A NOVEL BIOMARKER IN ACUTE HEART FAILURE AND OBESITY PARADOX IN ACUTE MEDICAL ILLNESS

A NOVEL BIOMARKER IN ACUTE HEART FAILURE

AND

OBESITY PARADOX IN ACUTE MEDICAL ILLNESS

by

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During the past two years of my education in the Master of Medical Sciences in Clinical Investigation Program at Harvard Medical School, my research has focused on acute medical illness. From a statistical perspective, I have primarily worked on regression analyses, including descriptive and predictive modeling, to estimate associations and answer the research questions outlined below.

OVERVİEW

Each year, approximately 8 million patients in the United States and 12 million patients in the European countries are hospitalized for acute medical illnesses such as heart failure, pneumonia and stroke.[1,2] VTE is an important cause of morbidity and mortality in acutely ill medical patients. Acute dyspnea is one of the most common symptoms of acutely ill patients presenting to the ER. It is a subjective symptom and often misleads the clinical diagnosis of acute heart failure.

Manuscript 1

Acute dyspnea is a common symptom among emergency department (ED) patients that may be caused by both cardiac and non-cardiac diseases.[3] Acute heart failure (HF) can be challenging to diagnose, as symptoms and signs often overlap with other conditions. The diagnosis of HF commonly relies on comprehensive analyses of medical history, symptoms, and results of echocardiography and biochemical tests.[4] Biomarker testing and cardiac imaging studies can be helpful for reaching the correct diagnosis and subsequently guiding patient management.[5-7]

Insulin like growth factor binding protein 7 (IGFBP7), is a cell cycle arrest biomarker associated with the senescence.[8] Among patients with chronic HF, elevated concentrations of IGFBP7 predict major adverse cardiovascular events and are correlated with multiple parameters associated with impaired myocardial relaxation.[9] The aims of the analysis were (i) to examine associations between IGFBP7 concentrations with clinically relevant

characteristics and cardiac structural relationships and (ii) to evaluate whether using IGFBP7 would optimize the diagnosis of acute HF in patients presenting to the ED with acute dyspnea enrolled in the International Collaborative of N-terminal pro-B-type Natriuretic Peptide Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department (ICON-RELOADED) study.

Manuscript 2

Obesity is an established risk factor for the development of many different diseases including cardiovascular and metabolic illnesses.[10-14] However, there is a growing data supporting the protective effect of obesity in certain medical conditions including acute heart failure[15], pneumonia[16], acute myocardial infarction[17], stroke[18], and hospitalization for critical illnesses[19] – the so called "obesity paradox". Acute illness is a hyper-catabolic state that increases the energy expenditure and requires an ample supply of calories which is stored in the adipose tissue.[20] Impaired metabolic response to acute stress and poor nutritional reserve may adversely impact the clinical outcome.

In the second analysis, we sought to investigate the association of body mass index (BMI) with venous thromboembolism (VTE) among medically ill hospitalized patients randomized in the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) trial.[21] We also tested the effect of comorbidity burden on the risk of VTE using the Charlson Comorbidity Index (CCI), a validated comorbidity assessment tool.[22]

Insulin-Like Growth Factor-Binding Protein-7, Cardiac Structure, and Function in Acute Dyspneic Patients with and Without Acute Heart Failure

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ABSTRACT

Aims: Concentrations of insulin-like growth factor-binding protein-7 (IGFBP7) have been linked to abnormal cardiac structure and function in patients with chronic heart failure (HF) but cardiovascular correlates of the biomarker in patients with more acute presentations are lacking. We aimed to determine the relationship between IGFBP7 concentrations and cardiac structure and to evaluate the impact of IGFBP7 on the diagnosis of acute HF among patients with acute dyspnea.

Methods: In this pre-specified subgroup analysis of the International Collaborative of N-terminal pro-B-type Natriuretic Peptide Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department (ICON-RELOADED) study we included 271 patients with and without acute HF. All patients presented to an emergency department with acute dyspnea, had blood samples for IGFBP7 measurement, and detailed echocardiographic evaluation.

Results: Higher IGFBP7 concentrations were associated with numerous cardiac abnormalities, including increased left atrial volume index (LAVi; $r = 0.49$, $p<0.001$), lower left ventricular ejection fraction (LVEF; $r = -0.27$, $p<0.001$), lower right ventricular (RV) fractional area change ($r = -0.31$, $p<0.001$), and higher tissue Doppler E/e' ratio ($r = 0.44$, $p<0.001$). In multivariable linear regression analyses, increased LAVi ($p= 0.01$), lower estimated glomerular filtration rate (eGFR, $p= 0.008$), higher body-mass index (BMI, $p= 0.001$), diabetes ($p= 0.009$), and higher concentrations of amino-terminal pro-B-type natriuretic peptide (NT-proBNP, $p= 0.01$) were independently associated with higher IGFBP7 concentrations regardless of other variables. In a multivariable logistic regression model, IGFBP7 remained a significant predictor of acute HF independent of other established risk factors. Dyspneic patients with supra-median IGFBP7 levels had a 76% acute HF; patients less than the median value had a 28% acute HF ($p< 0.001$).

Conclusion: Among acute dyspneic patients with and without acute HF increased IGFBP7 concentrations are associated with a range of cardiac structure and function abnormalities. Independent association with increased LAVi suggests elevated left ventricular filling pressure is an important trigger for IGFBP7 expression and release. IGFBP7 may enhance the diagnosis of acute HF.

Keywords

Dyspnea, Acute heart failure, Echocardiography, IGFBP7

Acute dyspnea is a common symptom amongst emergency department (ED) patients accounting for approximately 3-4 million visits (3%) in the ED each year in the United States.[1] Narrowing the diagnosis for patients with dyspnea may be challenging as the symptom can be caused by both cardiac and non-cardiac diseases. In this regard, biomarker testing and cardiac imaging studies can be helpful for reaching the correct diagnosis and subsequently guiding patient management. When a cardiac etiology is suspected, echocardiography is often the first imaging study (after chest x-ray) chosen to support clinical judgment, as it provides immediate information on left ventricular (LV) size and function, including ejection fraction (EF), diastolic parameters and valvular function.[2]

Circulating biomarkers may assist not only in diagnosis, but also in the understanding of disease pathophysiology and prognosis. For example, concentrations of B-type natriuretic peptide (BNP) and its amino-terminal precursor (NT-proBNP) are associated with a broad range of echocardiographic parameters, including systolic and diastolic LV function, filling pressures, and chamber size.[3-5] While such associations render natriuretic peptides nonspecific for individual cardiac structure and functional correlates, they help to demonstrate why both BNP and NT-proBNP are highly sensitive for a diagnosis of HF and contribute to prognostic understanding of such patients. However, they have insufficient specificity for the diastology, because of other conditions including valvular abnormalities and change in LVEF may contribute to their concentrations.[6] Several biomarkers that reflect different physiopathological pathways have been proposed for the diagnosis, prognosis, and risk stratification of patients with acute heart failure when natriuretic peptide levels are inconclusive. In this context, new and emerging biomarkers may be helpful to better define distinct pathophysiology and guide targeted therapeutic strategies.

IGFBP7, a cell cycle arrest biomarker associated with the senescence associated secretory phenotype, where senescent cells result in upregulation of inflammatory cytokines,

interluekins and growth factors. IGFBP7 was originally identified as a candidate HF biomarker in proteomic scans performed in a murine model of cardiac failure.[7] Among patients with chronic HF, elevated concentrations of IGFBP7 predict major adverse cardiovascular events[8] and are correlated with multiple parameters associated with impaired myocardial relaxation, notably including LAVi.[9] However, to date, all available data regarding IGFBP7 have been derived from patients with chronic HF. It is well-established that acute decompensated HF and chronic HF are distinct entities with different pathophysiology and treatment strategies. The goals of the present study were 1) to examine associations between IGFBP7 concentrations with clinically relevant baseline characteristics and cardiac structural relationships 2) to evaluate whether using IGFBP7 would optimize the diagnosis of acute HF in patients presenting to the ED with acute dyspnea enrolled in the recent ICON-RELOADED study.[10]

METHODS

Patient Population and Study Design

This study was performed in compliance with the Declaration of Helsinki and with approval of each institutional review board, and all patients provided written, informed consent before enrollment. Patients provided additional written, informed consent prior to giving the biorepository blood sample. The ICON-RELOADED study was a prospective, multicenter trial conducted at 19 sites in the United States and Canada. The design and primary results have been previously published.[10,11] In brief, patients aged 22 years or older presenting to emergency departments with complaints of dyspnea (defined as subjective feeling of shortness of breath, difficult or labored breathing, arising or worsening over the course of no longer than several days) were eligible for inclusion. Major exclusion criteria included, renal insufficiency requiring dialysis or known eGFR < 15.0 mL/min/1.73 m^2 prior to enrollment, dyspnea after chest trauma, patients who are unable to donate up to 50 mL of blood at one time, and known pregnancy. Overall, 1461 patients presenting at the ED with dyspnea were enrolled in a

prospective trial examining the age stratified cut-points of NT-proBNP for the diagnosis of acute HF. Adjudicated diagnosis of the cause of dyspnea was determined by a clinical events adjudication committee, blinded to NT-proBNP results, who independently reviewed and adjudicated the diagnosis of acute HF.

The present analysis is a pre-specified sub-study of the ICON-RELOADED trial, examining the subset of 271 patients from the overall cohort who underwent detailed echocardiographic examination during their index admission as part of standard of care; those with available echocardiograms and a blood sample for IGFBP7 measurement were included *(Figure 1).*

IGFBP7 Analysis

At enrollment, a blood sample was collected into EDTA-containing tubes, processed, and frozen at -80°C until measurement of IGFBP7 using a precommercial Elecsys assay (Roche Diagnostic, Penzberg, Germany) was performed. Assay of IGFBP7 was performed by Roche Diagnostics by laboratory personnel completely blinded to clinical information. Treating clinicians and those interpreting the echocardiograms were blinded to assay results.

Echocardiography

In the course of standard of care, echocardiography was determined to be indicated in 271 study participants, either in the ED or during the index hospitalization. Full image sets of each echocardiogram were exported in DICOM format onto suitable media (CD, DVD, etc.) or online portal to the designated Echocardiogram Core Laboratory at Massachusetts General Hospital. The readers were blinded to clinical picture and biomarker results.

Standard two-dimensional and color Doppler imaging was performed. Measurements were averaged over three cycles (five if atrial fibrillation was present). Structural indices included biplane LV end-diastolic and end-systolic volume indexed (LVEDVi, LVESVi) to body surface area (BSA), posterior wall thickness, LV mass by the modified American Society

of Echocardiography formula indexed to BSA, biplane LAVi; and RV end-diastolic and end-systolic area measured in the apical four-chamber view.[12] The LVEF was determined using biplane modified Simpson's measurements. Diastolic indices included early and late transmitral diastolic velocities (E and A), early deceleration time (DT), pulmonary venous systolic and diastolic velocities (PV S and D), and diastolic tissue Doppler velocities at the septal and lateral mitral annulus. RV indices included RV fractional area change; RV hypokinesis was qualitatively graded as none, mild, moderate and severe. Mitral regurgitation (MR) and tricuspid regurgitation (TR) severity were graded as none, trace, mild, moderate and severe based on visual assessment of structural and Doppler parameters and calculation of echocardiographic equations. Systolic dysfunction was defined as an LVEF <50%. Significant diastolic dysfunction was defined as E/e' ≥15 while diastolic dysfunction stages 1, 2, or 3 were used based on established criteria.[12]

Statistical Analysis

Analyses in this sub-study were pre-specified in the protocol of the ICON-RELOADED study.[11] Demographics and baseline characteristics were reported using frequencies and percentages for categorical variables and median and interquartile range (IQR) for continuous variables, respectively. Comparisons between groups were performed using the chi-square test for categorical variables and the Student's t-test or Wilcoxon rank-sum test for continuous variables. IGFBP7 and NT-proBNP levels were log-transformed because of their positively skewed distributions. For the purposes of analyzing the relationship between IGFBP7, NT-proBNP concentrations and echocardiographic parameters, patients were dichotomized as a function of being above or below median IGFBP7 and NT-proBNP values. Associations between IGFBP7, NT-proBNP and echocardiographic indices were assessed by Spearman's correlation coefficient.

Multivariable linear regression analysis was performed to determine the independent contributions of candidate variables to log IGFBP7 concentrations. Candidate predictor variables for the model were selected according to the clinical, biological plausibility and literature based associations. To avoid multicollinearity, nearly identical echocardiographic indices were not included into the model. Multicollinearity was assessed using variance inflation factor (VIF). The model was constructed with log-IGFBP7 as the dependent variable and the other candidate co-variates (age [as continuous], gender, log NT-proBNP levels [as continuous], BMI [as continuous], eGFR [as continuous], LV mass index [as continuous], LVEF [as continuous], RV fractional area change [as continuous], LAVI [as continuous], diastology grade [as categorical], atrial fibrillation, asthma, chronic obstructive pulmonary disease, history of diabetes, history of hypertension, history of heart failure, use of cardiovascular agents, lung cancer). Standardized β coefficients were generated and presented.

Multivariable logistic regression analysis was performed to identify independent predictors of acute HF. The model was constructed to estimate multivariable odds ratios (OR) and 95% confidence interval (CI) for IGFBP-7 and the other covariates for predicting the risk of acute HF. Predictors were selected based on their relevance in previous literature. The main explanatory variable was IGFBP-7 (log-transformed), and established risk factors (NT-proBNP [log-transformed], age [as continuous], gender, history of diabetes, history of hypertension, atrial fibrillation, GFR [as continuous], prior CAD, BMI [as continuous], and LVEF [as continuous]) were included into the model to assess associations with acute HF. Receiver-operating characteristic (ROC) analysis was used to measure and compare the performance of IGFBP7 and NT-proBNP for the diagnosis of acute HF.

In the present study, we have performed complete case analyses. The pattern of missingness was non-structured; thus, the data was considered to be missing at

random (MAR). Notably, most of the variables included in the models had less than 5% missing data.

For all statistical analyses, p-values reported are from two-sided tests and considered as statistically significant with a value of less than 0.05. All data analyses were performed using the STATA version 15.1 (StataCorp LLC, College Station, TX, USA).

