British Journal of Nutrition (2007), **98**, 332–336
doi: 10.1017/S0007114507701708

Malnutrition is an independent predictor of 1-year mortality following acute illness

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(Received 27 August 2006 – Revised 21 January 2007 – Accepted 2 February 2007)

Four hundred and forty-five randomly selected hospitalised patients had their nutritional status assessed from anthropometric, haematological and biochemical data. Nutritional status was compared between survivors and non-survivors at baseline, 6 weeks and 6 months. Using Cox's proportional hazard analysis, we measured the association between nutritional assessment variables and 1-year mortality after adjusting for disability, chronic illness, medications, smoking and tissue inflammation. Nutritional status was significantly worse amongst non-survivors compared with survivors, and non-survivors showed marked and significant deterioration in all measures of nutritional status compared with survivors. After adjusting for poor prognostic indicators the hazard ratios of death in the fourth, third and second quarters of both baseline serum albumin and mid-upper arm circumference distributions relative to the first were 0·68, 0·77 and 0·58 (trend $P=0·013$) and 0·61, 1·0 and 0·87 (trend $P=0·005$) respectively. Intervention studies are needed to determine whether the relationship between malnutrition and the poor outcome highlighted by the present study is causal or a mere association.

Malnutrition: Nutritional status: Prediction of mortality: Hospital patients

Studies of patients in hospitals and non-acute care settings are in agreement that food intakes are less than those reported for free-living older individuals and that malnutrition is prevalent and often unrecognised in patients admitted to hospitals and institutions (Gariballa & Sinclair, 1998; Akner & Cederholm, 2001). The effect of ill health on the nutritional status of hospitalised patients can often be limited to the time of acute illness, but older individuals are particularly at risk of prolonged malnutrition because of decreased nutritional reserves and the effect of repeated ill health (Gariballa & Sinclair, 1998). Nutritional depletion during recuperation and rehabilitation, however, may be more serious than during acute illness, since rehabilitation periods may extend over weeks and months, and deterioration in nutritional status, although less marked than in the early catabolic phase, may be greater overall (Sullivan & Walls, 1994; Gariballa & Sinclair, 1998). Although several studies have shown that some anthropometric and biochemical nutritional status indicators are predictive of post-discharge mortality, distinguishing underlying disease from undernutrition, and to separate their effects on patients' outcome is still a challenge for clinicians; therefore, a cause-and-effect relationship has not been definitely established (Klein *et al.* 1997; Liu *et al.* 2002; Massaia *et al.* 2003). The aim of the present study was to measure the impact of undernutrition of hospitalised patients on 1-year mortality following acute illness.

Subjects and methods

The study was conducted at a 650-bed Associate Teaching Hospital in the UK admitting unselected acutely ill patients on the basis of need. The methodology of the present study has been published before (Gariballa & Forster, 2006). Briefly 445 acutely ill older patients who took part in a study of nutritional supplementation were included. Admission diagnoses included IHD, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, chest and urinary tract infections, septicaemia, stroke, Parkinson's disease, anaemia, diabetes, osteoarthritis, rheumatoid arthritis, syncope, falls and fracture limbs. Inclusion criteria were: age ≥ 65 years; stable medical condition; able to swallow; able to sign an informed written consent form. Patients excluded from the study were those with severe medical or psychiatric illness including those with gastric surgery, malabsorption, or morbid obesity (BMI $\geq 40\,kg/m^2$), in a coma, diagnosed with severe dementia (abbreviated mental test <6) or malignancy, living in an institution and patients already on supplements. The study was approved by the local research ethics committee.

Clinical and nutritional assessment

Following informed written consent and recruitment to the study patients had assessments at baseline, 6 weeks and 6

Abbreviations: MUAC, mid-upper arm circumference.

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months. The assessment included demographic and medical data including current diagnosis, history of chronic illnesses, smoking, alcohol and drug intake, nutritional status and disability (Barthel score).

