Prevalence and Prognostic Significance of Malnutrition Using Three Scoring Systems Amongst Out-Patients with Heart Failure – A comparison with body mass index

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ABSTRACT

Background: Malnutrition may be common in heart failure (HF) and associated with adverse outcomes but few data exist.

Objectives: To report the prevalence, clinical associations and prognostic consequences of malnutrition in out-patients with HF.

Methods: We applied the geriatric nutritional risk index (GNRI), controlling nutritional status (CONUT) score and prognostic nutritional index (PNI), to consecutive patients referred with suspected HF to a clinic serving a local population (n≈550,000).

Results: Of 4,021 patients enrolled, HF was confirmed in 3,386 (61% men, median age 75 (interquartile range (IQR): 67-81) years, median NTproBNP 1,103 (IQR: 415-2,631) ng/L). Left ventricular ejection fraction (LVEF) was <40% in 35%. Using scores for GNRI ≤91, CONUT >4 and PNI ≤38, 6.7%, 10.0% and 7.5% patients were moderately or severely malnourished; 57% were at least mildly malnourished by at least one score. Worse scores were most strongly related to older age, lower body mass index (BMI), worse symptoms and renal function, atrial fibrillation, anaemia, and reduced mobility.

During a median follow-up of 1,573 days (interquartile range: 702-2,799 days), 1,723 (51%) patients died. For patients moderately or severely malnourished, one year mortality was 28% for CONUT, 41% for GNRI, and 36% for PNI, compared to 9% for those with mild malnutrition or normal nutritional status.

A model including only age, urea and logNTproBNP, predicted one year survival (c-statistic 0.719) and was slightly improved by adding nutritional indices (up to 0.724; P<0.001) but not BMI.

Conclusion: Malnutrition is common amongst out-patients with HF and is strongly related to increased mortality.

(250 words)

Key words: Heart failure, malnutrition, CONUT, GNRI, PNI, BMI, mortality.

Abbreviations: HF= heart failure, CONUT = COntrolling NUTritional Status index, PNI= prognostic nutritional index, GNRI = geriatric nutritional risk index, LVEF= left ventricular ejection fraction, NTproBNP= N-terminal pro-B-type natriuretic peptide, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction.

Introduction

Although often ignored, malnutrition is common in patients with chronic heart failure (HF)[1] and associated with a high mortality.[2-3] Severe HF may lead to loss of appetite, malabsorption and a catabolic state leading to malnutrition.[1] Malnutrition may also be a driver of disease progression as part of a vicious cycle associated with cytokine activation, autonomic dysfunction and cachexia.[4]

Screening patients with HF for malnutrition might identify patients at high risk of adverse outcomes who might benefit from tailored treatments or interventions to prevent deterioration in HF and improve prognosis.[5] There are many screening tools for malnutrition but no consensus on which to use for patients with HF.[6-8] Amongst malnutrition scores, the COntrolling NUTritional Status index **(**CONUT), the prognostic nutritional index (PNI)**Error! Bookmark not defined.** and the geriatric nutritional risk index (GNRI) have been studied in HF.[9] The prevalence of malnutrition varies depending on the screening tool used and has been reported to be as high as 69% in some HF populations.[9] Malnutrition determined by any of these scoring methods is an independent predictor of worsening HF and/or mortality.[9] However, the studies conducted so far have been small and may not have been epidemiologically representative of the general population with HF.

Accordingly, we investigated the prevalence and prognostic importance of malnutrition using three different scoring systems in a large, well-characterised cohort of ambulatory patients with HF.

Methods

Study population

Consecutive consenting patients referred to a community HF clinic between 2000 and 2016 with suspected HF were enrolled. HF was defined as the presence of symptoms or signs of HF **and** evidence of cardiac dysfunction; either a left ventricular ejection fraction (LVEF) <40% **or** a raised plasma concentration of N-terminal pro-B-type natriuretic peptide (NTproBNP) (>125ng/L).[10] We excluded patients from this analysis if they had no measurement of height, weight or NTproBNP recorded and six patients with a diagnosis of chronic lymphocytic leukaemia (Online figure 1).

Patients with HF were phenotyped as reduced ejection fraction (HeFREF: LVEF <40%, or at least moderate left ventricular systolic dysfunction by visual inspection on echocardiography if LVEF was not available); or normal ejection fraction (HeFNEF: LVEF ≥40%; or better than, or equal to, mild-moderate left ventricular systolic dysfunction by visual inspection on echocardiography if LVEF was not available and NTproBNP >125ng/L).[10] Patients with an LVEF ≥40% and NTproBNP ≤125ng/L were considered not to have HF. Patients with HF were stratified by plasma NTproBNP concentration: ≤400, 401-1000, 1001-2000, 2001-4000 and >4000 ng/L.

A medical history and findings on physical examination were recorded. 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 diagnosis of myocardial ischemia 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 evidence of extra-cardiac arterial disease at ultrasound, such as those of the lower limbs and abdominal aorta. Chronic obstructive pulmonary disease (COPD), hypertension (HTN) and active cancer were defined as a clinical history of the diagnoses recorded in patient's notes. Significantly deranged liver function test was defined as serum alanine aminotransferase (ALT) > 50% upper limit of normal.