RESULTS

Clinical Characteristics

Two hundred and seventy-one study participants (age 62.7±13.9 and 57% male) underwent echocardiography with data sufficient for analysis in the Core Laboratory. Among those with echocardiographic data, 143 (52.7%) had adjudicated acute HF. Both NT-proBNP (2700 [1247-5919] vs 317 [82-1083] pg/mL, p<0.001) and IGFBP7 (146 [116-188] vs 96 [81-119] ng/mL, p<0.001) concentrations were significantly higher in subjects with acute HF compared to subjects without HF.

IGFBP7 concentrations

The median IGFBP7 level in this sub-analysis was 119 ng/mL (IQR= 91–157 ng/mL). A summary of baseline clinical characteristics, dichotomized by the median IGFBP7 value, is presented in *Table 1*. Patients with an IGFBP7 level greater than the median value tended to be older, had worse kidney function, and more commonly had a history of diabetes mellitus (DM), HF, hypertension, prior coronary artery disease (CAD), prior myocardial infarction (MI), atrial fibrillation, significant aortic and mitral valve diseases and more frequent medication use for heart disease compared to those with an IGFBP7 level below the median value. Compared to patients with an inframedian level of IGFBP7, patients with a supramedian IGFBP7 level with pulmonary diseases (COPD and asthma) but without acute HF had an increased tissue Doppler E/e' ratio (*supplemental Table 1)*. Higher IGFBP7 concentrations were associated with prevalent echocardiographic abnormalities. For example, higher LAVi was observed in

patients with supra-median IGFBP7 levels across the study population irrespective of the diagnosis of acute HF. Baseline characteristics, dichotomized by median NT-proBNP values are summarized in *supplemental Table 2*.

Echocardiographic Findings

A summary of echocardiographic findings of acutely dyspneic patients, dichotomized by the median IGFBP7 value of 119 ng/mL is shown in *Table 2*. Cardiac structural and functional abnormalities were more common in those with higher IGFBP7 concentrations, including greater chamber sizes, worse systolic and diastolic function, higher filling pressures, and more severe valvular heart disease. A significant association was observed between increased IGFBP7 concentrations and worsening LV diastolic function ($p<0.001$, *Figure 2*). For comparison, the distribution of NT-proBNP concentrations according to LV diastolic dysfunction is presented in *supplemental Figure 1*.

Bivariate Spearman correlation analysis of echocardiographic indices and IGFBP7 concentrations are presented in *Table 3*. This shows modest correlation with a broad array of cardiac abnormalities. Notably, higher IGFBP7 was associated with an increased LAVi ($r = 0.49$, $p<0.001$), a reduced LVEF ($r = -0.27$, $p<0.001$), a lower RV fractional area change ($r = -0.31$, $p<0.001$), and a higher tissue Doppler E/e' ratio ($r = 0.44$, $p<0.001$). For comparison, echocardiographic indices, dichotomized by the median NT-proBNP value are summarized in *supplemental Table 3*.

A significant relationship was observed between atrial fibrillation and increased IGFBP7 concentrations in the univariate linear regression analysis (estimated β: 0.210, $p <0.001$). However, the association was not significant in the multivariable adjusted analysis ($p =0.73$)

Independent Predictors of log IGFBP7

Multivariable linear regression analysis was performed in order to determine the independent contributions of covariates to log-transformed IGFBP7 concentration. Diabetes (p= 0.009), log-NT-proBNP (p= 0.02), BMI (p= 0.001), eGFR (p= 0.008) and LAVi (p= 0.01) were significantly associated with log-IGFBP7 concentrations, regardless of other variables (*Table 4, Figure 4*).

IGFBP7 and Diagnosis of Acute Heart Failure

Out of 271 patients, 143 were diagnosed with acute HF and 128 were controls. Log-IGFBP7 (OR=12.08, 95% CI 2.42-60.15, p=0.02), log-NT-proBNP (OR=2.20, 95% CI 1.49-3.25, p<0.001), and BMI (OR=1.07, 95% CI 1.01-1.13, p=0.02) were found to be independently associated with acute HF in the multivariable logistic regression analysis (*Table 5*). The relationship between IGFBP7 and predicted probability of acute HF was illustrated by a Lowess curve in *Figure-3*. The diagnostic performance of NT-proBNP and IGFBP7 for acute HF was measured by ROC analysis. ROC curve analysis revealed 72% sensitivity and 79% specificity in the prediction of the risk for acute HF with the cut-off value of 121 pg/ml for IGFBP7 (AUC: 0.81, 0.75-0.86). The diagnostic performances of NT-proBNP and IGFBP7 for acute HF were comparable in the ROC curve comparison analysis (p=0.428, *Figure-5*).

DISCUSSION

IGFBP7 is an emerging biomarker that is strongly associated with cardiac structure, diastolic function, filling pressures and prognosis.[13] In our analysis of ED patients with acute dyspnea, we have identified that higher concentrations of IGFBP7 are associated with an increased indexed LA volume, worse kidney function, obesity, diabetes, and higher NT-proBNP concentrations. In addition, higher concentrations of IGFBP7 were clearly associated with more severe structural heart disease and HF diagnosis. Though associations between IGFBP7 and cardiac structural correlates have been examined in chronic HF[8,9,15-19], our study is the first to examine the biomarker in patients with acute dyspnea; our results further solidify

IGFBP7 as a plausible candidate cardiac marker. In many ways, higher IGFBP7 concentrations portray a commonly-encountered HF phenotype, namely the diabetic and obese patient with severe cardiac congestion and kidney dysfunction; the intersection between cellular senescence and these abnormalities has been recently highlighted[15], with some suggesting a specific cardiovascular phenotype of "metabolic senescent HF".[16] Indeed, in recent studies of chronic HF, higher concentrations of IGFBP7 were linked to aging, diabetes mellitus, and obesity.[17-21] Diabetes is presumed to have a role in increased myocardial stiffness through deposition of collagen and advanced glycation end products.[22] Diastolic dysfunction may be the earliest manifestation of diabetes-induced myocardial disease which leads to the progressive development of HF.[23] Previous studies reported an association of serum IGFBP7 concentrations with insulin resistance and diabetes.[24,25] Obesity is also a contributor to senescence, and expression of increased IGFBP7 has been found to be positively correlated with increase in BMI in HF patients.[17,18] Consistent with these findings, our data also demonstrate that higher levels of BMI and diabetes are independent predictors for increased IGFBP7 concentrations.

IGFBP7 has been defined as a biomarker of premature tissue aging and fibrosis[26,27] suggesting a contribution to increased myocardial stiffness and noncompliance. Higher concentrations of IGFBP7 may result in premature aging of the myocardium with consequent myocardial fibrosis.[18] Given the link between cardiac fibrosis, hypertrophy, and HF, several studies have demonstrated IGFBP7 as a novel biomarker of impaired myocardial relaxation in chronic HF with both reduced and preserved ejection fraction.[9,18,28] We found similar associations between IGFBP7 and measures of impaired relaxation; however, the extent of association between higher IGFBP7 and other abnormalities of cardiac structure and function was greater in our subjects with more acute presentations. This might imply acute expression of IGFBP7 in the setting of acute pressure and volume overload states. Whether specific

targeting of IGFBP7 to prevent or ameliorate adverse cardiac events in acute or chronic HF remains a speculative concept; it is worth noting that neprilysin inhibition reduced IGFBP7 concentrations in a randomized trial of patients with HF with preserved EF.[17]

Compared to prior studies of IGFBP7, we found differences in the patterns of imaging correlation. In stable, chronic HF patients IGFBP7 largely predicted variables consistent with impaired myocardial relaxation such as LAVi, transmitral E/A ratio, E/e' ratio, and estimated right ventricular systolic pressure.[18,29] In the present analysis IGFBP7 concentrations were associated with a broader range of cardiac abnormalities, including LV and RV systolic dysfunction and worse valve disease. We observed relationships between higher IGFBP7 levels and greater LV mass, higher LV filling pressures (E/e' ratio), impaired trans-mitral inflow velocities (mitral E/ A ratio), as well as more extensive LV diastolic relaxation abnormalities such as lower mean mitral annular e' velocity and right ventricular dysfunction. Impaired LV relaxation and increased LV diastolic stiffness are major causes of diastolic dysfunction that lead to elevated LV filling pressure and LA stretch.[30] Prior studies have reported that systolic RV shortening is highly sensitive to afterload which is typically elevated in diastolic dysfunction.[31,32] In the present study, RV fractional area change was negatively correlated with IGFBP7 concentrations showing an increased afterload due to pressure and volume overloaded LV and LA. On the other hand, increased RV afterload may also occur because of lung diseases as it is highly dependent on the distribution of blood flow in the lung and increased alveolar pressure.[33] Furthermore, severe mitral regurgitation was found to be correlated with higher IGFBP7 concentrations suggesting the regurgitant volume causes volume and pressure overload of LA and LV. Our study has demonstrated that acute elevated LV filling pressure and volume overload, diastolic stiffness as well as increased RV afterload are correlated with increased IGFBP7 concentrations.

In adjusted analyses, the association between LAVi and IGFBP7 remained robust, much as in prior studies.[17,18] Indexed LA volume has emerged as a prime imaging marker in HF given its very significant association with elevated LV end diastolic pressures with impaired myocardial relaxation.[28,29,34] Indeed, LAVi has been suggested as a marker of the severity and duration of diastolic dysfunction.[29,34-36] Upregulation of several senescence-associated biomarkers in cardiac fibroblasts and atrial myocytes along with notable atrial fibrosis has been observed in atrial tissue extracts of atrial fibrillation patients, indicating tissue aging associated with atrial enlargement.[37] In our study, simple linear regression analysis showed a significant relationship between atrial fibrillation and increased IGFBP7 concentrations, though the association did not reach statistical significance in the adjusted analysis. These observations are consistent with a potential role for IGFBP7 in mediating cardiac stiffness and potentially impeding diastolic filling resulting in a strong association with LAVi. With these strong associations, IGFBP7 may provide options for diagnosis, prognosis, and possibly even management strategies for patients whose primary mechanism of HF is abnormal diastolic function.[20]

Strengths of this analysis include the fact it is derived from a multicenter clinical trial population with diagnoses assigned with strict adjudication, and the echocardiograms were blindly interpreted in a core lab fashion. Nonetheless, our work has limitations. First, our study has a relatively small size; however, for imaging studies larger numbers of study participants are not as required as they are in outcome studies. Second, although we adjusted for a range of confounding variables, the effects of residual confounding cannot be excluded. Third, selection bias may have occurred due to the identification of the study population. Patients included in this study had clinical indications for detailed transthoracic echocardiography. Thus, cardiac structural and functional abnormalities may not be representative of a general acute dyspneic cohort. Though IGFBP7 was elevated in a manner consistent with a cardiac biomarker, it is

important to concede abnormal concentrations of cardiac biomarkers may be seen in non-cardiovascular presentations, presumably due to comorbid myocardial injury and stress. Indeed, Ruan et al identified that serum IGFBP7 levels are modestly increased during acute exacerbation of COPD.[38] Our data also demonstrated that among patients with asthma and COPD but without acute HF, those with higher IGFBP7 levels had higher LV filling pressures. Given our data includes acute dyspneic patients with suspected acute HF, we speculate that IGFBP7 concentrations might play a pivotal role in the response to acutely elevated LA and LV pressure and volume overload regardless of the underlying mechanism. The results of the present study have demonstrated that the biomarker may be a plausible candidate for use as a diagnostic test for acute HF, comparable to NT-proBNP. Therefore, a potential incremental benefit of adding IGFBP7 to NT-proBNP as a diagnostic tool for identifying acute HF as the cause of dyspnea is currently being further evaluated in the larger ICON-RELOADED dataset.

CONCLUSION

In this cohort of acutely dyspneic patients presenting to the ED, we found that concentrations of IGFBP7 were strongly associated with a broad range of cardiac abnormalities, most notably including increased LAVi (a marker of elevated LV filling pressure and myocardial stiffness). IGFBP7 may enhance the diagnosis of acute HF. The role of IGFBP7 as a diagnostic and prognostic biomarker for acute HF is being further explored.

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Table 1. Clinical Characteristics of the Study Population by the Median Value of IGFBP7

Patient Characteristic	IGFBP7 < Median (N=135)	IGFBP7 ≥ Median (N=136)	p-value
Age, years *	59 (51-68)	67 (56-76)	<0.001
Female (%)	46.6 (63/135)	39.7 (54/136)	0.24
eGFR (mL/min/1.73m^2) *	79.4 (65.2-101.3)	54 (42.5-74)	<0.001
BMI (kg/m^2) *	30.5 (26.4-36.9)	31.7 (26-37.7)	0.43
Body surface area (m^2) *	2.01 (1.79-2.21)	2.04 (1.85-2.28)	0.39
Medical history			
Diabetes mellitus (%)	26.3 (35/133)	46.3 (63/136)	0.001
Heart failure (%)	22.3 (29/130)	62.1 (82/132)	<0.001
Hypertension (%)	68.6 (92/134)	82.2 (111/135)	0.01
Prior CAD (%)	24.6 (33/134)	40.3 (54/134)	0.006
Previous MI (%)	11.4 (15/131)	22.1 (29/131)	0.02
Significant aortic valve disease (%)	0.8 (1/121)	8.4 (10/119)	0.005
Significant mitral valve disease (%)	3.25 (4/123)	10.4 (13/125)	0.03
COPD (%)	24.2 (32/132)	26.4 (36/136)	0.67
Asthma (%)	15.1 (20/132)	19.8 (27/136)	0.31
Atrial Fibrillation (%)	17.9 (24/134)	36.3 (48/132)	0.001
Medications at discharge			
Beta blockers (%)	29.6 (40/135)	45.5 (62/136)	0.007
Loop diuretic (%)	31.1 (42/135)	64.7 (88/136)	<0.001
ACEi or ARB (%)	25.9 (35/135)	35.2 (48/136)	0.12
Vital signs			
Pulse rate (bpm) *	95 (80-109)	87 (70-106.5)	0.02
SBP (mmHg) *	140 (126-165)	142 (127-165)	0.49
DBP (mmHg) *	83 (74-94)	81 (71-97)	0.35

* Median and IQR are presented.