Nutritional status was assessed from anthropometric, haematological and biochemical data. All anthropometrics measurements were performed by a single observer (S. F.) using standard methods with intra-observer differences assessed before the commencement of the study. Mid-upper arm circumference (MUAC) and triceps skinfolds were measured by a flexible tape and Harpenden skinfold callipers accurate to 0·2 mm (Practical Metrology, Lancing, West Sussex, UK) respectively and the mean of three measures was recorded (Gariballa *et al.* 1998). The local pathology laboratory performed routine tests including serum ferritin, albumin, transferrin and C-reactive protein measurements. Erythrocyte folate and plasma vitamin B_{12} were measured on the Architect (Abbott Laboratories, Chicago, IL, USA) using chemiluminescent microparticle immunoassay technology. The inter-assay CV were 12·6 and 8·4 % respectively. Plasma total ascorbic acid was measured by a fluorescence assay automated for the Cobas BioAutoanalyser (Roche Diagnostics, Basel, Switzerland), giving an inter-batch CV of 8·4 %.

Disability at baseline was assessed using the Barthel score on a twenty-point scale. The Barthel scores ten functions on a scale of 0 (fully dependent) to 20 (independent). For quality assurance, two researchers independently checked hospital and primary care records for all routinely collected outcome measures including 1-year mortality. Agreement was 99 %.

Statistical analyses

Statistical analyses were performed with SPSS software, version 11.0 (SPSS Inc., Chicago, IL, USA). Nutritional status between survivors and non-survivors at 6 weeks was analysed using an analysis of covariance model, with baseline values as a covariate. Cox's proportional hazard models were used to examine the 1-year mortality and nutritional status after controlling for poor prognostic indicators. The outcome variable was dichotomised (i.e. alive *v.* dead) and then analysed as the dependent variable against a number of independent nutritional variables including body weight, BMI, MUAC, triceps and biceps skinfolds, serum albumin and transferrin. Each independent nutritional status variable was first analysed separately against the dependent variable outcome. Then those variables with a significant association with the outcome variable ($P<0·05$) were entered with other variables recorded on admission (age, disability, chronic illness, drugs, smoking, and tissue inflammation) into the final model as the independent variables. All four MUAC and serum albumin quarters were entered in the model as a single variable or each quarter separately as an independent predictor variable. Survival times in relation to MUAC and serum albumin divided into four equal quarters are presented graphically using the Kaplan–Meier survival curve and assessed using the log rank test.

Results

Between July 2001 and May 2004, 445 patients were recruited. Table 1 shows baseline clinical characteristics including sex, smoking, alcohol consumption, chronic illness, drugs, disability, tissue inflammation (C-reactive protein), Hb, glucose and renal functions. Non-survivors were significantly older and had higher levels of co-morbidity and serum creatinine concentration compared with 1-year survivors; however, survivors had significantly higher fasting blood sugars (Table 1).

Table 1. Baseline characteristics of subjects according to survival status at 1 year (Number of subjects, percentages, mean values and standard deviations)

	Alive at 1 year (*n* 377)		Dead at 1 year (*n* 57)	
Variable	*n*	%	*n*	%
Age (years)*				
Mean	76·0		78·7	
SD	6		6	
Sex (female)	190	49	21	36
Alcohol >14 units/week†	34	9	8	14
Smoking				
Never smoked	127	33·7	10	17·5
Ex-smoker	179	47·5	37	65
Current smoker	71	18·8	10	17·5
Medications (per patient)	3·4		3·9	
Chronic diseases (per patient)‡	1·7		2·1	
COPD	68	18	16	28
IHD	136	36	26	46
Heart failure*	11	3	6	11
Chest infection	6	2	1	2
Stroke*	29	8	11	19
Admission diagnosis				
COPD*	48	12	16	28
IHD	52	13	7	12
Heart failure	23	6	13	22
Chest infection	31	8	8	14
Stroke	13	3	4	7
Barthel score*				
Mean	16		14·5	
SD	5		5	
C-reactive protein (mg/l)				
Mean	52		54	
SD	73		74	
Fasting blood glucose (mmol/l)*				
Mean	5·9		5·5	
SD	1·3		1·2	
Urea (mmol/l)				
Mean	8·2		8·4	
SD	16		4	
Serum creatinine (μmol/l)*				
Mean	101		110	
SD	30		37	