Blood was taken for standard haematology and biochemistry profiles and NTproBNP. Patients had an electrocardiogram and echocardiogram done by an experienced sonographer using a Vivid 5, 7 or 9 Scanner (GE, Fairfield, Connecticut, USA). All patients had left ventricular systolic function evaluated by visual assessment recorded (ranging from normal to severely impaired), whilst LVEF was calculated using Simpson's method. Patients were weighed in their casual wear without shoes. Body mass index (BMI) was calculated using the formula: BMI = weight in kilograms / (height in meters) squared, and patients were classified into 5 BMI (kg/m^2) categories: underweight (BMI<18.5), normal (BMI = 18.5-24.9), overweight (BMI = 25.0-29.9), obese (BMI = 30-39.9) and morbidly obese (BMI ≥40).[11]

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.

Malnutrition screening tools

Patients were screened for malnutrition using three indices (Online table 1).

a) *The geriatric nutritional risk index* (GNRI) is calculated using the formula: 1.489 x serum albumin (g/L) + 41.7 x (body weight in kilograms / ideal body weight).[7] We calculated the ideal body weight using the formula: 22 x square of height in meters.[12] A score of >98 is considered normal; scores of 92-98, 82-91 and <82 reflect mild, moderate and severe malnutrition, respectively.

b) *The controlling nutritional status score* (CONUT score) was developed by Ulibarri and colleagues in 2005 as a screening tool for the nutritional status of hospitalised patients.[6] The CONUT score takes into account serum albumin, cholesterol and total lymphocyte count. A score of 0-1 is considered normal; scores of 2-4, 5-8 and 9-12 reflect mild, moderate and severe malnutrition, respectively.

c) *The prognostic nutritional index* (PNI) is calculated using the formula: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (mm^3).[8] A score of >38 is considered normal; scores of 35-38 and <35 reflect moderate and severe malnutrition, respectively. Note there is no 'mild' category for PNI.

End points and follow-up

Patients were followed up until 19th July 2016. The primary endpoint was all-cause mortality. Our hospital is the only one in the region offering acute medical services. We have access to all primary and secondary care records. Outcome is censored at the point of last medical contact in primary or secondary care. Data regarding 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) (25^{th} to 75^{th} centiles) and categorical data are expressed as n (%). Independent t tests and non-parametric tests were used to compare medians across ordered groups for normally and non-normally distributed variables, respectively. The chi-squared test was used to compare proportions between groups. Pearson's correlation coefficients were used to assess the correlations between pairs of variables. Venn diagrams were used to illustrate the relationship between indices.

Time-to-event data are presented graphically using Kaplan-Meier curves. Log-rank-tests were used to compare survival between groups. Univariable and multivariable analyses with Cox proportional hazard regression were used to determine significant predictors of events. Log-transformation was applied when the data were very right-skewed.

Cross-validation, using an intuitive approach, brings both consistency and variability to prognostic model development.[13] The 'one-stop prognostic model' approach, although still favoured by many, fell into disrepute more than 30 years ago.[14] We therefore used k-fold cross-validation (k=25 here) to generate 25 prognostic models. Crossfold-validation splits the data randomly into 25 partitions. For each partition, the specified Cox regression model was fitted using the other *k*-1 (i.e., 24) groups, and the results were used to predict the dependent variable in the unused group.

The variables listed in Appendix 3 and 4 were included in the Cox models except: albumin, cholesterol and lymphocyte count which are included in the CONUT score and PNI; and weight, height and BMI which are included in the GNRI.

An arbitrary level of 5% statistical significance (two-tailed) was assumed for a covariate to be included in the model. The frequency of inclusion in all 25 prognostic models was calculated. Variables with an arbitrary inclusion frequency of ≥ 18 (in at least 70% of the 25 prognostic models) were used to form a malnutrition base model. Variables adjusted for in the base model included: age, sex, diastolic blood pressure, heart rate, New York Heart Association class III+ IV vs I+II, urea, logNTproBNP, CVA and PVD. We added each of the malnutrition indices and BMI alone (linear and decile) in turn to the base model and used Harrell's concordance (C) index[15] and log-likelihood ratio (LLR) to evaluate model discrimination in survival analysis, whilst noting that C-index is overoptimistic for censored survival data.[16] The C-index is defined as the probability that predictions and outcomes are concordant (the same). A C-index of 0.5 means that the relationship is no better than chance. The more negative the LLR, the bigger the improvement in model performance from addition of malnutrition indices to base model.

All statistical analyses were performed using SPSS 22 (SPSS INc.,Chicago, IL, USA) and The Stata (14th Version, StataCorp, TX, USA) statistical computer package.

Results

Patient characteristics

Of the 4,021 patients enrolled, 3,386 had HF: 1,198 (35%) patients had HeFREF, 2,188 (65%) patients had HeFNEF and 635 did not have HF. Most patients with HF were men (61%) and median age was 75 years (IQR: 67-81). Median LVEF was 44% (IQR: 33-56%) and median NTproBNP was 1,103 (IQR: 415-2,631) ng/L). A third of patients (30%) had

severe symptoms (New York Heart Association (NYHA) class III or IV), the most common co-morbid condition was IHD (48% of cases), and 36% were obese (BMI $\geq$ 30 kg/m^2). Baseline characteristics of patients with HeFREF, HeFNEF and patients without HF are shown in Table 1.

