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Is Acute heart failure a distinctive disorder? An analysis from BIOSTAT-CHF

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Abstract

Aims: This retrospective analysis sought to identify markers that might distinguish between acute heart failure (HF) and worsening HF in chronic outpatients.

Methods and Results: The BIOSTAT-CHF index cohort included 2516 patients with new or worsening HF symptoms: 1694 enrolled as inpatients (acute HF) and 822 as outpatients (worsening HF in chronic outpatients). A validation cohort included 935 inpatients and 803 outpatients. Multivariable models were developed in the index cohort using clinical characteristics, routine laboratory values, and proteomics data to examine which factors predict adverse outcomes in both conditions and to determine which factors differ between acute HF and worsening HF in chronic outpatients, validated in the validation cohort.

Patients with acute HF had substantially higher morbidity and mortality (6 months mortality was 12..3% for acute HF and 4..7% for worsening HF in chronic outpatients). Multivariable models predicting 180-day mortality and 180-day HF re-admission differed substantially between acute HF and worsening HF in chronic outpatients. CA-125 was the strongest single biomarker to distinguish acute HF from worsening HF in chronic outpatients, but only yielded a C-index of 0..71. A model including multiple biomarkers and clinical variables achieved a high degree of discrimination with a C-index of 0..913 in the index cohort and 0..901 in the validation cohort.

Conclusion: The study identifies different characteristics and predictors of outcome in acute HF patients as compared to outpatients with chronic HF developing worsening HF. The markers identified may be useful in better diagnosing acute HF and may become targets for treatment development.

Keywords

Acute heart failure; acute heart failure diagnosis; acute heart failure treatment.

Introduction

Acute heart failure (AHF) is defined as a worsening of symptoms and signs of heart failure (HF) requiring urgent care inclusive (but not limited to) intravenous therapy and hospital admission.(1) Following a series of neutral studies in which new interventions for AHF were not shown in large studies to be associated with improvements in either patients' symptoms or short- and long-term outcomes,(2) some opinion leaders have raised doubt whether AHF is a separate condition or just a part of the natural course of chronic heart failure.(3) At the same time doubts have been raised that some of the failure in demonstrating positive effects in large AHF studies relates to dilution of the patient population;(4) i.e., that patients enrolled in larger confirmatory studies may not have "true" AHF but have other disorders, chiefly chronic HF that has slightly deteriorated.(4) On the one hand some argue that the decision to admit a patient with AHF is subjective and variable and hence HF deterioration managed in the outpatient setting is not a different entity than AHF leading to hospital admission, while others argue that those are different conditions, the latter having a distinct pathophysiological mechanism – associated with inflammatory activation, more congestion, and end organ damage.(5) One of the obstacles in resolving these differences, and possibly developing effective therapies for AHF, is that there are no objective measures that help determine whether a patient is truly "acute", i.e., has AHF. All objective measures utilized in the diagnosis of AHF to date (natriuretic peptides levels, chest X-ray or lung ultrasound) can also be found to be affected in patients with stable chronic HF who have slight outpatient deterioration.

In the current analysis we have examined the characteristics of patients enrolled in the BIOSTAT-CHF study (A systems BIOlogy Study to Tailored Treatment in Chronic Heart

Failure) study where patients with both AHF requiring hospital admission and worsening of HF managed in an outpatient clinic were enrolled and followed.(6) While the absolute risk of adverse clinical outcomes overlapped in these two patient groups, the characteristics and prognosis of patients enrolled in the inpatient versus the outpatient setting in this study were found to differ.(7) The objective of this retrospective analysis was to identify markers that may distinguish between AHF and chronic HF patients with outpatient exacerbations and determine whether predictors of adverse outcomes in the two groups differed in the BIOSTAT-CHF database.