COPD, chronic obstructive pulmonary disease.
* Between-group difference was significant ($P<0·05$).
† One unit of alcohol in terms of UK 'standard drinks' is 0·5 pints (0·28 litres) beer, lager or cider, one measure of spirits or one glass of wine.
‡ Also includes falls, atrial fibrillation, syncope, urinary tract infection, anaemia, septicaemia, diabetes, osteoarthritis, rheumatoid arthritis and fractured limbs.

Both anthropometric and nutritional biochemical measures were significantly lower in non-survivors compared with survivors. For example, body weight, BMI, MUAC, serum albumin and plasma ascorbic acid were all significantly lower in non-survivors compared with survivors (Table 2).

Tables 3 and 4 summarise results of the multiple Cox's regression analysis for nutritional and other clinical variables on 1-year mortality. In the multiple Cox's regression analyses MUAC and serum albumin at baseline and 6 weeks were each divided into four quarters and analysed (separately or

Table 2. Baseline anthropometric and biochemical nutritional markers of survivors and non-survivors at 1 year following acute illness

(Mean values and standard deviations)

	Alive (*n* 377)		Dead (*n* 57)			
Nutritional variable	Mean	SD	Mean	SD	Mean difference	95% CI
Body weight (kg)	66·5	13	64	13	2·5	−1·5, 6
BMI (kg/m^2)	25·3	4	24	4	1·3*	0·5, 2·5
MUAC (cm)	28·4	4	26·2	3	2·2*	1·2, 3·2
TSF (mm)	16	7	13	6	2·9*	1·1, 4·7
Hb (g/l)	127	22	127	20	−0·1	−6, 6
Albumin (g/l)	38	5	35·8	4	2·4*	1·1, 3·6
Transferrin (μg/l)	2·2	0·5	2·0	0·6	0·13	−0·03, 0·3
Ascorbic acid (μmol/l)	24	21	20	21	4·2	−2·5, 11
Erythrocyte folate (nmol/l)	330	171	326	177	3	−70, 76
Vitamin B_{12} (pmol/l)	389	305	390	324	−1	−92, 91

MUAC, mid-upper arm circumference; TSF; triceps skinfold.
* Mean difference was significant ($P<0·05$).

as a single variable) against a number of poor prognostic variables including age, disability (Barthel), chronic illness, drugs, smoking and inflammatory response (C-reactive protein). After adjusting for poor prognostic indicators the hazard ratios of death in the fourth, third and second quarters of both baseline serum albumin and MUAC distributions relative to the first were 0·68, 0·77 and 0·58 (trend $P=0·013$) and 0·61, 1·0 and 0·87 (trend $P=0·005$) respectively. Overall the hazard ratios for an outcome of death associated with each quarter increase from the first in baseline serum albumin and MUAC were 0·73 (95% CI 0·56, 0·97) and 0·72 (95% CI 0·54, 0·97) respectively (Table 3). Corresponding hazard ratios for serum albumin and MUAC quarters at 6 weeks and 1-year mortality were 0·61 (95% CI 0·27, 1·38) ($P=0·06$) and 0·6 (95% CI 0·31, 1·18) ($P=0·23$) respectively (Table 4).

Although the unadjusted hazard ratios of death for body weight and BMI at baseline and 6 weeks were statistically significant, the adjusted hazard ratios were not statistically significant (hazard ratios for body weight at baseline and 6 weeks were 1·0 (95% CI 0·98, 1·03) and 0·99 (95% CI 0·94, 1·06) respectively; corresponding adjusted hazard ratios for BMI were 0·82 (95% CI 0·78, 2·1) and 0·93 (95% CI 0·72, 1·18) respectively).

