Agreement and classification performance of malnutrition tools in patients with chronic heart failure.

Short running head: Malnutrition in heart failure.

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Abbreviations: ACEi = angiotensin converting enzyme inhibitors, AF = atrial fibrillation, ARB = angiotensin receptor antagonist, BAPEN = British Association for Parenteral and Enteral Nutrition, BMI = body mass index, CHF = chronic heart failure, CONUT = COntrolling NUTritional status index, COPD = chronic obstructive pulmonary disease, GNRI = Geriatric Nutritional Risk Index, Hb= hemoglobin, HeFNEF = heart failure with normal ejection fraction, HeFREF = heart failure with reduced ejection fraction, HF = heart failure, JW = fourth author, K = Kappa coefficient, LVEF = left ventricular ejection fraction,

MNA = Mini Nutritional Assessment, MNA-SF = Mini Nutritional Assessment-Short Form, MUST = Malnutrition Universal Screening Tool, NTproBNP = N-terminal pro B-type natriuretic peptide, NYHA = New York Heart Association, PNI = Prognostic Nutritional Index, SGA = Subjective Global Assessment, SS = first author, UK = United Kingdom.

Abstract:

Background:

Malnutrition is common in patients with chronic heart failure (CHF) and is associated with adverse outcome, but few data exist.

Objectives:

To compare the agreement and classification performance of 6 malnutrition tools in patients with CHF.

Methods:

We evaluated the performance of 6 malnutrition tools: COntrolling NUTritional Status Index (CONUT); Geriatric Nutritional Risk Index (GNRI); Prognostic Nutritional Index (PNI); Malnutrition Universal Screening Tool (MUST); Mini Nutritional Assessment-Short Form (MNA-SF); and Subjective Global Assessment (SGA), in 467 consecutive patients with CHF who attended our clinic for follow up. We used Venn diagrams and Kappa statistics to study the agreement of different tools. Since there is no "gold-standard" for malnutrition evaluation, for each of the malnutrition tools, we used the results of the other 5 tools to produce a standard combined index for evaluating ≥moderate malnutrition. Subjects were considered having '≥moderate malnutrition' if so identified by ≥ 3/5 tools. We evaluated the sensitivity, specificity and predictive values of different tools in identifying significant malnutrition as defined by the combined index.

Results:

67% of patients were male, median age was 76 years and median N-terminal pro-B-type natriuretic peptide (NTproBNP) was 1156 ng/L. The prevalence of any degree and ≥moderate malnutrition ranged between 6-60% and 3-9% respectively, with CONUT classifying the highest proportion of subjects as malnourished.

Malnourished patients tended to be older, have worse symptoms, higher NT-proBNP and more co-morbidities. CONUT had the highest sensitivity (80%), MNA-SF and SGA had the highest specificity (99%) and MNA-SF had the lowest misclassification rate (2%) in identifying ≥moderate malnutrition as defined by the combined index.

Conclusion:

Malnutrition is common in patients with CHF. The prevalence of malnutrition varies depending on the tool used. Amongst the 6 malnutrition tools studied, MNA-SF has the best classification performance in identifying significant malnutrition as defined by the combined index.

(299 words)

Key words: heart failure, malnutrition, screening, assessment

Introduction:

Patients with chronic heart failure (CHF) are at risk of developing malnutrition. CHF is a condition characterised by systemic venous congestion. Malnutrition in CHF might be related to right heart dysfunction and congestion which predispose to bowel oedema, inflammatory activation and malabsorption, thereby leading to malnutrition and cachexia (1,2). CHF and malnutrition also share common risk factors such as depression and smoking (3,4). Once malnutrition develops, it might further contribute to progression of cardiac dysfunction, either due to lack of important nutrients or systemic inflammation (5,6). Although it is common in patients with chronic heart failure (CHF) with a prevalence of up to 62% and is associated with increased morbidity and mortality (7,8**)**, there is no standard method for evaluating malnutrition.

Several tools have been proposed and they can generally be categorised into *simple* versus *multi-dimensional* tools (7). *Simple* tools screens for malnutrition by considering laboratory tests and anthropometric measures; on the other hand, *multi-dimensional* tools offer a more comprehensive assessment of nutrition status by assessing a variety of factors, including acute illness, mobility, comorbidities and dietary intake. *Multi-dimensional* tools, such as Subjective Global Assessment (SGA), predict mortality in patients with heart failure (HF) (9), but are unlikely to be used in routine practice as they are too complex and time-

consuming. On the other hand, *simple* tools such as Geriatric Nutritional Risk Index (GNRI), are also of prognostic value in patients with HF (10,11); although rapid and easy to perform, they are also unlikely to be used in clinical practice if they don't offer the same information as the complex tools. It is therefore important to compare the two classes of tools to see if the ideal solution of a "quick and useful" tool is realisable.

Previous studies have mostly evaluated malnutrition using individual tools in different populations and settings (7). Few studies have simultaneously evaluated different tools in the same cohort of patients. We have previously evaluated malnutrition using 3 simple tools: GNRI, Prognostic Nutritional Index (PNI) and COntrolling NUTritional Status Index (CONUT), in two cohorts of patients with acute or chronic HF. We found that worsening malnutrition using each tool was independently related to an adverse prognosis (3,12).