Those with a supra-median IGFBP7 value were more likely to be older, have worse kidney function, and other chronic diseases.

Abbreviations: ***IQR*** denotes interquartile range, ***eGFR*** denotes estimated glomerular filtration rate, ***BMI*** denotes body mass index, ***CAD*** denotes coronary artery disease, ***MI*** denotes myocardial infarction, ***COPD*** denotes chronic obstructive pulmonary disease, ***ACEi*** denotes Angiotensin-converting enzyme inhibitors, ***ARB*** denotes Angiotensin II receptor blockers, ***SBP*** denotes systolic blood pressure, ***DBP*** denotes diastolic blood pressure, ***IGFBP7*** denotes insulin-like growth factor binding protein-7.

Table 2. Echocardiographic Indices of the Study Population by the Median Value of IGFBP7

Echocardiographic Indices	IGFBP7 < Median (N=135)	IGFBP7 ≥ Median (N=136)	p-value
Left ventricle			
Posterior wall thickness (mm) *	10 (8-11.5)	10 (9-12)	0.04
LV mass index (male, g/m^2) *	85.4 (67.9-106.2)	111.6 (92.2-130.2)	<0.001
LV mass index (female, g/m^2) *	77.9 (64.3-97.1)	96.6(81.5-111.6)	0.003
LVEDVi (mL/m^2) *	53.3 (44.9-65.7)	68.1 (51.2-86.5)	<0.001
LVESVi (mL/m^2) *	20.3 (15.3-28.7)	35.5 (18.3-56.3)	<0.001
LVEF (%) *	61.6 (51.9-69.2)	50 (30.4-64.7)	<0.001
LVEF			
LVEF *	61.6 (51.9-69.2)	50 (30.4-64.7)	<0.001
LVEF < 50 (%)	21 (25/117)	48 (53/110)	
LVEF ≥ 50 (%)	79 (92/117)	52 (57/110)	
Right ventricle			
RV diastolic area (cm^2) *	19 (14.8-23.4)	22.3 (18.6-27.4)	0.001
RV systolic area (cm^2) *	10.4 (8.1-13.9)	14.5 (10.6-18.6)	<0.001
RV fractional area change (%) *	43.2 (36.8-51.3)	36.3 (28.1-45.9)	<0.001
Right ventricular hypokinesis			0.003
None (%)	85.6 (107/125)	64.6 (73/113)	
Mild (%)	5.6 (7/125)	15 (17/113)	
Moderate (%)	4.8 (6/125)	11.5 (13/113)	
Severe (%)	4 (5/125)	8.6 (10/113)	
LAVi (mL/m^2) *	28.9 (21.9-36.2)	41.9 (33.1-51.2)	<0.001
Trans-mitral doppler			
E (cm/s) *	72 (61-92)	97.5 (80-121)	<0.001
A (cm/s) *	67 (55-85)	65.5 (46-87)	0.45
E/A*	1.04 (0.8-1.3)	1.3 (0.9-1.9)	<0.001
DT (ms) *	177 (145-210.5)	167 (129.4-199)	0.04
Pulmonary vein flow			
S (cm/s) *	45 (38-57)	35.5 (24-47.5)	0.001
D (cm/s) *	43 (32-52)	55.5 (42.5-68.5)	<0.001
S/D*	1.1 (0.8-1.4)	0.6 (0.5-0.9)	<0.001
Tissue doppler			
Mitral annular e' septal (cm/s) *	7 (6-9)	6 (5-7)	<0.001
Mitral annular e' lateral (cm/s) *	9 (6-11)	8 (6-10)	0.09
Mean mitral annular e' (cm/s) *	8 (6-10)	7 (5.2-9)	0.01
E/e'*	9.4 (7.4-13.6)	13.4 (10.7-19.6)	<0.001
E/e'≥15 (%)	19.6 (23/117)	42.5 (46/108)	<0.001
Diastology grade			<0.001
Normal (%)	59 (65/110)	19.8 (18/91)	

Grade I (%)	15.4 (17/110)	11 (10/91)	
Grade II (%)	18.1 (20/110)	36.2 (33/91)	
Grade III (%)	6.4 (7/110)	32.9 (30/91)	
Indeterminate (%)	0.9 (1/110)	0 (0/91)	
TR severity			0.001
None (%)	2.4 (3/127)	2.3 (3/130)	
Trace (%)	61.4 (78/127)	40 (52/130)	
Mild (%)	28.3 (36/127)	33 (43/130)	
Moderate (%)	7.9 (10/127)	21.5 (28/130)	
Severe (%)	0 (0/127)	3 (4/130)	
MR severity			<0.001
None (%)	11.8 (15/127)	3.1 (4/129)	
Trace (%)	59 (75/127)	36.4 (47/129)	
Mild (%)	19.7 (25/127)	40.3 (52/129)	
Moderate (%)	7.9 (10/127)	17 (22/129)	
Severe (%)	1.6 (2/127)	3.1 (4/129)	

* Median and IQR are presented.

Study participants with an IGFBP7 ≥ 119 ng/mL had prevalent cardiac abnormalities.

Abbreviations: ***IQR*** denotes interquartile range***,*** ***LV*** denotes left ventricle, ***LVEDVi*** denotes left ventricular end-diastolic volume index, ***LVESVi*** denotes left ventricular end-systolic volume index, ***LVEF*** denotes left ventricular ejection fraction, ***RV*** denotes right ventricle, ***LAVi*** denotes left atrial volume index, ***E*** denotes early transmitral diastolic velocities, ***A*** denotes late transmitral diastolic velocities, ***E/A*** denotes the ratio of early to late transmitral diastolic velocities, ***DT*** denotes early deceleration time, ***S*** denotes pulmonary venous systolic velocities, ***D*** denotes pulmonary venous diastolic velocities, ***S/D*** denotes the ratio of pulmonary venous systolic to diastolic velocities, ***E/e'*** denotes the ratio between early mitral inflow velocity and mitral annular early diastolic velocity, ***TR*** denotes tricuspid regurgitation, ***MR*** denotes mitral regurgitation, ***IGFBP7*** denotes insulin-like growth factor binding protein-7.

Table 3. Univariable Correlations of Echocardiographic Indices with IGFBP7 Levels

Echocardiographic Indices	Spearman Correlation Coefficient (ρ)	p-value
Left ventricle		
Posterior wall thickness (mm)	0.187	0.002
LV mass index (g/m^2)	0.342	<0.001
LVEDVi (mL/m^2)	0.285	<0.001
LVESVi (mL/m^2)	0.307	<0.001
LVEF (%)	-0.278	<0.001
Right ventricle		
RV diastolic area (cm^2)	0.342	<0.001
RV systolic area (cm^2)	0.391	<0.001
RV fractional area change (%)	-0.310	<0.001
LAVi (mL/m^2)	0.491	<0.001
Diastology grade	0.459	<0.001
Transmitral doppler		
E (cm/s)	0.435	<0.001
A (cm/s)	-0.084	0.25
E/A	0.311	<0.001
DT (ms)	-0.137	0.04
Pulmonary vein flow		
S (cm/s)	-0.353	<0.001
D (cm/s)	0.281	<0.001
S/D	-0.480	<0.001
Tissue doppler		
Mitral annular e' septal (cm/s)	-0.279	<0.001
Mitral annular e' lateral (cm/s)	-0.101	0.15
Mean mitral annular e' (cm/s)	-0.182	0.01
E/e'	0.442	<0.001
MR severity	0.320	<0.001

Abbreviations: ***LV*** denotes left ventricle, ***LVEDVI*** denotes left ventricular end-diastolic volume index, ***LVESVi*** denotes left ventricular end-systolic volume index, ***LVEF*** denotes left ventricular ejection fraction, ***RV*** denotes right ventricle, ***LAVi*** denotes left atrial volume index, ***E*** denotes early transmitral diastolic velocities, ***A*** denotes late transmitral diastolic velocities, ***E/A*** denotes the ratio of early to late transmitral diastolic velocities, ***DT*** denotes early deceleration time, ***S*** denotes pulmonary venous systolic velocities, ***D*** denotes pulmonary venous diastolic velocities, ***S/D*** denotes the ratio of pulmonary venous systolic to diastolic velocities, ***E/e'*** denotes the ratio between early mitral inflow velocity and mitral annular early diastolic velocity, ***TR*** denotes tricuspid regurgitation, ***MR*** denotes mitral regurgitation, ***IGFBP7*** denotes insulin-like growth factor binding protein-7.

Table 4. Multivariable Correlations of Clinical and Echocardiographic Indices with log transformed IGFBP7 Levels

Patient Characteristic	Estimated β	Standard Error	p-value
Age	0.003	0.002	0.14
Gender (female vs male)	-0.037	0.050	0.46
Log-NT-proBNP	0.048	0.020	0.02
BMI	0.010	0.003	0.001
eGFR (mL/min/1.73m)	-0.003	0.001	0.008
LV mass index*	-0.01	0.01	0.09
LVEF*	-0.01	0.02	0.59
RV fractional area change*	-0.01	0.02	0.62
LAVI*	0.05	0.02	0.01
Diastology grade	0.035	0.020	0.08
Atrial fibrillation	0.020	0.060	0.73
Asthma	-0.090	0.077	0.24
COPD	-0.034	0.059	0.56
Diabetes	0.139	0.053	0.009
Hypertension	-0.038	0.058	0.50
Heart failure	0.073	0.054	0.18
Loop diuretics	0.003	0.056	0.95
Beta blockers	0.062	0.055	0.25
ACEI/ARBs	-0.086	0.056	0.12
Lung cancer	-0.001	0.112	0.99

The association between IGFBP7 concentrations and LAVi remained significant, even after adjusting for atrial fibrillation, diastolic abnormalities, LVEF, and NT-proBNP levels.

*Each 10-unit change was presented.

LV mass index, n=258; **LVEF,** n=229; ***RV fractional area change,*** n=195; ***LAVI***, n=238; ***Diastology grade,*** n= 242

Abbreviations: NT-proBNP denotes N-terminal pro b-type natriuretic peptide, ***BMI*** denotes body mass index, ***eGFR*** denotes estimated glomerular filtration rate, ***LV*** denotes left ventricle, ***LVEF*** denotes left ventricular ejection fraction, ***RV*** denotes right ventricle, ***LAVi*** denotes left atrial volume index, ***COPD*** denotes chronic obstructive pulmonary disease, ***ACEI/ARB*** denotes angiotensin-converting-enzyme inhibitors/ angiotensin receptor blockers.

Table-5. Adjusted Odds Ratios for Individual Predictors Included in Logistic Regression Model

Variables	Multivariable OR, 95% CI	p-value
logIGFBP7 Level	12.08 (2.42 to 60.15)	0.002
logNT-proBNP Level	2.20 (1.49 to 3.25)	<0.001
Age (Each increase in 1 year)	0.99 (0.96 to 1.03)	0.71
Gender (Female vs male)	1.11 (0.49 to 2.50)	0.80
History of diabetes (Yes vs. No)	1.41 (0.55 to 3.65)	0.47
GFR (Each increase in 1 mg/dL)	1.001 (0.98 to 1.02)	0.95
History of hypertension (Yes vs. No)	1.52 (0.53 to 4.35)	0.43
Atrial fibrillation (Yes vs. No)	0.85 (0.32 to 2.30)	0.75
Prior CAD (Yes vs. No)	0.63 (0.23 to 1.75)	0.38
BMI (Each increase in 1 kg/m^2)	1.07 (1.01 to 1.13)	0.02
LVEF (Each increase in %)	0.97 (0.95 to 1.001)	0.06

Abbreviations: **OR** denotes odds ratio, **CI** denotes confidence interval, **IGFBP7** denotes insulin-like growth factor-binding protein-7, **NT-proBNP** denotes, N-terminal pro b-type natriuretic peptide, **eGFR** denotes estimated glomerular filtration rate, **CAD** denotes coronary artery disease, **BMI** denotes body mass index, ***LVEF*** denotes left ventricular ejection fraction

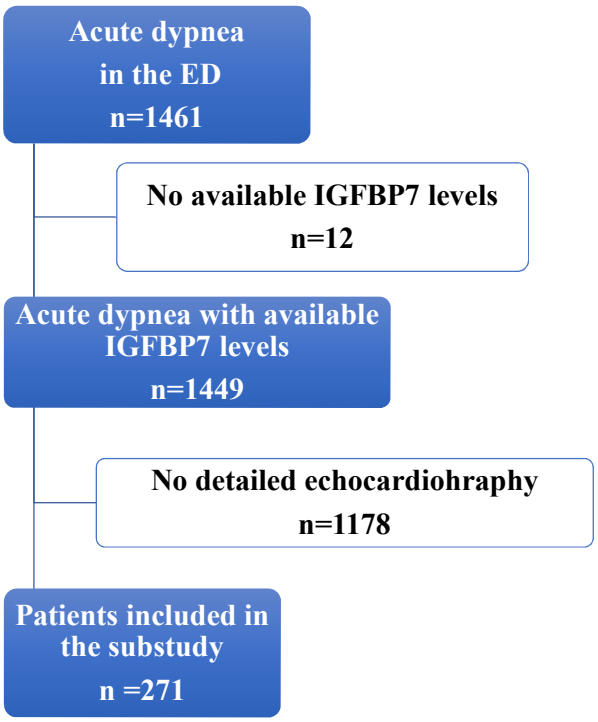


Figure 1. Flow of the study inclusion and exclusion criteria

Abbreviation: IGFBP7 denotes insulin-like growth factor binding protein-7, ***ED*** denotes emergency department.