The Kaplan–Meier curves clearly demonstrate graded relationships between MUAC and serum albumin at baseline and 6 weeks and 1-year mortality (Figs. 1–4).

Discussion

The present study shows a strong and independent association between nutritional status as measured by MUAC and serum albumin and 1-year mortality of older patients following acute illness. We also observed a graded and significant relationship between MUAC, serum albumin and mortality.

Previously we observed a similar association between serum albumin and 3-month stroke mortality; however, in the present study we have found a similar relationship between MUAC and 1-year mortality in a heterogeneous group of acutely ill patients.

Even though serum albumin is frequently considered a nutritional marker and has been shown to predict outcome in many settings, there are many conditions, such as catabolism, liver and renal disease which may reduce serum albumin levels (Sullivan & Walls, 1994; Gariballa *et al.* 1998). The catabolic state and the associated neuroendocrine response which is likely to follow an acute illness may lead to altered serum albumin concentrations. It may therefore be

Table 3. Cox's proportional hazard analysis of the relationship between baseline nutritional status and other prognostic variables and hospitalised patients' 1-year mortality

Variable	Regression coefficient	SE	*P*	Hazard ratio for unit change	95% CI
Age (years)	0·034	0·026	0·187	1·04	0·98, 1·09
Barthel score (0–20)	−0·054	0·031	0·077	0·95	0·89, 1·02
Chronic illnesses	0·146	0·102	0·152	1·16	0·95, 1·41
Smoking (never, ex, current)	0·368	0·205	0·072	1·45	0·97, 2·12
All medications	0·087	0·080	0·279	1·07	0·93, 1·28
C-reactive protein (≤10, > 10 mg/l)	−0·001	0·002	0·522	0·99	0·99, 1·003
MUAC quarters (cm)†§	−0·309	0·140	0·028*	0·73	0·56, 0·97
Serum albumin quarters (g/l)‡§	−0·329	0·151	0·029*	0·72	0·54, 0·97

MUAC, mid-upper arm circumference.
* $P<0·05$.
† MUAC quarters (cm): 1st <25·8; 2nd = 25·8–28; 3rd = 28·1–30·5; 4th >30·5.
‡ Albumin quarters (g/l): 1st <35; 2nd = 35–38; 3rd = 38·1–41; 4th >41.
§ 1st quarter <25%; 2nd quarter = 25–50%; 3rd quarter = 51–75%; 4th >75%.

Table 4. Cox's proportional hazard analysis of the relationship between nutritional status at 6 weeks and other prognostic variables and hospitalised patients' 1-year mortality

Variable	Regression coefficient	SE	*P*	Hazard ratio for unit change	95% CI
Age (years)	0·156	0·067	0·019*	1·17	1·03, 1·33
Barthel score (0–20)	−0·037	0·078	0·638	0·96	0·86, 1·12
Chronic illnesses	0·177	0·208	0·393	1·2	0·80, 1·80
Smoking (never, ex, current)	0·742	0·525	0·158	2·1	0·68, 5·88
All medications	0·141	0·185	0·446	1·2	0·80, 1·66
C-reactive protein (mg/l)	0·007	0·004	0·142	1·0	0·99, 1·02
MUAC quarters (cm)†§	−0·495	0·416	0·062	0·61	0·27, 1·38
Serum albumin quarters (g/l)‡§	−0·507	0·342	0·231	0·60	0·31, 1·18

MUAC, mid-upper arm circumference.
* $P<0·05$.
† MUAC quarters (cm): 1st <25·5; 2nd = 25·5–28; 3rd = 28·1–30·5; 4th >30·5.
‡ Albumin quarters (g/l): 1st <39; 2nd = 39–41; 3rd = 41·1–43; 4th >43.
§ 1st quarter <25%; 2nd quarter = 25–50%; 3rd quarter = 51–75%; 4th >75%.