Prevalence and clinical associations of malnutrition

By GNRI and CONUT score, 316 (9%) and 1,486 (44%) patients with HF had mild malnutrition, respectively. By GNRI, CONUT score and PNI, 228 (7%), 339 (10%) and 255 (8%) patients had moderate to severe malnutrition, respectively (Table 1 and Online tables 2a-c). Although malnutrition scores correlated with each other (CONUT vs GNRI: correlation coefficient (r) = 0.36; CONUT vs PNI: r = 0.72; GNRI vs PNI: r = 0.42, all p<0.001), only 5% were classified as malnourished (any degree of malnutrition) by all three scores, and only 42% were *not* malnourished by any (Online figure 2). Because PNI has no "mild" category for malnutrition, the overlap amongst patients identified as moderately or severely malnourished by the different scores is more striking.

Compared to those with normal nutritional status, patients with malnutrition measured by any of the three malnutrition scores were older, more likely to be men, had lower BMI, worse symptoms and renal function; they were also more likely to have atrial fibrillation, anaemia and reduced mobility. (Online tables 2a-c) By CONUT score, 54% of patients with HeFREF and HeFNEF were malnourished, whilst fewer than 30% of those without HF were malnourished. By GNRI, malnutrition was more common in patients with HeFREF (19%) than HeFNEF (14%) or patients without HF (4%). By PNI, malnutrition was equally common in patients with HeFREF (8%) and HeFNEF (7%), whilst it was rare in patients

without HF (Table 1). The prevalence of moderate to severe malnutrition measured by any of the three indices was much higher in patients with plasma NTproBNP >4000 ng/L (Table 2).

Not surprisingly, the highest prevalence of malnutrition was found in patients who were underweight (BMI<18.5kg/m^2; 1.4% of patients with HF). A substantial proportion of patients with BMI $\geq$30 kg/m^2 (36% of patients with HF) were malnourished defined by CONUT (50%) or PNI (5%) scores but none by GNRI. (Table 2)

Malnutrition scores and mortality

During a median follow-up of 1,573 days (interquartile range: 702-2,799 days), 1,723 (50.9%) patients died; 351 (10%), 600 (18%) and 818 (24%) after one, two and three years, respectively. Worsening malnutrition status was associated with worse outcome regardless of the malnutrition screening tool used (Figure 1).

Univariable and multivariable predictors of mortality for the overall population and for the different HF phenotypes are shown in table 3 and Online tables 3a-b. Worsening malnutrition was associated with worse outcome regardless of left ventricular ejection fraction.

The following variables were independently associated with adverse outcome in 100% of the 25 prognostic Cox regression models developed using cross-validation: increasing age, urea, NTproBNP, NYHA class (III/IV vs I/II), worse CONUT or GNRI score, male sex, CVD, PVD and diastolic blood pressure; PNI was an independent predictor in 20 models (80%) (Online table 4).

A base model (including age, sex, diastolic blood pressure, heart rate, NYHA class III/IV vs I&II, urea, logNTproBNP, CVA and PVD) for predicting mortality achieved a Harrell's concordance (C) index = 0.719. (Table 4) Each malnutrition score, when added individually, improved the performance of the base model, with GNRI improving model performance most. Addition of BMI (linear or decile) alone did not improve performance of the base mode. Online table 5 summarised the findings from other studies which reported the role of malnutrition scores in predicting outcomes using different risk models.

Patients with any indication of malnourishment who were also underweight had the worst outcome. For those with higher BMI, one year mortality was substantially higher in the presence of moderate-severe malnutrition by any of the indices used. Patients with an NTproBNP >4000 ng/L and moderate or severe malnutrition had a particularly high one year mortality, ranging from 37 to 57% by different indices (Table 2).

Discussion

Malnutrition, as defined by existing scores, is common in out-patients with chronic heart failure and is associated with a poor prognosis regardless of the screening tools used, and regardless of the left ventricular systolic function, circulating levels of natriuretic peptides or body mass index. Although, malnutrition scores provided only a modest increase in the statistical accuracy of multi-variable prognostic models they may be important for at least two reasons; the wide availability of the variables required for their calculation and malnutrition as a potentially modifiable risk and therapeutic target.

The prevalence of malnutrition is, however, highly dependent upon the tool used, ranging from 8% (by PNI) to 54% (by CONUT) in the same cohort of patients. According to Lin et al. who conducted a systematic review on nutritional screening and assessment tools in heart failure, the prevalence of malnutrition in patients with chronic HF ranged from 16-62%.[9] The differences amongst studies in the prevalence of reported malnutrition might be due either to differences in the severity of heart failure or the use of different scoring systems. In our cohort, concordance amongst scores for milder degrees of malnutrition was rather poor, suggesting that they are not interchangeable. However, there was a greater degree of concordance for moderate to severe malnutrition amongst the three scores; perhaps reflecting the similarity of the variables on which they are based.

