitalized with acute HF and volume **O**verload to assess **T**reatment **E**ffect on **C**ongestion and renal func**T**ion (PROTECT) in order to evaluate the prevalence of abnormal LFTs, a pattern of changes in LFTs over time (from baseline to day 14) and their prognostic importance.

Methods

Inclusion/exclusion criteria and study design

PROTECT was a global, prospective, multicentre, randomized, double-blind, placebo-controlled trial that recruited 2033 patients hospitalized for AHF. A detailed description of the study design as well as results of the main study has been published elsewhere (11,12). For entry, patients were required to have dyspnea at rest or with minimal activity, at least one symptom of fluid overload (JVP>8cm or pulmonary rales ≥1/3 up the lung fields, not clearing with cough or ≥2+ peripheral edema, or pre-sacral edema) and elevated natriuretic peptide levels [brain natriuretic peptide (BNP) ≥500 pg/mL or N-terminal-pro-BNP (NT-proBNP) ≥2000 pg/mL]. All patients required intravenous (i.v.) loop diuretic therapy and had impaired renal function (as evidenced by estimated creatinine clearance of 20–80 mL/min by the Cockcroft–Gault equation corrected for weight in oedematous or obese subjects ≥100 kg). Relevant for the analysis exclusion criteria were known hepatic impairment (total bilirubin >3 mg/dL, albumin <2.8 mg/dL, or increased ammonia levels if performed), history of drug or alcohol abuse, clinical evidence of acute coronary syndrome in the 2 weeks prior to screening, ongoing or planned i.v. therapy for AHF with positive inotropic agents, vasopressors, vasodilators, or mechanical support with the exception of IV nitrates. Other exclusion criteria are outlined in the design paper (11).

Patients were randomized in a 2:1 ratio to receive either rolofylline 30 mg or placebo administered as a daily 4-hour infusion for 3 days in a double-blind manner.

Clinical assessments (heart failure signs and symptoms) were performed and blood for laboratory assessments was drawn daily just prior to the initial study drug/placebo administration, through discharge and on days: 7 and 14. All laboratory tests were performed in a core laboratory. The study protocol included the following LFTs to be collected: AST [Aspartate aminotransferase], ALT [Alanine Aminotransferase] and albumin.

PROTECT fulfilled the requirements stated in the Declaration of Helsinki and it was independently approved by the Ethics Committees at each participating centre; written informed consent was obtained from each participant.

Endpoints of the present analysis

The primary and secondary endpoints of PROTECT are presented in the design paper (11). The outcomes for this analysis were worsening of heart failure, worsening of renal failure within 7 days of index hospital admission, in-hospital death and 180-day mortality. Worsening heart failure was reported based on worsening signs and symptoms of heart failure with resulting intensification of intravenous therapy for heart failure or mechanical circulatory or ventilator support. Worsening of renal failure was defined as a serum creatinine increase of ≥0.3 mg/dL (26.5 mmol/L) from randomization to Day 7, confirmed at Day 14, or the initiation of renal replacement therapy through Day 7.

For this analysis we defined the following cutoffs for abnormal LFTs: above upper limit of normal for AST or ALT (>37 U/L, and >47 U/L, respectively) or below lower limit of normal for albumin (<3.7 g/dL).

PROTECT showed a favorable effect of rolofylline neither with respect to the primary and secondary clinical composite end points, nor 60-day and 180-day mortality (12). As we were not aware of any data confirming that rolofylline may affect LFTs, the analysis was performed in the entire trial population.

Statistical analyses

Continuous variables are reported as mean ± standard deviation for normally distributed variables and median (interquartile range, IQR) for non-normally distributed variables; categorical variables are reported as percentages. Differences between patients with abnormal and normal LFTs at baseline were tested for by using a two-sample t-test or Kruskal-Wallis rank test for continuous data and a Chi-square test for categorical data.

The association between baseline LFTs and worsening of HF, worsening of renal failure within 7 days of the index admission, and in-hospital death was assessed using logistic regression analysis; the association between baseline and discharge LFTs and 180 day mortality was assessed using Cox

proportional hazards regression. The analyses were first performed by dichotomizing the LFTs into normal and abnormal and then repeated by including the LFTs as continuous variables. For the continuous analysis, possible non-linearity in the relationship between the LFTs and the outcomes of interest was explored using fractional polynomials, but this did not reveal any significant non-linear relationships. The LFTs were therefore included as linear terms in the final models. To explore whether the associations in the univariable models were independent of other covariates, the following confounding factors were adjusted for in the multivariable analyses: gender, age, NYHA class, creatinine, sodium, systolic blood pressure, and hemoglobin. The analyses were performed on all patients from the PROTECT study for which complete covariate and outcome data were available. This resulted in a study population of 1,652 patients.