To the best of our knowledge, no study has compared *simple* versus *multi-dimensional* tools for evaluating malnutrition in patients with CHF. We therefore prospectively compared the prevalence of malnutrition, agreement and classification performance of 3 *simple* versus 3 *multi-dimensional* malnutrition tools in a well characterized cohort of patients with CHF.

Methods

Study population

Consecutive ambulatory patients with CHF attending a community heart failure clinic were enrolled between September 2016 and March 2017 (Figure 1). All patients had a pre-existing (>1 year) clinical diagnosis of CHF. Patients had to have **either** a low left ventricular ejection fraction (LVEF) <40% or at least moderate left ventricular systolic dysfunction by visual inspection if LVEF was not calculated, defined as heart failure with reduced ejection fraction, HeFREF; **or** normal left ventricular systolic function (LVEF ≥40% or better than, or equal to, mild left ventricular systolic dysfunction by visual inspection) and raised N-terminal pro-B-type natriuretic peptide (NTproBNP) of >400 ng/L, defined as heart failure with normal ejection fraction, HeFNEF (13). All patients had already been initiated on HF treatment.

Individuals who had previously consented to take part in research were recruited as controls. Control subjects were older than 65 years of age, with no previous or current symptoms or signs of HF; with normal left ventricular systolic function on echocardiography and NT-proBNP of < 400 ng/L. They also had risk factors for development of HF, including coronary artery disease, diabetes mellitus or hypertension (Figure 1).

All patients had a full medical history, physical examination, blood tests (full blood count, urea and electrolytes and NT-proBNP), an electrocardiogram and a consultation with a HF specialist. The New York Heart Association (NYHA) functional classification was used to assess the severity of HF symptoms (14).

Malnutrition evaluation

All patients and controls were evaluated by the same researcher (SS) for malnutrition (Supplemental material 1a).

The *simple* screening tools used were listed below. These tools only take into account laboratory tests and anthropometric measures and can be completed within a minute.

1) Geriatric Nutritional Risk Index (GNRI)

GNRI was calculated using the formula: [1.489 x albumin (g/L)] + [41.7 x current weight/ ideal weight] (15). Ideal body weight was calculated using the formula: 22 x square of height in meters (16). Subjects with GNRI >98 have normal nutritional status, those with GNRI 92-98, 82-91, <82 have mild, moderate and severe malnutrition respectively (15). GNRI ≤ 98 is classified as malnourished.

2) COntrolling NUTritional Status (CONUT score; scored between 0-12):

The CONUT score was developed by Ignacio de Ulibarri and colleagues in 2005 as a screening tool for assessment of nutritional status of in-patients (17). It uses serum albumin, cholesterol and total lymphocyte count. Subjects with a CONUT score 0-1 have normal nutritional status, those with CONUT score 2-4, 5-8, 9-12 have mild, moderate and severe malnutrition respectively (17). Subjects with CONUT score ≥2 are classified as malnourished.

3) Prognostic Nutritional Index (PNI)

PNI is calculated using the formula: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (mm^3) (18). Subjects with PNI >38 have normal nutritional status; those with PNI 35-38 and <35 have moderate and severe malnutrition respectively (18). Subjects with PNI ≤38 are classified as malnourished.

The *multi-dimensional* tools used were listed below. These tools take into account different factors that affect nutritional status including: the effect of acute illness, mobility, comorbidities and dietary intake. They are more time consuming to perform (on average 20 minutes for SGA)

1) *Malnutrition Universal Screening Tool (*MUST; scored between 0-2): (Supplemental material 1b)

MUST is a 3-step screening tool developed by the multidisciplinary malnutrition advisory group of the British Association for Parenteral and Enteral Nutrition (BAPEN) in 2003 to identify malnutrition in adults (19). MUST uses 3 simple steps: body mass index (BMI), weight loss and the effect of acute illness on food intake to generate an overall risk of malnutrition. Subjects with MUST score 0 have normal nutritional status (low malnutrition risk); those with MUST score 1 and ≥ 2 have mild (medium risk) and ≥ moderate (high risk) malnutrition respectively (19). Subjects with MUST ≥ 1 are classified as malnourished. The researcher who assessed nutrition status completed the "Nutritional Screening using MUST" BAPEN e-learning module available at https://www.bapen.org.uk/e-learning-portal.

2) *Mini Nutritional Assessment Short Form* (MNA-SF; scored between 0-14): (Supplemental material 1c)

Mini Nutritional Assessment (MNA) was developed in 1996 as a tool to identify malnutrition in elderly patients (20). MNA-short form (MNA-SF) (21), a shorter version of MNA, consists of 6 questions which assess food intake, weight loss, mobility, acute events, neuro-psychological problems and BMI. Subjects with MNA-SF score 12-14 have normal nutritional status, those with MNA-SF score 8-11 and ≤7 have mild and ≥ moderate

153 malnutrition respectively (21). Subjects with MNA-SF score ≤11 are classified as
154 malnourished.