Methods

Index and validation cohorts

The BIOSTAT-CHF project provided access to data from an index cohort of 2516 heart failure patients enrolled between December 2010 and December 2012 in 69 centers in 11 European countries. In the Index Cohort adult patients with new or worsening heart failure symptoms, objective evidence of cardiac dysfunction, treated with at least 40 mg/day furosemide or equivalent, and receiving 50% or less the target doses of evidence-based therapies were enrolled in either the inpatient or outpatient setting and patients were followed for a median of 21 months.(6). For the Validation cohort inclusion criteria were similar, although outpatients could have been recruited without worsening of heart failure. Data were available from a validation cohort of 1738 patients enrolled in either the inpatient or outpatient setting between October 2010 and April 2014 in six centers in Scotland, UK. Patients in the validation cohort had a heart failure diagnosis and a previous admission with heart failure requiring diuretic therapy, and were treated with at least 20 mg/day furosemide or equivalent and 50% or less the target doses of

evidence-based therapies at entry. The study design of BIOSTAT-HF, baseline characteristics of the two cohorts and various modeling results have been described previously (6-8).

Patient characteristics and clinical outcomes

In order to develop a discriminatory model for acute HF and outpatient worsening HF (OP-WHF) we used reported hospitalization status (inpatient or outpatient) as surrogate. Model development was based on basic patient characteristics collected at study entry and baseline (age, sex, LVEF, BMI, vital signs, medical history), as well as baseline laboratory test values from blood samples analyzed locally or from blood samples that were frozen for shipment to central laboratories for analysis:

1. Local and routine central laboratory: Local laboratory results considered in the models included white blood cell count, red blood cell count, platelet count, hemoglobin, urea, glomerular filtration rate estimated from local creatinine using the CKD-EPI equation,(9) sodium, potassium, total bilirubin, glucose, AST, ALT, GGT, ALP, HDL, LDL, and triglycerides. NT-proBNP, high-sensitivity troponin T (hsTnT), and GDF-15 were centrally measured using a Roche Elecsys® cobas analyzer (Roche Diagnostics, Mannheim, Germany); aldosterone, renin, FGF23, urea, creatinine, calcium, phosphate, albumin, iron, ferritin, transferrin, hepcidin, and sTFR were also measured centrally.
2. Specialty biomarkers: Three biomarkers (TnI, ET-1, and IL-6) were measured using enzyme-linked immunosorbent assays (Singulex Inc.) on a Luminex platform. pro-ENK and bio-ADM were measured on a Sphingotec platform (Spingotec GmbH). CA125 was measured using a chemiluminescent microparticle immunoassay on an ARCHITECTi system (Abbott Laboratories).

3. Proteinomics/Olink panels: The BIOSTAT-CHF project included a comprehensive proteomic database measured by the Olink Proseek analysis service (Olink Proteomics, Uppsala, Sweden). The Olink platform utilizes a high-throughput multiplex immunoassay based on a proprietary Proximity Extension Assay (PEA) technology, where each biomarker is addressed by a matched pair of antibodies, coupled to unique, partially complementary oligonucleotides, and measured by quantitative real-time polymerase chain reaction (PCR). Results are expressed in the form of relative quantification (Normalized Protein eXpression or NPX) which are logarithmically related to protein concentration but cannot be converted to absolute protein concentrations. The BIOSTAT-CHF database comprised data from four Olink panels: Cardiovascular II, Cardiovascular III, Immune Response, and Oncology II, providing baseline measurements for a total of 368 proteins for most patients of both cohorts. Proteins can be recognized by a UniProt identifier.(10) For model development, we excluded 4 biomarkers from analysis as the same proteins were measured on more than 1 panel (1 copy each of AREG and SCF, and two copies of IL-6), leaving a total of 364 unique proteins for analysis.

In a preliminary step, we excluded baseline parameters with mostly missing observations in the index cohort and selected representative parameters in case of highly correlated or collinear variables. Olink measures were nearly perfectly correlated with other central measures of the same parameter. When both were available models were developed considering only the Olink parameter; for example, only MUC16 and not CA125 was considered in multivariable Model 3 for distinguishing AHF from OP-WHF. A differential expression analyses of the Olink proteins was performed using the Linear Models for Microarray data analysis (Limma) software (version 3.34.9).(11) Proteins were considered differentially expressed in inpatients relative to outpatients

