The impact of malnutrition on short-term morbidity and mortality in ambulatory patients with heart failure

Short Title: Prognostic value of malnutrition in heart failure

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Abbreviations: AF = atrial fibrillation, AIC = Akaike Information Criterion, BAPEN = British Association for Parenteral and Enteral Nutrition, BIC = Bayesian Information Criterion, BMI = body mass index, CHF = chronic heart failure, CONUT = controlling nutritional status index, COPD = Chronic obstructive pulmonary disease, CVA = Cerebrovascular accident, eGFR = estimated glomerular filtration rate, GNRI = geriatric nutritional risk index, Hb = hemoglobin, HeFREF = heart failure with reduced ejection fraction, HeFNEF = heart failure with normal ejection fraction, HF = heart failure, IQR= interquartile range, LVEF = left ventricular ejection fraction, MI = myocardial infarction, MNA-SF = mini nutritional assessment-short form, MUST = malnutrition universal screening tool, NT-proBNP = N-terminal pro B-type natriuretic peptide, NYHA = New York Heart Association, PNI = prognostic nutritional index, PVD = peripheral vascular disease, SGA = subjective global assessment.

Abstract

Background:

Malnutrition is common in patients with chronic heart failure (CHF) and is associated with adverse outcome, but it is uncertain how malnutrition should best be evaluated.

Objectives:

This prospective cohort study aims to compare the short-term prognostic value of 9 commonly used malnutrition tools in CHF patients.

Methods:

We assessed, simultaneously: 3 simple tools (controlling nutritional status (CONUT) score, geriatric nutritional risk index (GNRI), prognostic nutritional index (PNI)); 3 multi-dimensional tools (malnutrition universal screening tool (MUST), mini nutritional assessment-short form (MNA-SF), subjective global assessment (SGA)); and 3 laboratory tests (serum cholesterol, albumin and total lymphocyte count) in consecutive patients with CHF attending a routine follow-up. The primary end point was all-cause mortality; the secondary end point was the combination of all-cause hospitalization and all-cause mortality.

Results:

467 patients (67% male, median age 76 years (range: 21-98 years), median N-terminal pro-B-type natriuretic peptide (NT-proBNP) 1156 ng/L) were enrolled. During a median follow-up of 554 days, 82 (18%) patients died and 201 (43%) patients had either a non-elective hospitalization or died.

In models corrected for age, hemoglobin (Hb), renal function, New York Heart Association (NYHA) class, NTproBNP, body mass index and comorbidities, all malnutrition tools, except total lymphocyte count and serum cholesterol, were independently associated with worse morbidity and mortality.

A base model for predicting mortality including age, NYHA class, log [NT-proBNP], Hb, renal function and comorbidities had a C-statistic of 0.757. Among simple tools: CONUT (C-statistic=0.777); among multi-dimensional tools, MNA-SF (C-statistic=0.776) and among biochemical tests: albumin (C-statistic=0.773), increased model performance most compared to base model. Patients with serum albumin <30 g/L was associated with a 6-fold increase in mortality compared to patients with albumin ≥35 g/L.

Conclusion:

Malnutrition is strongly associated with adverse outcomes in CHF patients. Measuring serum albumin provides comparable prognostic information to simple or multi-dimensional malnutrition tools.

(300 words)

Key words: heart failure, malnutrition, prognosis, mortality, hospitalization

Introduction

Malnutrition is the lack of intake or uptake of nutrients, which ultimately results in altered body composition, leading to reduced physical function and worse clinical outcomes (1).

Malnutrition is common in patients with heart failure (HF), and is associated with significant disability, morbidity and mortality (2). The relationship between malnutrition and HF is complex. On one hand, nutritional deficiencies might cause atrophy and fibrosis of cardiac myocytes, leading to reduced left ventricular mass and function (3,4). The lack of nutrients secondary to poor lifestyles and habits such as chronic and severe alcoholism, might also contribute to the development of overt HF. On the other hand, HF itself predisposes to congestive enteropathy and malabsorption (5). The sustained neurohormonal activation and chronic inflammation associated with HF lead to hypercatabolism, which, in turn, predisposes to sarcopenia and cachexia (6). Older age, polypharmacy, and other co-morbidities, such as dementia or frailty (7), might further increase the risk of malnutrition in patients with HF.

Current guidelines recommend assessment of nutritional status in patients with HF(8), but there is no consensus as to how malnutrition should best be measured. We therefore performed a comprehensive malnutrition evaluation in a cohort of well-characterised ambulatory patients with chronic heart failure (CHF) and compared the short-term prognostic significance of 9 commonly used malnutrition tools.

Methods

Study population (Supplementary Figure 1)

Between September 2016 and March 2017, we enrolled prospectively consecutive ambulatory patients with CHF who attended a community HF clinic for a routine follow-up appointment. All patients had a pre-existing (>1 year) clinical diagnosis of HF, confirmed by either evidence of left ventricular systolic dysfunction on echocardiography (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%) and N-terminal pro-B-type natriuretic peptide (NTproBNP) >400 ng/L, defined as heart failure with normal ejection fraction, HeFNEF (9). All patients gave consent to take part in research and had been initiated on treatment for HF according to the Heart Failure Association of the European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure (8).

During the visit, 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.

Malnutrition evaluation

All patients were screened by the same researcher (SS) for malnutrition. (Supplementary Table 1a)

The simple tools used were:

1) The geriatric nutritional risk index (GNRI)

GNRI was calculated using the formula: [1.489 x albumin (g/L)] + [41.7 x current weight/ ideal weight] (10). Ideal body weight was calculated using the formula: 22 x square of height in meters (11). Subjects with GNRI >98 have normal nutritional status, those with GNRI 92-98, 82-91, <82 have mild, moderate and severe malnutrition respectively. GNRI ≤ 98 is classified as malnourished (10).