155

156 *3)* *Subjective Global Assessment* (SGA; scored as A, B or C)*:* (Supplemental material
157 1d)

158 SGA is a nutritional assessment tool that is widely used in a variety of clinical settings (22,
159 23, 24). It includes an assessment of medical history (weight loss, changes in dietary intake,
160 gastrointestinal symptoms and functional capacity) and a physical examination (wasting of
161 large muscle groups as determined by low bulk that is detectable on palpation; low
162 subcutaneous fat measured in the triceps, biceps and peri-orbital region; degree of sacral or
163 ankle oedema and ascites). The four features of the physical examination are scored as either
164 normal (A), mild to moderate (B) or severe (C) malnutrition. These measurements are not
165 precise, but are merely a subjective impression. Subjects with SGA- A have normal
166 nutritional status, those with SGA-B and C have mild and ≥ moderate malnutrition
167 respectively (22). Subjects with SGA-B or C are classified as malnourished.

168

169 During data analysis, it quickly became apparent that CONUT score was reporting a
170 disproportionately large number of subjects as having malnutrition of some degree. We

therefore performed detailed analyses to study subjects identified by different tools as having "*any degree of malnutrition"* and "*at least (≥) moderate* malnutrition".

Co-morbidities

Co-morbidities were measured using the Charlson co-morbidity index. (25) Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or a pre-existing diagnosis (26). Anaemia was defined as hemoglobin (Hb) <13.0 g/dL in men and < 12.0 g/dL in women) (27). Diabetes mellitus was defined according to the Diabetes United Kingdom (UK) guideline (28). Patients consented to the use of electronic medical records to identify previous clinical history of myocardial infarction, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), dementia, rheumatological disease, peptic ulcer, hemiplegia/ paraplegia, liver/renal disease or malignancy. None of the patients had dementia sufficiently severe as to be lacking capacity.

Statistical analysis

Continuous data are expressed as a median with 25^{th} to 75^{th} centiles and categorical data are expressed as n (%). Independent t tests and Mann-Whitney U tests were used to compare two

189 continuous variables for normally and non-normally distributed data. The chi-squared test
190 was used to compare proportions between groups. Pearson's correlation or Spearman's
191 correlation coefficients were used to assess the relationship between two variables.

192

193 We studied the prevalence of any degree of malnutrition and at least moderate malnutrition in
194 subjects using the different malnutrition tools described in detail in the "malnutrition
195 evaluation" section. We used Venn diagrams to illustrate the relationship between
196 malnutrition tools and Kappa statistics to study the agreement between simple versus multi-
197 dimensional malnutrition tools.

198

199 We then studied the classification performance of different malnutrition tools (simple and
200 multi-dimensional tools). Since there is no gold standard in evaluating malnutrition in
201 patients with CHF, for each of the tools, we used the results of the *other* 5 tools to produce a
202 single combined malnutrition index which we assumed to be the standard. This methodology
203 has been previously suggested by Pablo et al (29).

204

205 We created two sets of combined indices, one for evaluation of any degree of malnutrition
206 and the other for evaluation of at least moderate malnutrition. The combined index for any

degree of malnutrition classifies subjects into malnourished (any degree) versus not malnourished: subjects were considered as malnourished (any degree) if so identified by at least 3 of the 5 tools. Similarly, the combined index for at least moderate malnutrition classifies subjects into < moderate malnutrition versus ≥ moderate malnutrition: subjects were considered as having at least moderate malnutrition if so identified by at least 3 of the 5 tools.

In a separate analysis, in order to assess the value of single laboratory tests (albumin, lymphocyte count and cholesterol) in defining any degree of malnutrition or at least moderate malnutrition, we compared each with two similar combined indices as described above (one for evaluation of any degree of malnutrition and another for evaluation of at least moderate malnutrition) derived from the tools that did not contain the variable in question.

The sensitivity, specificity and predictive values for each of the individual tools and single laboratory tests in identifying malnutrition as defined by the combined index were calculated.

To investigate the bias associated with SGA being a subjective malnutrition tool, in addition to the principal investigator (SS), a second investigator (JW) also completed the SGA for a

random sample of 23 patients. Kappa statistics was used to determine the inter-operator agreement.

All statistical analyses were performed using SPSS 24 (SPSS INc.,Chicago, IL, USA) and The Stata (14th 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 the Yorkshire and the Humber- South Yorkshire Research Ethics Committee (Study reference number: 03/02/044). All subjects gave their written informed consent for their data to be used for research.

Results

A total of 467 consecutive patients with CHF and 87 controls was studied. The agreement and classification performance of different malnutrition tools were evaluated and compared. Table 1 shows the baseline characteristics of the HF cohort vs controls. The majority of patients and controls were male and elderly; 17% of those with CHF were older than 85 years

(vs 2% of controls). Most of the patients with CHF had HeFREF (62%) with a median NTproBNP of over 1100ng/L; around one fifth had severe symptoms (NYHA class III/IV).