if the absolute value of the fold change exceeded 1.24 ($|\log_2 FC|>0.31$), the p-value for the t-test that the $\log_2$FC differs from zero and the false discovery rate (FDR) <0.05. A volcano plot [a plot of $-\log_{10}$(p-value) versus $\log_2$ fold change] was used to visualize the differential expression of these markers in patients enrolled in the inpatient versus the outpatient setting. Clinical endpoints considered for analysis were the two components of the primary endpoint of BIOSTAT-CHF: all-cause death and first re-admission for heart failure. For the development of prognostic models, the time to the first occurrence of each clinical endpoint was evaluated through 180 days after baseline. Partially missing re-admission or death dates were imputed with the 15th of the month if only day was missing, or July 1st if both day and month were missing. Re-admission dates before and up to (≤) the respective baseline visit dates were excluded from analysis. Time to event was computed for all patients with a recorded event. Time to event for patients without a recorded event was censored at the earlier of 180 days after baseline or the individual end of study date. For the analysis of time to first occurrence of HF re-admission, time was censored at date of death for subjects who were not re-admitted for HF as the primary cause.

Statistical model development

Hospitalization status (inpatient versus outpatient) was analyzed using logistic regression. Time to all-cause death through 180 days and time to first HF re-admission through 180 days were analyzed using Cox proportional hazards models. We examined a number of classification methods in addition to logistic and Cox regression including Boosted Logistic Regression (LogitBoost), linear discriminant analysis with stepwise feature selection (stepLDA), neural networks (nnet), k-nearest neighbors (knn), CART (rpart), C5.0, and random forest (rf) (Supplementary Tables 1-5). We noted that performance characteristics of C5.0 and random

forest appeared best, with generally the highest area under the receiver operator characteristic curves (AUCs) and highest scaled Brier scores (which can be interpreted as correlation coefficients). Thus, pre-selection of Olink candidate predictors for the logistic regression models was based on the average variable importance rank for these two methods. We used the set of index cohort patients with complete Olink data as a training set for building classifiers that would predict inpatient status. Variable importance for each Olink marker was calculated by independently using C5.0(12) as well as Random Forests(13) as classification methods in a repeated 5-fold cross-validation approach using R package "caret"(14). Variable importance measures within each method were ranked using sports ranking; markers were then sorted by their average rank across the two methods. The top 50 Olink markers were selected as candidates for the inpatient status model (Supplementary Table 6), and the top 20 markers as candidates for the outcome models except for the top 10 in the case of outpatient mortality.

The full set of candidate predictors for each of the five models is given in Supplementary Table 11. For discriminating between in- and outpatients, in Model 1 we considered only patient characteristics, vital signs and locally- and centrally-measured laboratory values; we additionally considered medical history for prognostic models. For model 2, we further considered specialty biomarker measures; for model 3, we added the pre-selected Olink proteins. Missing values in the final analysis data set were imputed using a multi-chain Monte Carlo approach (R package "mice"(15)) and 10 imputed data sets were generated for the index cohort.

For each model, each continuous candidate baseline variable was first tested for non-linearity of its association with the model outcome by assessing the significance of the non-linear components of a restricted cubic spline transformation applied to the baseline variable in the index cohort while adjusting for the remaining candidate variables. In cases where the

association was deemed significantly non-linear and this behavior was observed consistently across the 10 imputed data sets of the index cohort, appropriate non-linear transformations were selected from a set of pre-specified transformations (such as quadratic, cubic, or linear spline transformations). Selection was based on values of Akaike's Information Criterion and visual inspection of plotting the predicted outcome against the baseline values. Baseline variables with highly skewed distributions were log2 transformed for analysis. Logistic or Cox regression with backwards selection was run on the 10 imputed data sets computing pooled p-values according to Rubin's algorithm(16) in each selection step and with the p-value criterion of 0.01 for staying in the inpatient models, and 0.05 for staying in the prognostic models. Estimated effect sizes, their 95% confidence intervals and p-values were pooled using Rubin's algorithm.

As a measure of discriminatory ability, the C-index pooled across the 10 imputed data sets was computed for each model. We further derived "final" models by combining the regression coefficients using Rubin's algorithm, applied each final model on the imputed data sets and derived the C-index for the final models as the average C-index across the imputed data sets. For internal validation, bootstrap samples of the imputed data sets of the index cohort were drawn, each time using the same random sample of patients for all imputations. Backwards selection and model fitting were repeated for each bootstrap sample in order to estimate bias-corrected C-indices and confidence intervals for each multivariable model. For external validation, the final models were applied to the imputed data sets of the validation cohort and pooled C-indices estimated. We further examined discrimination and calibration of our models through receiver-operator characteristics (ROC) curves and calibration plots.