The CONUT score is calculated from variables reflecting protein and lipid metabolism as well as immune function measured from blood tests. PNI is similar to CONUT but does not include cholesterol. The CONUT score suggested that many more patients were 'malnourished' compared to GNRI or PNI but this may reflect low plasma cholesterol due to statin therapy. Although the benefits of statins are dubious in heart failure,[17] they are still commonly prescribed, and thus CONUT score is perhaps not the ideal tool. PNI identifies far fewer patients as malnourished compared to CONUT because it does not include cholesterol. However, as PNI only identifies patients as moderately or severely malnourished and may therefore underestimate the overall prevalence of malnutrition.

Amongst the three screening tools used, GNRI had the greatest incremental value in predicting risk. GNRI is the only tool of the three malnutrition indices we studied which takes into account both anthropometric factors (the ratio of body weight to ideal body weight) and

serum markers (albumin level). The CONUT score and PNI both consider serum markers only. GNRI might be a better malnutrition screening tool than CONUT or PNI because it is multidimensional. However, because GNRI considers low body weight to be a marker of malnutrition, it might underestimate malnutrition in overweight patients.

Although we found that indices of malnutrition increased the prognostic value of the models we constructed, the modest increase in c-index is of little value for the individual patient. However, given the effect in a substantial population of patients, the increase in c-statistic does emphasise that there is some component of "malnutrition" that is related to prognosis above and beyond the usual clinical variables taken into account when constructing prognostic models. In turn, that statistical result suggests that there may be some value in exploring malnutrition – and, perhaps, its treatment – further.

In patients with heart failure, BMI is not an ideal measure of body size and composition, and should not be used a surrogate of nutritional status. Patients with HF and higher BMI have, on average, lower plasma concentrations of natriuretic peptides and better outcomes than those with lower BMI, a phenomenon sometimes termed the 'obesity paradox'.[18] Using CONUT and PNI criteria, malnutrition is not only common in underweight patients, but is also highly prevalent in those who are overweight, obese, or even morbidly obese. We have found that the malnutrition scores we used were more highly related to outcome than BMI, and that their inclusion in predictive models of outcome increased the predictive power of the models, whereas including BMI did not. Despite the apparent protective effects of greater BMI, overweight patients who are malnourished by these two indexes have a higher mortality

than those who do not, highlighting that malnutrition does not simply manifest as being underweight.

Once present, malnutrition may progress to overt cardiac cachexia, a global wasting process affecting all body compartments including skeletal muscle, fat and bone.[1] The causes of cachexia in HF are multifactorial, and might arise as a result of malnutrition, impaired protein and calorie balance, pro-inflammatory immune activation, neurohormonal derangement, physical deconditioning and prolonged immobilisation leading to catabolic anabolic imbalance.[19] Screening for malnutrition using the most appropriate tool for patients with heart failure might enable early identification and characterisation of patients at risk of developing cachexia. Future studies should focus on studying whether better use of available treatments or novel treatments might improve nutritional status and eventually outcomes in these at-risk HF patients.

Study limitations

This is a single-centre study which has advantages and disadvantages. It is much easier to develop a system to enrol a large number of consecutive patients and apply consistent criteria and evaluations in a single centre. On the other hand, our patients and processes may differ from other centres. However, variations in patient selection amongst centres, often coupled with poor enrolment may make multi-centre studies less epidemiologically representative than a well-conducted single centre study. Nonetheless, confirmation of our findings by other investigators and other countries with different healthcare and social systems would be welcome. We used only three of the large number scores developed to screen for

malnutrition. We did not compare the prognostic value of nutritional screening tools with more complex comprehensive nutritional assessments.[20]

Whether it is appropriate to attribute low serum albumin solely to malnutrition is unclear. Hepatic disease and congestion or protein-losing gastro-intestinal or renal disease could cause serum albumin to fall. Indeed, in CONUT, scores for mild malnutrition appeared to be driven largely by statin therapy. Some of our patients were naïve to, or required optimisation of treatment for heart failure, which might improve nutritional status, and outcome, particularly those with HeFREF. Not everyone will agree with our definition of HeFNEF, for which there is no universal diagnostic agreement. However, malnutrition was much more common and prognosis much worse for patients who fulfilled our definition of HeFNEF compared to patients considered not to have HF.

We did not investigate the changes in nutritional status over time and the relationship between malnutrition scores and body composition. As reduced mobility occurred significantly in patients with HF who were classified as malnourished it might also be worthwhile to investigate whether an association between malnutrition and physical deconditioning exists.

Conclusion

Recognition of the high prevalence (and poor prognosis associated with) malnutrition in patients with heart failure should stimulate further research into its definition and management. We found that simple malnutrition scores were more closely related to outcome

than BMI, which is thus not an ideal measure of body size and composition. BMI should not be used as surrogate of nutritional status in patients with heart failure.

Perspectives:

Competency in Medical Knowledge 1: Malnutrition is common in ambulatory patients with HF, with a prevalence of up to 54% depending on severity and screening tool used. Malnutrition was more common when BMI was low or plasma NTproBNP was high and in older patients.

Competency in Medical Knowledge 2: Malnutrition is associated with a poor prognosis regardless of the screening tools used, LVEF, NTproBNP or BMI.