Prevalence of malnutrition

Malnutrition of any degree

The prevalence of malnutrition of any degree in patients with CHF was highly variable, ranging from 6-60%, depending on the malnutrition tool used (Supplemental material 2). The CONUT score classified a much larger proportion of subjects (both patients with CHF and controls) as malnourished by any degree than other tools [patients: N=279 (60%), controls: N=43 (49%)].

Amongst the simple screening tools, CONUT score graded the greatest proportion while PNI graded the lowest proportion of patients as malnourished by any degree (Figure 2a & Supplemental material 2). Only 3% (N=15) of patients were classified as malnourished by any degree by **all** 3 *simple screening* tools (Figure 2a, top right).

Amongst the multi-dimensional tools, MNA-SF graded the greatest proportion while the MUST score graded the lowest proportion of patients as malnourished by any degree (Figure 2a & Supplemental material 2). Only 11% (N=51) of patients were classified as malnourished by any degree by **all** 3 multi-dimensional tools (Figure 2a, top left).

The prevalence of malnutrition of any degree was similar in patients with HeFNEF versus HeFREF but was generally more common in patients with atrial fibrillation (AF) versus sinus rhythm (Supplemental material 3). The prevalence of malnutrition of any degree increased with decreasing BMI and increasing NYHA class, age and NTproBNP (Supplemental material 3).

At least moderate malnutrition

The prevalence of at least moderate malnutrition in patients with CHF ranged from 3-9%, depending on the malnutrition tool used (Supplemental material 2). It was much more common in patients with CHF than in controls.

Amongst the simple screening tools, the CONUT score graded the greatest proportion of patients as having at least moderate malnutrition (Figure 2b & Supplemental material 2). Only 2% (N=9) of patients were classified as having at least moderate malnutrition by **all** 3 *simple screening* tools (Figure 2b, top right).

Amongst the multi-dimensional tools, the MUST score graded the greatest proportion of patients as having at least moderate malnutrition (Figure 2b & Supplemental material 2). Only 1.3% (N=6) of patients were classified as having at least moderate malnutrition by **all** 3 multi-dimensional tools (Figure 2b, top left).

The prevalence of at least moderate malnutrition was similar in patients with HeFNEF versus HeFREF and in patients with AF versus sinus rhythm (Table 2). The prevalence of at least moderate malnutrition increased with decreasing BMI and increasing NYHA class and NTproBNP (Table 2).

Relationship between malnutrition and clinical data

Malnutrition of any degree

Compared to those with normal nutritional status, patients with malnutrition of any degree were older, had a lower BMI; more co-morbidities, worse symptoms, higher NTproBNP and lower haemoglobin. They were also less likely to be on angiotensin converting enzyme inhibitors (ACEi)/ angiotensin receptor antagonist (ARB) or statins. (Supplemental material 4a)

At least moderate malnutrition

Compared to those with normal nutritional status or mild malnutrition, patients with at least moderate malnutrition were older, had a lower BMI, more co-morbidities, worse symptoms, higher NTproBNP and lower haemoglobin (Supplemental material 4b). They were also less likely to be on ACEi/ ARB or statins.

<u>Agreement between simple and multi-dimensional tools</u>

Malnutrition of any degree

Of the simple screening tools, GNRI had the highest, and CONUT score the lowest, agreement with multi-dimensional tools in identifying malnutrition of any degree

(Supplemental material 5a). There was a greater degree of agreement in identifying patients with any degree of malnutrition using the multi-dimensional tools compared to simple screening tools.

At least moderate malnutrition

Of the simple screening tools, GNRI had the highest, and CONUT score the lowest, agreement with multi-dimensional tools in identifying at least moderate malnutrition (Supplemental material 5b). There was a greater degree of agreement in identifying patients with at least moderate malnutrition using the multi-dimensional tools compared to simple screening tools.

Classification performance of different malnutrition tools according to the combined index

Malnutrition of any degree

Amongst the patients with CHF, the MNA-SF score had the greatest sensitivity while MUST and PNI had the highest specificity in identifying malnutrition of any degree defined by the combined index (Supplemental material 6). SGA had the lowest, and CONUT had the

highest, misclassification rate. Single tests generally had higher misclassification rates compared to either simple or multi-dimensional tools.

In non-obese patients (BMI<30 kg/m^2), GNRI had a sensitivity of 73% in identifying malnutrition of any degree, but its sensitivity was zero in obese patients (BMI≥30 kg/m^2) (Supplemental material 7a & b). Similarly, in non-obese patients, SGA had a sensitivity of 94% in identifying malnutrition of any degree, but its sensitivity was 38% in obese patients (Supplemental material 7a & b).

At least moderate malnutrition

Amongst the patients with CHF, the CONUT score had the greatest sensitivity while MNA-SF and SGA had the highest specificity in identifying at least moderate malnutrition defined by the combined index (Table 3). MNA-SF had the lowest, and CONUT the highest, misclassification rate. Single tests (serum albumin, cholesterol or total lymphocyte levels) generally had higher misclassification rates compared to either simple or multi-dimensional tools.