The model for inpatient versus outpatient status was externally validated in the validation cohort. A few of the baseline characteristics included in the final models were not accessible or not

reported in the validation cohort and were thus multiply imputed. We successively added a small random sample of validation patients (n=11) to each of the 10 imputed data sets of the index cohort. We then imputed missing data for each subset of 11 validation patients in each imputed data set, repeated this step 158 times, thus generating 10 imputed data sets for the 1738 subjects in the validation cohort as well.

To further explore differences in prognostic factors between inpatients and outpatients, we applied the final multivariable models in inpatients to the outpatients. For HF readmission, all variables in the final model were used, while for death due to the limited number of events in outpatients the top 8 predictors were chosen. We further compared the fit of the final inpatient and outpatient models in the inpatients using partial likelihood ratio tests(17) as implemented in R package nonnestcox; for each clinical endpoint, the two final models were fitted within the inpatients and separately for 10 imputed data sets.

SAS® version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.5.1(18) software was used for all analyses.

Data availability

The data that support the findings of this study are available from University Medical Center Groningen but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of University Medical Center Groningen.

Results

Inpatients versus outpatients

Summary statistics for selected baseline characteristics are presented in Table 1 by cohort and patient status. A volcano plot showing the differential expression of the Olink panel proteins in inpatients versus outpatients is presented in Figure 1. Mucin-16 (MUC16), also known as CA125, appears to be the most differentially expressed, when considered without simultaneous adjustment for other proteins (i.e., univariably). In BIOSTAT-CHF, a doubling of CA125 (ARCHITECTi) as a continuous measure increased the odds of being an inpatient by 50% (OR 1.50, 95% CI 1.42-1.58, p<0.0001) with an AUC of 0.6983 (Table 2); results for MUC-16 measured on the Olink platform were similar (OR 1.58, 95% CI 1.48-1.69, p<0.0001). MUC-16 was selected for inclusion in the multivariable model (Table 3) with a somewhat smaller association with inpatient status (OR 1.30, 95% CI 1.17-1.46). At a threshold of 100 U/mL,(19) CA125 (ARCHITECTi) greater than the threshold had an AUC of 0.6278, sensitivity of 0.3832, specificity 0.8725, positive predictive value (PPV) 0.8610 and negative PV (NPV) 0.4070. .....

We also examined the ability of the traditional marker of HF severity – NT-proBNP – to discriminate between inpatients and outpatients. A doubling of NT-proBNP (cobas) was associated with an OR of 1.32 (95% CI 1.25-1.39, p<0.0001) for inpatient status with an AUC of 0.6395. Using a cut-point of 400 pg/mL(20) resulted in an AUC of 0.5421, sensitivity 0.9400, specificity 0.1442, PPV 0.6936, and NPV 0.5384. Thus, the traditional cut-point displayed high sensitivity and very low specificity. Note that when adjusted simultaneously for other proteins (Table 3), patients with a higher NT-proBNP were less likely to be an in-patient (OR 0·87 per 1-log increase, 95% CI 0·78-0·96).

We examined the ability of other biomarkers identified as potential markers of acutely ill heart failure patients including ST2, troponin T, troponin I, GDF-15, and ADM. Each of these markers

individually was unable to discriminate between inpatients and outpatients, with AUCs of about 0.500 signifying an ability no better than chance to predict the status.

Table 3 presents the selected multivariable logistic regression models for inpatient versus outpatient; Supplementary Figures 1 and 2 show in the index and validation cohorts the receiver-operator-characteristic (ROC) and calibration curves, respectively. The discrimination of the final multivariable model 3, which included 21 of the 50 Olink proteins considered, was excellent, with a c-index (AUC) of 0.9133 in the index cohort and of 0.9011 in the validation cohort. The performance characteristics of this model – including AUC and scaled Brier score – were better than those using classification methods (Supplementary Table 1).