2) The COntrolling NUTritional Status index (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 (12). 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. Subjects with CONUT score ≥2 are classified as malnourished (12).

3) The prognostic nutritional index (PNI)

PNI is calculated using the formula: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (mm^3) (13). Subjects with PNI >38 have normal nutritional status; those with PNI 35-38 and <35 have moderate and severe malnutrition respectively. Subjects with PNI ≤38 are classified as malnourished (13).

The multi-dimensional tools used were:

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

MUST is a 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 (14). 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. Subjects with MUST ≥ 1 are classified as malnourished (14). The researcher who assessed nutrition status completed the BAPEN's e-learning available at www.bapen.org.uk.

2) Mini Nutritional Assessment Short Form (MNA-SF; scored between 0-14): (Supplementary Table 1c)

MNA was developed in 1996 as a tool to identify malnutrition in elderly patients (15). MNA-short form (MNA-SF) (16), 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 malnutrition respectively. Subjects with MNA-SF score ≤11 are classified as malnourished (16).

3) Subjective global assessment (SGA; scored as A, B or C)*:* (Supplementary Table 1d)

SGA is a nutritional assessment tool that is widely used in a variety of clinical settings (17,18). It includes an assessment of medical history (specifically evaluating weight loss, changes in dietary intake, gastrointestinal symptoms and functional capacity) and a physical examination (specifically evaluating large muscle wasting as determined by palpable loss of

bulk; subcutaneous fat loss as determined by arm circumference; peripheral edema and ascites: graded as none; mild to moderate or severe). The measurements are not precise, but are a subjective impression. Each component of the SGA is ranked as either 'A', 'B' or 'C' according to specific set criteria, with 'A' reflecting normal nutritional status and 'C' reflecting significant malnutrition. The ranking with the highest frequency among individual components of SGA was determined as the overall SGA score. We classified subjects with SGA- A as having normal nutritional status, those with SGA-B and C, we classified as having mild and ≥ moderate malnutrition respectively. Subjects with SGA-B or C are malnourished (17).

The laboratory tests chosen were based on the components of the CONUT score as these have been studied in prior work (19):

1) Serum cholesterol level (mmol/L): (Supplementary Table 1a)

Subjects with serum cholesterol level >4.65 have normal nutritional status according to the CONUT score cut-off, those with serum cholesterol level 3.62-4.65, 2.59-3.61, <2.59 have mild, moderate and severe malnutrition respectively (12). Subjects with serum cholesterol level ≤ 4.65 are classified as malnourished.

2) Serum albumin level (g/L): (Supplementary Table 1a)

Subjects with serum albumin level ≥35 have normal nutritional status according to the CONUT score cut-off, those with serum albumin level 30-34, 25-29 and <25 have mild, moderate and severe malnutrition respectively (12). Subjects with serum albumin level <35 are classified as malnourished.

3) Serum total lymphocyte count ($x10^9/L$): (Supplementary Table 1a)

Subjects with serum total lymphocyte count of ≥1.6 have normal nutritional status according to the CONUT score cut-off, those with total lymphocyte count 1.20-1.59, 0.80-1.19 and <0.80 have mild, moderate and severe malnutrition respectively (12). Subjects with serum total lymphocyte count <1.6 are classified as malnourished.

Co-morbidities

Co-morbidities were recorded using the Charlson co-morbidity index/score (20). Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or a previous clinical diagnosis (21). Current hemoglobin (Hb) levels were used to define anemia (Hb<13.0 g/dL in men and <12.0 g/dL in women) (22). Diabetes mellitus was defined according to the Diabetes UK guidelines (23). Patients consented to the use of electronic medical records to identify previous clinical history of myocardial infarction (MI), peripheral vascular disease (PVD), cerebrovascular accidents (CVA), chronic obstructive pulmonary disease (COPD), dementia, rheumatological disease, peptic ulcer disease, liver or renal disease or malignancy.

End points and follow-up

Patients were followed until the 1st of August 2018. All patients were followed for a minimum of one year. The primary end point was all-cause mortality and the secondary end point was the combination of all-cause hospitalization and all-cause mortality.

Mortality was ascertained by using medical records (updated systematically onto a NHS electronic database), autopsy reports and death certificates. Hospitalization was ascertained

by using electronic medical records and discharge letters. Hospitalizations refer to non-elective admissions to hospital with length of stay of at least 24 hours.

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 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.

Time-to-event data are presented graphically using Kaplan-Meier curves. Log-rank-tests were used to compare survival between groups. To understand the prognostic value of different malnutrition tools, we performed two types of analyses: 1) etiological analysis and 2) predictive analysis.[24] The aim of the etiological analysis is to understand the causal relationship between malnutrition tools and outcomes, with adjustment for possible confounders. On the other hand, the aim of the predictive analysis is to predict accurately the risk of outcomes using multiple predictors collectively.

For etiological analysis, the relation between a variable and outcome was explored using Cox regression analysis. The Schoenfeld and scaled Schoenfeld residuals were used to check the proportional hazards assumption in multivariable Cox regression analyses (Supplementary Table 2). Since there is no significant relationship between residuals and time, we assumed the proportional hazards (Supplementary Figure 2). Univariable and multivariable analyses with Cox proportional hazard regression were used to determine significant predictors of events. Variables with $p<0.05$ in univariable analysis, which are known predictors of