In non-obese patients (BMI<30 kg/m^2), GNRI had a sensitivity of 62% in identifying at least moderate malnutrition, but its sensitivity was zero in obese patients (BMI≥30 kg/m^2) (Supplemental material 8a & b). Similarly, in non-obese patients, SGA had a sensitivity of 60% in identifying at least moderate malnutrition, but its sensitivity was zero in obese patients (Supplemental material 8a & b).

Inter-operator agreement of SGA

The agreement between the two operators' judgements on degree of malnutrition in a random sample of subjects (N=23) using the SGA had a Kappa coefficient (K) of 0.65 (95% CI: 0.59-0.71, p=0.001).

Discussion

Ours is the first paper to compare directly several commonly used simple versus multi-dimensional malnutrition tools in patients with CHF. We found that malnutrition is common, with a prevalence of malnutrition by any degree and moderate to severe malnutrition ranging between 6-60% and 3-9% respectively, depending on the tool used. Our findings are similar to those from a recent meta-analysis which evaluated the role of different malnutrition tools in patients with acute and chronic heart failure (7). The prevalence of malnutrition in patients

with CHF was between 16 and 62% depending on the malnutrition tool used and the population studied.

Our results showed that the variation in prevalence of malnutrition (of any degree and at least moderate) is much greater amongst simple screening tools (any degree: 6-60%; at least moderate: 6-9%) compared to multi-dimensional tools (any degree: 12-29%; at least moderate: 3-4%). The CONUT score in particular suggested that many more patients were 'malnourished' compared to GNRI or PNI. There was a greater degree of agreement in identifying malnourished patients using the multi-dimensional tools compared to *simple* screening tools. The agreement between the simple and multi-dimensional tools was weak for some tools, suggesting that the tools are measuring different aspects of malnutrition as they certainly do not identify the same group of patients as being malnourished. The heterogeneity of the tools was further demonstrated by our finding that the prevalence of malnutrition was higher in patients with AF than in patients with sinus rhythm according to some malnutrition tools but not others.

We found that malnutrition was equally common in patients with HeFREF and those with HeFNEF. Malnutrition was more common in patients with worse NYHA classes and higher

natriuretic peptide levels, suggesting that malnutrition is more closely related to the severity of HF rather than to the HF phenotype.

Different tools have their own strengths and weaknesses. Amongst the simple screening tools, CONUT score has the highest sensitivity, but it also has the highest false positive rate in identifying at least moderate malnutrition compared with the combined index. The CONUT score is confounded by the use of statins (62% of patients with CHF were on statins), which causes lower cholesterol levels irrespective of nutritional status. Furthermore, of the 3 components of CONUT score, cholesterol level and lymphocyte count treated as single measures misclassified a significant proportion of patients compared with the combined index. Further studies are needed to determine the optimal cut-offs for each component of the CONUT score to improve its classification performance.

PNI (although specific) has the highest false negative rate in identifying malnutrition of any degree, hence underestimating malnutrition compared to other tools. This is because PNI does not have a mild malnutrition category and only identifies patients with at least moderate malnutrition. GNRI seems to be the best screening tool for malnutrition in patients with CHF, but only when BMI is <30 kg/m^2.

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395 The multi-dimensional tools offer a more comprehensive evaluation of nutritional status
396 compared to the simple screening tools. They have more stringent criteria for identifying
397 malnutrition compared to simple tools; although they classify a smaller proportion of subjects
398 as malnourished, they are likely to be more accurate in detecting malnutrition. MUST score
399 and MNA are both commonly used in different settings: hospital wards, clinics, general
400 practice and care homes. (30,31) MNA-SF, a shorter version of MNA, is quicker to complete
401 and has similar validity and accuracy as the MNA in detecting malnutrition in older adults
402 (15, 32, 33). In our study, amongst all the malnutrition tools studied, MNA-SF had the
403 lowest misclassification rate in detecting at least moderate malnutrition compared with the
404 combined index, therefore might be appropriate to use in patients with CHF. Compared to the
405 MUST score, apart from considering BMI, weight loss and the effect of acute illness on
406 nutritional intake, MNA-SF also takes into account the impact of mobility and
407 neuropsychological problems.

408

409 SGA is the most comprehensive of the 3 multi-dimensional tools. It considers weight change,
410 dietary changes, gastrointestinal symptoms and functional capacity; and a significant
411 proportion of the assessment depends on the results of a comprehensive physical
412 examination. Similar to MNA-SF, SGA also has a low misclassification rate in detecting

413 significant malnutrition compared with the combined index. However, SGA is subjective and
414 is not sensitive in detecting malnutrition in obese patients. It also requires significant time to
415 perform (on average about 20 minutes).

416

417 Biomarkers e.g. lymphocyte count, albumin or cholesterol have long been used in isolation to
418 evaluate nutritional status but they might be affected by treatments, social conditions, or other
419 diseases rather than malnutrition alone. They thus are unlikely to be able to evaluate
420 nutritional status accurately (34,35). We found that individual biomarkers had higher
421 misclassification rates than simple and multi-dimensional tools.