Death through Day 180

In the Index cohort a total of 208 (12.3%) patients enrolled in the inpatient setting, and 39 (4.7%) patients enrolled in the outpatient setting, died by day 180. In the validation cohort 162 (17.3%) of the patients enrolled in the inpatient setting died at 6 months versus 25 (3.1%) in the outpatient setting. Final multivariable prognostic models are presented in Tables 4 and 5 for inpatients and outpatients, respectively. The full models (Model 3) had good discrimination with c-indexes of 0.8281 and 0.8460, respectively. Although difficult to compare directly because the paucity of events among outpatients restricted the number of candidate predictors that could be considered for that outcome, the prognostic factors differed for the two patient groups. When only considering patient characteristics and local and central laboratory data (Model 1), for example, FGF23, NT-proBNP, renin, and troponin T were all highly prognostic in inpatients, while platelet count, peripheral arterial disease, and age were most prognostic in outpatients.

The 8 most prognostic factors from the inpatient multivariable Model 3 for death provided much less discrimination in outpatients with a c-index 0.7464 (Supplementary table 12). And the inpatient and outpatient models were found to be distinguishable, and the fit of the inpatient model significantly better than the outpatient model, in inpatients.

Heart failure hospitalization through Day 180

In the Index Cohort, a total of 254 (15.0%) patients enrolled as inpatients, and 73 (8.9%) patients enrolled as outpatients, were hospitalized for heart failure by day 180. In the Validation Cohort, 6-month HF admission was observed in 166 (17.8%) inpatients and 57 (7.1%) outpatients. Final multivariable prognostic models are presented in Tables 6 and 7 for inpatients and outpatients, respectively. Model discrimination was modest in inpatients, with a c-index of 0.7322 for the full model (Model 3); the model including only patient characteristics and local or central laboratory data (Model 1) and the model additionally considering specialty laboratory parameters (Model 2) had similar discrimination with a c-index of 0.7395 for both. Discrimination for the models in outpatients was better, with c-indexes of 0.7966, 0.7984, and 0.8234 for Models 1, 2, and 3, respectively. NT-proBNP was a strong prognostic factor in both inpatients and outpatients.
The inpatient Model 3 applied to outpatients provided less discrimination than the model developed in the outpatients, with a c-index of 0.8055 (Supplementary table 13). And the inpatient and outpatient models were found to be distinguishable, and the fit of the inpatient model significantly better than the outpatient model, in inpatients.

Discussion

AHF research has been limited in the last decades by three major issues. The first is the lack of an objective definition of AHF. The currently used definition is a subjective one (worsening

symptoms and signs requiring urgent care) which has been an impediment to distinguishing between patients with “true” AHF versus those with out-patient HF exacerbations not requiring urgent care. This had led to significant problems in enrolling AHF patients in large studies.(4) Second, related to the lack of ability to define AHF we also know little of its pathophysiology. And third, as a consequence of our lack of ability to define AHF and our lack of knowledge of its pathophysiology the treatment targets for AHF are also not defined. In the last two decades, most therapies developed for AHF were either vasodilators or diuretics – which have both failed to show substantial benefit beyond some improvement in very short-term symptoms.

In the current analysis, AHF and OP-WHF were found to differ in three major domains. First, patients with AHF had much higher morbidity and mortality rates. The 180-day mortality and HF readmission rates were 12.3% and 15% for the AHF cohort and 4.7% and 8.9% for the OP-WHF cohort, respectively. Second, prognostic models for adverse outcomes differ for patients with AHF versus outpatient exacerbation of HF and models that predict adverse outcomes in AHF do not predict well adverse outcomes in outpatient exacerbations of HF. Third and lastly, the characteristics and prognosis of patients enrolled in the inpatient versus the outpatient setting in this study were found to differ.(7) The current analysis suggests that patients admitted for AHF have a different biomarker profile from patients with HF exacerbation not requiring admission.