outcomes in patients with HF, were entered into a multivariable analysis with each malnutrition tool both as a continuous and binary variable. In order to determine accurately the association between malnutrition tools and outcomes, multivariable adjustment was performed for the following variables: age, BMI, cardiac rhythm [atrial fibrillation (AF) vs sinus rhythm], New York Heart Association (NYHA) class (III/IV vs I/II), Charlson score, log[NTproBNP], Hb and estimated glomerular filtration rate (eGFR). Potential effect-modification was tested by fitting models containing both main effects and their cross-product terms. Specifically, effect-modification was tested between the following variables: age and BMI; age and cardiac rhythm; age and NYHA class; age and log[NTproBNP]; age and Charlson score; age and Hb; age and eGFR; malnutrition tool and age; malnutrition tool and BMI; malnutrition tool and cardiac rhythm; malnutrition tool and NYHA class; malnutrition tool and log[NTproBNP]; malnutrition tool and Charlson score; malnutrition tool and Hb; and malnutrition tool and eGFR in multivariable Cox regression analysis for predicting all-cause mortality (Supplementary Table 3). Further analyses were performed to study the relationship between the degree of malnutrition and outcome. We used the malnutrition tool from each category (simple tools, multi-dimensional tools and single laboratory test) which best predicted all-cause mortality (highest Wald χ^2). Log-transformation was applied when the data were very right-skewed.

For predictive analysis, in order to compare the performance of different malnutrition tools in predicting outcomes, we created a common base model including age, NYHA class (III/IV vs I/II), log [NT-proBNP], Hb, eGFR, AF, CVA and COPD for predicting mortality. These variables are all significant predictors of mortality in univariable Cox regression analysis. The base model was standardised so that a fair comparison can be made regarding the prognostic performance of different malnutrition tools. Although BMI, dementia and falls

were significant univariable predictors of mortality, they were excluded from the base model as they are contained in some of the malnutrition tools. We added each of the malnutrition tools in turn to the base model and used Harrell's C-statistic to evaluate model discrimination in survival analysis. A C-statistic of 0.5 indicates no discriminative ability at all while a C-statistic of 1 indicates perfect discrimination. The likelihood ratio was used to determine if there was any significant difference in model fit between the base model and models including different malnutrition tools. We performed additional sensitivity analyses where we constructed different base models for evaluating the prognostic performance of different malnutrition tools, based on the components of each tool (Supplementary Table 4). To compare the prognostic performance of models including different malnutrition tools, we used the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). The lower the AIC or BIC value, the better the model fit (Supplementary Table 5).

To evaluate length of stay during hospitalization, we only included patients with at least one hospitalization and hospitalizations resulting in death were excluded.

All statistical analyses were performed using SPSS 26 (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.

311 **Results**

312 A total of 467 consecutive ambulatory patients with HF was approached and all patients
313 consented to participate in the study. No patient was lost to follow up as we regularly receive
314 information on admissions and deaths from the two regional hospitals which provide
315 emergency care, in turn linked with our research database.

316

317 Baseline characteristics

318 The majority of patients were male and elderly; most patients had HeFREF (62%) with
319 median NT-proBNP of 1156 (496-2463) ng/L; around 20% had severe symptoms (NYHA
320 class III/IV). (Table 1)

321

322 Compared to patients who were alive at 1 year, those who died were older, had more severe
323 symptoms and were more likely to be malnourished at baseline. They also had higher NT-
324 proBNP levels, lower BMI and more co-morbidities. (Table 1)

325

326 Relation between malnutrition and mortality

327 During a median follow-up of 554 days (interquartile range 511-629 days), 18% of patients
328 died. The influence of malnutrition measures considered as univariable predictors of
329 mortality are shown in Supplementary Table 6a with Supplementary Table 6b showing the
330 results for other clinical variables. The presence of malnutrition, as determined by any tool,
331 was associated with increased risk of mortality. Clinical variables included in multivariable
332 analyses for predicting mortality are shown in Supplementary Table 7. All malnutrition tools,
333 with the exception of total lymphocyte count, and GNRI, PNI and MUST score as binary

variables, were significant predictors of all-cause mortality when evaluated individually in multivariable analysis (Table 2).

A base model (including age, NYHA (III/IV vs I/II), log [NT-proBNP], Hb, eGFR, AF, CVA and COPD) for predicting mortality achieved a C-statistic of 0.757 (Table 3). Each malnutrition tool, when added individually, except total lymphocyte count, led to better model fit compared to the base model. Among the simple tools: CONUT score (C-statistic=0.777); among the multi-dimensional tools: MNA-SF (C-statistic=0.776); and among the single laboratory tests: albumin (C-statistic=0.773), all as continuous variables, increased model performance most compared with base model.

Patients who were at least moderately malnourished according to CONUT score, MNA-SF and albumin, had a 6-10 times greater mortality risk than those who were not malnourished. (Figure 1)

The 3-month, 6-month and 12-month mortality according to worsening malnutrition categories is shown in Figure 2, top panel. Patients with the worst nutritional status, had a much higher 1-year mortality rate (33-47%) than patients with the best nutritional status (2-4%).

<u>Relation between malnutrition and combined all-cause hospitalization and mortality</u>

During follow up, 43% of patients were either hospitalised or died. The influence of malnutrition measures considered as univariable predictors of the combined outcome are shown in Supplementary Table 6a with Supplementary Table 6b showing the results for other clinical variables. The presence of malnutrition, as determined by any malnutrition tool, was

associated with increased risk of combined outcome. Clinical variables included in multivariable analysis for predicting combined outcome are shown in Supplementary Table 7. All malnutrition tools, with the exception of total lymphocyte count and serum cholesterol level, were significant predictors of the combined outcome when evaluated individually in multivariable analysis (Table 2).

Patients who were at least moderately malnourished according to CONUT score, MNA-SF and albumin, had a 5-11 times greater risk of combined outcome than those who were not malnourished (Figure 3).

The 3-month, 6-month and 12-month combined event rates according to malnutrition categories is shown in Figure 2, bottom panel. Patients with the worst nutritional status, had a much higher 3-month combined event rate (27-47%) than patients with the best nutritional status (5-8%). A similar trend was seen in 6-month and 12-month combined event rates.