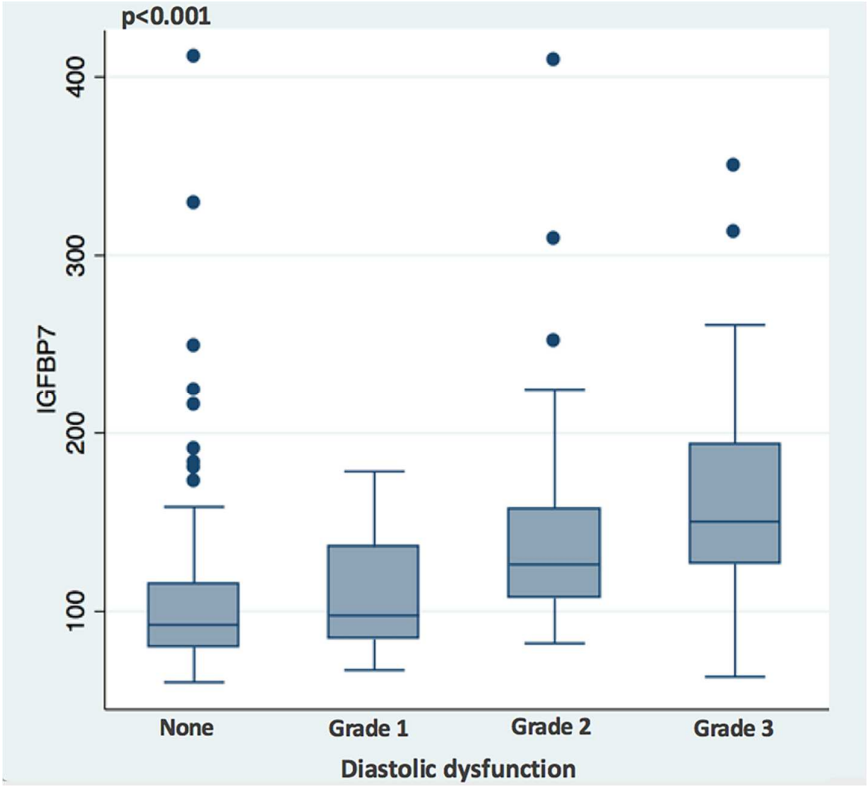


Figure 2. Box-plots of IGFBP7 concentrations according to the left venticular diastolic dysfunction grading ($p < 0.001$)

Diastolic Dysfunction, *n*= 242

Abbreviation: IGFBP7 denotes insulin-like growth factor binding protein-7.

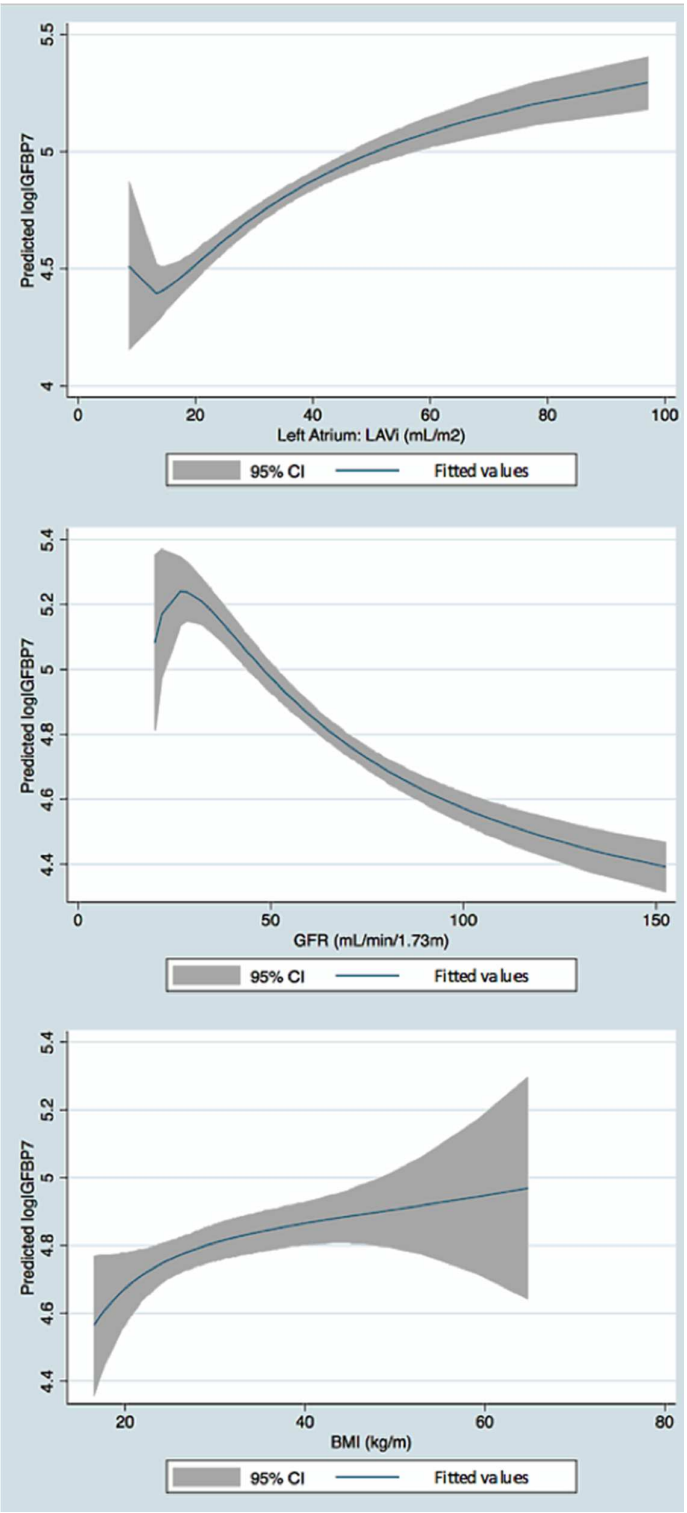


Figure 3. Associations between predicted logIGFBP7 and LAVi, eGFR, BMI and age were plotted with smooth curves

Abbreviations: IGFBP7 denotes insulin-like growth factor binding protein-7, ***LAVi*** denotes left atrial volume index, ***eGFR*** denotes estimated glomerular filtration rate, ***BMI*** denotes body mass index.

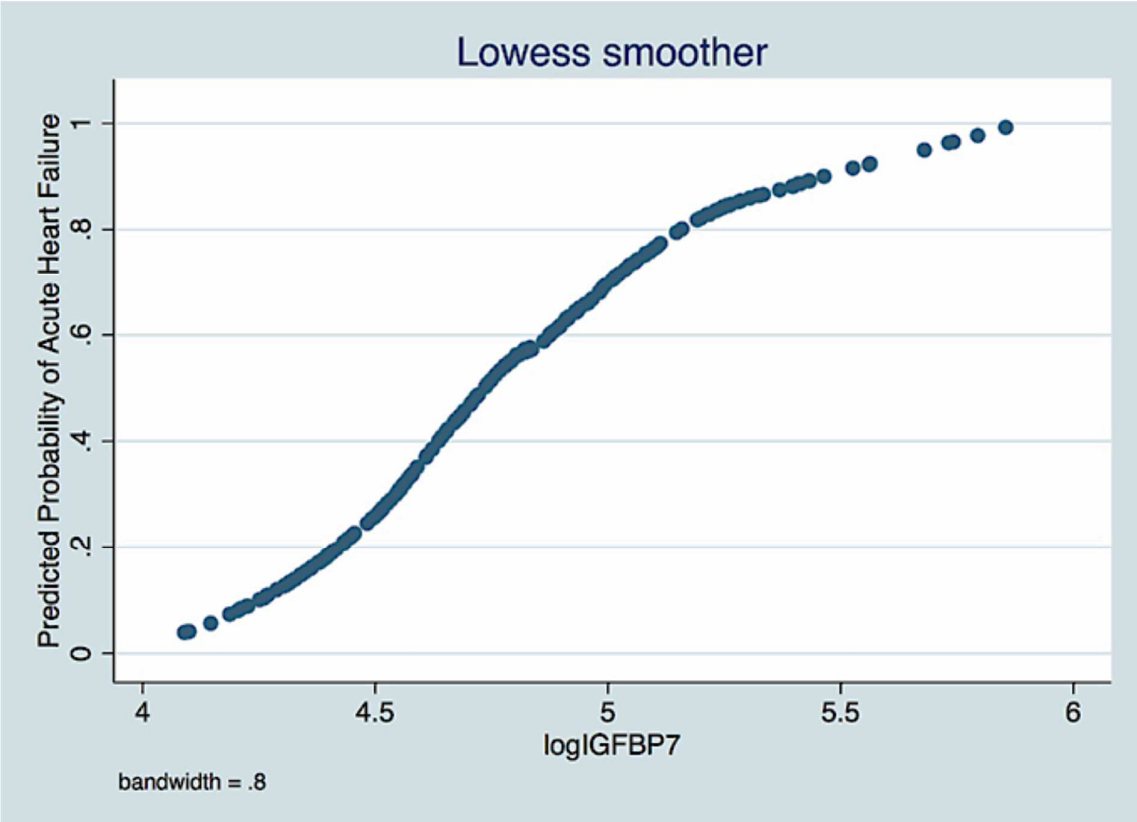


Figure 4. Association between predicted risk of acute heart failure and insulin-like growth factor-binding protein-7 (IGFBP7) was plotted with smooth curves

Abbreviation: IGFBP7 denotes insulin-like growth factor binding protein-7

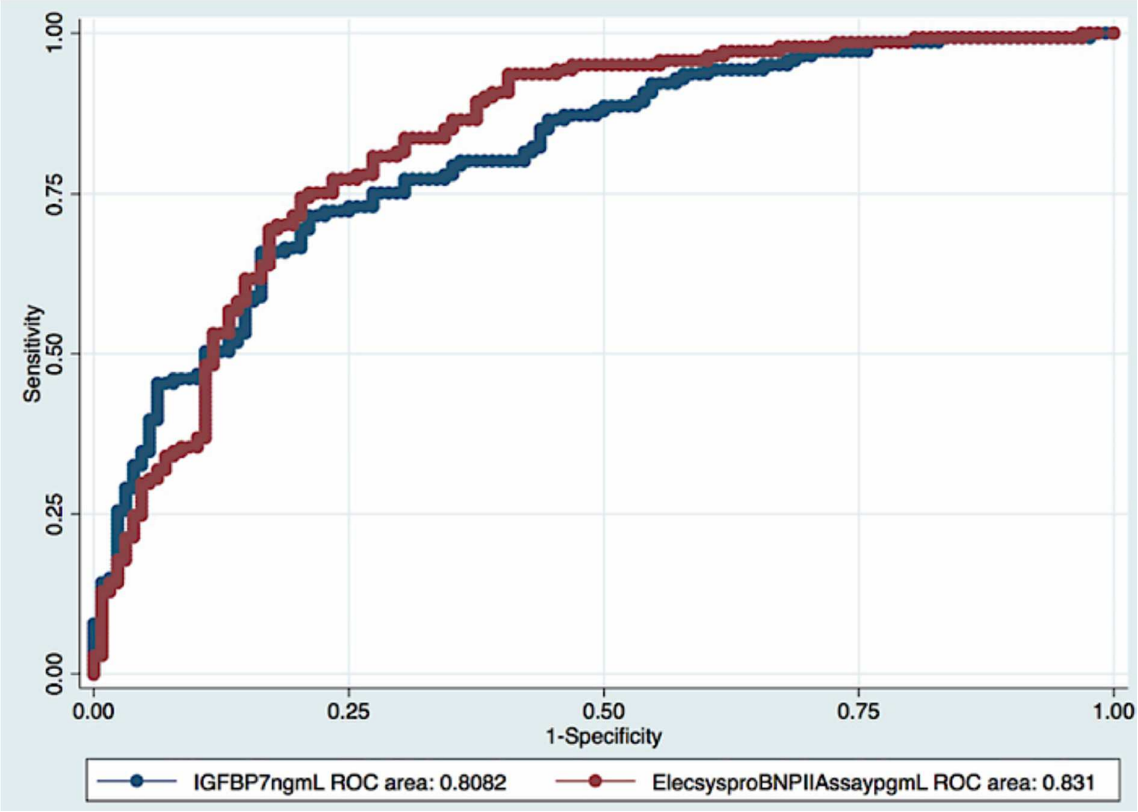


Figure 5. Comparison of ROC curves for IGFBP7 and NT-proBNP for the diagnosis of acute HF.

Abbreviations: ***ROC*** denotes receiver operating characteristic, ***IGFBP7*** denotes insulin-like growth factor-binding protein-7, ***NT-proBNP*** denotes, N-terminal pro b-type natriuretic peptide

SUPPLEMENTAL FILE

Supplementary Table-1. Echocardiographic Indices of Patients with Asthma and COPD, without Acute Heart Failure by the Median Value of IGFBP7

Echocardiographic Indices	IGFBP7 < Median (n= 27)	IGFBP7 ≥ Median (n= 16)	p value
LV mass index (g/m^2)	83.6 (66.3 – 104.9)	102 (83.6 – 126.8)	0.21
RV fractional area change (%)	43.2 (36.8 – 51.3)	36.3 (28 – 46)	0.09
RV diastolic area (cm^2)	19.4 (14.8 – 23.4)	22.4 (18.7 – 27.6)	0.34
RV systolic area (cm^2)	10.48 (8.2 – 13.9)	14.7 (10.7 – 18.6)	0.14
LAVi (mL/m^2)	28.8 (21.8 – 36.1)	41.4 (33.1 – 51.2)	0.13
E/A	1 (0.8 – 1.3)	1.32 (0.89 – 1.96)	0.34
E/e'	9.3 (7.4 – 13.7)	13.5 (11 – 19.7)	0.01
Mean mitral annular e' (cm/s)	8 (6 – 10)	7 (5.2 – 8.5)	0.37

Median and IQR are presented.

Abbreviations: IQR denotes interquartile range, ***COPD*** denotes chronic obstructive pulmonary disease, ***LV*** denotes left ventricle, ***RV*** denotes right ventricle, ***LAVi*** denotes left atrial volume index, ***E/A*** denotes the ratio of early to late transmitral diastolic velocities, ***E/e'*** denotes the ratio between early mitral inflow velocity and mitral annular early diastolic velocity, ***IGFBP7*** denotes insulin-like growth factor binding protein-7.

