MALNUTRITION, CONGESTION AND MORTALITY IN AMBULATORY PATIENTS WITH HEART FAILURE

Shirley Sze, MBBS[1] ; Pierpaolo Pellicori, MD, FESC[1] ; Jufen Zhang PhD[1,3]; Andrew L Clark, MA, MD, FRCP.[1]

[1]Department of Cardiology, Castle Hill Hospital, Hull York Medical School (at University of Hull), Kingston upon Hull, HU16 5JQ, UK

[2] Faculty of Medical Science, Anglia Ruskin University, CB1 1PT, UK

Corresponding author: Shirley Sze

Department of Cardiology,

Hull York Medical School

Hull and East Yorkshire Medical Research and Teaching Centre

Castle Hill Hospital, Cottingham, Kingston upon Hull, HU16 5JQ, UK

Tel: + 44 1482 461811

Fax: +44 1482 461779

Email: Shirley.sze@nhs.net

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ABSTRACT

Background: In patients with chronic heart failure (CHF), malnutrition might be related to right heart dysfunction and venous congestion, which predispose to bowel oedema and malabsorption, thereby leading to malnutrition. We explored the relation between congestion, malnutrition and mortality in a large cohort of ambulatory patients with CHF.

Methods: We assessed malnutrition using the geriatric nutritional risk index (GNRI). Congestion was defined by echocardiography (raised right atrial pressure (RAP) = dilated inferior vena cava (IVC) ≥21 mm/ raised pulmonary artery systolic pressure (PAsP) = trans-tricuspid gradient of ≥ 36mmHg/ right ventricular systolic dysfunction (RVSD) = TAPSE <17mm).

Results: Of the 1058 patients enrolled, CHF was confirmed in 952 (69% males, median age 75 (interquartile range (IQR):67-81) years, median NTproBNP 1141 (IQR: 465-2562) ng/L). 39% had HF with reduced (HeFREF, LVEF<40%) and 61% had HF with normal (HeFNEF, LVEF≥40% and NTproBNP>125 ng/l) LVEF.

Overall, 14% of patients were malnourished (GNRI ≤98). 35% had raised RAP, 23% had raised PAsP and 38% had RVSD. Congestion was associated with malnutrition.

During a median follow-up of 1683 days (IQR: 1096-2230 days), 461 (44%) patients died. Malnutrition was an independent predictor of mortality. Patients who were malnourished with both RVSD and increased RAP had much worse outcome compared to non-malnourished patients without RVSD who had normal RAP.

Conclusion: Malnutrition and congestion are modestly correlated and each is independently associated with increased mortality in patients with CHF. HF patients with both malnutrition

and congestion as evidenced by right heart dysfunction should be managed with additional vigilance.

(250 words)

Key words: Heart failure, malnutrition, congestion, echocardiography, right atrial pressure, pulmonary hypertension.

Key Messages:

What is already known about this subject?

Malnutrition is common amongst patients with chronic heart failure (CHF) and is associated with worse prognosis, but its pathophysiology is not fully understood. Weight loss in CHF is associated with right heart dysfunction and intestinal congestion.

What does this study add?

We explored the relation between *malnutrition* and congestion (assessed clinically or by echocardiography) in a large cohort of well-characterised ambulatory patients with CHF and found that malnutrition and congestion are modestly associated with each other. The concomitant presence of malnutrition and congestion is strongly associated with high mortality.

How might this impact on clinical practice?

Patients with malnutrition and congestion are at high risk and should be managed with additional vigilance. Studies are needed to see if treating malnutrition specifically is helpful.

Introduction

Malnutrition is common amongst patients with chronic heart failure (CHF). It has been implicated in the origin of cachexia, [1,2] and is associated with worse prognosis. [3,4,5] However, its pathophysiology is not fully understood.

CHF is characterised by congestion and high systemic venous pressures. Previous work has suggested that cachexia in CHF is associated with both high right atrial pressure and tricuspid regurgitation.[6,7,8] There is an association between RV dysfunction and intestinal and liver congestion[9,10] and abnormal body composition[11] in cachectic patients with CHF. However, the relation between *malnutrition*, RV dysfunction and systemic venous congestion in patients with CHF has not been studied.

We hypothesized that patients with CHF who have significant clinical congestion, high right heart pressures and right ventricular (RV) dysfunction might be at risk of developing congestive enteropathy, malabsorption and anorexia, thereby leading to clinical malnutrition and worse outcome. We studied the relation between congestion (assessed clinically and with echocardiography) and malnutrition, and the relation between these features and outcome in a large cohort of well-characterised ambulatory patients with CHF.

Methods

Study population

From 2000, patients referred by either primary or secondary care physicians to a community CHF clinic serving a local population of about 500,000 people were enrolled in a longitudinal observational study of patients with CHF (The Hull LifeLab). Some patients had no prior

diagnosis of CHF and were treatment naive, therefore requiring initiation of guideline-recommended therapy; many others had a pre-existing diagnosis of CHF and had already been initiated on treatment that might, however, require optimisation. We have previously reported the prevalence of moderate to severe malnutrition amongst patients with CHF is 7-10%, depending upon the screening tool and definition used.[12] In patients hospitalised for HF, up to 46% were malnourished.[13] In the present paper, we focused on a subset of patients from the Hull LifeLab who were enrolled between 2008 and 2012 for whom we have detailed echocardiographic images, and studied the relation between congestion and malnutrition.

All patients had a full medical history, physical examination, blood tests (including full blood count, urea and electrolytes and NTproBNP), an electrocardiogram and an echocardiogram. Weight was measured with the patients wearing their casual clothes but without shoes. Body mass index (BMI) was calculated using the formula: BMI = weight in kilograms / (height in meters) squared.