The relation between malnutrition and all-cause hospitalization alone is shown in supplementary tables 8-9.

Discussion

Our study is the first to comprehensively compare the prognostic value of several commonly used malnutrition tools in a well-characterised cohort of ambulatory patients with CHF. In order to eliminate possible bias regarding time between HF diagnosis and enrollment on the association between malnutrition and outcomes, we recruited consecutive ambulatory patients who attended our HF clinic for a routine follow up appointment. All patients had a pre-existing clinical diagnosis of HF for at least one year and all have been started on guideline-

indicated HF treatment. From etiological analyses, we found that malnutrition as determined by any malnutrition tools as a continuous variable except total lymphocyte count and serum cholesterol level, was associated with worse morbidity and mortality, after adjustment for age, co-morbidities, HF symptoms and severity. Our results confirm, and expand, previous findings from other HF cohorts, which demonstrated malnutrition as a predictor of worse outcome (25). From predictive analyses, we found that malnutrition as determined by any tool apart from total lymphocyte count, improved the performance of a base model including age, NYHA (III/IV vs I/II), log [NT-proBNP], Hb, eGFR, AF, CVA and COPD, for predicting mortality, although the degree of improvement is small. This is likely due to the fact that malnutrition is associated with variables forming the base model, such as increasing age, worsening HF and complex comorbidities. (26)

It is important to distinguish between analyses performed using an etiological versus a predictive approach. (24) Although both approaches make use of multivariable modelling, the underlying research aim and interpretation of results are different. We performed etiological analyses to determine the effect of malnutrition on outcomes after adjusting for confounders. On the other hand, predictive analyses aim at predicting accurately the risk of mortality using a combination of factors. The final prediction model is based on statistical significance and not necessarily causal associations.

Many novel malnutrition tools incorporating different combinations of clinical and biochemical factors have been developed and are strong predictors of adverse outcomes (2). However, the impact of individual factors on the overall prognostic performance of combination tools is unclear. Up to 25% of ambulatory patients with HF have hypoalbuminemia, and the proportion is greater among those requiring recurrent

hospitalizations. We found that serum albumin has a similar prognostic value as the more complex malnutrition tools. Albumin may reflect the overall clinical status of patients with HF. Apart from being a marker of malnutrition, albumin levels can fluctuate with acute illness, congestion or liver dysfunction, all of which are common in patients with HF and predispose to malnutrition via mechanisms such as bowel congestion, increased basal metabolism or reduced dietary intake. Given its simplicity and easy accessibility, albumin may be useful as a screening tool of patients at risk of malnutrition who may benefit from more detailed nutrition assessment.

Simple malnutrition tools such as the CONUT score, GNRI and PNI, measure malnutrition using a combination of laboratory tests and anthropometric measures in addition to albumin. They can generally be completed within a minute. The CONUT score uses serum albumin, cholesterol and lymphocyte count. Its use in patients with HF is potentially limited by statin use. PNI only classifies patients as either non-malnourished or at least moderately malnourished, and therefore underestimates the prevalence of milder degrees of malnutrition. GNRI takes into account weight, which might be confounded by fluid status, and underestimate malnutrition in obese patients (27).

Multi-dimensional tools, such as MUST score, MNA-SF and SGA, offer a more comprehensive approach to assess nutritional status by taking into account a variety of clinical and dietary factors, but have subjective components and are time-consuming to perform (5-20 minutes, depending on mobility of patients). A recent systematic review which included 28 observational studies on malnutrition tools and clinical outcomes in patients with stable or acute HF, concluded that among 11 malnutrition tools, MNA has the best predictive ability for mortality (2). However, the reliability of these results is limited as they were

generated from a meta-analysis of observational studies investigating different malnutrition tools.

The pathophysiology of malnutrition in patients with HF is not well understood. Several theories have been proposed. One possibility is that fluid retention might cause gut edema leading to nausea, anorexia and possibly malabsorption (28). A second possibility is that change in gut morphology and function disrupts the immunological barrier of the bowel wall, triggering release of pro-inflammatory cytokines. Chronic inflammation and neurohormonal activation in HF also promote catabolism, leading to protein and fat tissue degradation, and thus weight loss and cachexia (27,29).

Malnutrition predisposes to cachexia which is associated with functional impairment, reduced quality of life, increased morbidity and mortality (30). Early identification of malnutrition in patients with HF may allow initiation of potential treatment to prevent the development of cachexia. Firstly, optimisation of HF therapy might help stabilise systemic haemodynamics and improve bowel edema (31). Secondly, regular nutritional counselling and promotion of a high caloric and high protein diet might help ensure adequate dietary intake (31). Micronutrient and vitamin supplementation might also be helpful (31,32). Regular physical exercise has anti-inflammatory effect and might ameliorate progressive tissue wasting (31). Other mechanistically appealing treatments include appetite stimulants, anti-inflammatory agents and anabolic hormones, but their role in the treatment of malnutrition is unclear (30).

Study limitations

This is a single-centre study conducted in the UK with limited sample size, and so external validation of our results from other populations with different healthcare and social systems

is needed. Secondly, we have limited follow up. We are unable to comment on long-term prognostic significance of malnutrition in the HF population. However, the majority of patients identified as malnourished had had an end-point by the end of the study. Thirdly, we did not study the change in nutritional status over time. Lastly, the type I error rate of the Cox regression analyses may be increased due to multiple testing.

Conclusions

Malnutrition, measured by any of the malnutrition tools studied, with the exception of total lymphocyte count and serum cholesterol level, is a strong predictor of morbidity and mortality in stable ambulatory patients with CHF. Measuring serum albumin provides comparable prognostic information to simple or multi-dimensional malnutrition tools.