Supplemental Table 2. Clinical Characteristics of the Study Population by the Median Value of NT-proBNP

Patient Characteristic	NT-proBNP < Median (N=135)	NT-proBNP ≥ Median (N=136)	p-value
Age, years *	59 (51-68)	67 (56-77)	<0.001
Female, n (%)	46.2 (62/134)	40.1% (55/136)	0.86
eGFR (mL/min/1.73m^2) *	78.3 (64.7-101.1)	56.1 (42.6-75.9)	<0.001
BMI (kg/m^2) *	32.2 (26.6-39.6)	30 (25.7-35.2)	0.03
Body surface area (m^2) *	2.07 (1.89-2.29)	2 (1.79-2.22)	0.07
Medical history			
Diabetes Mellitus (%)	32.3 (43/133)	40.4% (55/136)	0.16
Heart Failure (%)	22.3 (29/130)	62.1% (82/132)	<0.001
Hypertension (%)	70.1 (94/134)	80.7% (109/135)	0.04
Prior CAD (%)	20.4 (27/132)	44.1% (60/136)	<0.001
Previous MI (%)	6.1 (8/130)	27.2% (36/132)	<0.001
Significant Aortic Valve Disease (%)	1.6 (2/119)	7.4% (9/121)	0.03
Significant Mitral Valve Disease (%)	6.6 (8/121)	7% (9/127)	0.88
COPD (%)	25 (33/132)	25.7% (35/136)	0.89
Asthma (%)	18.9 (25/132)	16.1% (22/136)	0.55
Medications at discharge			
Beta Blockers (%)	27.4 (37/135)	47.7% (65/136)	0.001
Loop Diuretic (%)	26.6 (36/135)	69.1% (94/136)	<0.001
ACEi or ARB (%)	23.7 (32/135)	37.5% (51/136)	<0.001
Vital signs			
Pulse Rate (bpm) *	91 (76-107)	88.5 (74-110)	0.74
SBP (mmHg) *	140 (126-168)	143 (126-162)	0.99
DBP (mmHg) *	82 (73-94)	83 (71-98)	0.91

The median NT-proBNP value is 1229 pg/dl.
* Median and IQR are presented.

Abbreviations: IQR denotes interquartile range, ***eGFR*** denotes estimated glomerular filtration rate, ***BMI*** denotes body mass index, ***CAD*** denotes coronary artery disease, ***MI*** denotes myocardial infarction, ***COPD*** denotes chronic obstructive pulmonary disease, ***ACEi*** denotes Angiotensin-converting enzyme inhibitors, ***ARB*** denotes Angiotensin II receptor blockers, ***SBP*** denotes systolic blood pressure, ***DBP*** denotes diastolic blood pressure, ***NT-proBNP*** denotes N-terminal pro b-type natriuretic peptide.

Supplemental Table 3. Echocardiographic Indices of the Study Population by the Median Value of NT-proBNP

Echocardiographic Indices	NT-proBNP < Median (N=135)	NT-proBNP ≥ Median (N=136)	p-value
Left ventricle			
Posterior wall thickness (mm) *	10 (8.3-11)	10 (8.9-12)	0.06
LV mass index (g/m^2) *	82.7 (65.6-98.5)	108.1 (83.6-129.3)	<0.001
LVEDVi (mL/m^2) *	52.7 (43.9-62.1)	72.6 (51.2-95.4)	<0.001
LVESVi (mL/m^2) *	17.3 (13.7-23.8)	41 (22.3-66.5)	<0.001
LVEF (%)*	63.4 (51.9-72.3)	40.3 (26.2-59.7)	<0.001
Right ventricle			
RV diastolic area (cm^2) *	19.8 (15.7-23.4)	22.3 (17.4-27)	0.001
RV systolic area (cm^2) *	10.3 (8.1-13.8)	14.5 (10.8-18.6)	<0.001
RV fractional area change (%)*	44.5 (39.1-52.2)	36.1 (26.5-45.1)	<0.001
RV hypokinesis			<0.001
None (%)	88.6 (109/123)	61.7 (71/115)	
Mild (%)	6.5 (8/123)	13.9 (16/115)	
Moderate (%)	3.2 (4/123)	13 (15/115)	
Severe (%)	1.6 (2/123)	11.3 (13/115)	
LAVi (mL/m^2) *	27.7 (21.2-34.2)	42.4 (34.9-51.9)	<0.001
Trans-mitral doppler			
E (cm/s) *	77 (63-96)	96 (76-121)	<0.001
A (cm/s) *	69.5 (58-89)	59 (41-82)	<0.001
E/A*	1.02 (0.8-1.2)	1.5 (0.9-2.2)	<0.001
DT (ms)*	188 (163-216)	153 (123-184)	<0.001
Pulmonary vein flow			
S (cm/s) *	47 (38-60)	35.5 (27-46)	<0.001
D (cm/s) *	44 (32-56)	53 (37-65)	0.04
S/D*	1.1 (0.8-1.3)	0.6 (0.5-1)	<0.001
Tissue doppler			
Mitral annular e' septal (cm/s) *	7 (6-9)	5.5 (4-7)	<0.001
Mitral annular e' lateral (cm/s) *	9 (7-12)	8 (6-9)	<0.001
Mean mitral annular e' (cm/s) *	8.2 (6.7-10.5)	6.5 (5-8.5)	<0.001
E/e' *	9.2 (7.4-12.9)	14 (11-19.3)	<0.001
E/e'≥15 (%)	14.7 (17/115)	47.2 (52/110)	<0.001
Diastology grade			<0.001
Normal (%)	65 (69/106)	14.7 (14/95)	
Grade I (%)	15 (16/106)	11.5 (11/95)	
Grade II (%)	14.1 (15/106)	40 (38/95)	
Grade III (%)	4.7 (5/106)	33.6 (32/95)	
Indeterminate (%)	0.9 (1/106)	0 (0/95)	

TR severity			<0.001
None (%)	3.9 (5/128)	0.7 (1/129)	
Trace (%)	67.1 (86/128)	34.1 (44/129)	
Mild (%)	25.7 (33/128)	35.6 (46/129)	
Moderate (%)	3.1 (4/128)	26.3 (34/129)	
Severe (%)	0 (0/128)	3.1 (4/129)	
MR severity			<0.001
None (%)	12.7 (16/126)	2.3 (3/130)	
Trace (%)	62.7 (79/126)	33 (43/130)	
Mild (%)	19.8 (25/126)	40 (52/130)	
Moderate (%)	3.1 (4/126)	21.5 (28/130)	
Severe (%)	1.5 (2/126)	3 (4/130)	

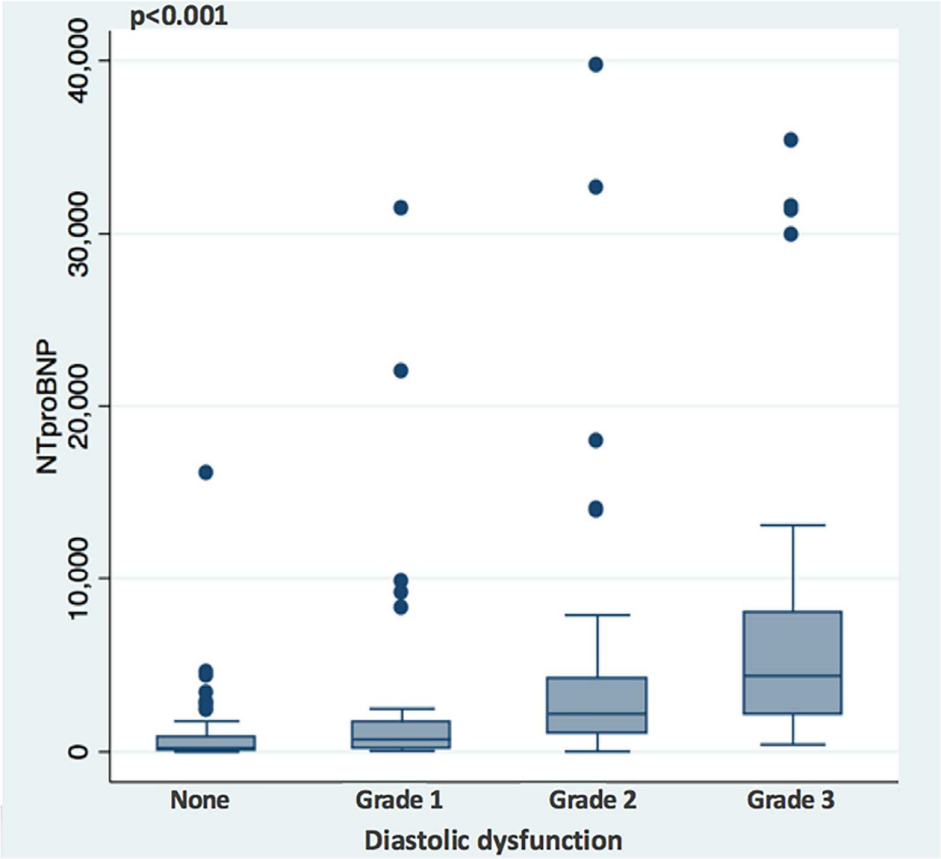
The median NT-proBNP value is 1229 pg/dl.
* Median and IQR are presented.

Abbreviations: ***IQR*** denotes interquartile range, ***LV*** denotes left ventricle, ***LVEDVi*** denotes left ventricular end-diastolic volume index, ***LVESVi*** denotes left ventricular end-systolic volume index, ***LVEF*** denotes left ventricular ejection fraction, ***RV*** denotes right ventricle, ***LAVi*** denotes left atrial volume index, ***E*** denotes early transmitral diastolic velocities, ***A*** denotes late transmitral diastolic velocities, ***E/A*** denotes the ratio of early to late transmitral diastolic velocities, ***DT*** denotes early deceleration time, ***S*** denotes pulmonary venous systolic velocities, ***D*** denotes pulmonary venous diastolic velocities, ***S/D*** denotes the ratio of pulmonary venous systolic to diastolic velocities, ***E/e'*** denotes the ratio between early mitral inflow velocity and mitral annular early diastolic velocity, ***TR*** denotes tricuspid regurgitation, ***MR*** denotes mitral regurgitation, ***NT-proBNP*** denotes N-terminal pro b-type natriuretic peptide.

Supplemental Table-4. Diagnostic Performance of IGFBP7 Across Subgroups

Chronic Diseases	**AUC Diagnosis (+)**	**AUC Diagnosis (-)**
Diabetes	0.81 (n=96)	0.81 (n=171)
Hypertension	0.78 (n=65)	0.86 (n=202)
Atrial Fibrillation	0.80 (n=72)	0.80 (n=194)
Gender	**Female**	**Male**
AUC	0.84	0.76
Age Categories	**AUC**	
≥ 22 - < 53 (n= 61)	0.81	
≥ 53 - < 63 (n= 72)	0.80	
≥ 63 - < 73 (n= 67)	0.90	
≥ 73 - ≤ 93 (n= 69)	0.70	

Abbreviations: ***AUC*** denotes area under curve, ***IGFBP7*** denotes insulin-like growth factor binding protein-7.



Supplemental Figure 1. Box-plots of NT-proBNP concentrations according to the left ventricular diastolic dysfunction grading

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The Body Mass Index Paradox in Venous Thromboembolism:

Observations from the APEX (Acute Medically Ill VTE Prevention

With Extended-Duration Betrixaban) Trial

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Keywords: venous thrombosis; body mass index; obesity paradox

Abbreviations

APEX, Acute Medically Ill VTE Prevention with Extended Duration Betrixaban trial

BMI, body mass index

CCI, Charlson Comorbidity Index

COPD, chronic obstructive pulmonary disease

CRNM, clinically relevant non-major

DVT, deep vein thrombosis

HF, heart failure

ICU, intensive care unit

PE, pulmonary embolism

VTE, venous thromboembolism

WBC, white blood cell

Abstract

Obesity is associated with cardiovascular complications such as diabetes and hypertension. However, obesity and high body mass index (BMI) can also be linked with improved clinical outcomes in certain patient populations. This counterintuitive observation is called the "obesity paradox." The effect of BMI on the risk of developing venous thromboembolism (VTE) in acutely ill medical patients remains unclear. In the Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) trial, acutely ill hospitalized medical patients were randomized to receive either extended-duration betrixaban or shorter-duration enoxaparin. A total of 7,372 patients with evaluable VTE endpoints had BMI measured at baseline. The association between BMI and VTE risk was assessed after adjusting for potential confounders. The multivariable adjusted odds ratios for VTE endpoint associated with BMI levels (20-15, 20-18.5, 20 [reference BMI value], 20-25, 20-30, 20-35, 20-40, 20-45) were 1.80 (95% confidence interval [CI], 1.20 – 2.70), 1.19 (95% CI, 1.06 – 1.35), 0.62 (0.44 – 0.88), 0.76 (0.53 – 1.08), 0.86 (0.61 – 1.24), and 0.73 (0.49 – 1.08), 0.56 (0.32 – 0.99) respectively (p=0.021). In conclusion, acutely ill hospitalized patients with higher BMI had a lower VTE risk, which appears to be a manifestation of the obesity paradox.

Introduction

Obesity is an established risk factor for the development of cardiovascular and metabolic illnesses.[1-5] Nevertheless, increasing evidence suggests a protective effect of obesity in certain medical conditions such as acute heart failure[6], pneumonia[7], acute myocardial infarction[8], stroke,[9] and hospitalization for critical illnesses[10,11] – the so-called "obesity paradox". A hallmark of acute illness is a hypercatabolic state that increases energy expenditure and requires an ample supply of calories stored in the adipose tissue.[12] An impaired metabolic response to acute stress and poor nutritional reserve may adversely impact the clinical outcome.

In this study, we sought to investigate the association of BMI with VTE among medically ill hospitalized patients randomized in the APEX trial.[13] We also tested the effect of comorbidity burden on the risk of VTE using the Charlson Comorbidity Index (CCI), a validated comorbidity assessment tool.[14]

Methods

Study Population

The APEX trial design and principal results have been published.[15] APEX is a multicenter, double-blind, randomized controlled trial that enrolled 7,513 acutely ill hospitalized medical patients. Subjects were randomized in a 1:1 ratio to receive VTE prophylaxis with either extended-duration betrixaban for 35 to 42 days or shorter-duration enoxaparin for 10 ± 4 days. Key eligibility criteria included: (1) hospitalization for acute medical illness; (2) older age or elevated D-dimer with a history of VTE or cancer; (3) anticipated severe immobilization for ≥ 24 hours followed by moderate or severe immobilization for 3 or more days; and (4) anticipated hospitalization for 3 or more days.