Liver function trajectories in PROTECT.

Changes in AST, ALT and albumin over time were modeled using linear mixed effects models, which assume the change in values over time can be described by a linear regression model including population-specific effects (fixed effects) and subject-specific effects (random effects). After visual inspection of the change in mean levels over time, several candidate models were fitted based on maximum likelihood maximization, assuming any missing data was missing at random. The best fitting model was subsequently selected by examining Akaike's information criterion (AIC) and Bayesian information criterion (BIC) values for the models, which provide a measure for the relative quality of a model by balancing goodness-of-fit and model complexity. Due to the non-normality of both AST and ALT distributions, a double log transformation was performed to allow more accurate modeling. For all three LFTs, the changes in mean levels over time (fixed-effects structure) were best described by a quadratic function. The random-effects structure of the models provided subject-specific intercepts and slopes for both linear and quadratic time effects. Both fixed and random effects were used to estimate subject-specific values and slopes at various time points. The effect of individual, subject-specific slopes at various time points – representing the rate of

change at those times – and change in LFTs on survival were examined using cox proportional hazards regression. All regression models were corrected for baseline values of the LFT in question. Multivariable models were corrected for covariates (as listed above). A two-sided p-value ≤ 0.05 was considered to be statistically significant. All analyses were conducted using R-2.14.2.
We applied this novel statistical modeling to describe trajectories of renal function in the PROTECT study and the method with detailed clinical interpretation is presented elsewhere (13).

Results

Prevalence of abnormal LFTs at baseline and during follow-up

Among 2033 patient enrolled in PROTECT, baseline AST, ALT and albumin were available in 92%, 90% and 96% of patients, respectively. Baseline median (IQR) were for AST: 25 (14) U/L, for ALT: 21 (13) U/L and mean±SD albumin was: 3.84± 0.43 g/dL. Abnormal baseline AST, ALT and albumin were present in 20%, 12% and 40% of patients, respectively. We observed decrease of prevalence of abnormal LFT reaching 15%, 9% and 26%, respectively at 14th day (Figure 1)**.**

Patients characteristics

Baseline characteristics of the PROTECT population has been presented in detail elsewhere (12). Table 1 shows a comparison of baseline characteristics between patients with abnormal vs normal LFTs. Patients with elevated AST and ALT were younger, had lower incidence of comorbidities (hypertension, coronary artery disease and diabetes), lower systolic blood pressure and higher heart rate, higher hemoglobin, BUN and lower sodium on admission, they received more often inotropes or vasopressors during hospital stay when compared to patients with normal AST or ALT. Patients with low albumin levels were slightly older, had more frequent incidence of diabetes, significantly elevated jugular venous pressure and magnitude of peripheral edema on physical examination, higher NT-proBNP, creatinine, and lower hemoglobin levels, received higher

doses of diuretics and more frequently inotropes or vasopressors during hospital stay when compared to those with normal albumin (see Table 1).

Clinical profile of patients with opposite LFTs trajectories

On day 3, the majority of patients (1320 (67%)) had decreasing trajectory of AST. This group did not differ in demographics, baseline clinical examination as well as in most biochemical parameters (creatinine, BUN, haemoglobin, natriuretic peptides values) when compared to patients with increasing trajectory of AST (see Table 2). However, we found that this group had higher baseline transaminases and albumin on admission, although the median/mean values remained within normal ranges (all $p<0.001$). Interestingly those two groups did not differ in treatment during hospitalization: diuretic doses, inotropes and vasodilatators use (see Table 2).

Sixty-one percent of patients (1197) had increasing trajectory of albumin on day 4. This group was significantly younger, had better renal function, lower haemoglobin and albumin on admission (all $p<0.05$) (see Table 2). Those patients had higher weight change during first 4 days of hospitalization (-3±3 vs -2.5±2.8, $p<0.001$). Interestingly patients with increasing trajectories of albumin received lower total dose of furosemidu within 7 days of hospitalization 260 [120-540] vs 280 [160-560] $p<0.02$, whereas there was no difference in total dose of diuretic they received during first 3 days of treatment 240 [140-410] vs 240 [156-388.8] $p=0.2$ (see Table 2). Moreover, changes in albumin level between admission and discharge/day 7 significantly correlated with changes in hemoglobin levels (Rho= 0.542, $p<0.001$) and inversely in changes in body weight during first 4 days of hospital stay (Rho= -0.102, $p<0.001$).