CHF was defined as the presence of symptoms or signs of CHF and evidence of cardiac dysfunction, with either: left ventricular systolic dysfunction (left ventricular ejection fraction (LVEF) <40%; heart failure with reduced ejection fraction, HeFREF); **or** normal left ventricular systolic function (LVEF $\geq$40%) and raised N-terminal pro-B-type natriuretic peptide (NTproBNP) of >125ng/L (heart failure with normal ejection fraction, HeFNEF).[14] Patients whose LVEF was $\geq$40% and who had NTproBNP $\leq$125ng/L were considered not to have CHF.

A congestion score was constructed, based on lung auscultation (normal, presence of basal, mid-zone or diffuse crackles), JVP (not visible, raised 1-4 cm, raised to earlobe), peripheral

oedema (none, ankles, below or above knees) and liver examination (not palpable, palpable) with one point attributed for each degree of severity and a total possible score of 9. Patients with a score of 3 or more were defined as severely congested.[15]

Echocardiograms were performed by an experienced sonographer using a Vivid 5 or 7 scanner (GE, Fairfield, Connecticut) with a 2.5-MHz phased-array transducer. Left ventricular (LV) systolic function was measured by calculating LVEF using Simpson's method. Right ventricular (RV) systolic function was measured by tricuspid annular plane systolic excursion (TAPSE). Patients with TAPSE <17mm were defined as having RV systolic dysfunction (RVSD).[16] RV systolic pressure and right atrial pressure (RAP) were estimated from the maximal tricuspid regurgitation velocity (TR Vmax) and inferior vena cava (IVC) diameter respectively. Patients with IVC diameter of <21mm were considered to have normal RAP, whereas those with IVC diameter of ≥ 21 mm were considered to have an increased RAP.[16] Patients with trans-tricuspid gradient of ≥ 36mmHg were considered to have raised pulmonary arterial systolic pressure (PAsP).[16] Mitral and tricuspid regurgitation were assessed semi-quantitatively and expressed in 4 grades (absent, mild, moderate or severe).

Ischaemic heart disease (IHD) was defined as any previous medical history of acute coronary syndrome (ACS), percutaneous coronary intervention or coronary artery bypass surgery, or a diagnosis of myocardial ischaemia based on invasive or non-invasive diagnostic tests. Cerebrovascular disease (CVD) was defined as any previous history of stroke or transient ischaemic attack (TIA). Peripheral vascular disease (PVD) was defined as a clinical history of the diagnosis.

Malnutrition screening

Patients were screened for malnutrition using the geriatric nutritional risk index (GNRI),[17] which we have previously shown[12] to have the greatest prognostic value compared to two other commonly used malnutrition screening tools: the controlling nutritional status (CONUT) score[18] and the prognostic nutritional index (PNI).[19]

The GNRI was calculated using the formula: 1.489 x serum albumin (g/L) + 41.7 x (body weight in kilograms / ideal body weight).[16] Ideal body weight was calculated using the formula: 22 x square of height in meters.[20] Patients with GNRI >98 have normal nutritional status, those with GNRI 92-98, 82-91, <82 have mild, moderate and severe malnutrition, respectively.

End points and follow-up

Patients were followed up until 1st May 2016. The primary endpoint was all-cause mortality. Our hospital is the only one in the region offering acute medical services. With previous consent from patients, we could access all their primary and secondary care records. Outcome was censored at the point of last medical contact in primary or secondary care. Data regarding hospitalisations and deaths were collected from the hospital's electronic systems and were entered into a dedicated database, stored on a secure NHS server.

Statistical analysis

Continuous data are expressed as a median with interquartile range (IQR) (25th to 75th centiles) and categorical data are expressed as N (%). Independent t tests and Mann-Whitney U tests were used to compare two continuous variables for normally and non-normally distributed data. The chi-squared test was used to compare proportions between

groups. Pearson's correlation or Spearman's correlation coefficients were used to assess the relationships between two variables. Log-transformation was applied when the data were very skewed. Logistic regression analysis was used to estimate associations between other variables and malnutrition.

The impact of variables on survival was investigated using the Cox proportional hazards model. Additionally, we created a base model for predicting mortality after adjusting for the following variables which are commonly available in clinical practice and are significantly associated with outcome: age, systolic blood pressure, New York Heart Association (NYHA) class, urea and NTproBNP. We added the malnutrition score (GNRI), markers of congestion (clinical and echocardiographic) and combinations of malnutrition and markers of congestion in turn to the base model and used C-index (the area under receiver operating characteristic (ROC) curves) and net reclassification index (NRI) to evaluate model discrimination in logistic regression analysis. The C-index is defined as the probability that predictions and outcomes are the same. A C-index of 0.5 means that the relationship is no better than chance.

All statistical analyses were performed using SPSS 22 (SPSS INc.,Chicago, IL, USA) and The Stata (14^{th} Version, StataCorp, TX, USA) statistical computer package. A two-tailed P-value of <0.05 was considered significant in all analyses.

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by relevant ethical bodies. All subjects gave their written informed consent for their data to be used for research.

Results

Patient characteristics

Baseline characteristics (clinical data and measures of congestion) of the overall cohort are shown in Table 1 (Appendix 1a, 1b). Baseline characteristics by GNRI (malnourished vs not malnourished), by RVSD and clinical congestion are shown in tables 2a-c. (Appendix 2) Of the patients with CHF, 10% had mild malnutrition and 4% had moderate to severe malnutrition. (Table 1and Appendix 2). Malnutrition was more common in patients with HeFREF than HeFNEF (17% vs 12%, p=0.01) (Appendix 1a).

Prevalence of clinical signs of congestion

Although a small proportion of patients without CHF had signs of congestion on clinical examination, patients with CHF were much more likely to have these signs (Table 1). Patients with HeFREF were as likely to have clinical signs of congestion as patients with HeFNEF (Appendix 1a).

Prevalence of RV dysfunction and increased PAsP & RAP

Compared to patients without CHF, those with CHF were more likely to have RVSD, raised PAsP and raised RAP. RVSD and increased RAP were more common in patients with HeFREF than in those with HeFNEF. (Appendix 1b)

Clinical associations of malnutrition

Compared to patients with normal nutritional status, patients with malnutrition were older, had lower BMI, worse renal function and HF symptoms, and higher NTproBNP levels (Table 2a, Appendix 2).