Study Endpoints

The primary efficacy endpoint was a composite of asymptomatic proximal deep vein thrombosis (DVT) detected by ultrasonography between days 35 and 47, symptomatic

proximal or distal deep vein thrombosis, symptomatic nonfatal pulmonary embolism, or fatal pulmonary embolism through 42 days after randomization. The primary safety outcome included major bleeding through 7 days after discontinuation of all study medications. All randomized patients with non-missing baseline BMI values and evaluable VTE endpoints (N=7372) were included in the analysis *(Figure 1)*.

Events were adjudicated by an independent clinical events committee blinded to thromboprophylaxis allocation. The study was approved by the local institutional review committees, and all enrolled participants provided informed consent.

Definition of Adiposity

BMI was assessed at baseline in kg/m^2 and was the measure of adiposity. In compliance with the conventional World Health Organization (WHO) BMI classification, patients were categorized as follows: underweight (BMI < 18.5 kg/m^2), normal weight (BMI ≥ 18:5, <25 kg/m^2), pre-obesity (BMI ≥ 25, <30 kg/m^2), obesity class I (BMI ≥ 30, <35 kg/m^2), obesity class II (BMI ≥ 35, <40 kg/m^2), and obesity class III (BMI ≥ 40 kg/m^2). We have also divided the data into BMI quartiles to present it in four equal parts.

Charlson Comorbidity Index (CCI)

The CCI[19] predicts the risks of short-term and long-term patient mortality. It has been used extensively for comorbidity assessment.[20,21] There are three components: disease assessment, severity assessment, and scoring. It includes 16 diseases: myocardial infarction, heart failure, peripheral arterial obstructive disease, cerebrovascular disease, senile dementia, chronic obstructive pulmonary disease (COPD), connective tissue disease, gastroduodenal ulcer, diabetes, chronic kidney disease, hemiplegia, leukemia, malignant lymphoma, tumor and metastasis, liver disease, and AIDS. Each comorbidity has an associated weight (either between 1 and 3 or 6), based on the adjusted risks of mortality. The sum of all weights results in a single

comorbidity score. Age-based scoring starts at the age of 50 years, with a 1-point increase for every 10 years above age 50.

CCI was used to quantify patients' comorbidities and was included in the logistic regression model to adjust for comorbid conditions.

Statistical Analysis

Analyses in this sub-study were post hoc and exploratory. Baseline characteristics were reported using medians and interquartile range (IQR) for continuous variables, and frequencies and percentages for categorical variables. The baseline characteristics of study participants were compared across BMI categories using the chi-squared test for categorical variables and the one-way ANOVA or Kruskal-Wallis test for continuous variables, as appropriate.

A logistic regression model was fitted to compute odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Restricted cubic splines with 4 knots were used to allow for non-linear relationships between continuous variables and outcome. Variable selection was conducted considering clinical knowledge, previous literature, and biological plausibility. The explanatory variable was BMI (as continuous). Other covariates were treatment allocation, and established risk factors (CCI [as categorical], sex, history of VTE, heart failure, respiratory failure, ischemic stroke, rheumatic disorder, serum D-dimer [as continuous], C- Reactive Protein [as continuous], albumin [as continuous], hemoglobin [as continuous], WBC [as continuous]) were included into the model to assess associations with primary efficacy outcome. Variables that are included as components of the CCI score (i.e., age, malignancy) with a high variance inflation factor (> 10) were not included in the model in order to avoid multicollinearity. Variables with a very high frequency or a very low frequency were not included in the model (i.e., thrombophilia, hormone replacement therapy). Treatment effects were compared in a separate model according to BMI (as continuous, using restricted cubic splines), by adding interaction terms into the model including BMI and treatment allocation.

In the present study, we have performed a complete case analysis since most of the variables included in the model had minimal (< 3%) missing data.

A two-sided P-value of 0.05 was considered statistically significant. *All* statistical *analyses were performed using R* version 3.6.3.

Results

Baseline characteristics

Baseline characteristics across WHO BMI categories and BMI quartiles are presented in *Table 1* and *Table 2*, respectively. Compared with lower BMI, patients with a higher BMI were younger, more likely to be female, and less likely to be of Asian ethnicity. Further, patients with increased BMI had lower levels of D-dimer and C-reactive protein, higher levels of albumin and hemoglobin, and were more likely to have a history of heart failure and VTE. Patients with a higher BMI also had lower baseline CCI scores.

Impact of Body Mass Index on VTE risk

A total of 384 (5.2%) patients suffered the composite VTE endpoint of asymptomatic DVT, symptomatic DVT, non-fatal pulmonary embolism (PE), or VTE-related death within 42 days after randomization. The incidence of the composite VTE endpoint across BMI categories is presented in *Table 3.* Composite VTE endpoint was mainly driven by the occurrence of asymptomatic DVT (79%). Underweight patients (<18.5 kg/m^2) proportionally had a higher composite VTE event (7.9%) and asymptomatic VTE occurrence (9%) compared to other groups. The multivariable adjusted ORs of VTE risk associated with BMI levels (15, 18.5, 20 [reference BMI value], 25, 30, 35, 40, 45) were 1.80 (95% CI, 1.20 – 2.70), 1.19 (95% CI, 1.06 – 1.35), 0.62 (0.44 – 0.88), 0.76 (0.53 – 1.08), 0.86 (0.61 – 1.24), and 0.73 (0.49 – 1.08), 0.56 (0.32 – 0.99) respectively. Higher BMI was associated with a lower risk of VTE (p=0.021; p for non-linearity=0.010; *Table 4, Figure 2, Figure 3*).

The present analysis of the non-linear relationship revealed a remarkable decrease in VTE risk throughout the BMI levels from underweight to overweight, followed by a slight increase within the BMI levels of class I obesity. Continued VTE risk reduction was observed across the BMI levels of class II and class III obesity categories. The multivariable-adjusted associations for predictor variables are presented in *Table 4*.

Body Mass Index and Primary Efficacy Outcome

Overall, 384 patients experienced a VTE event (5.2%). Patients treated with both betrixaban and enoxaparin had lower rates of VTE as BMI increased (*Figure 3*). There was no significant interaction between BMI and the treatment groups for the primary efficacy outcome (p for interaction= 0.274).

Body Mass Index and Safety Outcome

A total of 46 patients experienced major bleeding (0.6%). Gastrointestinal bleeding was the most common type of major bleeding, occurring in 25 patients (54%). The distribution of major bleeding across BMI categories was similar (p = 0.466). Further, clinically relevant non-major (CRNM) bleeding was observed in 128 patients (1.7%). There was no significant imbalance across BMI categories with respect to the CRNM bleeding (p = 0.980) (*Table 3*).

Charlson Comorbidity Index and VTE risk

Higher CCI scores were associated with a higher risk of VTE (OR: 1.25; 95% CI: 1.02 to 1.54, p=0.034). A stepwise increase in higher CCI scores (≥6) was observed toward the lower BMI category (p for trend <0.001). In the adjusted analysis, however, the interaction between BMI and CCI scores did not reach statistical significance (p for interaction= 0.262) (*Figure 4*).

Discussion

The present study demonstrates that among patients hospitalized with an acute medical illness, a higher baseline BMI level was associated with a lower risk of VTE. The observed benefit of both betrixaban and enoxaparin was incremental with increasing BMI. Bleeding risk was

similar across the BMIs and did not differ between the two treatment arms. Higher CCI scores were associated with an increased risk of VTE.

Previous studies have reported a "BMI paradox" manifested by an inverse relationship between overweight population and outcomes in cardiovascular[6,8,16-21] and non-cardiovascular conditions.[7,22-24] Our data now document the existence of a 'BMI paradox' in a large cohort of acutely ill hospitalized medical patients who are receiving anticoagulant prophylaxis.

There are several possible explanations for the BMI paradox with regard to VTE risk in acutely ill medical patients. Acute illness is a hypercatabolic state and alters energy expenditure. The severity of these alterations is associated with adverse outcomes.[12,25] The adaptive catabolism is orchestrated by a coordinated neuroendocrine and cytokine response. Although the primary metabolic role of adipose tissue is to serve as a key energy reservoir, it can also respond to an acute illness by increasing its storage capacity to absorb circulating toxic metabolites.[26] Furthermore, higher BMI may be associated with a better nutritional reserve, favorable immune function, and better tolerability of required therapies compared with lean patients with poor nutritional status and/or cachexia.[25,27] In addition, malignancy is the main example of an underlying disease exhibiting prominent thrombogenicity that can even overcome the protective effect of anticoagulants. It is noteworthy that the distribution of cancer patients numerically but not significantly increased toward the lower BMI category. The lack of statistical significance may be attributable to the very small number of cancer patients in our study population.

In the literature, the BMI paradox is usually characterized by U- or J-shaped curves, with elevated risk levels at both the low and high ends of the BMI continuum. Still, the optimal BMI range associated with the lowest adverse events varies according to patient characteristics and the nature of the underlying illness.[28-31] In the present analysis of acutely ill hospitalized patients, a dramatic decrease in VTE risk was observed from underweight to overweight.

Hospitalized medical patients with varying BMIs can respond to medications differently as they may have an altered pharmacokinetic and pharmacodynamic profile due to the nature and burden of underlying medical conditions. Therefore, the reduction in VTE risk in relation to a higher BMI can also be attributable to the incremental benefit of anticoagulant therapy with increasing BMI.

The principal strengths of this analysis include the large sample size that was derived from a multicenter clinical trial population. The diagnoses assigned followed a strict protocol and were independently adjudicated.

Limitations

First, this study is an exploratory analysis from a population that agreed to participate in a clinical trial with specific enrollment criteria. Second, although we adjusted for a range of confounding variables, the effects of residual confounding cannot be excluded. Third, the evaluation of body weight using BMI is a valuable tool to provide a standardized definition of obesity; however, BMI alone may not provide a good estimate of fat distribution in the body. Finally, BMI was only measured at baseline and was assumed to be stable during the course of the study.

Conclusions

Our data suggest that among acutely ill hospitalized patients who received anticoagulation, VTE risk is paradoxically lower in patients with a higher BMI compared to lean patients. Higher BMI may be protective and associated with a decreased VTE risk in the setting of acute illness.

Table 1. Baseline characteristics across BMI categories

Characteristics	BMI Categories						p value
	Underweight (BMI <18.5) (n = 101)	Normal Weight (BMI = 18.5–24.9) (n = 1833)	Pre-obesity (BMI = 25–29.9) (n = 2557)	Obesity class I (BMI = 30–34.9) (n = 1473)	Obesity class II (BMI = 35–39.9) (n = 904)	Obesity class III ((BMI ≥40) (n = 504)	
Age, yr*	78 (72 - 85)	78 (74 - 83)	78 (75 -83)	77 (73 - 81)	73 (67 - 79)	69 (63 - 77)	<0.001
Male, n (%)	53 (52)	946 (52)	1241 (49)	605 (41)	368 (41)	148 (29)	<0.001
Duration of Hospitalization*	9 (6 -13)	10 (7 - 14)	10 (8 -14)	10 (8 -14)	10 (8 -14)	10 (8 -14)	0.451
Strong P-gp Inhibitor, n (%)	21 (21)	340 (19)	472 (18)	252 (17)	148 (16)	104 (21)	0.313
Previous thromboprophylaxis ≤ 96 hours, n (%)	49 (49)	918 (50)	1336 (52)	708 (48)	463 (51)	279 (55)	0.045
Serum Creatinine Level*	0.91 (0.70 - 1.10)	0.94 (0.80 - 1.30)	1.02 (0.87 - 1.31)	1.02 (0.80 - 1.30)	1 (0.87 - 1.31)	1 (0.80 - 1.30)	<0.001
Serum D-Dimer*	1.48 (0.74 - 2.46)	1.41 (0.73 - 2.41)	1.31 (0.66 - 2.39)	1.34 (0.69 - 2.33)	1.01 (0.49 - 1.97)	1.11 (0.54 – 1.94)	<0.001
C-Reactive Protein*	47.8 (7.95 - 81.5)	15.7 (3.70 - 70.3)	11.8 (3.30 - 61.1)	10.7 (3.89 - 41.3)	9.9 (3.87 - 41.3)	15.3 (6.10 - 52.4)	<0.001
Albumin*	36 (32 - 40)	38 (34 - 41)	39 (35 - 42)	39 (36 - 42)	40 (36 - 42)	39 (36 - 42)	<0.001
WBC*	8.7 (6.67 - 11.52)	8.2 (6.35 - 10.70)	7.9 (6.30 - 10.30)	8.1 (6.5 - 10.4)	8 (6.4 - 10)	8.4 (6.8 - 10.4)	0.010
Hemoglobin*	12.6 (11.3 - 14.1)	12.8 (11.7 - 13.9)	13 (12 - 14.1)	13.1 (12 – 14.1)	13.2 (12 – 14.4)	13.1 (11.9 – 14.4)	<0.001
Race, n (%)							<0.001
White **Asian** **Black** **Other¥**	87 (86) 0 (0.0) 5 (5) 9 (8.9)	1699 (91) 11 (0.6) 39 (2.1) 114 (6.2)	2414 (94) 2 (0.1) 37 (1.4) 104 (4)	1394 (95) 1 (0.1) 20 (1.4) 58 (3.9)	866 (96) 1 (0.1) 17 (1.9) 20 (2.2)	463 (92) 1 (0.2) 22 (4.4) 18 (3.6)	
Acute Medical Condition, n (%)							
Heart Failure **Infectious Disease** **Respiratory Failure** **Ischemic Stroke** **Rheumatic Disorder**	18 (18) 45 (45) 31 (31) 3 (3.0) 4 (4.0)	700 (38) 565 (31) 284 (15) 228 (12) 56 (3.1)	1140 (45) 693 (27) 279 (11) 357 (14) 87 (3.4)	717 (49) 426 (29) 135 (9.2) 157 (11) 37 (2.5)	482 (53) 226 (25) 109 (12) 65 (7.2) 22 (2.4)	275 (55) 123 (24) 62 (12) 28 (5.6) 16 (3.2)	<0.001 <0.001 <0.001 <0.001 0.547