422

423 The double burden of malnutrition is a novel concept which emphasizes the coexistence of
424 undernutrition and overnutrition (overweight and obesity) (36). Most of the malnutrition tools
425 we studied regard malnutrition as “undernutrition without overnutrition”; classifying patients
426 as ‘malnourished’ based on factors such as low body weight or BMI, weight loss, decline in
427 food intake, low cholesterol level, low muscle bulk or subcutaneous fat on physical
428 examination. GNRI and SGA focus on anthropometric measures; they have a much lower
429 sensitivity in detecting malnutrition in obese compared to non-obese patients. Apart from
430 anthropometric measures, MNA-SF also takes into account other factors affecting nutrition
431 such as acute illness, cognition and mobility, and is thus the only tool that is effective at

identifying malnutrition in the obese [prevalence of malnutrition by any degree according to MNA-SF was 19% in patients with BMI≥ 30kg/m^2, much higher than that determined by other tools apart from CONUT (Supplementary material 3)]. The new malnutrition reality is that it has varied manifestations and should not be managed with a siloed approach.

Study limitations

This is a single-center study conducted in the UK with limited sample size, which mainly enrolled Caucasians. External validation of our results in other populations is needed. Our study is, however, the largest study which directly compared several commonly used malnutrition tools in consecutive, unselected, patients with CHF.

Secondly, we have only studied 6 of the most commonly used malnutrition tools in literature. A large number of other malnutrition tools have been proposed.

Thirdly, this study only focuses on studying the agreement and classification performance of different malnutrition tools. The prognostic role of these tools will be presented in subsequent manuscript due to the vastness of information already presented in this paper. Furthermore,

some might not agree with our approach of creating a combined index, invented for comparison of the different tools. However, given the fact that there is currently no consensus on how malnutrition should be evaluated in patients with CHF, we think this approach is a reasonable way to allow comparisons to be made. A consensus definition of malnutrition is needed in order to determine how best to measure it.

Lastly, aging is a risk factor for the development of malnutrition (37); in our cohort, old age might have partially contributed to the higher prevalence of malnutrition in patients with CHF compared to controls.

Conclusion

Malnutrition is common in patients with CHF and is associated with increasing age, comorbidities and severity of HF. The prevalence is variable depending on the malnutrition tool used. The agreement amongst malnutrition tools varies from weak to moderate. Amongst the 6 tools studied, MNA-SF has the best classification performance in identifying significant malnutrition compared to the combined index and might be useful in screening for malnutrition in patients with CHF.

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Legends

Tables

Table 1. Baseline characteristics of HF cohort vs controls

Table 2. Prevalence of at least moderate malnutrition in different subgroups of patients with CHF.

Table 3. Sensitivity, specificity and misclassification rates of different malnutrition tools in identifying at least moderate malnutrition in patients with CHF as defined by the combined index (the assumed gold standard).

Figures

Figure 1: Participant flow chart. Key for abbreviation: CHF= chronic heart failure, HF= heart failure, LV= left ventricular, NT-proBNP= N-terminal pro-B-type natriuretic peptide.

Figure 2a: Venn diagrams showing the relationship between different simple and multi-dimensional screening tools in detecting any degree of malnutrition in patients with HF and in controls. Key for abbreviations: HF= heart failure, CONUT= COntrolling NUTritional Status Index, GNRI= Geriatric Nutritional Risk Index, PNI= Prognostic Nutritional Index, MUST= Malnutrition Universal Screening Tool, MNS-SF = Mini Nutritional Assessment-Short Form, SGA= Subjective Global Assessment.

Figure 2b: Venn diagrams showing the relationship between different simple and multi-dimensional screening tools in detecting at least moderate malnutrition in patients with HF and in controls. Key for abbreviations: HF= heart failure, CONUT= COntrolling NUTritional Status Index, GNRI= Geriatric Nutritional Risk Index, PNI= Prognostic Nutritional Index, MUST= Malnutrition Universal Screening Tool, MNS-SF = Mini Nutritional Assessment-Short Form, SGA= Subjective Global Assessment.

Supplemental material

Supplemental material 1a. Evaluation of malnutrition by malnutrition screening tools

Supplemental material 1b. Evaluation of malnutrition by malnutrition universal screening tool (MUST)

Supplemental material 1c. Evaluation of malnutrition by mini nutritional assessment-short form (MNA-SF)

Supplemental material 1d. Evaluation of malnutrition by subjective global assessment (SGA)

Supplemental material 2: Bar graph showing prevalence of malnutrition by different malnutrition tools in the HF cohort. Key for abbreviations: HF= heart failure, CONUT= COntrolling NUTritional Status Index, GNRI= Geriatric Nutritional Risk Index, PNI=

Prognostic Nutritional Index, MUST= Malnutrition Universal Screening Tool, MNS-SF = Mini Nutritional Assessment- Short Form, SGA= Subjective Global Assessment, Mod= moderate malnutrition.

Supplemental material 3. Prevalence of malnutrition of any degree in different subgroups of patients with CHF.

Supplemental material 4a. Baseline characteristics of malnourished (by any degree) vs non-malnourished patients with CHF categorised according to multi-dimensional malnutrition screening tools.