Malnutrition and clinical signs of congestion

Patients with CHF and malnutrition were more likely to have signs of congestion on clinical examination than those without malnutrition. Malnourished patients with HeFREF or HeFNEF were equally likely to have signs of congestion. (Appendix 2) Of the 4 clinical signs of congestion, peripheral oedema and raised JVP were the two commonest.

Malnutrition and echocardiographic findings

Patients with malnutrition were more likely to have RVSD and increased PAsP and RAP compared to those with normal nutrition. (Table 2a) The simultaneous presence of RVSD and increased RAP was much more common in malnourished patients than in non-malnourished patients (33% vs 17%, $p<0.001$). The prevalence of LV systolic dysfunction and LA dilation was not related to malnutrition (Table 2a). Box plot figures comparing the key echocardiographic measures in malnourished versus non-malnourished patients with HeFREF versus HeFNEF were shown in Appendix 3a-e.

Correlations between malnutrition and echocardiographic findings

Worsening malnutrition correlated with increasing NTproBNP levels, increasing age and worsening right ventricular dysfunction by ultrasound: decreasing TAPSE, increasing RAP and PAsP (Appendix 4). Malnutrition was more strongly linked to elevated right-sided pressures than to either right or left ventricular dysfunction (Appendix 4).

If we used an NT-proBNP cut-off of >400 ng/l to diagnose HeFNEF, in accordance to NICE guidelines[21], the prevalence of congestion and malnutrition would have been slightly higher amongst patients with HeFNEF (congestion: from 15% to 18%; RVSD: from 30% to 34%, malnutrition from 12% to 15%). However, the change of cut-off does not alter the modest

relationship between congestion, RVSD and malnutrition (worsening malnutrition correlated with decreasing TAPSE (correlation coefficient from 0.21 to 0.17 (both p <0.001) and increasing congestion score (correlation coefficient remains the same: 0.05, p = 0.15 and p=0.16 respectively).

Logistic regression analysis of clinical and echocardiographic variables associated with malnutrition is shown in Table 3. NTproBNP (OR 5.7, 95% CI 3.2-10.1, p<0.001) had the strongest association with malnutrition, followed by trans-tricuspid gradient (OR 1.11, 95% CI 1.0-1.2), p=0.03). (Table 3)

Malnutrition, echocardiographic findings and hospitalisation in the year before recruitment

539 (57%) of patients were admitted to hospital in the year before recruitment, of which 181 (34%) were HF admissions. Patients with previous hospitalisations for HF were more likely to be malnourished and have raised RAP / PAsP or RVSD compared to patients with previous cardiovascular but non-HF hospitalisations or no hospitalisations. (Appendix 5)

Malnutrition, RVSD and mortality

During a median follow-up of 1683 days (interquartile range: 1096-2230 days), 461 (44%) patients died.

Univariable and multivariable predictors of mortality for the overall population and for the different HF phenotypes are shown in table 4 and Appendix 6a-b. In univariable analysis, the

presence of malnutrition, signs of congestion, increasing PASP, RAP and left atrial volume index (LAVI) and decreasing TAPSE and LVEF were associated with worse outcome.
In a multivariable model including all the patients, malnutrition was independently associated with an increased risk of all-cause mortality. Of the echocardiographic variables, only increasing RAP and LAVI were significant predictors of mortality. (Table 4, Appendix 7)

The Kaplan-Meier curves for the relationship between malnutrition, RV dysfunction, increased RAP and outcome is shown in figure 1. Compared to patients who were not malnourished with normal RV function and RAP, those with malnutrition and normal RV function and RAP had a 2 fold increase in the risk of death for any cause. Those who were malnourished with RV dysfunction and raised RAP had the worst outcome.(Figure 1)

A base model (including age, systolic blood pressure, NYHA class, urea and NTproBNP) for predicting mortality achieved a C-index = 0.79. (Table 5) Moderate to severe malnutrition by GNRI and markers of congestion (both clinical and echocardiographic), when added individually, did not improve performance of the base model. The net reclassification index (NRI) produced similar results. Addition of moderate to severe malnutrition by GNRI and clinical congestion (congestion score $\geq$3) in combination and addition of moderate to severe malnutrition by GNRI and IVC diameter in combination improved performance of base model (C = 0.80 and 0.81 respectively, p =0.02 for both).

Discussion

Ours is the one of the few studies [9,10, 22,23] to explore the relation between malnutrition and congestion in patients with CHF. Our study comprehensively investigated the associations

between malnutrition, right heart dysfunction and venous congestion assessed clinically, biochemically and by echocardiography.

We hypothesised that malnutrition might be caused by congestion, but only found a modest relation between malnutrition and measures of congestion. Although ours is a study of associations of malnutrition, and thus few conclusions can be drawn about causation, the weakness of the correlation between the two suggests that one does not directly cause the other. Congestion and malnutrition were independent predictors of mortality, again suggesting that they are measures of different aspects of the heart failure syndrome and may not be causally related.

One explanation for our findings might be that it is *historical* congestion that causes malnutrition and that the malnutrition we measured at the time of the assessment would not be related to any congestion present at the time. We found that patients with previous admissions for HF were more likely to be malnourished or have raised RAP, PAsP or RVSD compared to patients with previous cardiovascular but non-HF hospitalisations or no hospitalisation, which might imply a closer link between malnutrition and previous congestion.

Our findings are similar to those from Valentova et al, who studied the relationship between congestion and cardiac *cachexia* in 169 outpatients with heart failure due to left ventricular systolic dysfunction.[9] They found that cachexia was more common in patients with reduced RV function and elevated RAP than in patients with either reduced RV function but normal RAP or preserved RV function (67 vs. 15 vs. 7%). They also found that cachexia was associated with thicker bowel wall (odds ratio (OR) 1.3; 95% CI: 1.1–1.6; P = 0.002).