Prognostic significance of baseline LFTs

There were 32 (1.9%) in-hospital deaths and 291 (17.6%) at 180 day follow-up, respectively. Abnormal baseline LFTs impacted neither the risk of worsening heart failure (odds ratios (OR), 95% Confidence Interval (CI) – for AST: 1.3 (0.92 - 1.89), for ALT: 1.3 (0.85 - 2.04), for albumin:

1.19 (0.88 - 1.61), respectively, all p>0.05) nor worsening renal function during hospitalization (OR (95% CI) – for AST: 1.0 (0.71 - 1.40), for ALT: 0.70 (0.44 - 1.12), for albumin: 1.05 (0.80 - 1.38), respectively, all p>0.05).

We found a relationship between risk of in-hospital death and baseline levels of AST, ALT, and albumin, which remained significant after adjustment for the other prognosticators (details – see statistical analyses section) (Table 3a). Moreover, the multivariate model revealed that patients with abnormal LFTs on admission had significantly higher risk of in-hospital death when compared to patients with normal LFTs – ORs (95% CI) for abnormal AST, ALT, albumin were: 3.53 (1.70-7.32), 3.89 (1.80-8.41), and 2.78 (1.32-5.87), respectively, (all p<0.01) (Table 3a).

Baseline values of AST, ALT and albumin were also related to the risk of 180-day all-cause mortality (Table 3b). After adjustment for other prognostic variables, we found that patients with abnormal baseline AST and albumin (but not ALT) had increased risk of 180-day mortality with hazard ratio (HR, 95%CI) of 1.33 (1.01-1.74) for AST and 1.44 (1.14-1.82) for albumin (both p<0.05) (Table 3b).

Prognostic significance of discharge LFTs

Values of AST, ALT and albumin on discharge/day 7 (whichever occurred first) were independently related to the risk of 180-day mortality (Table 4). Analogously, patients with abnormal LFTs at discharge had worse 180 day outcome in comparison to group with normal LFTs with HR (95%CI) for AST: 1.46 (1.07-1.98), for ALT: 1.50 (1.04-2.17), and for albumin: 1.61 (1.24-2.11), respectively, all p<0.05 (Table 4).

Associations of LFTs trajectories and 180-day survival

To analyze the clinical consequences of rates of LFTs change during hospitalization we have examined the trajectories of LFTs change on day 3 (for transaminases) and on day 4 (for albumin) in relation to outcome.

AST/ALT

AST and ALT slopes on day 3 were associated with 180-day mortality in univariable models (table 4), which remained significant after correction for covariates known to be associated with mortality HR (95% CI): 1.012 (1.006-1.019) and 1.008 (1.003-1.013), respectively (both $p<0.001$) (table 5). In other words, the steeper trajectory of AST/ALT increase at day 3 the higher risk of 180 day mortality.

Albumin

Albumin slope on the 4th day of hospitalization showed a association with 180-mortality HR(95% CI): 0.342 (0.243-0.482) ($p<0.001$) (table 4), which persisted significant after multivariable correction HR(95% CI): 0.364 (0.245-0.541) $p<0.001$ (table 5). Patients with decreasing albumin trajectories on day 4 had significantly worse 180 day prognosis and the risk is increasing with decreasing albumin slope.

Figures 2 a-c show Kaplan-Meier curves for 180-day mortality stratified by trajectories categorized into rise versus fall on day 3 (for AST/ALT) and day 4 (for albumin).

Discussion

There are three major findings of the present analysis. Firstly, we found that abnormal LFTs are common in AHF, such abnormalities are present already on admission and decrease during 14 day observation. Secondly, an assessment of simple LFTs – AST, ALT and albumin performed at baseline and on discharge provides an important prognostic information. Thirdly, change of LFTs values during hospitalization is associated with clinical outcome.

We found relatively high prevalence of abnormal LFTs at baseline, although patients with known significant hepatic impairment (defined as total bilirubin >3 mg/dL, albumin <2.8 mg/dL, or increased ammonia levels if performed) were excluded from the study. Interestingly, we observed a much higher percentage of patients with hypoalbuminemia as compared to elevated

aminotransferases which may be explained by the patients' profile. As the PROTECT study recruited AHF patients with dyspnea and signs of fluid overload, low albumin concentration may not only reflect hepatic synthesis insufficiency, but also constitute a biomarker of overhydratation, whereas elevated AST and ALT are rather markers of hepatocellular injury.