Translational outlook: Recognition of the high prevalence and poor prognosis of malnutrition in patients with HF should stimulate further research into its definition and management. (91 words)

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Legends:

Figure 1: Upper left panel: characteristics of malnourished patients. Upper right panel: prevalence of malnutrition in different subgroups of patients with HF: overweight/obese vs underweight/normal weight; HeFREF vs HeFNEF. Lower panel: Kaplan Meier curves for all-cause mortality by CONUT, GNRI and PNI categories.

Table 1: Baseline characteristics of all patients referred with suspected HF.

Table 2: Prevalence of malnutrition and 1-year mortality of the HF cohort according to BMI categories and NTproBNP categories.

Table 3: Univariable and multivariable analyses for mortality in patients with chronic HF (overall population).

Table 4: Addition of malnutrition indices to base model improves model performance in predicting all-cause mortality.

Supplementary Figures:

Online figure 1: Recruitment of chronic HF patients.

Online figure 2: Prevalence of malnutrition (any degree versus moderate to severe) in our HF cohort according to CONUT score, GNRI and PNI.

Online table 1: Procedures for evaluation of each nutritional index.

Online table 2a: Baseline characteristics of the HF cohort by CONUT categories.

Online table 2b: Baseline characteristics of the HF cohort by GNRI categories.

Online table 2c: Baseline characteristics of the HF cohort by PNI categories.

Online table 3a: Univariable and multivariable analyses of factors predicting outcomes in patients with CHF with HeFREF.

Online table 3b: Univariable and multivariable analyses of factors predicting outcomes in patients with CHF with HeFNEF.

Online table 4. Crossvalidation (x) for all patients with chronic HF. Crossvalidation (z) for patients chronic HF with baseline treatment excluded.

Online table 5: Summary of findings from other studies which reported the role of malnutrition scores in predicting outcomes using different risk models.

MALNUTRITION PHENOTYPE

- Elderly
- Male
- Anemia
- Atrial fibrillation
- ↓ Renal function
- ↓ Mobility
- ↓ BMI
- ↑ NYHA class
- ↑ NTproBNP
- Takes loop diuretic

PREVALENCE

HeFREF (35%)

	Degree of malnutrition		
	Mild	Mod	Sev
CONUT	42%	11%	1%
GNRI	11%	6%	2%
PNI	-	4%	4%

Under- or normal weight (27%)

	Degree of malnutrition		
	Mild	Mod	Sev
CONUT	45%	13%	1%
GNRI	28%	17%	5%
PNI	-	6%	5%

HeFNEF (65%)

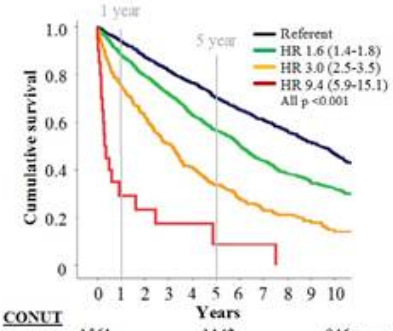
	Degree of malnutrition		
	Mild	Mod	Sev
CONUT	45%	9%	1%
GNRI	8%	5%	1%
PNI	-	4%	3%

Overweight or obese (73%)

	Degree of malnutrition		
	Mild	Mod	Sev
CONUT	44%	8%	<1%
GNRI	2%	1%	<1%
PNI	-	3%	3%

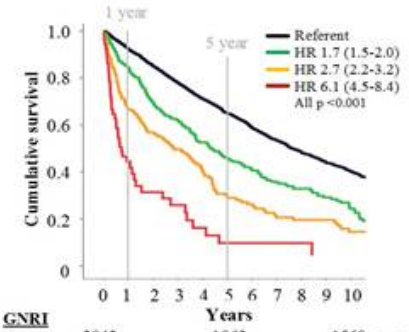
OUTCOME

CONUT



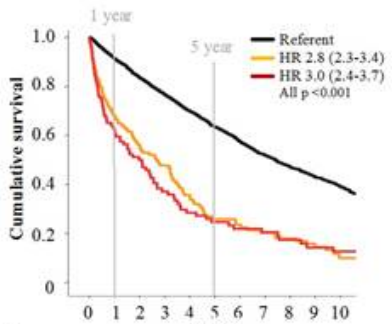
CONUT			
Normal	1561	1142	946
Mild	1486	919	712
Moderate	319	136	102
Severe	20	3	2

GNRI



GNRI			
Normal	2842	1962	1568
Mild	316	167	127
Moderate	177	72	57
Severe	51	11	10

PNI



PNI			
Normal	3131	2123	1694
Moderate	139	49	36
Severe	116	40	32

Table 1. Baseline characteristics of all patients referred with suspected heart failure.