Previous work has mainly focused on identifying mechanistically plausible explanations for the association between cachexia/ malnutrition and congestion/cardiac dysfunction in patients with CHF. Congestion and cardiac dysfunction have been implicated as a cause of malnutrition. Systemic venous congestion in the hepatic and splanchnic beds cause intestinal congestion and dysmotility, anorexia, malabsorption and increased intestinal permeability with protein loss and endotoxin translocation.[24] Neuro-hormonal activation exacerbates renal dysfunction, leading to more salt and water retention, contributing to bowel congestion and development of malnutrition.[8] Chronic intestinal congestion might cause persistent lipopolysaccharide translocation which might induce systemic release of pro-inflammatory cytokines and worsen the underlying intestinal congestion.[8] In addition, RV dysfunction and pulmonary hypertension cause the release of natriuretic peptides,[25] which stimulates lipolysis of adipose tissue[26] and indirectly stimulate secretion of adiponectin which promotes glucose and fatty acid utilisation,[27] resulting in weight loss and increased mortality.

Malnutrition might itself aggravate underlying left and right heart dysfunction, leading to a vicious spiral of deterioration. Metabolites and cytokines released secondary to malnourishment state might adversely affect cardiac performance. Cytokines such as TNF-α, raised in patients with cachexia, have potent negative inotropic effects and might subsequently impair RV and LV systolic function.[28]

Although we found that malnutrition is associated with congestion, the association is modest, suggesting that they are two distinct entities. Other factors such as advanced age and severity of CHF might also have important roles to play in the pathogenesis of malnutrition. Patients with CHF often suffer from multiple comorbidities, such as osteoarthritis, airways disease,

renal dysfunction, cognitive impairment, anxiety and depression, which might interact with and/or modify the course of CHF and have negative impact on medication adherence, self-care ability and food intake.[29] Lack of social support and financial constraints negatively impact on activities of daily living, such as shopping and preparing meals, hence predisposing to malnutrition.

Limitations

This is a single-centre study conducted in the UK; external validation of our results from other countries with different healthcare and social systems is needed. Secondly, we have only studied one of the large number of tools available to screen for malnutrition. Thirdly, this is an observational study, and thus causality cannot be addressed.

Additionally, up-titration of anti-HF medications during follow-up for patients with HeFREF might have led to an improved congestive and nutritional status, and perhaps outcome, in some.

Furthermore, this study is an explorative analysis using a comprehensive prospective data collection undertaken as part of the Hull LifeLab database between 2008 and 2012. The analysis plan was decided post-hoc, and results might have changed overtime, particularly as newer treatments have become available.

The GNRI is derived from serum albumin and the ratio of body weight to ideal body weight. Although it is questionable whether an ideal BMI of 22 kg/m^2 as used in our formula to calculate ideal body weight applies to a UK population, as it might underestimate prevalence

of malnutrition in our population, a recent report from UK Biobank enrolling more than 200,000 UK residents without cardiovascular risk factors supports these findings.[30]

Lastly, we have included patients with HeFNEF, for which there is no universally agreed diagnostic definition and some might not accept our definition based only on the evidence of signs or symptoms supported by a natriuretic peptide level above the diagnostic level suggested by current ESC-HF guidelines (125 ng/L).

Conclusion

Malnutrition and congestion are both common but are only modestly associated with each other in patients with chronic heart failure. The concomitant presence of malnutrition and congestion is strongly associated with a high mortality in patients with CHF; these patients should thus be managed with additional vigilance.

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Legends

Appendices:

Tables:

Table 2c: Baseline characteristics of HF patients (clinical congestion vs no clinical congestion)

Table 3: Logistic regression analysis of clinical and echocardiographic variables associated with malnutrition in HF subjects (Backward selection).

Table 4: Univariable and multivariable analyses of factors predicting outcomes in patients with heart failure.

Table 5: Effect of addition of clinical congestion and echocardiographic markers of right cardiac dysfunction to base model in predicting mortality.

Figure:

Figure 1: Kaplan meier curve showing the relation amongst malnutrition, right ventricular systolic dysfunction and increased right atrial pressure and all-cause mortality.

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Table 1. Baseline characteristics of the entire cohort.

	No HF (N=102)	**HF** (N=952)	Missing	**P-value**
Demographics				
Age (years)	64 (50-70)	75 (67-81)	0	<0.001
Sex (male), n (%)	71 (70)	655 (69)	0	0.87
Weight (kg)	88 (76-100)	80 (68-95)	0	0.002
BMI (kg/m^2)	30 (27-34)	28 (25-32)	0	0.002
BP systolic (mmHg)	133 (118-151)	126 (111-144)	0	0.01
HR (bpm)	71 (63-80)	70 (61-78)	0	0.27
Sinus rhythm, n (%)	102 (100)	606 (64)	0	<0.001
NYHA III, n (%)	11 (11)	317 (33)	0	<0.001
Comorbidities				
IHD, n (%)	33 (32)	579 (61)	0	<0.001
Diabetes, n (%)	28 (28)	285 (30)	0	0.60
Hypertension, n(%)	57 (56)	498 (52)	0	0.49
CVA, n (%)	5 (5)	90 (10)	0	0.13
COPD, n (%)	11 (11)	109 (11)	0	0.84
Blood tests				
Hb (g/dL)	14.1 (13.2-15.4)	13.3 (12.0-14.3)	0	<0.001
Urea (mmol/L)	4.9 (3.9-6.1)	7.3 (5.5-10.2)	0	<0.001
Creatinine (umol/L)	84 (70-98)	103 (84-134)	0	<0.001
Na+ (mmol/L)	139 (138-140)	138 (136-140)	1	0.12
Albumin (g/L)	41 (38-42)	38 (36-40)	0	<0.001
NTproBNP (ng/L)	59 (33-93)	1141 (465-2562)	1	<0.001
Treatment				
Loop diuretic, n (%)	36 (35)	661 (69)	0	<0.001
MRA, n (%)	21 (21)	344 (36)	0	0.002
ACEi or ARB, n (%)	67 (66)	805 (85)	0	<0.001
BB, n (%)	44 (43)	736 (77)	0	<0.001
Malnutrition				
GNRI			0	0.07
Normal (>98)	97 (95)	820 (86)		
Mild malnutrition (92-98)	5 (5)	98 (10)		
Moderate malnutrition (82-91)	0	30 (3)		
Severe malnutrition (<82)	0	4 (1)		

HF= heart failure, BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA = New York Heart Association Class, IHD = ischaemic heart disease, CVA = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, Na+ = sodium, NTproBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoids receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, GNRI = Geriatric nutritional risk index.