Further to this end, we observed decreased prevalence of abnormally elevated AST and ALT during 14 days of observation (although they were still present in about 10-15% of patients). It may well suggest that hepatocellular dysfunction/damage may constitute an integral element of several pathophysiological processes accompanying AHF, and standard therapies currently applied in AHF seem not to be able to reverse these abnormalities completely. We have previously reported lack of correlation between invasively monitored hemodynamic indices and AST/ALT in AHF patients (14), thus hemodynamic stabilization alone may not adequately improve LFTs. Although Ambrosy et al (9) found pattern of unchanged prevalence of abnormal LFTs (apart from bilirubin) within first 7 days of hospitalization in AHF patients, the authors observed decrease of prevalence of abnormal LFTs (except AP) during 8 week follow-up.

To the best of our knowledge, this is the first study showing that baseline as well as discharge/day 7 LFTs (AST/ALT and albumin) are independent predictors of short- and long-term mortality in AHF population. Earlier, post-hoc analysis of the EVEREST study revealed that low baseline albumin and elevated bilirubin, but not elevated AST/ALT were associated with clinical outcome (9). Van Deursen (10) reported changes in albumin from baseline to day 5 as predictors of mortality, but due to small number of events no multivariable adjustment was performed in this study. On the other hand retrospective analysis of SURVIVE study (the study included AHF patients that would be excluded from PROTECT as they required inotrope support) revealed that abnormal baseline transaminases were related to poor outcome (15). Although, patients with significant liver dysfunction were excluded from the PROTECT study we found that even mild to

moderate abnormalities in LFTs indentify patients at higher risk of death: in-hospital as well as during first 180 days of the follow-up.

Pathophysiological mechanisms explaining the relationship between abnormal LFTs and poor outcome remain unclear. Surprisingly, abnormal baseline LFTs were not associated with higher risk of either heart failure or renal function worsening during hospitalization, which are traditionally linked with higher risk of short- and longer-term mortality (5,16). We may speculate that elevated AST/ALT and low albumin at baseline are laboratory surrogates reflecting some clinical characteristics which may be potentially associated with poor outcome (for AST/ALT - lower systolic blood pressure, higher heart rate, lower sodium, more frequent use of inotropes or vasopressors, for albumin – low hemoglobin, low sodium, more severe fluid overload, higher dose of diuretics) (17). Since low ALT may be related to worse outcome in some populations (especially in elderly), there were premises to believe that risk related to transaminases can have a U-shape pattern (18). Based on our data there is no evidence to support such a hypothesis, as we have confirmed linear increase in risk of death with increasing transaminases and decreasing albumin. Moreover, we found that categorization into normal and abnormal LFTs identifies groups of patients with much worse prognosis, i.e. patients with abnormal baseline LFTs had approximately three times higher risk of in-hospital death in comparison to patients with normal LFTs. We decided to show these analyses as they provide simple and useful clinical information that can be helpful in everyday practice.

As we believe that day to day changes in absolute values of LFTs during hospitalization are complex to calculate and difficult to interpret in a meaningful biological context, we focused our interest on analysis of LFTs' trajectories during first days of hospitalization. The slopes of LFTs' change were analyzed on the 3rd day (for AST/ALT) and the 4th day for albumin as that may reflect the effectiveness of the initial treatment. The trajectories as a result of complex calculations not only describe the direction of LFTs' change (increase vs decrease) but also the rate of change (the

higher trajectory value (the steeper the trajectory) the greater and the faster change of LFT). We have previously reported interesting clinical findings using this approach directed towards changes renal function in PROTECT study (13).

Our results support the hypothesis that increasing AST/ALT as well as decreasing albumin early during hospitalization are independent biochemical signs of poor prognosis. Moreover the analysis revealed that the greater change of LFTs (increase of AST/ALT, decrease of albumin) the worse the prognosis is. Presented Kaplan-Meier curves showed that simple categorization of LFTs trajectories as increase vs decrease at examined time points can identify patients with significantly worse outcome (for AST and albumin). However this was not true for ALT, for which different cutoff should be found. As we remember that serial assessments of LFTs during hospitalization is not a routine or recommended procedure in AHF patients, based on our results, it seems reasonable to monitor LFTs values (at least in some patients) as it may bring additional clinical information. To the best of our knowledge, this is the first study showing that dynamic change of LFTs and rate of its change during hospitalization has significant prognostic importance.

Interestingly, comparison of patients with opposite trajectories of albumin showed that the group with increasing albumin received lower total dose of furosemide during 7 days of hospitalization, whereas the same dose within first 3 days of treatment. That observation may suggest that those patients had better early response to the same doses of furosemide that lead to lower furosemide demand after the 3rd day. That speculation is also supported by observation that those patients had significantly higher weight loss during first 4 days of hospitalization.