Risk Factors for VTE, n (%)							
D-dimer*	1.48 (0.74 - 2.46)	1.41 (0.73 - 2.41)	1.31 (0.66 - 2.39)	1.34 (0.69 - 2.33)	1.01 (0.49 - 1.97)	1.11 (0.54 – 1.94)	<0.001
Age ≥ 75	70 (69)	1347 (73)	1958 (77)	1025 (70)	413 (46)	173 (34)	<0.001
Malignancy	5 (5.0)	81 (4.4)	91 (3.6)	48 (3.3)	35 (3.9)	16 (3.2)	0.490
Previous VTE	4 (4.0)	114 (6.2)	159 (6.2)	134 (9.1)	106 (12)	77 (15)	<0.001
History of HF	14 (14)	449 (24)	741 (29)	451 (31)	272 (30)	134 (27)	<0.001
Severe Varicosis	8 (7.9)	172 (9.4)	254 (9.9)	216 (15)	156 (17)	94 (19)	<0.001
HRT	4 (4)	24 (1.3)	24 (0.9)	12 (0.8)	6 (0.7)	3 (0.6)	0.020
Known thrombophilia	0 (0.0)	1 (0.1)	3 (0.1)	3 (0.2)	0 (0.0)	1 (0.2)	0.668
Lower limb paralysis	4 (4)	144 (7.9)	226 (8.8)	114 (7.7)	46 (5.1)	29 (5.8)	0.003
ICU admission	9 (8.9)	162 (8.8)	265 (10.4)	135 (9.2)	78 (8.6)	53 (10.5)	0.444
CCI score, n (%)							<0.001
0	0 (0.0)	1 (0.1)	3 (0.1)	3 (0.2)	2 (0.2)	2 (0.4)	
1	1 (1)	8 (0.4)	15 (0.6)	8 (0.5)	8 (0.9)	6 (1.2)	
2	2 (2)	78 (4.3)	63 (2.5)	69 (4.7)	65 (7.2)	56 (11.1)	
3	13 (13)	289 (15.9)	391 (15.4)	261 (17.7)	179 (19.9)	119 (23.7)	
4	37 (37)	556 (30.6)	720 (28.3)	412 (28)	242 (26.9)	134 (26.6)	
5	18 (18)	403 (22.2)	640 (25.1)	307 (20.9)	182 (20.2)	89 (17.7)	
6	15 (15)	240 (13.2)	393 (15.4)	194 (13.2)	117 (13)	56 (11.1)	
7	5 (5.0)	143 (7.9)	194 (7.6)	144 (9.8)	58 (6.5)	21 (4.2)	
8	5 (5.0)	61 (3.4)	86 (3.4)	51 (3.5)	26 (2.9)	12 (2.4)	
9	1 (1.0)	26 (1.4)	26 (1.0)	17 (1.2)	16 (1.8)	6 (1.2)	
10	1(1.0)	9 (0.5)	10 (0.4)	4 (0.3)	3 (0.3)	1 (0.2)	
11	2(2.0)	2 (0.1)	5 (0.2)	1 (0.1)	1 (0.1)	1 (0.2)	
12	0 (0.0)	1 (0.1)	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
CCI score, n (%)							<0.001
<6	71 (71)	1335 (73)	1832 (72)	1060 (72)	678 (75)	406 (81)	
≥6	29 (29)	482 (27)	715 (28)	411 (28)	221 (25)	97 (19)	

Abbreviations: WBC denotes white blood cell, ***VTE*** denotes venous thromboembolism, ***HF*** denotes heart failure, ***ICU*** denotes intensive care unit, ***CCI*** denotes Charlson Comorbidity Index. * Median and IQR are presented. ¥Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Multiple, Data Collection Prohibited by Regulation

Table 2. Baseline characteristics across BMI quartiles

Characteristics	BMI Quartiles				p value
	Quartile 1 (n = 1843)	Quartile 2 (n = 1843)	Quartile 3 (n = 1843)	Quartile 4 (n = 1843)	
Age, yr*	78 (74 - 83)	79 (75 - 83)	77 (74 -82)	74 (66 - 79)	<0.001
Male, n (%)	949 (51)	904 (49)	823 (45)	685 (37)	<0.001
Duration of Hospitalization*	10 (7 -14)	10 (7 - 14)	10 (8 -14)	10 (8 -14)	0.067
Strong P-gp Inhibitor, n (%)	349 (19)	354 (19)	302 (16)	332 (18)	0.181
Previous thromboprophylaxis ≤ 96 hours, n (%)	920 (50)	968 (53)	915 (50)	950 (52)	0.249
Serum Creatinine Level*	0.93 (0.79 - 1.20)	1 (0.80 - 1.30)	1 (0.80 - 1.30)	1 (0.82 - 1.30)	<0.001
Serum D-Dimer*	1.42 (0.73 - 2.45)	1.36 (0.67 - 2.44)	1.28 (0.68 - 2.26)	1.13 (0.55 - 2.06)	<0.001
C-Reactive Protein*	17.3 (4.09 - 72.1)	12.1 (3.40 - 67.2)	10.8 (3.40 - 52.3)	11.6 (4.40 - 48.9)	<0.001
Albumin*	37 (34 - 41)	39 (35 - 42)	39 (36 - 42)	39 (36 - 42)	<0.001
WBC*	8.3 (6.4 - 10.8)	7.9 (6.3 - 10.3)	7.9 (6.4 - 10.3)	8.1 (6.5 - 10.2)	0.010
Hemoglobin*	12.8 (11.7 - 13.9)	13.0 (11.9 - 14.1)	13.1 (12 - 14.1)	13.2 (12 – 14.3)	<0.001
Race, n (%)					<0.001
White	1672 (94)	1730 (95)	1749 (96)	1742 (96)	
Asian	11 (0.6)	1 (0.1)	1 (0.1)	3 (0.2)	
Black	41 (2.3)	28 (1.5)	25 (1.4)	46 (2.5)	
Other¥	57 (3.1)	54 (3.4)	38 (2.5)	27 (1.3)	
Acute Medical Condition, n (%)					
Heart Failure	687 (37)	814 (44)	846 (46)	985 (53)	<0.001
Infectious Disease	585 (32)	510 (28)	514 (28)	469 (25)	<0.001
Respiratory Failure	310 (17)	200 (11)	185 (10)	205 (11)	<0.001
Ischemic Stroke	207 (11)	249 (14)	249 (14)	133 (7.2)	<0.001
Rheumatic Disorder	54 (2.9)	70 (3.8)	47 (2.6)	51 (2.8)	0.127
Risk Factors for VTE, n (%)					
D-dimer*	1.42 (0.73 - 2.45)	1.36 (0.67 - 2.44)	1.28 (0.68 - 2.26)	1.13 (0.55 - 2.06)	<0.001
Age ≥ 75	1346 (73)	1420 (77)	1350 (73)	870 (47)	<0.001
Malignancy	80 (4.3)	72 (3.9)	63 (3.4)	61 (3.3)	0.325
Previous VTE	113 (6.1)	117 (6.3)	135 (7.3)	229 (12)	<0.001
History of HF	442 (24)	542 (29)	522 (28)	555 (30)	<0.001
Severe Varicosis	174 (9.4)	173 (9.4)	241 (13)	312 (17)	<0.001
HRT	27 (1.5)	18 (1.0)	15 (0.8)	13 (0.7)	0.095
Known thrombophilia	1 (0.1)	1 (0.1)	4 (0.2)	2 (0.1)	0.391
Lower limb paralysis	139 (7.5)	145 (7.9)	174 (9.4)	105 (5.7)	<0.001
ICU admission	157 (8.5)	194 (10.5)	181 (9.8)	170 (9.2)	0.196
CCI score, n (%)					<0.001
1	1 (0.1)	3 (0.2)	3 (0.2)	4 (0.2)	
2	9 (0.5)	10 (0.5)	11 (0.6)	16 (0.9)	
3	79 (4.3)	38 (2.1)	76 (4.1)	140 (7.6)	
4	285 (15.6)	284 (15.5)	311 (16.9)	372 (20.3)	
5	571 (31.3)	512 (27.9)	521 (28.3)	497 (27.1)	
6	401 (22)	450 (24.5)	423 (23)	365 (19.9)	

7	242 (13.3)	291 (15.9)	254 (13.8)	228 (12.4)	
8	141 (7.7)	147 (8.0)	151 (8.2)	126 (6.9)	
9	62 (3.4)	61 (3.3)	64 (3.5)	54 (2.9)	
10	22 (1.2)	25 (1.4)	19 (1.0)	26 (1.4)	
11	8 (0.4)	10 (0.5)	4 (0.2)	6 (0.3)	
12	4 (0.2)	3 (0.2)	3 (0.2)	2 (0.1)	
	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	

Abbreviations: WBC denotes white blood cell, ***VTE*** denotes venous thromboembolism, ***HF*** denotes heart failure, ***ICU*** denotes intensive care unit, ***CCI*** denotes Charlson Comorbidity Index.
* Median and IQR are presented.
¥Other includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Multiple, Data Collection Prohibited by Regulation

Table 3. Clinical outcomes across BMI categories

	BMI Categories						p value
	Underweight (BMI <18.5) (n = 101)	Normal Weight (BMI = 18.5–24.9) (n = 1833)	Pre-obesity (BMI = 25–29.9) (n = 2557)	Obesity class I (BMI = 30–34.9) (n = 1473)	Obesity class II (BMI = 35–39.9) (n = 904)	Obesity class III ((BMI ≥40) (n = 504)	
Primary Efficacy Endpoint, n (%)	8 (7.9)	105 (5.7)	120 (4.7)	87 (5.9)	43 (4.8)	21 (4.2)	0.235
Asymptomatic DVT, n (%)	6 (9.0)	83 (5.6)	95 (4.4)	72 (5.7)	33 (4.2)	16 (3.9)	0.133
Major Bleeding, n (%)	0 (0.0)	16 (0.9)	17 (0.7)	7 (0.5)	5 (0.6)	1 (0.2)	0.466
CRNM Bleeding, n (%)	2 (2.0)	32 (1.7)	44 (1.7)	28 (1.9)	13 (1.4)	9 (1.8)	0.980

Abbreviations: BMI denotes body mass index***, DVT*** denotes deep vein thrombosis***, CRNM*** denotes clinically relevant non-major, ***OR*** denotes odds ratio

Table 4. Associations of VTE risk with clinical and laboratory factors in acutely ill hospitalized patients

	Multivariable OR (95% CI) *	p-value
BMI (kg/m^2)		0.021
15 **18.5** **20** **25** **30** **35** **40** **45**	1.80 (1.20 – 2.70) 1.19 (1.06 – 1.35) **1.0 (Reference)[a]** 0.62 (0.44 – 0.88) 0.76 (0.53 – 1.08) 0.86 (0.61 – 1.24) 0.73 (0.49 – 1.08) 0.56 (0.32 – 0.99)	
Charlson Comorbidity Index (from 3 to 6)	1.25 (1.02 – 1.54)	0.038
Treatment (Betrixaban vs Enoxaparin)	1.46 (1.16 - 1.84)	0.001
Gender (Female vs male)	1.07 (0.85 - 1.37)	0.565
History of VTE (Yes vs. No)	3.51 (2.60 - 4.74)	< 0.001
Heart Failure (Yes vs. No)	0.93 (0.68 - 1.28)	0.684
Respiratory Failure (Yes vs. No)	1.21 (0.81 - 1.82)	0.366
Stroke (Yes vs. No)	1.59 (1.04 - 2.42)	0.026
Rheumatic Disorder (Yes vs. No)	1.33 (0.68 - 2.61)	0.402
Serum D-Dimer (mg/L, from 0.7 to 2.3)	2.18 (1.74 - 2.73)	< 0.001
C-Reactive Protein (mg/L, from 3.8 to 60.2)	1.07 (0.79 -1.45)	0.240
Albumin (g/L from 26 to 33)	0.72 (0.51 - 1.01)	0.049
Hemoglobin (g/dl, from 9 to 13)	0.87 (0.47 - 1.61)	0.310
WBC (10^3/µl, from 6.4 to 10.4)	1.41 (1.07 - 1.87)	0.022

*Adjusted odds ratios for individual predictors included in the logistic regression model.
[a]The reference BMI value was 20 kg/m^2.

Logistic regression model was used to examine the independent role of BMI in relation to 42-day primary efficacy outcome (a composite of asymptomatic proximal DVT, symptomatic proximal or distal deep vein thrombosis, symptomatic nonfatal pulmonary embolism, or fatal pulmonary embolism).

Abbreviations: ***OR*** denotes odds ratio, ***CI*** denotes confidence interval, ***BMI*** denotes body mass index, ***VTE*** denotes venous thromboembolism, ***WBC*** denotes white blood cell.

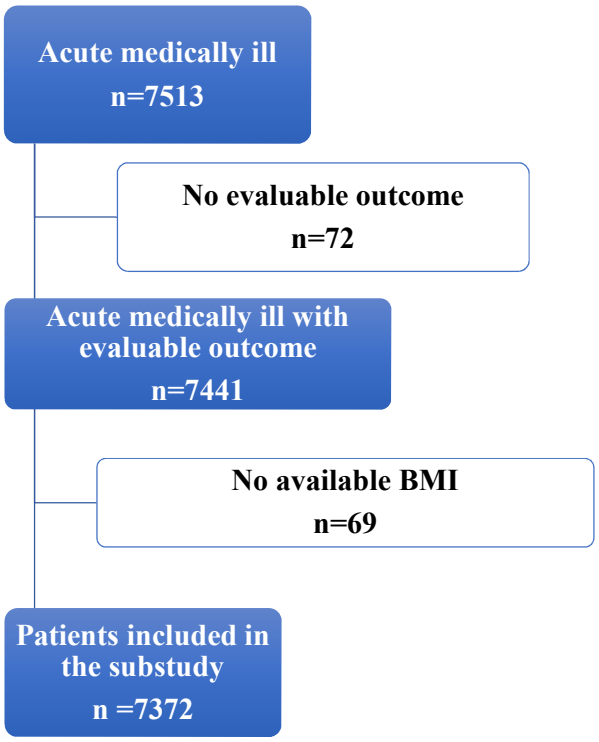


Figure 1. Flow of the study inclusion and exclusion criteria

Abbreviation: BMI denotes body mass index.