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481 **Table 1**

Baseline characteristics of patients with CHF (Died by 1 year vs alive at 1 year). [1]

	HF patients N=467	Died by 1 year N=56	Alive at 1 year N=411	P (Died vs alive)	Missing
Demographics					
Age	76 (69-82)	82 (77-87)	75 (68-82)	<0.001	0
Sex (male), % (N)	67 (313)	68 (38)	67 (275)	0.88	0
HR (bpm)	70 (60-80)	70 (60-82)	70 (60-80)	0.84	0
Rhythm (AF), % (N)	46 (215)	66 (37)	43 (178)	0.001	0
BP systolic (mmHg)	139 (126-162)	136 (127-160)	140 (125-162)	0.89	0
BP diastolic (mmHg)	75 (66-83)	74 (66-83)	75 (66-83)	0.63	0
NYHA III/IV, % (N)	22 (103)	43 (24)	19 (79)	<0.001	0
HeFREF, % (N)	62 (291)	63 (35)	62 (256)	0.37	0
LVEF (%)	45 (35-54)	44 (34-51)	45 (35-54)	0.31	160
Height (m)	1.68 (1.61-1.75)	1.69 (1.60-1.75)	1.68 (1.61-1.75)	0.68	0
Weight (kg)	83 (69-99)	77 (66-89)	83 (69-100)	0.009	0
BMI (kg/m^2)	29 (25-33)	27 (23-30)	29 (26-33)	0.004	0
Comorbidities					
Charlson score	8 (6-10)	10 (9-12)	8 (6-10)	<0.001	0
MI, % (N)	42 (198)	38 (21)	43 (177)	0.43	0
PVD, % (N)	15 (72)	25 (14)	14 (58)	0.03	0
HTN, % (N)	67 (313)	66 (37)	67 (276)	0.87	0
CVA, % (N)	15 (71)	23 (13)	14 (58)	0.08	0
Diabetes, % (N)	35 (163)	39 (22)	34 (141)	0.46	0
Dementia, % (N)	10 (48)	36 (20)	7 (28)	<0.001	0
COPD, % (N)	30 (140)	41 (23)	29 (117)	0.05	0
Depression, % (N)	20 (93)	29 (16)	19 (77)	0.08	0
Anemia, % (N)	47 (218)	79 (44)	42 (174)	<0.001	0
Recurrent falls, % (N)	37 (173)	59 (33)	34 (140)	<0.001	0
Urinary incontinence, % (N)	7 (33)	14 (8)	6 (25)	0.03	0

Medications					
BB, % (N)	84 (392)	79 (44)	85 (348)	0.24	0
ACEi/ARB, % (N)	83 (389)	63 (35)	86 (354)	<0.001	0
MRA, % (N)	46 (214)	41 (23)	47 (191)	0.45	0
Digoxin, % (N)	21 (100)	32 (18)	20 (82)	0.04	0
Loop diuretic, % (N)	74 (347)	88 (49)	73 (298)	0.02	0
Thiazide, % (N)	4 (17)	4 (2)	4 (15)	0.98	0
≥ 5 medications, % (N)	87 (404)	95 (53)	85 (351)	0.06	0
Blood tests					
NTproBNP (ng/L)	1156 (496-2463)	2507 (1434-5825)	1001 (428-2150)	<0.001	0
Hb (g/L)	131 (118-142)	117 (106-131)	132 (120-143)	<0.001	0
Na (mmol/L)	137 (135-138)	136 (133-138)	137 (135-138)	0.04	0
K (mmol/L)	4.4 (4.2-4.7)	4.4 (4.1-4.7)	4.4 (4.2-4.7)	0.40	0
eGFR (mL/min per 1.73m^2)	55 (40-73)	39 (28-58)	58 (42-74)	<0.001	0
Malnutrition tools					
CONUT (mal), % (N)	60 (279)	93 (52)	55 (227)	<0.001	0
GNRI (mal), % (N)	19 (89)	36 (20)	17 (69)	0.001	0
PNI (mal)[2], % (N)	6 (29)	14 (8)	5 (21)	0.008	0
MUST (mal), % (N)	12 (58)	30 (17)	10 (41)	<0.001	0
MNA-SF (mal), % (N)	29 (137)	66 (37)	24 (100)	<0.001	0
SGA (mal), % (N)	21 (100)	54 (30)	17 (70)	<0.001	0
Cholesterol (mal), % (N)	60 (282)	71 (40)	59 (242)	0.07	0
Albumin (mal), % (N)	25 (116)	59 (33)	20 (83)	<0.001	0
Lymphocyte (mal), % (N)	44 (203)	63 (35)	41 (168)	0.002	0

HF= heart failure, HR= heart rate, AF= atrial fibrillation, BP= blood pressure, NYHA= new York heart association, HeFREF= heart failure with reduced ejection fraction, LVEF= left ventricular ejection fraction, BMI= body mass index, MI= myocardial infarction, PVD= peripheral vascular disease, HTN= hypertension, CVA= cerebrovascular accident, COPD= chronic obstructive pulmonary disease, 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= hemoglobin, Na= sodium, K= potassium, eGFR = estimated glomerular filtration rate, Mal= malnourished, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF= mini nutritional assessment –short form, SGA = subjective global assessment.

[1] 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.