As already mentioned, hypoalbuminemia may not only reflect liver function itself, but also effectiveness of dehydration. Indeed, we found a correlation between makers of body fluid status (changes in body weight and hemoglobin concentration) and changes in albumin levels during hospitalization. Moreover patients with increasing trajectory of albumin had lower baseline albumin as well as haemoglobin which can suggest that those phenomena were at least in part a results of

overhydratation. It has been already shown that hemodilution may be responsible for low hematorcrit (dilutional anemia) in patients with advanced heart failure (19). Similarly, some patients with low albumin at baseline may in fact have dilutional (relative) hypoalbuminemia due to fluid overload. They do not necessarily have at the same time liver dysfunction (defined as abnormal liver synthesis capacity) and the absolute albumin amount may well be within normal range. Baseline characteristics of patients with hypoalbuminemia (higher NT-proBNP, lower hemoglobin and sodium concentration, clinical evidence of more extensive fluid overload) as well as fact that patients with increasing trajectory of albumin had lower albumin at baseline also indicate that dilution may play an important role in developing hypoalbuminemia. Hypoalbuminemia has already been shown to be a strong prognosticator of adverse long-term outcome in patients with chronic heart failure (20,21), but prognostic significance of low albumin in the AHF settings has not yet been adequately explored.

Thus, patients with low albumin on discharge/day 7 might have either ineffective decongestion or real hypoalbuminemia due to liver dysfunction, which was independently related to worse outcome (at 180 days). In accordance with previous data, we found that patients with decreasing albumin during hospitalization (reflecting ineffective decongestion or lack of liver function improvement) had significantly higher risk of death during follow-up when compared to patients with an increase in albumin.

Study limitations.

As this is a post-hoc analysis of the selected population included into clinical trial, it may not completely reflect the scale of the problem of liver dysfunction in the whole spectrum of AHF patients. Additionally, we have only assessed 3 LFTs – albumin (reflecting liver synthesis capacity) and AST/ALT (reflection hepatocellular injury). For more comprehensive characteristics additional LFTs reflecting cholestatic pattern would be useful.

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Figure legends

Figure 1.

Percentage of patients with abnormal LFTs overtime (until day 14).

Figure 2.

Kaplan Meier curves for 180-day mortality by LFTs slopes rise vs fall (on Day 3 for AST/ALT and day 4 for albumin). a) AST, b) ALT, c) albumin.

Table 1.

Comparison of characteristics of patients with abnormal vs normal LFTs at baseline.

Variable	Elevated AST n = 370	Normal AST n = 1508	p-value	Elevated ALT n = 221	Normal ALT n = 1609	p-value	Low albumin n = 788	Normal albumin n = 1167	p-value
Demographics									
Age (years)	69+/-12.9	70.5+/-11.2	0.05	67.7+/-13.1	70.4+/-11.4	<0.01	70.8+/-11.3	69.7+/-11.8	0.04
Sex (male, %)	63.8	67.4	0.18	67.9	66.7	0.73	65.2	67.7	0.26
White race (%)	94.3	95.8	0.21	94.5	95.6	0.47	92.7	97.4	<0.01
Measurments									
Body-mass index	28.3 +/-6.2	28.9+/-6.1	0.09	27.9+/-6.2	29+/-6.2	0.02	28.8+/-6.5	28.9+/-5.9	0.74
LVEF (%)	31.2+/-14.4	32.3+/-12.7	0.35	27.1+/-12.2	32.8+/-13	<0.01	32.2+/-13.3	32.2+/-12.8	0.95
NTproBNP (pg/ml)	3000 [606]	3000 [935]	0.13	3000 [1083]	3000 [922]	0.1	3000 [1191]	3000 [712]	<0.01
BUN (mg/dl)	31 [19]	29 [19]	<0.01	32 [22]	29 [19]	0.06	32 [21]	28 [17]	<0.01
HGB (g/dL)	13.2+/-2	12.5+/-2	<0.01	13.1+/-2.1	12.6+/-2	<0.01	12.2+/-2	13+/-1.9	<0.01
Na (mmol/l)	138.5+/-4.6	139.5+/-4	<0.01	138.6+/-4.4	139.4+/-4.1	0.01	138.8+/-4.4	139.7+/-3.9	<0.01