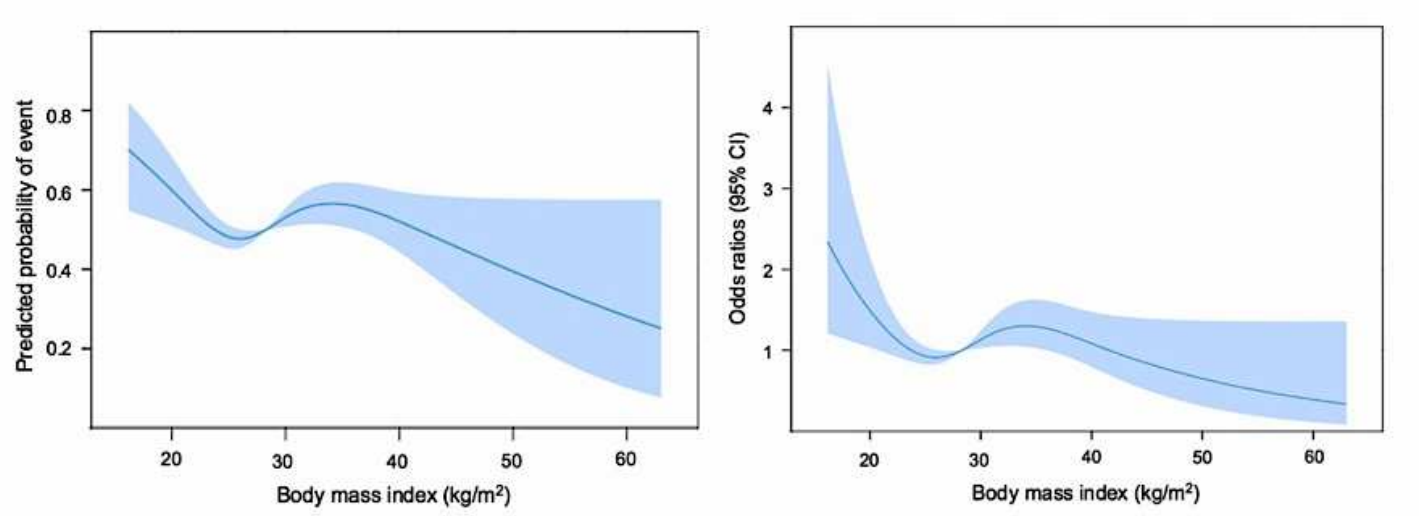


Figure 2. Smooth curves of the predicted probability and odds ratios for the primary efficacy outcome across each unit increase in body mass index in the overall study population. The primary efficacy outcome included a composite of asymptomatic proximal DVT, symptomatic proximal or distal deep vein thrombosis, symptomatic nonfatal pulmonary embolism, or fatal pulmonary embolism.

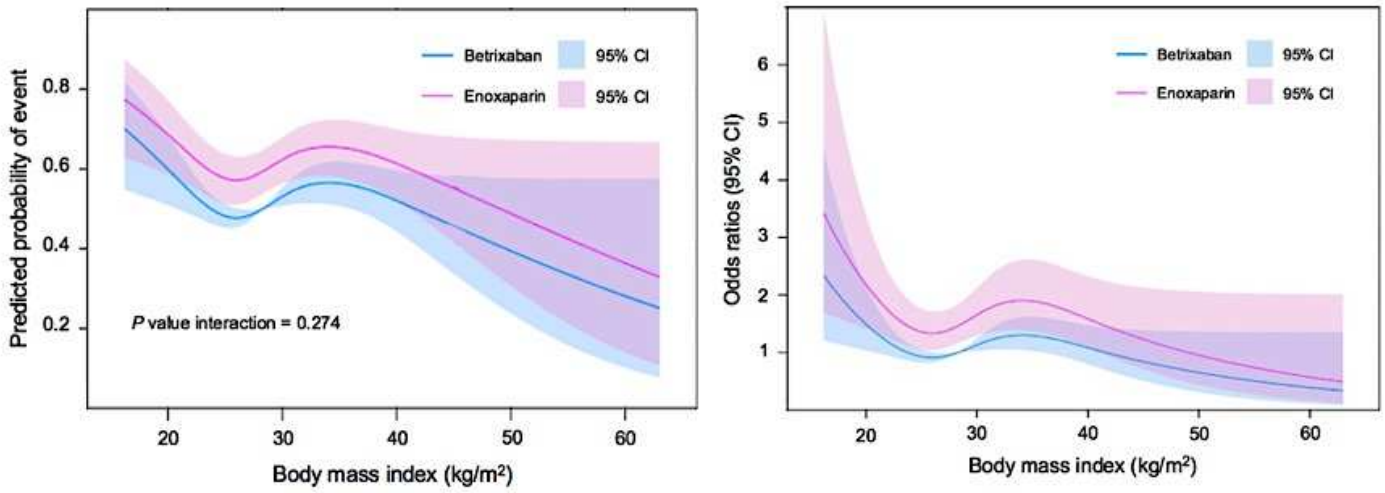
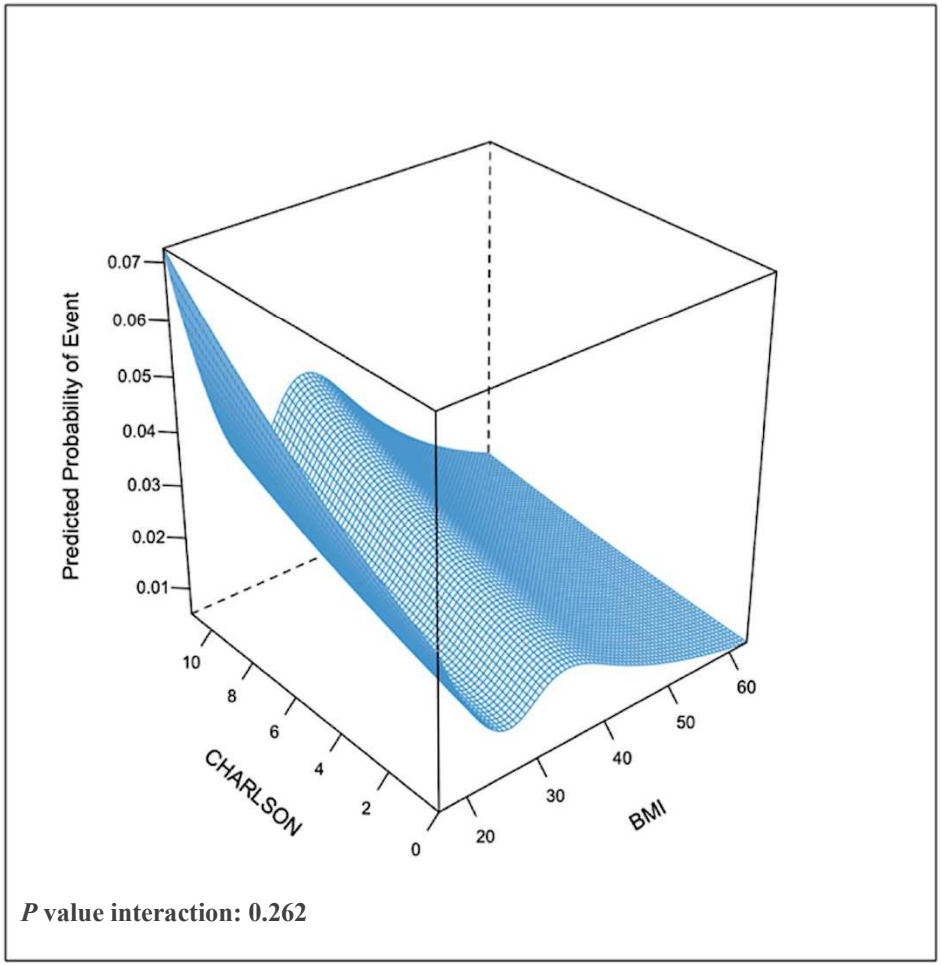


Figure 3. Smooth curves of the predicted probability and odds ratios for the primary efficacy outcome across each unit increase in body mass index according to study treatment. The primary efficacy outcome included a composite of asymptomatic proximal DVT, symptomatic proximal or distal deep vein thrombosis, symptomatic nonfatal pulmonary embolism, or fatal pulmonary embolism.



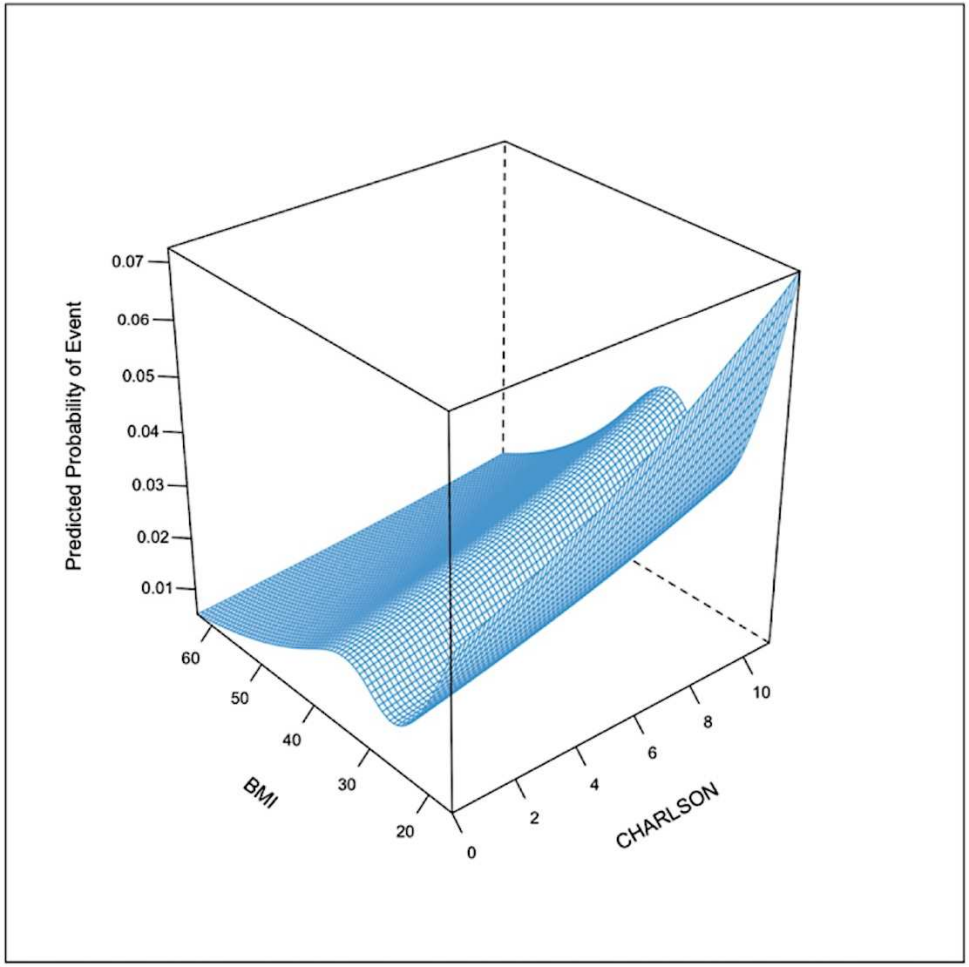


Figure 4. 3D surface plot of the predicted probability for the primary efficacy outcome across each unit change in body mass index and Charlson comorbidity score. The primary efficacy outcome included a composite of asymptomatic proximal DVT, symptomatic proximal or distal deep vein thrombosis, symptomatic nonfatal pulmonary embolism, or fatal pulmonary embolism.

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SUMMARY AND PERSPECTIVES

These analyses shed light on two important aspects in acute medically ill patients.

In our first analysis, among patients enrolled in the ICON-RELOADED study who presented to ED with acute dyspnea with and without acute HF, we found that acute elevated left ventricular (LV) filling pressure and volume overload, diastolic stiffness as well as increased right ventricular (RV) afterload were correlated with increased IGFBP7 concentrations. Indexed left atrial (LA) volume has emerged as a prime imaging marker in HF given its very significant association with elevated LV end diastolic pressures with impaired myocardial relaxation.[23-25] Independent association with increased left atrial volume index (LAVi) suggests elevated left ventricular filling pressure is an important trigger for IGFBP7 expression and release. Given our data includes acute dyspneic patients with suspected acute HF, we speculate that IGFBP7 concentrations might play a pivotal role in response to acutely elevated LA and LV pressure and volume overload regardless of the underlying mechanism. The results of the present study have demonstrated that the biomarker may be a plausible candidate for use as a diagnostic test for HF, comparable with N-terminal pro-brain natriuretic peptide (NT-proBNP). With these associations, IGFBP7 may provide options for diagnosis, prognosis, and possibly even management strategies for patients whose primary mechanism of HF is abnormal diastolic function.

In our second analysis, among patients enrolled in the APEX study who were hospitalized for an acute medical illness, VTE risk was found to be paradoxically lower in patients with a higher BMI compared to lean patients. We also reported that higher CCI scores were associated with a higher VTE risk, suggesting the comorbidity burden might be an indicator for VTE risk in the setting of acute illness. Previous studies have reported a "BMI paradox" manifested by an inverse relationship between overweight population and outcomes in cardiovascular[26-33] and non-cardiovascular conditions.[34-37] We reported another

manifestation of "BMI paradox" in a large cohort of acutely ill hospitalized medical patients who were receiving anticoagulant prophylaxis. There are biological mechanisms explaining these findings. We speculate that higher BMI may be associated with a better nutritional reserve, favorable immune function, and better tolerability of required therapies compared with lean patients with poor nutritional status and/or cachexia. Hospitalized medical patients with different BMIs can respond to medications differently as they may have an altered pharmacokinetic and pharmacodynamic profile due to the nature and burden of underlying medical conditions. Therefore, the reduction in VTE risk in relation to a higher BMI can also be attributable to the incremental benefit of anticoagulant therapy with increasing BMI. The present analysis furthers our understanding of the relationship between varying BMIs and VTE risk in acutely ill hospitalized patients. Future analyses examining longitudinal changes in BMI and its impact on outcomes are warranted.

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