	No HF	**HF**		**Missing**	**P-value*** **HF vs no HF**	**P-value*** **HeFREF vs HeFNEF**
	(LVEF ≥40 % & NTProBNP ≤125 ng/L) (N=635)	HeFREF (LVEF <40%) (N=1198)	HeFNEF (LVEF ≥40% & NTProBNP >125 ng/L) (N=2188)			
Demographics						
Age (years)	67 (59-73)	73 (64-79)	76 (70-82)	0	<0.001	<0.001
Sex (male), n (%)	342 (54)	895 (75)	1168 (53)	0	0.001	<0.001
Height (m)	1.67 (1.60-1.74)	1.69 (1.62-1.76)	1.65 (1.58-1.73)	0	0.06	<0.001
Weight (kg)	85 (73-97)	78 (66-90)	79(67-92)	0	<0.001	0.01
BMI (kg/m^2)	30 (27-34)	27 (24-31)	29 (25-33)	0	<0.001	<0.001
BP systolic (mmHg)	144 (129-159)	128 (113-143)	145 (127-162)	5	<0.001	<0.001
BP diastolic (mmHg)	82 (74-91)	76 (67-87)	78 (70-89)	5	<0.001	<0.001
HR (bpm)	72 (64-82)	75 (64-88)	72 (62-83)	13	0.08	<0.001

NYHA, n (%) I II III IV	 302 (48) 244 (38) 83 (13) 5 (1)	 165 (14) 598 (50) 401 (33) 34 (3)	 547 (25) 1062 (49) 551 (25) 29 (1)	0	<0.001	<0.001
Comorbidities						
CVA, n (%)	20 (3)	104 (9)	133 (6)	0	<0.001	0.004
IHD, n (%)	153 (24)	768 (64)	838 (38)	0	<0.001	<0.001
PVD, n (%)	13 (2)	72 (6)	74 (3)	0	0.007	<0.001
Diabetes, n (%)	169 (27)	274 (23)	546 (25)	0	0.19	0.18
HTN, n (%)	252 (40)	367 (31)	878 (40)	0	0.16	<0.001
COPD, n (%)	63 (10)	113 (9)	212 (10)	0	0.80	0.81
Cancer, n (%)	33 (5)	94 (8)	208 (10)	0	0.002	0.11
Significantly deranged liver function test, n (%)	2 (0)	9 (1)	7 (0)	0	0.59	0.08
Reduced mobility, n (%)	210 (33)	620 (52)	1203 (55)	0	<0.001	0.07
Blood tests						
Hb (g/dL)	14.0 (13.2-15.0)	13.5 (12.3-14.7)	13.2 (12.0-14.3)	10	<0.001	<0.001
Urea (mmol/L)	5.2 (4.2-6.3)	7.1 (5.4-9.9)	6.6 (5.1-9.1)	1	<0.001	<0.001

Creatinine (umol/L)	82 (71-96)	105 (88-133)	95 (79-121)	7	<0.001	<0.001
K+ (mmol/L)	4.3 (4.0-4.5)	4.4 (4.1-4.7)	4.3 (4.0-4.6)	24	<0.001	0.003
Na+ (mmol/L)	139 (137-141)	139 (136-140)	139(137-140)	6	<0.001	0.009
Lymphocyte ($x10^9$/L)	1.9 (1.6-2.3)	1.6 (1.2-2.1)	1.7 (1.3-2.1)	0	<0.001	0.46
Albumin (g/L)	40 (37-41)	38 (35-40)	38 (35-40)	0	<0.001	0.09
Cholesterol (mmol/L)	4.9 (4.1-5.8)	4.4 (3.7-5.3)	4.5 (3.7-5.4)	0	<0.001	0.08
NTproBNP (ng/L)	64 (38-92)	1974 (831-4534)	812(309-1845)	0	NA	<0.001
Treatment at Referral						
Loop diuretic, n (%)	184 (29)	904 (76)	1243 (57)	42	<0.001	<0.001
MRA, n (%)	23 (4)	369 (31)	262 (12)	42	<0.001	<0.001
ACEi, n (%)	226 (36)	858 (72)	1094 (51)	42	<0.001	<0.001
ARB, n (%)	69 (11)	112 (9)	280 (13)	42	0.63	0.003
ACEi or ARB, n (%)	292 (47)	966 (81)	1349 (62)	42	<0.001	<0.001
BB, n (%)	169 (27)	758 (64)	1119 (52)	42	<0.001	<0.001
Statin, n (%)	299 (48)	634 (53)	1093 (51)	42	0.09	0.10
Digoxin, n (%)	10 (2)	203 (17)	384 (18)	42	<0.001	0.65
ECG and echocardiography						

Cardiac rhythm, n (%) AF Sinus Unknown	 0 628 (99) 6 (1)	 278 (23) 833 (70) 87 (7)	 695 (32) 1382 (63) 112 (5)	0	<0.001	<0.001
EF (%)	59 (54-64)	30 (25-35)	54 (46-60)	1779	<0.001	NA
LV impairment , n (%) None/trivial Mild / mild- moderate Moderate to severe	 581 (91) 54 (9) 0	 0 108 (9) 1090 (91)	 1499 (69) 634 (29) 55 (2)	0	<0.001	<0.001
LVEDD (cm)	4.8 (4.4-5.2)	6.2 (5.7-6.8)	5.0 (4.5-5.5)	619	<0.001	<0.001
Malnutrition						
Prevalence of malnutrition <u>CONUT</u> Normal (0-1) Mild malnutrition (2-4) Moderate malnutrition (5-8) Severe malnutrition (9-12) <u>GNRI</u> Normal (>98) Mild malnutrition (92-98) Moderate malnutrition (82-91) Severe malnutrition (<82) <u>PNI</u> Normal (>38) Moderate malnutrition (35-38) Severe malnutrition (<38)	 450 (71) 181 (29) 3 (<1) 0 614 (96) 16 (3) 4 (1) 0 633 (100) 1 (0) 0	 552 (46) 507 (42) 129 (11) 10 (1) 969 (81) 133 (11) 71 (6) 25 (2) 1101 (92) 53 (4) 44 (4)	 1010 (46) 979 (45) 190 (9) 10 (<1) 1874 (86) 183 (8) 106 (5) 26 (1) 2023 (93) 86 (4) 72 (3)	 0 0 0	 <0.001 <0.001 <0.001	 0.09 0.003 0.65