These findings suggest that different pathophysiological mechanisms leading to different patterns of activation of neurohormonal and inflammatory protein markers may be involved in AHF and differ from those in out-patient exacerbations of heart failure. If confirmed, these may enable development of new diagnostic platforms that would lead to better ability to diagnose patients with true AHF. The exact components and details of such diagnostic platforms should be

elucidated in further prospective studies. In line with this limitation, as seen above, none of the currently proposed biomarkers (natriuretic peptides, CA125, ST2 or troponin) by itself can differentiate between AHF and outpatient exacerbation to the degree that the full model can. However, more data are required to better elucidate which variables and biomarkers would best discriminate the different disorders. As described in the current manuscript the models provided may help illuminate new paths in developing better models, but are not in themselves ready to be applied immediately in clinical studies.

In addition, some biomarkers that are differentially activated in AHF or those that seem to be associated with adverse outcomes in AHF patients specifically may become targets for therapeutic interventions or proxies to therapeutic intervention success enabling more targeted therapy for AHF to be developed. Oncological development plans have for the last 20 years been successful in targeting specific phenotypes with specific tailored therapies targeting the pathways most activated in those phenotypes. Novel approaches assessing in parallel multiple targeted interventions in specific phenotypes should be adopted in AHF research. It is possible that the lack of success we have encountered in developing new therapies for AHF is not related to the proposal that AHF does not exist, but rather to our limited attempts to develop tailored phenotype specific treatments.

Study Limitations

The current analysis is limited by the moderate size of the BIOSTAT study which was designed mainly to examine the importance of treatment optimization in patients with worsening HF. Some of the outcomes were sparse – especially in the group of patients with exacerbation of HF not requiring admission –. This was especially true in the Validation Cohort where some patients

could have been enrolled in the outpatient setting without worsening of HF. Moreover, the BIOSTAT study included a cohort of European mostly Caucasian patients mostly with left ventricular systolic dysfunction. Therefore, our models need validation in other cohorts of more diverse patient populations. The prognostic models developed have relatively low predictive value especially when it comes to HF readmissions. Therefore, they cannot be suggested to replace currently validated models in acute and chronic HF.

Conclusions

Our analysis suggests that patients who present with AHF differ from patients who develop HF exacerbation not requiring hospital admission. Patients with AHF are characterized by different clinical and biomarker profiles, have substantially worse outcomes and different predictors of adverse outcomes. The biomarkers that differ between patients with AHF and outpatients with HF exacerbation as well as the predictors of adverse outcome in AHF patients can serve to improve AHF diagnosis and potentially become therapeutic targets for AHF.

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Conflicts of Interest

B.A.D. is an employee of Momentum Research who received research grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Roche Diagnostics, Sanofi, and Windtree Therapeutics Inc.

S.S. is a former employee of Momentum Research who received research grants from Abbott Laboratories, Amgen, Celyad, Cirius Therapeutics, Roche Diagnostics, Sanofi, and Windtree Therapeutics Inc.

I.S. reports no conflicts.

G.G.K. is the principal investigator of a biostatistical agreement between Momentum Research, Inc. and the University of North Carolina at Chapel Hill, and that agreement provided the structure for his activity for this article. He is also the principal investigator of many such biostatistical agreements with other biopharmaceutical sponsors, including AbbVie, Amgen, Arena, AstraZeneca, Eli Lilly & Co., Forest Research Institute (Allergan), GlaxoSmithKline, Merck, Novartis, Otsuka, Pfizer, and Sanofi, although his activities for those sponsors are not related to the content of this article. Information concerning all biostatistical agreements for which Gary Koch is the principal investigator is publicly available through the University of North Carolina at Chapel Hill.

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Author contributions

The study was conceived by G.C. and designed by G.C., B.A.D., S.S., I.E.S., and A.A.V..

B.A.D., S.S., C.E., and I.E.S. analyzed the data.

G.C., B.A.D., and S.S. drafted the manuscript.

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All authors critically reviewed the manuscript and contributed to the interpretation of results.

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Figure Legends

Figure 1 (Central Illustration). Differential protein expression in inpatients relative to outpatients

Presented is a volcano plot of differential protein expression showing the fold change, i.e. the ratio of average expression in inpatients to average expression in outpatients, versus the corresponding t-test p-value per protein and on logarithmic scales. Higher values on the y-axis indicate stronger statistical significance, values >0 on the x-axis indicate upregulation in inpatients, and values <0 on the x-axis indicate downregulation in inpatients. Significantly differentially expressed proteins have been labeled.