that in catabolic states the synthesis of acute-phase proteins has a priority over serum albumin, and this may partly account for some of the features of the plasma protein profile observed during the acute-phase response after injury. This process is likely to lead to erosion of nutritional reserves. It is also well known that malnutrition negatively affects protein synthesis (Rothschild *et al.* 1972; Gariballa *et al.* 1998). In the present study and a previous one (Gariballa *et al.* 1998), we have demonstrated that low serum albumin levels were related to poor outcome not just during the acute phase following acute illness but throughout the recovery period, an effect unlikely to be explained by the catabolic state alone. On the other hand, MUAC is a composite measure of muscle and fat stores. Studies which have investigated MUAC either alone or as part of corrected arm muscle area calculated from MUAC and triceps skinfolds found that it has a better ability to discriminate between degrees of malnutrition and is also simple and feasible, and if classified by percentiles may have a good prognostic value in acute care settings (Campbell *et al.* 1990; Muhethaler *et al.* 1995). When used as part of corrected arm muscle area in community settings it has also been found useful in assessing undernutrition in older adults and that it has better prognostic value than BMI in predicting death in older adults (Miller *et al.* 2002).

Many studies have evaluated several nutritional and non-nutritional clinical and biochemical prognostic indicators in older adults in acute care settings such as general medical wards and intensive care facilities (Sullivan & Walls, 1994; Gariballa *et al.* 1998; Liu *et al.* 2002; Massaia *et al.* 2003). For example, Sullivan and co-workers (Sullivan & Walls, 1994; Sullivan *et al.* 1995) studied the nutritional status and energy intake of 350 randomly selected admissions to a geriatric rehabilitation unit and found that protein–energy malnutrition was a strong predictor of in-hospital and post-discharge mortality. Another observational study which analysed data of 18 316 hospitalised Italian patients found low BMI to be a significant and independent predictor of shortened survival in older patients (Landi *et al.* 2000).

The challenge is to distinguish underlying co-morbidity from undernutrition, and to separate their effects on older patients' outcome. For patients admitted to intensive care units the risk stratification involve the use of several acute physiological parameters. However, for less critically ill older patients admitted to general medical wards, as is the

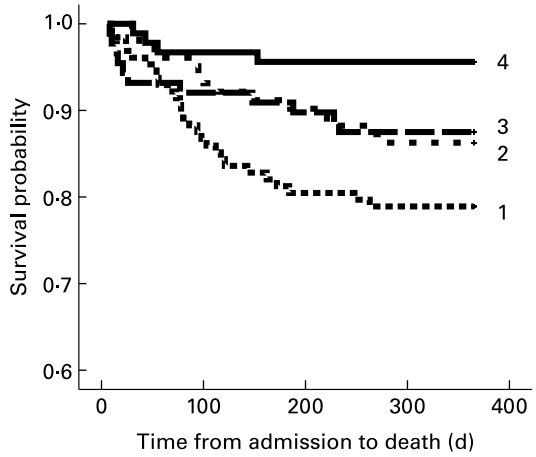

Fig. 1. Survival at 1 year according to serum albumin quarters (1, 2, 3,4) on admission. The relationship between serum albumin on admission and 1-year survival was significant ($P<0·01$).

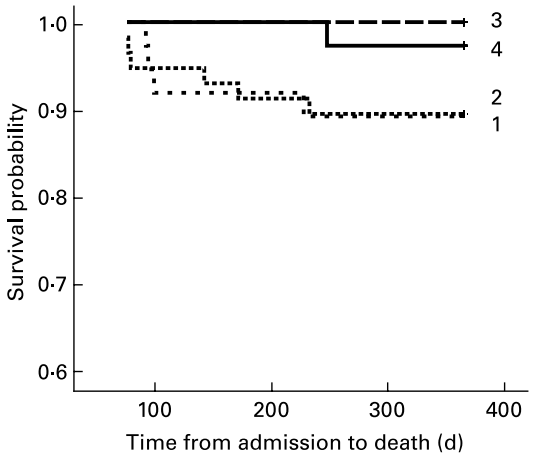

Fig. 2. Survival at 1 year according to serum albumin quarters (1, 2, 3,4) at 6 weeks. The relationship between serum albumin at 6 weeks and 1-year survival was not significant ($P<0·095$).