Creatinine (mg/dl)	1.5+/-0.5	1.5+/-0.6	0.08	1.5+/-0.6	1.5+/-0.6	0.95	1.6+/-0.6	1.5+/-0.5	<0.01
Medical history (%)									
Hypertension	74.3	80.4	<0.01	71	80.4	<0.01	81.5	77.9	0.06
Ischemic heart disease	64.1	70.6	0.02	58.8	70.8	<0.01	69.1	69.8	0.73
Myocardial infarction	42.2	50.6	<0.01	43.4	49.6	0.09	48.3	50.2	0.43
Atrial fibrillation	56.6	53.9	0.35	52.7	54.7	0.58	54.1	54.7	0.77
Diabetes	34.6	48.6	<0.01	36.2	47.4	<0.01	49	43.2	0.01
Clinical examination at baseline									
Systolic Blood Pressure (mmHg)	121.5+/-17.4	124.9+/-17.7	<0.01	120.1+/-16.8	124.8+/-17.8	<0.01	124+/-18	124.7+/-17.4	0.39
Diastolic Blood Pressure (mmHg)	74.4+/-12.2	73.6+/-11.9	0.27	74.1+/-11.9	73.7+/-12	0.66	73.5+/-12.3	74.1+/-11.5	0.32
HR (beat/min.)	83.4+/-16.6	79.5+/-15.1	<0.01	83.8+/-17.2	79.8+/-15.2	<0.01	81.3+/-15.9	79.5+/-15.1	0.02
JVP (%)			0.69			0.64			0.05
< 6 cm	11.4	12.3		11.6	12.1		11	12.4	
6 - 10 cm	46.3	48		45.3	48.3		44.5	49	

> 10 cm	42.3	39.7		43.2	39.6		44.5	38.6	
Edema (%)			0.55			0.54			<0.01
0	13	14.5		12.2	14.2		10	17	
1+	17.3	18.6		18.6	18.2		14.6	20.6	
2+	43.5	39.5		44.3	39.8		39.2	41	
3+	26.2	27.4		24.9	27.7		36.2	21.4	
Pulmonary congestion (%)			0.8			0.53			0.23
No rales	9.2	9.6		11.8	9.2		10.4	8.9	
Rales < 1/3	28.9	29.6		29.9	29.5		30.5	28.2	
Rales 1/3 - 2/3	50.5	51.2		47.5	51.5		48.7	53.4	
Rales > 2/3	11.4	9.6		10.9	9.8		10.3	9.5	
Treatment before hospital admission (%)									
ACE-inhibitor /ARB	75.7	75.2	0.84	77.4	74.9	0.43	72.1	78	<0.01
Beta blockers	75.4	77.4	0.42	79.6	76.7	0.33	74.1	78.2	0.04
Nitrates	24.6	25.8	0.63	19	26.5	0.02	27.4	24.7	0.18
Aldosterone inhibitor	44.1	44.1	0.98	43.9	44.2	0.93	40.7	46.7	<0.01

Prior digoxin	26.2	28.7	0.34	27.1	28.4	0.71	26.6	29.7	0.15
Treatment through day 7									
Total loop diuretics (mg)	287 [495]	280 [432]	0.06	280 [500]	280 [420]	0.8	320 [559]	240 [360]	<0.01
Inotropes or vasopressors	10	6.6	0.02	9.5	6.9	0.16	9.4	5.7	<0.01
Vasodilators	9.5	8.8	0.7	9.5	8.5	0.6	9.8	8.1	0.19
Medications at discharge (or day 7, if earlier) (%)									
ACE-inhibitor /ARB	81.1	82.1	0.68	83.4	81.6	0.52	79.8	84.2	0.01
Beta blockers	84.5	85.2	0.75	87.2	85.1	0.42	81.6	86.7	<0.01
Nitrates	19.2	20.6	0.53	14.2	21.3	0.02	23.2	18.4	<0.01
Aldosterone inhibitor	61.4	59.3	0.46	63	59.2	0.28	58.9	61.5	0.24
Digoxin	32.4	33	0.82	35.1	32.5	0.46	33.1	33.2	0.97

Table 2

Comparison of characteristics of patients by opposite AST and albumin trajectories.