Table 2a: Baseline characteristics of HF patients (malnourished vs not malnourished)

	Malnutrition		Missing	P-value
	Yes (N=132)	**No** (N=820)		
Demographics				
Age (years)	80 (74-84)	74 (66-80)	0	<0.001
Sex (male), n (%)	83 (63)	572 (70)	0	0.11
Weight (kg)	59 (53-68)	84 (73-97)	0	<0.001
BMI (kg/m^2)	22 (20-24)	29 (26-33)	0	<0.001
BP systolic (mmHg)	118 (103-138)	129 (112-146)	0	<0.001
HR (bpm)	70 (60-78)	70 (61-79)	0	0.73
Sinus rhythm, n (%)	89 (67)	517 (63)	0	0.33
NYHA III, n (%)	60 (46)	257 (31)	0	0.001
Comorbidities				
IHD, n (%)	84 (64)	495 (60)	0	0.48
Diabetes, n (%)	23 (17)	262 (32)	0	0.001
Hypertension, n(%)	55 (42)	443 (54)	0	0.008
CVA, n (%)	14 (11)	76 (9)	0	0.63
COPD, n (%)	21 (16)	88 (11)	0	0.08
Blood tests				
Hb (g/dL)	12.4 (10.9-13.7)	13.3 (12.2-14.5)	0	<0.001
Urea (mmol/L)	9.0 (6.4-12.6)	7.2 (5.4-9.9)	0	<0.001
Creatinine (umol/L)	114 (86-145)	102 (84 -132)	0	<0.001
Na+ (mmol/L)	137 (135-140)	138 (137-140)	1	<0.001
Albumin (g/L)	35 (32-37)	39 (37-41)	0	<0.001
NTproBNP (ng/L)	2884 (1444-4973)	1015 (406-2089)	1	<0.001
Treatment				
Loop diuretic, n (%)	98 (74)	563 (69)	0	0.20
MRA, n (%)	50 (38)	294 (36)	0	0.65
ACEi or ARB, n (%)	99 (75)	706 (86)	0	0.001
BB, n (%)	102 (77)	634 (77)	0	0.99
Clinical congestion				
Lung crackles (≥1)	28 (21)	92 (11)	0	0.001
Raised JVP (≥1)	31 (24)	94 (12)	0	<0.001
Peripheral oedema (≥1)	40 (30)	162 (20)	0	0.006
Palpable liver	17 (13)	34 (4)	0	<0.001
Congested (congestion score ≥3)	36 (27)	105 (13)	0	<0.001
Echocardiography				
Increased RAP (IVC ≥21mm)	64 (50)	254 (32)	33	<0.001
RVSD (TAPSE<17mm)	65 (49)	295 (36)	0	0.004
Increased PAsP	53 (41)	155 (20)	35	<0.001

(Trans-tricuspid gradient ≥36mmHg)				
LA dilatation (LAVI >34 mL/m^2)	94 (71)	535 (65)	0	0.18
LVSD (LVEF <40%)	61 (46)	308 (38)	0	0.06
Mitral regurgitation (mod to sev)	32 (24)	113 (14)	1	0.002
Tricuspid regurgitation (mod to sev)	28 (21)	57 (7)	0	<0.001

HF= heart failure, BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA = New York Heart Association Class, IHD = ischaemic heart disease, CVA = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, Na+ = sodium, NTproBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoids receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, GNRI = Geriatric nutritional risk index, LVEF= left ventricular ejection fraction, LAVI= left atrial volume index, TAPSE= tricuspid annular plane systolic excursion, IVC= inferior vena cava, RVSD= right ventricular systolic dysfunction, PAsP= pulmonary artery systolic pressure, RAP= right atrial pressure.

Table 2b: Baseline characteristics of HF patients (RVSD vs no RVSD)

	RVSD		Missing	P-value
	Yes (N=360)	**No** (N=592)		
Demographics				
Age (years)	76 (70-82)	74 (66-81)	0	0.006
Sex (male), n (%)	262 (73)	393 (66)	0	0.04
Weight (kg)	77 (66-89)	82 (70-97)	0	<0.001
BMI (kg/m^2)	27 (24-31)	29 (25-33)	0	<0.001
BP systolic (mmHg)	121 (105-139)	130 (115-148)	0	<0.001
HR (bpm)	121 (105-139)	68 (60-76)	0	<0.001
Sinus rhythm, n (%)	177 (49)	429 (73)	0	<0.001
NYHA III, n (%)	156 (43)	161 (27)	0	<0.001
Comorbidities				
IHD, n (%)	241 (67)	338 (57)	0	0.003
Diabetes, n (%)	106 (29)	179 (30)	0	0.80
Hypertension, n(%)	163 (45)	335 (57)	0	0.001
CVA, n (%)	37 (10)	53 (9)	0	0.50
COPD, n (%)	44 (12)	65 (11)	0	0.56
Blood tests				
Hb (g/dL)	13.2 (12.0-14.2)	13.3 (12.1-14.4)	0	0.15
Urea (mmol/L)	8.3 (6.1-11.3)	7.0 (5.3-9.7)	0	<0.001
Creatinine (umol/L)	109 (88-141)	100 (82-131)	0	0.27
Na+ (mmol/L)	138 (136-140)	139 (137-140)	1	0.05
Albumin (g/L)	38 (36-40)	38 (36-40)	0	0.07
NTproBNP (ng/L)	1926 (882-3907)	800 (364-1784)	1	<0.001
Treatment				
Loop diuretic, n (%)	285 (79)	376 (64)	0	<0.001
MRA, n (%)	162 (45)	182 (31)	0	<0.001
ACEi or ARB, n (%)	302 (84)	503 (85)	0	0.66
BB, n (%)	458 (77)	278 (77)	0	0.96
Clinical congestion				
Lung crackles (≥1)	58 (16)	62 (11)	0	0.01
Raised JVP (≥1)	79 (22)	46 (8)	0	<0.001
Peripheral oedema (≥1)	89 (25)	113 (19)	0	0.04
Palpable liver	33 (9)	18 (3)	0	<0.001
Congested (congestion score ≥3)	81 (23)	60 (10)	0	<0.001
Echocardiography				
Increased RAP (IVC ≥21mm)	179 (51)	139 (24)	33	<0.001
Increased PAsP	126 (36)	82 (14)	35	<0.001