ACEi = Angiotensin-converting enzyme inhibitor, AF= atrial fibrillation, ARB = Angiotensin receptor blocker, BB= betablocker, BMI= body mass index, BP= blood pressure, CONUT = Controlling nutritional status, CVA = cerebrovascular disease, ECG= electrocardiogram. EF= ejection fraction, GNRI = Geriatric nutritional risk index, Hb = Haemoglobin, HF= heart failure, HeFREF = heart failure with reduced ejection fraction, HeFNEF = heart failure with normal ejection fraction, HR= heart rate, IHD = ischaemic heart disease, HTN= hypertension, COPD = chronic obstructive pulmonary disease, K+ = potassium, LVEDD= left ventricular end diastolic diameter, MRA = Mineralocorticoids receptor antagonists, Na+ = sodium, NYHA = New York Heart Association Class, NTproBNP = N-terminal Pro Brain Natriuretic Peptide, PNI = Prognostic nutritional Index, PVD = peripheral vascular disease.

*P-value for trend except when there are $\geq$ 2 categories (e.g. NYHA class, cardiac rhythm etc)

Table 2: Prevalence of malnutrition and 1-year mortality of patients with heart failure stratified by BMI and NTproBNP.

		BMI Categories (kg/m^2)				
		Underweight <18.5 (N=48)	**Normal 18.5-24.9** (N=854)	**Overweight 25-29.9** (N=1256)	**Obese 30-39.9** (N=1061)	**Morbidly obese ≥40** (N=167)
CONUT	% malnourished (any degree)	77	59	54	49	56
	% malnourished (mod-sev)	21	15	9	7	11
	1 year mortality (%) Malnutrition (mod-sev vs mild vs none)	56 vs 42 vs 9	38 vs 17 vs 8	23 vs 11 vs 6	17 vs 9 vs 5	33 vs 5 vs 9
GNRI	% malnourished (any degree)	96	49	6	0	0
	% malnourished (mod-sev)	88	20	1	0	0
	1 year mortality (%) Malnutrition (mod-sev vs mild vs none)	40 vs 0 vs 50	41 vs 15 vs 8	43 vs 9	NA	NA
PNI	% malnourished (mod-sev)	26	11	7	4	7
	1 year mortality (%) Malnutrition (mod-sev vs none)	50 vs 32	50 vs 12	26 vs 9	24 vs 7	36 vs 8

		NTproBNP categories (ng/L)				
		≤400 (N=822)	**401-1000** (N=776)	**1001-2000** (N=697)	**2001-4000** (N=553)	**>4000** (N=538)
CONUT	% malnourished (any degree)	39	47	54	62	78
	% malnourished (mod-sev)	3	4	8	12	31
	1 year mortality (%) Malnutrition (mod-sev vs mild vs none)	10 vs 4 vs 3	19 vs 8 vs 5	20 vs 11 vs 5	25 vs 12 vs 11	37 vs 31 vs 20
GNRI	% malnourished (any degree)	5	10	15	22	38
	% malnourished (mod-sev)	2	4	5	7	20
	1 year mortality (%) Malnutrition (mod-sev vs mild vs none)	29 vs 7 vs 3	25 vs 5 vs 6	25 vs 13 vs 8	28 vs 14 vs 12	57 vs 30 vs 22
PNI	% malnourished (mod-sev)	2	3	6	9	23
	1 year mortality (%) Malnutrition (mod-sev vs none)	20 vs 3	27 vs 6	26 vs 8	30 vs 12	47 vs 25

*There are only two underweight (BMI < 18.5 kg/m^2) patients classified as not malnourished by GNRI. There is no underweight patient classified as mildly malnourished by GNRI.

CONUT = Controlling nutritional status, GNRI = Geriatric nutritional risk index, HF= heart failure, Mod-sev = moderate to severe, NTproBNP = N-terminal Pro Brain Natriuretic Peptide, PNI = Prognostic nutritional Index.