[2]moderate malnutrition vs no malnutrition (PNI classifies patients as non-malnourished, moderately or severely malnourished)

485 **Table 2**

Multivariable Cox proportional hazards regression analyses of malnutrition tools predicting all-cause mortality and combined outcome.[1]

Worse outcome per unitary increase		**All-cause mortality[3]**			**Combined outcome[4]**		
		HR (95% CI)	Wald χ^2	P	HR (95% CI)	Wald χ^2	P
Laboratory tests	Albumin (g/L)	0.87 (0.81,0.93)	14.7	<0.001	0.90 (0.86,0.95)	18.5	<0.001
	Albumin (Mal vs not mal)	2.05 (1.28,3.28)	9.0	0.003	1.96 (1.45,2.65)	18.9	<0.001
	Cholesterol (mmol/L)	0.72 (0.58,0.90)	8.0	0.005	0.91 (0.80,1.03)	2.1	0.15
	Cholesterol (Mal vs not mal)	1.64 (1.00,2.69)	3.9	0.05	1.27 (0.95,1.70)	2.5	0.11
	Lymphocyte ($x10^9$/L)	0.89 (0.61,1.30)	0.4	0.55	0.91 (0.73,1.14)	0.7	0.41
	Lymphocyte (Mal vs not mal)	0.99 (0.62,1.58)	0.001	0.97	0.94 (0.70,1.25)	0.2	0.66
Simple	CONUT	1.28 (1.13,1.45)	15.4	<0.001	1.23 (1.13,1.34)	23.5	<0.001
	CONUT (Mal vs not mal)	3.05 (1.58,5.85)	11.2	0.001	1.52 (1.10,2.11)	6.3	0.01
	GNRI	0.98 (0.96,1.00)	4.9	0.03	0.99 (0.97,1.00)	5.9	0.02
	GNRI (Mal vs not mal)	1.18 (0.69,2.02)	0.4	0.55	1.84 (1.31,2.59)	12.4	<0.001
	PNI	0.92 (0.88,0.98)	8.4	0.004	0.95 (0.92,0.98)	10.7	0.001
	PNI (Mal vs not mal)[2]	1.45 (0.73,2.88)	1.1	0.29	2.18 (1.36,3.48)	10.6	0.001
Multi-dimensional	MUST	1.38 (1.03,1.84)	4.6	0.03	1.27 (1.05,1.53)	5.8	0.02
	MUST (Mal vs not mal)	1.32 (0.74,2.33)	0.9	0.35	2.01 (1.38,2.95)	13.0	<0.001
	MNA-SF	0.84 (0.75,0.93)	10.2	0.001	0.85 (0.79,0.91)	21.2	<0.001
	MNA-SF (Mal vs not mal)	2.09 (1.26,3.47)	8.2	0.004	2.12 (1.55,2.90)	21.9	<0.001
	SGA	1.83 (1.12,3.00)	5.8	0.02	1.97 (1.41,2.76)	15.9	<0.001
	SGA (Mal vs not mal)	2.06 (1.10,3.88)	5.1	0.03	2.37 (1.58,3.54)	17.6	<0.001

Mal= malnourished, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST= malnutrition universal screening tool, MNA-SF= mini nutritional assessment –short form, SGA = subjective global assessment.

[1]Separate multivariable analysis was performed for each tool as both binary and continuous variable, with Supplementary Table 3 showing clinical variables included in multivariable analysis for predicting all-cause mortality and combined outcome. No significant interactions were found between variables included in the multivariable Cox regression models

[2]moderate malnutrition vs no malnutrition (PNI classifies patients as non-malnourished, moderately or severely malnourished)

[3] Variables in multivariable analysis predicting all-cause mortality included: Age, BMI, AF vs sinus rhythm, NYHA (III/IV vs I/II), Charlson score, log[NT-proBNP], Hb, eGFR. (BMI is not included in multivariable analysis involving MNA-SF, GNRI or MUST as it is part of these scores).

[4] Variables in multivariable analysis predicting combined outcome included: Age, BMI, NYHA (III/IV vs I/II), Charlson score, log[NT-proBNP], Hb, eGFR (AF vs sinus rhythm is not included as it is not a significant predictor of combined outcome in univariable analysis; BMI is not included in multivariable analysis involving MNA-SF, GNRI or MUST as it is part of these scores).

487 **Table 3**

488 Addition of malnutrition tools and its impact on performance of base model containing age,
489 NYHA (III/IV vs I/II), Log [NTproBNP], Hb, eGFR, atrial fibrillation, CVA and COPD in
490 predicting all-cause mortality.[1]

Model	**C-statistics (95% CI)**	**Likelihood ratio test** Compared to base model (P value)
Base model[2]	0.757 (0.71, 0.81)	-
Base[2] + BMI	0.760 (0.71, 0.81)	0.27
Simple tools		
Base[2] + CONUT	0.777 (0.73, 0.83)	0.0001
Base[2] + GNRI	0.766 (0.71, 0.82)	0.009
Base[2] + PNI	0.770 (0.72, 0.82)	0.0007
Multi-dimensional tools		
Base[2] + MUST	0.762 (0.71, 0.82)	0.02
Base[2] + MNA-SF	0.776 (0.72, 0.83)	0.0003
Base[2] + SGA	0.768 (0.71, 0.82)	0.002
Single tests		
Base[2] + Cholesterol	0.767 (0.72, 0.82)	0.003
Base[2] + Albumin	0.773 (0.72, 0.82)	<0.001
Base[2] + Total lymphocyte count	0.758 (0.71, 0.81)	0.44

491
492 AF= atrial fibrillation, SR= sinus rhythm, NYHA= New York Heart Association, NT-proBNP= N-terminal pro-B-type natriuretic peptide,
493 Hb= hemoglobin, eGFR = estimated glomerular filtration rate, CVA= cerebrovascular accident, COPD= chronic obstructive pulmonary
494 disease, CONUT = Controlling nutritional status score, GNRI = geriatric nutritional risk index, PNI = prognostic nutritional index, MUST=
495 malnutrition universal screening tool, MNA-SF= mini nutritional assessment –short form, SGA = subjective global assessment, CI=
496 confidence interval.
497
498 [1]Harrell's C-statistic was used to evaluate model discrimination in survival analyses. The likelihood ratio test was used to determine if there
499 was any significant difference in model fit between the base model and models including different malnutrition tools.