(Trans-tricuspid gradient ≥36mmHg)				
LA dilatation (LAVI >34 mL/m^2)	272 (76)	357 (60)	0	<0.001
LVSD (LVEF <40%)	184 (51)	185 (31)	0	<0.001
Mitral regurgitation (mod to sev)	86 (24)	59 (10)	1	<0.001
Tricuspid regurgitation (mod to sev)	63 (18)	22 (4)	0	<0.001
Malnutrition				
GNRI Normal (>98) Mild malnutrition (92-98) Moderate malnutrition (82-91) Severe malnutrition (<82)	 295 (82) 51 (14) 12 (3) 2 (1)	 525 (89) 47 (8) 18 (3) 2 (0)	0	0.02

HF= heart failure, BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA = New York Heart Association Class, IHD = ischaemic heart disease, CVA = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, Na+ = sodium, NTproBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoids receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, GNRI = Geriatric nutritional risk index, LVEF= left ventricular ejection fraction, LAVI= left atrial volume index, TAPSE= tricuspid annular plane systolic excursion, IVC= inferior vena cava, RVSD= right ventricular systolic dysfunction, PAsP= pulmonary artery systolic pressure, RAP= right atrial pressure.

Table 2c: Baseline characteristics of HF patients (clinical congestion vs no clinical congestion)

	Clinical Congestion		Missing	P-value
	Yes (N=141)	**No** (N=811)		
Demographics				
Age (years)	79 (74-84)	74 (66-80)	0	<0.001
Sex (male), n (%)	96 (68)	559 (69)	0	0.84
Weight (kg)	77 (67-95)	80 (69-95)	0	0.51
BMI (kg/m^2)	28 (25-32)	28 (25-33)	0	0.66
BP systolic (mmHg)	124 (108-142)	127 (111-144)	0	0.15
HR (bpm)	72 (63-86)	70 (60-78)	0	<0.001
Sinus rhythm, n (%)	63 (45)	543 (67)	0	<0.001
NYHA III, n (%)	95 (67)	222 (27)	0	<0.001
Comorbidities				
IHD, n (%)	83 (59)	496 (61)	0	0.61
Diabetes, n (%)	45 (32)	240 (30)	0	0.58
Hypertension, n(%)	72 (51)	426 (53)	0	0.75
CVA, n (%)	74 (9)	16 (11)	0	0.41
COPD, n (%)	16 (11)	93 (12)	0	0.97
Blood tests				
Hb (g/dL)	12.4 (11.1-13.8)	13.3 (12.2-14.4)	0	<0.001
Urea (mmol/L)	9.7 (6.8-13.2)	7.1 (5.4-9.8)	0	<0.001
Creatinine (umol/L)	118 (91-152)	101 (83-131)	0	0.05
Na+ (mmol/L)	138 (135-140)	138 (137-140)	1	0.19
Albumin (g/L)	36 (34-39)	38 (37-40)	0	<0.001
NTproBNP (ng/L)	2810 (1357-4787)	1014 (409-2064)	1	<0.001
Treatment				
Loop diuretic, n (%)	125 (89)	536 (66)	0	<0.001
MRA, n (%)	58 (41)	286 (35)	0	0.18
ACEi or ARB, n (%)	109 (77)	696 (86)	0	0.01
BB, n (%)	104 (74)	632 (78)	0	0.28
Echocardiography				
Increased RAP (IVC ≥21mm)	93 (67)	225 (29)	33	<0.001
RVSD (TAPSE<17mm)	81 (57)	279 (34)	0	<0.001
Increased PAsP (Trans-tricuspid gradient ≥36mmHg)	71 (53)	137 (18)	35	<0.001
LA dilatation (LAVI >34 mL/m^2)	120 (85)	509 (63)	0	<0.001
LVSD (LVEF <40%)	51 (36)	318 (39)	0	0.49

Mitral regurgitation (mod to sev)	33 (24)	112 (14)	1	0.003
Tricuspid regurgitation (mod to sev)	41 (29)	44 (5)	0	<0.001
Malnutrition				
GNRI			0	<0.001
Normal (>98)	105 (75)	715 (88)		
Mild malnutrition (92-98)	24 (17)	74 (9)		
Moderate malnutrition (82-91)	10 (7)	20 (3)		
Severe malnutrition (<82)	2 (2)	2 (0)		

HF= heart failure, BMI= body mass index, BP= blood pressure, HR= heart rate, NYHA = New York Heart Association Class, IHD = ischaemic heart disease, CVA = cerebrovascular disease, COPD= chronic obstructive pulmonary disease, Hb = Haemoglobin, Na+ = sodium, NTproBNP = N-terminal Pro Brain Natriuretic Peptide, MRA = Mineralocorticoids receptor antagonists, ACEi = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin receptor blocker, BB= betablocker, GNRI = Geriatric nutritional risk index, LVEF= left ventricular ejection fraction, LAVI= left atrial volume index, TAPSE= tricuspid annular plane systolic excursion, IVC= inferior vena cava, RVSD= right ventricular systolic dysfunction, PAsP= pulmonary artery systolic pressure, RAP= right atrial pressure.