Table 3: Univariable and multivariable analyses of factors predicting mortality in patients with CHF (overall population)

Worse outcome per unitary increase	**Overall HF population**					
	Univariate			**Multivariate**		
	HR(95%CI)	Wald X^2	P-value	HR(95%CI)	Wald X^2	P-value
Age (years)	1.055 (1.05-1.06)	362.8	<0.001	1.05 (1.04-1.06)	209.0	<0.001
Sex (male vs female)	1.17 (1.06-1.29)	10.0	0.002	1.29 (1.15-1.45)	18.1	<0.001
Height (m)	0.26 (0.17-0.42)	32.4	<0.001			
Weight (kg)	0.99 (0.986-0.991)	70.5	<0.001			
BMI (kg/m^2)	0.97 (0.96-0.98)	41.6	<0.001			
BP systolic (mmHg)	0.99 (0.99-1.00)	34.1	<0.001			
BP diastolic (mmHg)	0.98 (0.98-0.98)	129.6	<0.001	0.99 (0.99-1.00)	14.7	<0.001
HR (bpm)	1.01 (1.00-1.01)	22.9	<0.001	1.01 (1.00-1.01)	9.7	0.002
NYHA III/IV vs I/II	2.03 (1.84-2.24)	200.7	<0.001	1.56 (1.40-1.74)	64.4	<0.001
Hb (g/dL)	0.82 (0.80-0.85)	195.4	<0.001			

Urea (mmol/L)	1.06 (1.05-1.06)	343.2	<0.001	1.03 (1.02-1.04)	21.8	<0.001
Creatinine (umol/L)	1.00 (1.00-1.00)	183.1	<0.001			
K+ (mmol/L)	1.01 (0.91-1.11)	0.02	0.90			
Na+ (mmol/L)	0.94 (0.93-0.95)	76.8	<0.001			
Lymphocyte ($x10^9$/L)	0.67 (0.62-0.72)	100.7	<0.001			
Albumin (g/L)	0.90 (0.88-0.91)	328.1	<0.001			
Cholesterol (mmol/L)	0.94 (0.90-0.97)	12.0	0.001			
Log NTproBNP (ng/L)	2.80 (2.57-3.06)	524.7	<0.001	1.75(1.56-1.97)	93.0	<0.001
Loop diuretic (Y vs N)	2.10 (1.90-2.40)	180.6	<0.001			
MRA (Y vs N)	1.21 (1.08-1.37)	9.9	0.002			
ACEi (Y vs N)	1.04 (0.94-1.14)	0.5	0.46			
ARB (Y vs N)	0.89 (0.75-1.04)	2.2	0.14			
ACEi or ARB (Y vs N)	1.00 (0.90-1.11)	0.003	0.96			
BB (Y vs N)	0.70 (0.64-0.77)	53.3	<0.001			

Statin (Y vs N)	0.77 (0.70-0.84)	30.0	<0.001			
Digoxin (Y vs N)	1.43 (1.27-1.60)	35.2	<0.001			
Cardiac rhythm AF vs Sinus	1.32 (1.19-1.47)	26.3	<0.001			
EF (%)	0.99 (0.98-0.99)	36.7	<0.001			
LVEDD (cm)	1.05 (1.00-1.11)	4.0	0.046			
CVA (Y vs N)	1.55 (1.31-1.83)	26.8	<0.001			
IHD (Y vs N)	1.11 (1.01-1.22)	4.8	0.029			
PVD (Y vs N)	1.80 (1.48-2.20)	34.0	<0.001	1.66 (1.35-2.05)	22.7	<0.001
Diabetes (Y vs N)	1.13 (1.01-1.27)	4.2	0.04			
Reduced mobility (Y vs N)	2.11 (1.89-2.36)	175.1	<0.001			
Prevalence of malnutrition <u>CONUT</u> Normal Mild malnutrition Moderate malnutrition Severe malnutrition	 1 1.58 (1.43-1.75) 2.96 (2.54-3.45) 9.41 (5.89-15.06)	 - 76.0 195.3 87.5	 <0.001 <0.001 <0.001			

GNRI				1.26 (1.15-1.37)	27.2	<0.001
Normal	1	-	-			
Mild malnutrition	1.72 (1.48-2.00)	50.8	<0.001			
Moderate malnutrition	2.68 (2.23-3.22)	111.4	<0.001			
Severe malnutrition	6.14 (4.49-8.40)	129.2	<0.001			
PNI						
Normal	1	-	-			
Moderate malnutrition	2.75 (2.26-3.36)	101.2	<0.001			
Severe malnutrition	2.99 (2.41-3.72)	97.4	<0.001			

ACEi = Angiotensin-converting enzyme inhibitor, AF= atrial fibrillation, ARB = Angiotensin receptor blocker, BB= betablocker, BMI= body mass index, BP= blood pressure, CONUT = Controlling nutritional status, CVA = cerebrovascular disease, ECG= electrocardiogram. EF= ejection fraction, GNRI = Geriatric nutritional risk index, Hb = Haemoglobin, HF= heart failure, HeFREF = heart failure with reduced ejection fraction, HeFNEF = heart failure with normal ejection fraction, HR= heart rate, IHD = ischaemic heart disease, K+ = potassium, LVEDD= left ventricular end diastolic diameter, MRA = Mineralocorticoids receptor antagonists, Na+ = sodium, NYHA = New York Heart Association Class, NTproBNP = N-terminal Pro Brain Natriuretic Peptide, PNI = Prognostic nutritional Index, PVD = peripheral vascular disease, Y= yes, N=No.