500 [2] Base model: Age, NYHA (III/IV vs I/II), Log [NTproBNP], Rhythm (AF vs SR), Hb, eGFR, CVA, COPD

501

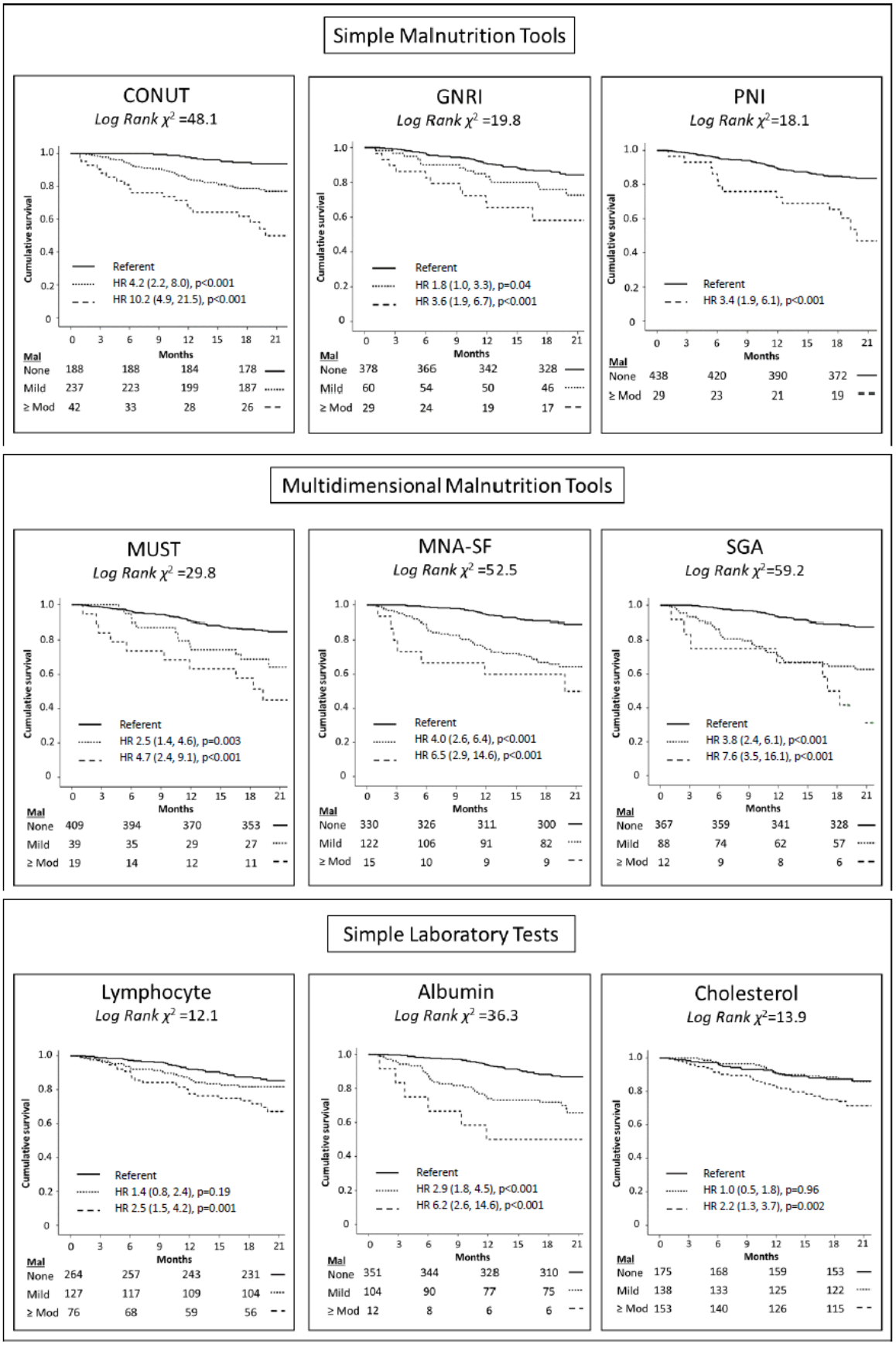
Figure Legend

Figure 1: Kaplan Meier curves illustrating the relation between malnutrition tools and all-cause mortality (Top panel: simple tools; middle panel: multi-dimensional tools; bottom panel: single laboratory tests). Log rank test was used to compare survival between groups.

Figure 2: 3 month, 6 month & 12 month mortality (top panel) and combined event rates (bottom panel) according to malnutrition categories of the CONUT score, MNA-SF and serum albumin level. The chi-squared test was used to compare proportions between groups.

Figure 3: Kaplan Meier curves illustrating the relation between malnutrition tools and combined outcome (Top panel: simple tools; middle panel: multi-dimensional tools; bottom panel: single laboratory tests). Log rank test was used to compare survival between groups.

513 **Figure 1**



514

Figure 2

A, All-cause mortality

CONUT

	Worsening malnutrition				P
	0-1 N=187	2-3 N=190	4-5 N=68	≥ 6 N=22	
3 m	0	1% (N=2)	6% (N=4)	9% (N=2)	<0.001
6 m	0	4% (N=8)	19% (N=13)	18% (N=4)	<0.001
12 m	2% (N=4)	13% (N=25)	28% (N=19)	36% (N=8)	<0.001

MNA-SF

	Worsening malnutrition				P
	13-14 N=241	11-12 N=132	9-10 N=61	≤ 8 N=30	
3 m	0	0	7% (N=4)	13% (N=4)	<0.001
6 m	0 (N=1)	4% (N=5)	18% (N=11)	23% (N=7)	<0.001
12 m	4% (N=10)	11% (N=15)	32% (N=20)	33% (N=10)	<0.001