Table 3: Logistic regression analysis of clinical and echocardiographic variables associated with malnutrition in all HF subjects. (Backward selection)

	Univariable			Multivariable		
	OR (95% CI)	Wald X^2	P	OR (95% CI)	Wald X^2	P
Age	1.06 (1.04-1.08)	27.4	<0.001	1.03 (1.01-1.06)	7.9	0.005
Log NTproBNP	6.15 (4.04-9.36)	71.8	<0.001	5.68 (3.20-10.06)	35.4	<0.001
LVEF (per 5% increase)	0.93 (0.86-0.99)	4.8	0.03			
LAVI (per 10 mL/m^2 increase)	1.10 (1.02-1.19)	5.8	0.02			
TAPSE (per 5mm increase)	0.69 (0.56-0.85)	12.4	<0.001			
Trans-tricuspid gradient (per 5 mmHg increase)	1.24 (1.15-1.33)	32.5	<0.001	1.11 (1.01-1.22)	4.7	0.03
IVC diameter (per 5 mm increase)	1.42 (1.18-1.71)	14.0	<0.001			

HF= heart failure, NYHA = New York Heart Association Class , NTproBNP= N-terminal Pro Brain Natriuretic Peptide , LVEF= left ventricular ejection fraction, LAVI= left atrial volume index, IVC= inferior vena cava, TAPSE= tricuspid annular plane systolic excursion.

Table 4: Univariable and multivariable analysis of factors predicting outcomes in patients with HF (overall population)

Worse outcome per unitary increase	Overall HF population (N=952)					
	Univariate			Multivariate		
	HR(95%CI)	Wald X^2	P-value	HR(95%CI)	Wald X^2	P-value
Demographics						
Age (years)	1.05 (1.04-1.06)	97.2	<0.001	1.04 (1.03-1.06)	43.5	<0.001
Sex (male vs female)	1.20 (0.98-1.47)	3.0	0.08	1.46 (1.14-1.85)	9.3	0.002
BP systolic (per 10 mmHg)	0.92 (0.89-0.96)	16.3	<0.001	0.94 (0.90-0.98)	9.1	0.003
HR (bpm)	1.01 (1.00-1.01)	4.1	0.04			
Sinus rhythm (Y vs N)	0.78 (0.65-0.94)	6.6	0.01	0.71 (0.55-0.91)	7.5	0.006
Clinical examination						
Congested (Y vs N)	2.77 (2.23-3.43)	85.5	<0.001			
NYHA (III/IV vs I/II)	2.65 (2.20-3.18)	108.3	<0.001	1.61 (1.31-1.99)	20.1	<0.001
Comorbidities						
IHD (Y vs N)	1.23 (1.01-1.49)	4.3	0.04			
CVA (Y vs N)	1.76 (1.35-2.30)	17.3	<0.001	1.41 (1.06-1.89)	5.5	0.02

Blood test						
Hb (g/dL)	0.78 (0.74-0.82)	86.6	<0.001			
Urea (mmol/L)	1.08 (1.06-1.09)	91.3	<0.001			
Na+ (mmol/L)	0.93 (0.90-0.96)	27.5	<0.001	0.96 (0.93-0.99)	9.2	0.002
Log NTproBNP (ng/L)	3.48 (2.89-4.18)	175.9	<0.001	1.49 (1.13-1.96)	8.0	0.005
Echocardiography						
LVEF (%)	0.99 (0.99-1.00)	4.6	0.03			
LVEDD (cm)	1.01 (1.00-1.02)	2.7	0.10			
TAPSE (mm)	0.93 (0.91-0.95)	48.4	<0.001			
LAVI (mL/m^2)	1.02 (1.01-1.02)	87.8	<0.001	1.01 (1.00-1.01)	5.8	0.02
Trans-tricuspid gradient (mmHg)	1.03 (1.03-1.04)	84.0	<0.001			
IVC diameter (mm)	1.09 (1.08-1.11)	98.6	<0.001	1.04 (1.01-1.06)	5.6	0.02
Malnutrition						
GNRI (mod/sev) (Y vs N)	1.75 (1.14-2.68)	6.5	0.01	2.32 (1.49-3.62)	13.8	<0.001

HF= heart failure, BP= blood pressure, HR= heart rate, NYHA = New York Heart Association Class, IHD = ischaemic heart disease, CVA = cerebrovascular disease, Hb = Haemoglobin, Na+ = sodium, NTproBNP = N-terminal Pro Brain Natriuretic Peptide, LVEF= left ventricular ejection fraction, LVEDD= left ventricular end diastolic diameter, TAPSE= tricuspid annular plane systolic excursion, LAVI= left atrial volume index, TR Vmax= maximal tricuspid regurgitation velocity, Mod/sev= moderate or severe, GNRI = Geriatric nutritional risk index, Y= yes, N=No.

For continuous variables, HR relate to the hazard associated per unitary increase in the variable except for systolic BP, where HR relates to the hazard associated per10 unitary increase. For categorical variables (*), HR quoted compares groups specified in brackets.

Lung crepitations, Raised JVP, Peripheral oedema, Palpable liver are excluded as these are included in congested.

Weight, BMI, BSA are excluded as these are included in GNRI.

WCC, lymphocyte, albumin, cholesterol are excluded as these are included in PNI, CONUT.

Creatinine is excluded as urea is considered as a marker of renal function.

LA diameter and volume are excluded as LAVI is considered as a marker of LA dimensions.