Supplemental material 4b. Baseline characteristics of patients with ≥ moderate vs < moderate malnutrition categorised according to multi-dimensional screening tools.

Supplemental material 5a. Agreement between simple vs multi-dimensional screening tools in identifying any degree of malnutrition.

Supplemental material 5b. Agreement between simple vs multi-dimensional screening tools in identifying at least moderate malnutrition.

Supplemental material 6. Sensitivity, specificity and misclassification rates of different malnutrition tools in identifying any degree of malnutrition in patients with CHF as defined by the combined index (the assumed gold standard).

Supplemental material 7a. Sensitivity, specificity and misclassification rates of different malnutrition tools in identifying any degree of malnutrition in patients with CHF who are not obese (BMI<30 kg/m^2) as defined by the combined index (the assumed gold standard).

Supplemental material 7b. Sensitivity, specificity and misclassification rates of different malnutrition tools in identifying any degree of malnutrition in patients with CHF who are obese (BMI≥30 kg/m^2) as defined by the combined index (the assumed gold standard).

Supplemental material 8a. Sensitivity, specificity and misclassification rates of different malnutrition tools in identifying at least moderate malnutrition in patients with CHF who are not obese (BMI<30 kg/m^2) as defined by the combined index (the assumed gold standard).

Supplemental material 8b. Sensitivity, specificity and misclassification rates of different malnutrition tools in identifying at least moderate malnutrition in patients with CHF who are obese (BMI≥30 kg/m^2) as defined by the combined index (the assumed gold standard).

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Table 1. Baseline characteristics of HF cohort vs controls.

	Controls (N=87)	**HF** (N=467)	Wilcoxon test statistic (W)	p
Demographics				
Age (years); median (25^{th} -75^{th} centiles)	73 (69-77)	76 (69-82)	19952	0.11
Male, n (%)	69 (79)	313 (67)	-	0.02
HR (bpm); median (25^{th} -75^{th} centiles)	61 (55-70)	70 (60-80)	16193	<0.001
BP systolic (mmHg); median (25^{th} -75^{th} centiles)	144 (130-152)	139 (126-162)	128931	0.98
BP diastolic (mmHg); median (25^{th} -75^{th} centiles)	76 (70-82)	75 (66-83)	128433	0.40
NYHA III/IV, n (%)	-	103 (22)	-	-
HeFREF, n (%)	-	291 (62)	-	-
HeFNEF, n (%)	-	176 (38)	-	-
Height (m); median (25^{th} -75^{th} centiles)	1.71 (1.63-1.75)	1.68 (1.61-1.75)	127866	0.20
Weight (kg); median (25^{th} -75^{th} centiles)	81 (73-92)	83 (69-99)	23016	0.22
BMI (kg/m^2); median (25^{th} -75^{th} centiles)	27.8 (25.2-30.8)	29.0 (25.0-33.2)	21848	0.08
Charlson score; median (25^{th} -75^{th} centiles)	6 (4-7)	8 (6-10)	12643	<0.001
Medications				
BB, n (%)	57 (66)	392 (84)	-	<0.001
ACEi/ARB, n (%)	51 (59)	389 (83)	-	<0.001
MRA, n (%)	1 (1)	214 (46)	-	<0.001
Digoxin, n (%)	0	100 (21)	-	<0.001
Loop diuretic, n (%)	3 (3)	347 (74)	-	<0.001
Thiazide, n (%)	8 (9)	17 (4)	-	0.02
Statin, n (%)	67 (77)	290 (62)	-	0.008
≥5 medications, n (%)	58 (67)	404 (87)	-	<0.001
Blood tests				
NTproBNP (ng/L); median (25^{th} -75^{th} centiles)*	170 (99-278)	1156 (496-2463)	7180	<0.001
Hb (g/dL); median (25^{th} -75^{th} centiles)	139 (127-147)	131 (118-142)	123648	0.007

Na (mmol/L); median (25^{th} -75^{th} centiles)	137 (136-139)	137 (135-138)	125823	0.01
K (mmol/L); median (25^{th} -75^{th} centiles)	4.4 (4.2-4.6)	4.4 (4.2-4.7)	22212	0.11
eGFR (mL/min per 1.73 m^2); median (25^{th} -75^{th} centiles)	77 (64-87)	55 (40-73)	119721	<0.001

HF= heart failure, HR= heart rate, BP= blood pressure, NYHA= New York Heart Association, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, BMI= body mass index, BB= beta-blocker, ACEi= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, MRA= mineralocorticoid receptor antagonist, NTproBNP= N-terminal pro-B-type natriuretic peptide, Hb= haemoglobin, Na= sodium, K= potassium, eGFR = estimated glomerular filtration rate.