Albumin

	Worsening malnutrition				P
	≥ 40 N=75	35-39 N=276	31-34 N=99	≤ 30 N=17	
3 m	0	0 (N=1)	4% (N=4)	18% (N=3)	<0.001
6 m	3% (N=2)	2% (N=5)	13% (N=13)	29% (N=5)	<0.001
12 m	4% (N=3)	7% (N=20)	25% (N=25)	47% (N=8)	<0.001

Mortality Rate: <5% 5-10% 10-20% 20-50%

B, Combined event rates

CONUT

	Worsening malnutrition				P
	0-1 N=187	2-3 N=190	4-5 N=68	≥ 6 N=22	
3 m	8% (N=15)	12% (N=23)	28% (N=19)	32% (N=7)	<0.001
6 m	13% (N=25)	20% (N=38)	50% (N=34)	73% (N=16)	<0.001
12 m	24% (N=45)	32% (N=60)	68% (N=46)	82% (N=18)	<0.001

MNA-SF

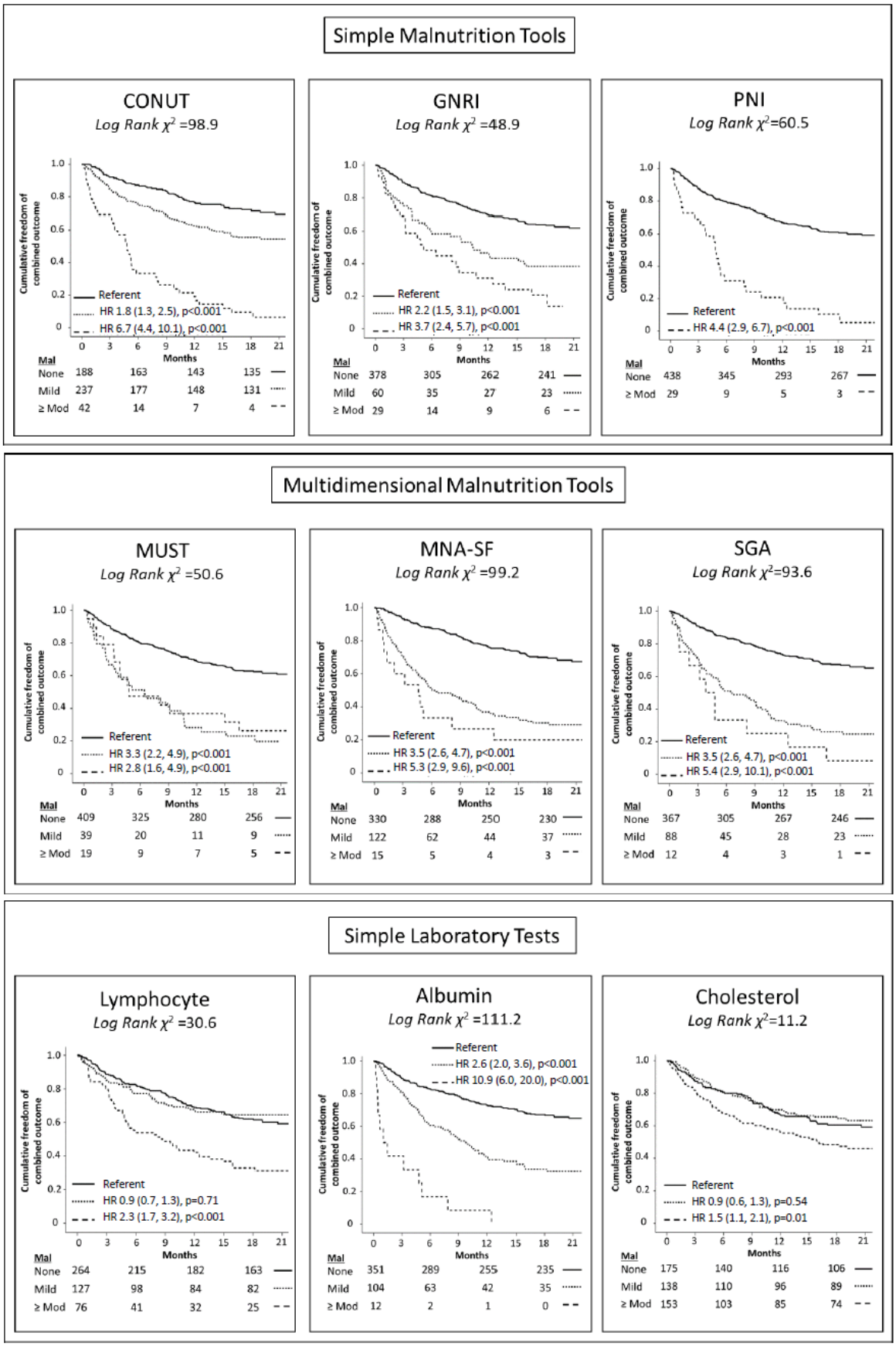
	Worsening malnutrition				P
	13-14 (N=241)	11-12 (N=132)	9-10 (N=61)	≤ 8 (N=30)	
3 m	5% (N=13)	15% (N=20)	38% (N=23)	27% (N=8)	<0.001
6 m	10% (N=23)	27% (N=35)	61% (N=37)	57% (N=17)	<0.001
12 m	22% (N=54)	36% (N=48)	71% (N=43)	73% (N=22)	<0.001

Albumin

	Worsening malnutrition				P
	≥ 40 N=75	35-39 N=276	31-34 N=99	≤ 30 N=17	
3 m	8% (N=6)	11% (N=31)	19% (N=19)	47% (N=8)	<0.001
6 m	12% (N=9)	19% (N=53)	39% (N=39)	71% (N=12)	<0.001
12 m	23% (N=17)	29% (N=79)	60% (N=59)	82% (N=14)	<0.001

Combined event rate: <10% 10-20% 21-40% 41-70% >70%

517 **Figure 3**



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