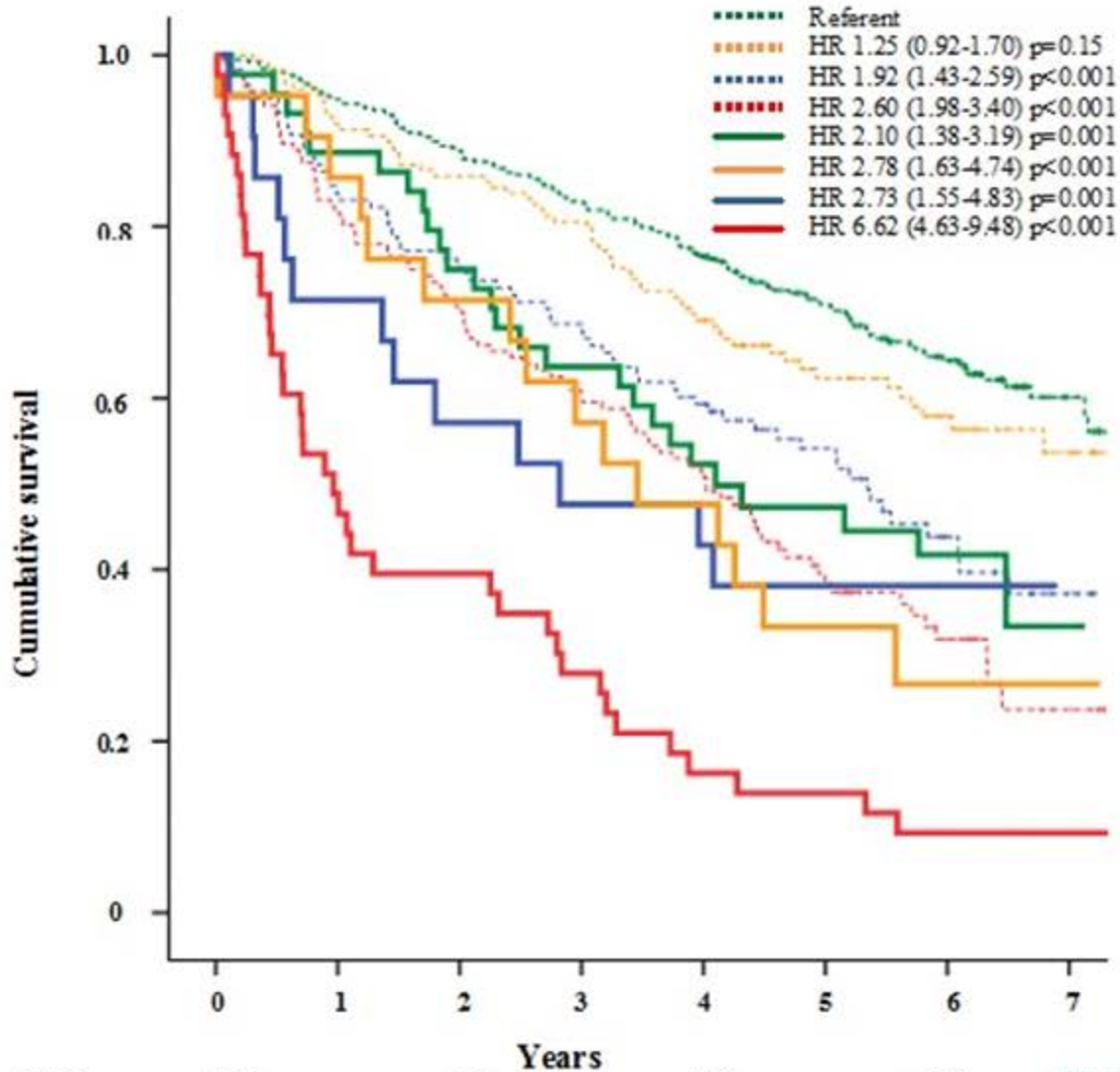
GLS and e/e’ are excluded due to large amount of missing values.

Table 5: Effect of addition of clinical congestion and echocardiographic markers of right cardiac dysfunction to base model in predicting mortality.

Model	c-statistics (Compared to model 1, p-value)	c-statistics (compared to model 6)	cNRI (standard error) (compared to model 1, p-value)
1. Base model*	0.789 (0.754-0.823)	-	-
2. Base + clinical congestion**	0.796 (0.762-0.830) P=0.10	-	0.03 (0.08) P=0.69
3. Base + TAPSE	0.789 (0.75-0.82) P=0.83	-	0.013 (0.08) P=0.87
4. Base + IVC	0.796 (0.76-0.83) P=0.18	-	0.14(0.08) P=0.07
5. Base + Trans-tricuspid gradient	0.791 (0.756-0.826) P=0.60	-	-0.0003 (0.08) P=1.0
6. Base + GNRI***	0.797 (0.762-0.831) P=0.12	0.797 (0.762-0.831)	0.08(0.08) P=0.29
7. Base + GNRI*** + clinical congestion	0.80 (0.77-0.84) P=0.018	0.803 (0.770-0.837) P=0.08	-
8. Base + GNRI*** + IVC	0.807 (0.77-0.84) P=0.017	0.807(0.772-0.832) P=0.075	-
9. Base + GNRI*** + TAPSE	0.797(0.76-0.83) P=0.11	0.797 (0.763-0.831) P=0.78	-
10. Base + GNRI***+ Trans-tricuspid gradient	0.798(0.76-0.83) P=0.12	0.798 (0.763-0.833) P=0.78	-

** clinical congestion (congestion score ≥3 vs congestion score <3), ***GNRI (moderate to severe malnutrition vs mild or no malnutrition)

TAPSE= tricuspid annular plane systolic excursion, IVC=inferior vena cava diameter, NRI= net reclassification index



Not mal, N RAP, no RVSD	387	344	296	261
Not mal, N RAP, RVSD	149	128	103	91
Not mal, increased RAP, no RVSD	118	89	70	57
Not mal, increased RAP, RVSD	136	96	70	50
Mal, N RAP, no RVSD	44	33	23	19
Mal, N RAP, RVSD	21	15	10	6
Mal, increased RAP, no RVSD	21	12	9	8
Mal, increased RAP, RVSD	43	17	7	4