Variable	Decreasing slope	Increasing slope	P-value	Decreasing slope	Increasing slope	P-value
	AST			ALBUMIN		
Number of patients	1320	642		766	1197	
Demographics						
Age (years)	70.4±11.7	69.4±11.4	0.064	70.9±11.4	69.5±11.7	0.005
Sex (male, %)	66.4 (876)	68.5 (440)	0.363	64.9 (497)	68.5 (820)	0.106
Measurments						
LVEF (%)	32.3±13.3	32.2±12.4	0.939	33.2±13.2	31.7±12.9	0.091
Creatinine (mg/dL)	1.4 [1.1-1.8]	1.4 [1.1-1.8]	0.610	1.4 [1.2-1.9]	1.4 [1.1-1.7]	<0.001
Creatinine Clearance (ml/min)	48.4 [36.7-63.4]	49.5 [36.6-63.4]	0.801	45.9 [35.8-59.9]	51.5 [37.8-65.2]	<0.001
Blood Urea Nitrogen (mg/dL)	29 [22-41]	29 [21-41]	0.363	31 [23-44]	28 [21-39]	<0.001
Sodium (mmol/L)	140 [137-142]	140 [137-142]	0.639	140 [137-142]	140 [137-142]	0.601
Hemoglobin (g/dL)	12.7±2	12.7±2	0.930	12.9±2.1	12.5±1.9	<0.001
Total Cholesterol (mmol/L)	149.2±44.8	143.7±42.9	0.010	152.2±44.8	144.2±43.6	<0.001

Triglycerides (mmol/L)	103.6±56.7	98.4±52.2	0.048	104.8±58.4	100±53.2	0.065
NT-proBNP (pg/mL)	3000 [3000-3864.8]	3000 [3000-3853]	0.642	3000 [3000-4033.8]	3000 [3000-3781.8]	0.966
BNP (mg/dL)	1301.5 [812.5-2265]	1198.5 [834-2094.8]	0.353	1158.1 [761.2-2090]	1304 [841.2-2260.2]	0.127
AST (U/L)	26 [21-36]	22 [17-28]	<0.001	25 [20-33]	24 [19-33]	0.104
ALT (U/L)	22 [16-36]	19 [13-26]	<0.001	21 [15-32]	21 [14-32]	0.311
Albumin (mg/dL)	3.9±0.4	3.8±0.4	<0.001	4±0.4	3.8±0.4	<0.001
Clinical examination at baseline						
Systolic Blood Pressure (mmHg)	124.3±17.4	124.8±18.1	0.625	125.2±17.3	124±17.8	0.121
Diastolic Blood Pressure (mmHg)	73.7±11.5	74.2±12.4	0.391	74.4±11.2	73.4±12.2	0.053
Heart Rate (beats/min)	79.6±15.1	80.8±16	0.135	80.5±15.7	79.7±15.2	0.275
Rolofylline administration (%)	66.4 (877)	67.9 (436)	0.549	65.1 (499)	68.1 (815)	0.193
Atrial fibrillation on presentaiton	39.7 (212)	45.6 (115)	0.134	43.1 (127)	40.7 (200)	0.573
Orthopnea (%)	96.9 (1261)	94.3 (597)	0.011	96.3 (731)	95.8 (1128)	0.688
Rales (%)	61.2 (806)	59.5 (381)	0.510	63.4 (486)	58.9 (702)	0.049

Edema (%)	66.7 (880)	69.3 (444)	0.280	66.8 (512)	68 (813)	0.616
NYHA Class			0.105			0.128
I-II	17.7 (233)	15.4 (99)		17.8 (136)	16.4 (196)	
III	49.1 (648)	46.9 (301)		45.4 (348)	50.3 (602)	
IV	28 (370)	32.4 (208)		31.2 (239)	28.3 (339)	
Clinical Outcomes						
Weight change day 1 - 4 (kg)	-2.7±2.8	-3±3.2	0.037	-2.5±2.8	-3±3	<0.001
Total diuretic dose, day 1 - 3 (mg)	240 [140-400]	240 [140-400]	0.703	240 [156-388.8]	240 [140-410]	0.219
Total IV diuretic dose through day 7 (mg)	280 [133.3-560]	280 [120-539.8]	0.738	280 [160-560]	260 [120-540]	0.015
Inotropics (%)	5.8 (76)	7 (45)	0.326	8.9 (68)	4.4 (53)	<0.001
Inotropics or vasodilators (%)	14.8 (195)	17.6 (113)	0.121	17.2 (132)	14.7 (176)	0.150
Residual Congestion on day 7 (%)	57.8 (355)	61.9 (185)	0.526	70.6 (229)	51.7 (311)	<0.001
WRF, day 7 (%)	20.7 (264)	25.2 (158)	0.032	20.4 (154)	23.3 (268)	0.148
WRF, day 14 (%)	22.9 (292)	24.4 (153)	0.504	23.2 (175)	23.5 (271)	0.897
Persistent WRF (%)	12.9 (165)	14 (88)	0.556	13.1 (99)	13.4 (154)	0.915

Treatment failure due to Worsening Heart Failure (%)	8.7 (115)	10 (64)	0.410	12.4 (95)	7 (84)	<0.001
Treatment failure due to WRF (%)	12.6 (161)	13.6 (85)	0.616	13 (98)	12.9 (148)	0.972

Table 3.