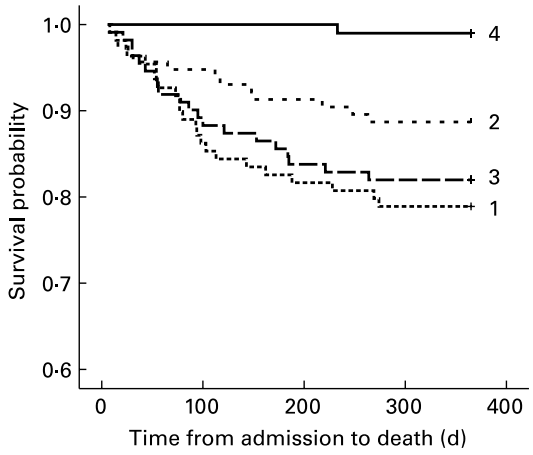

Fig. 3. Survival at 1 year according to mid-upper arm circumference (MUAC) quarters (1, 2, 3, 4) on admission. The relationship between MUAC on admission and 1-year survival was significant ($P<0·001$).

case in the present study, other functional and co-morbidity measures should be included in models of predictors of clinical outcome. Furthermore, nutritional indices in ageing patients are affected by age-related changes, disability, illness and injury (Klein *et al.* 1997; Dionigi *et al.* 2000). In attempting to overcome some of the above challenges we excluded from the study all patients with severe medical and psychiatric illnesses such as liver, gastrointestinal, kidney or neoplasm. Also by adjusting for underlying disease state, age, drugs, functional capacity and acute-phase response on mortality it was possible to identify a potential independent effect of poor nutritional status on patients' outcome.

The present study lacked information on pre-morbid and long-term post-discharge dietary intake. Another important limitation is inherent difficulties in measuring anthropometric and biochemical nutritional indices in ageing patients. The purpose of assessing intra-observer differences on anthropometric measurements, the longitudinal design of the study and the use of multiple Cox's regression analyses to adjust for poor prognostic clinical indicators was to overcome some of these weaknesses.

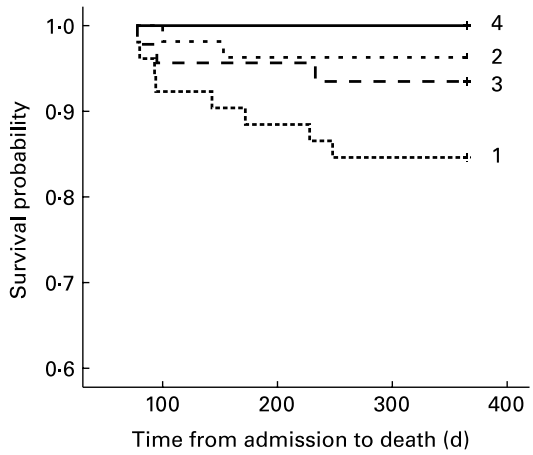

Fig. 4. Survival at 1 year according to mid-upper arm circumference (MUAC) quarters (1, 2, 3,4) at 6 weeks. The relationship between MUAC at 6 weeks and 1-year survival was significant ($P=0·03$).

In the present study of hospitalised acutely ill patients, we found that baseline nutritional status was worse among those who later died at 1 year and their nutritional status deteriorated further following acute illness compared with those alive at 1 year.

The heterogeneous nature of the patient population in the present study gave us the opportunity to study and adjust for the contribution of underlying disease and co-morbidity, as well as the catabolic state of acute illness to the erosion of macro- and micronutrient nutritional status. Whether the relationship between malnutrition and the poor outcome highlighted by the present study is a causal one or a mere association can also be determined by robust intervention studies.

Acknowledgements

The present study was funded by The Health Foundation project grant. There are no conflicts of interest.

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