**2 values are missing for NTproBNP.

Table 2: Prevalence of at least moderate malnutrition in different subgroups of patients with CHF

		AT LEAST MODERATE MALNUTRITION					
		Multi-dimensional tools			Simple tools		
		MUST (N=19)	**MNA-SF** (N=15)	**SGA** (N=12)	**GNRI** (N=29)	**CONUT** (N=41)	**PNI** (N=29)
Heart rhythm	**SR** (N=252)	4% (N=10)	2% (N=5)	2% (N=4)	7% (N=17)	6% (N=16)	4% (N=11)
	AF (N=215)	4% (N=9)	5% (N=10)	4% (N=8)	6% (N=12)	12% (N=25)	8% (N=18)
	P (SR vs AF)	0.91	0.10	0.15	0.60	0.04	0.07
BMI categories (kg/m^2)	**<24.9** (N=111)	13% (N=14)	10% (N=11)	9% (N=10)	26% (N=29)	18% (N=20)	10% (N=11)
	25.0-29.9 (N=158)	2% (N=3)	1% (N=2)	1% (N=2)	0	8% (N=12)	7% (N=11)
	≥30 (N=198)	1% (N=2)	1% (N=2)	0	0	5% (N=9)	4% (N=7)
	P (BMI categories)	<0.001	<0.001	<0.001	<0.001	<0.001	0.07
HF phenotype	**HeFREF** (N=291)	5% (N=13)	3% (N=9)	2% (N=6)	6% (N=18)	9% (N=26)	6% (N=17)
	HeFNEF (N=176)	3% (N=6)	3% (N=6)	3% (N=6)	6% (N=11)	9% (N=15)	7% (N=12)
	P (HeFREF vs HeFNEF)	0.58	0.85	0.37	0.98	0.89	0.67
NYHA	**I/II** (N=364)	3% (N=12)	2% (N=7)	1% (N=5)	6% (N=21)	6% (N=22)	4% (N=16)
	III/IV (N=103)	7% (N=7)	8% (N=8)	7% (N=7)	8% (N=8)	18% (N=19)	13% (N=13)
	P (I/II vs III/IV)	0.11	0.003	0.002	0.46	<0.001	0.002

Table 2: Prevalence of at least moderate malnutrition in different subgroups of patients with CHF (continued)

		AT LEAST MODERATE MALNUTRITION					
		Multi-dimensional tools			Simple tools		
		MUST (N=19)	**MNA-SF** (N=15)	**SGA** (N=12)	**GNRI** (N=29)	**CONUT** (N=41)	**PNI** (N=29)
NTproBNP (ng/L)	**<1000** (N=215)	1% (N=2)	1% (N=1)	0	3% (N=7)	5% (N=10)	3% (N=7)
	1000-2000 (N=108)	4% (N=4)	1% (N=1)	1% (N=1)	7% (N=8)	6% (N=6)	5% (N=5)
	>2000 (N=144)	9% (N=13)	9% (N=13)	8% (N=11)	10% (N=14)	18% (N=25)	12% (N=17)
	P (NTproBNP categories)	0.001	<0.001	<0.001	0.04	<0.001	0.003
Age (years)	**<65** (N=82)	1% (N=1)	0	0	2% (N=2)	2% (N=2)	2% (N=2)
	65-75 (N=139)	2% (N=3)	2% (N=3)	2% (N=3)	3% (N=4)	6% (N=8)	6% (N=8)
	>75 (N=246)	6% (N=15)	5% (N=12)	4% (N=9)	9% (N=23)	13% (N=31)	8% (N=19)
	P (Age categories)	0.06	0.07	0.18	0.01	0.006	0.22

MUST= malnutrition universal screening tool, MNA-SF = mini nutritional assessment – short form, SGA= subjective global assessment, GNRI= geriatric nutritional risk index, CONUT= CONtrolling NUTritional Status Index, PNI= Prognostic Nutritional index, SR= sinus rhythm, AF= atrial fibrillation, BMI= body mass index, HeFREF= heart failure with reduced ejection fraction, HeFNEF= heart failure with normal ejection fraction, NYHA= New York heart association classification, NTproBNP= N-terminal pro B type natriuretic peptide.

Table 3. Sensitivity, specificity and misclassification rates of different malnutrition tools in identifying at least moderate malnutrition in patients with CHF as defined by the combined index (the assumed gold standard)

HF patients	**Malnutrition screening**								
	Simple			**Multi-dimensional**			**Single Tests**		
	CONUT	GNRI	PNI	MUST	MNA -SF	SGA	Lymph <1.2x10^9/L	Albumin <30 g/L	Chol <3.62 mmol/L
Sensitivity (%)	80	57	73	56	69	56	56	38	60
Specificity (%)	94	95	96	98	99	99	84	98	68
PPV (%)	29	28	38	47	73	75	7	42	6
NPV (%)	99	99	99	98	99	98	99	98	98
False positive (%)	6	5	4	2	1	1	15	2	31
False negative (%)	1	1	1	2	1	2	1	2	1
Misclassification rate (%)	7	6	5	4	2	3	16	4	32

MUST= Malnutrition Universal Screening Tool, MNA-SF = Mini Nutritional Assessment – Short Form, SGA= Subjective Global Assessment, GNRI= Geriatric Nutritional Risk Index, CONUT= COntrolling NUTritional Status Index, PNI= Prognostic Nutritional Index, Lymph = lymphocyte, Chol= cholesterol, PPV= positive predictive value, NPV= negative predictive value.