Baseline LFTs as predictors of:

a) in hospital mortality

	Univariate model		**Multivariate model***	
Baseline LFTs	OR (95% CI)	p-value	OR (95% CI)	p-value
AST (for a unit increase of 100U)	1.583 (1.219 – 2.057)	<0.001	1.486 (1.107 – 1.996)	0.008
ALT (for a unit increase of 100U)	1.297 (1.048 – 1.605)	<0.001	1.293 (1.047 – 1.597)	0.017
Albumin (per decrease of 1 g/dl)	4.65 (2.23-9.6)	<0.001	5.4 (2.49- 11.76)	<0.001
Baseline LFTs as categorized variables				
Abnormal AST *(cut-off value of 37 U/L)***	4.205 (2.079 – 8.504)	<0.001	3.525 (1.697 – 7.322)	<0.001
Abnormal ALT *(cut-off value of 47 U/L)***	4.071 (1.931 – 8.583)	<0.001	3.891 (1.800 – 8.413)	<0.001
Low Albumin *(cut-off value of 3.7 g/dL)***	2.619 (1.271 – 5.395)	<0.001	2.784 (1.320 – 5.874)	0.007

* adjusted for (age, gender, NYHA class, serum creatinine, serum Na+, Blood pressure, HGB);

** group of patients with normal AST, ALT, albumin are reference.

b) 180 day mortality

	Univariate model	**Multivariate model***

Baseline LFTs	HR (95% CI)	p-value	HR (95% CI)	p-value
AST (for a unit increase of 100U)	1.253 (1.128 – 1.391)	<0.001	1.132 (1.016 – 1.262)	0.025
ALT (for a unit increase of 100U)	1.154 (1.066 – 1.250)	<0.001	1.115 (1.026 – 1.213)	0.011
Albumin (per decrease of 1 g/dl)	1.89 (1.47-2.445)	<0.001	1.675 (1.279-2.198)	<0.001
Baseline LFTs as categorized variables				
Abnormal AST *(cut-off value of 37 U/L)***	1.464 (1.120 – 1.947)	0.005	1.325 (1.006 – 1.744)	0.0453
Abnormal ALT *(cut-off value of 47 U/L)***	1.242 (0.886 – 1.742)	0.21	1.137 (1.024 – 1.047)	0.46
Low Albumin *(cut-off value of 3.7 g/dL)***	1.631 (1.296 – 2.053)	<0.001	1.437 (1.137 – 1.818)	0.002

* adjusted for (age, gender, NYHA class, serum creatinine, serum Na+, Blood pressure, HGB)

** group of patients with normal AST, ALT, albumin are reference.

Table 4.

Discharge LFTs as predictors of 180-days mortality.

	Univariate model		**Multivariate model***	
Baseline LFTs	HR (95% CI)	p-value	HR (95% CI)	p-value
AST (for a unit increase of 100U)	1.160 (1.053 – 1.279)	0.003	1.156 (1.034 – 1.294)	0.011
ALT (for a unit increase of 100U)	1.170 (1.087 – 1.259)	<0.001	1.114 (1.031 – 1.205)	0.007
Albumin (per decrease of 1 g/dl)	2.165 (1.63-2.865)	<0.001	1.786 (1.32-2.4)	<0.001
Discharge LFTs as categorized variables				
Abnormal AST *(cut-off value of 37 U/L)***	1.481 (1.097 – 1.999)	0.01	1.456 (1.072 – 1.976)	0.016
Abnormal ALT *(cut-off value of 47 U/L)***	1.65 (1.151 – 2.366)	0.006	1.504 (1.042 – 2.169)	0.029
Low Albumin *(cut-off value of 3.7 g/dL)***	1.928 (1.484 – 2.505)	<0.001	1.613 (1.235 – 2.108)	<0.001

* adjusted for (age, gender, NYHA class, serum creatinine, serum Na+, Blood pressure, HGB)

** group of patients with normal AST, ALT, albumin are reference.

Table. 5

LFTs trajectories as predictors of 180 day outcomes.

LFTs trajectories	HR (95% CI)	P	HR (95% CI)	P
Univariate Cox regression			**Multivariable Cox regression**	
AST (day 3)	1.015 (1.009-1.02)	<0.001	1.012 (1.006-1.019)	<0.001
ALT (day 3)	1.01 (1.007-1.014)	<0.001	1.008 (1.003-1.013)	0.001
Albumin (day 4)	0.342 (0.243-0.482)	<0.001	0.364 (0.245-0.541)	<0.001

models are all corrected for the baseline value of LFTs