Original Research Paper

Title: The Relationship between Malnutrition Risk and Clinical Outcomes in a Cohort of Frail Older Hospital Patients

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Abstract

Background & Aims: Malnutrition has an adverse effect on clinical outcomes and frail older people may be at greater risk of malnutrition. The purpose and aims of this study was to investigate the relationship between markers of malnutrition risk and clinical outcomes in a cohort of frail older hospital patients.

Methods: 78 frail older hospital patients had the following measurements recorded; length of stay (LOS), time to medical fitness for discharge (TMFFD), body mass index (BMI), malnutrition universal screening tool (MUST) and mini-nutritional assessment short-form (MNA-SF) scores, blood urea, C-reactive protein (CRP), albumin, CRP-albumin ratio; and bioelectrical impedance assessment (BIA) measurements (n=66). Patients were grouped by mortality status 12 months post hospital admission. Grouping by albumin classification was performed (n=66) whereby, <30 g/l indicated severe malnutrition, 30-34.9, moderate and >35, low. Receiver-operating characteristic (ROC) curve analysis was performed on variables as potential predictors of mortality.

Results: After 12 months, 31% (n=24) of patients died. LOS was significantly greater in this group (25.0±22.9 vs 15.4±12.7d, $P<0.05$). BMI (23.8±4.9 vs 26.4±5.5kg/m^2); fat mass (FM) (17.2±9.9 vs 25.5±10.5kg), fat mass index (FMI) (9.3±4.1 vs 17.9±2.4kg/m^2); and MNA-SF score (6.6±2.4 vs 8.6±2.7) were significantly lower ($P<0.05$), and urea significantly higher (11.4±8.7 vs 8.8±4.4mmols/l, $P=0.05$). Albumin was typically low across the entire group (30.5±5.9 g/l) and a potential relationship was identified between albumin and MNA-SF score. MNA-SF, FM, and FMI were significant predictors of mortality outcome by ROC curve analysis, whereas MUST was a poor predictor.

Conclusion: This study highlights a potential relationship between indicators of malnutrition risk and clinical outcomes in frail older hospital patients which should be studied in larger cohorts with an aim to improve patient care.

(275 words)

Keywords: *malnutrition, frailty, cachexia, malnutrition universal screening tool (MUST), mini nutritional assessment (MNA), bioelectrical impedance assessment.*

Introduction

Frail older people may be admitted to hospital wards suffering from a range of acute and chronic disease/s, with signs and symptoms of physical and/or cognitive frailty and be on multiple medications. Identifying possible nutritional risk/malnutrition is important and may affect trajectory of health, morbidity, and mortality[1-4]. Different screening methods exist including the '*malnutrition universal screening tool'* (MUST)[1,5], the '*mini-nutritional assessment'* (MNA)[1,6-8] and the '*geriatric nutritional risk index',* (GNRI)[9]. In the United Kingdom (UK), the MUST is the standard routine method of screening in all hospital wards and care homes, although in reality there is no universal gold standard tool[4]. We showed recently in a cohort of frail older hospital patients that there is a significant discordance between MUST and 'MNA-short form' (MNA-SF) malnutrition screening categorisation[10]. The MUST predominantly categorized patients as 'low risk' (77%) and MNA-SF predominantly as 'at risk' (46%) and 'malnourished' (45%). Reliability assessment found poor reliability between the screening tools and bioelectrical impedance assessment (BIA)

assessment was in general agreement with MNA-SF scoring patterns, especially in male patients. A potential body mass index (BMI) paradox was also highlighted whereby some patients who were 'at risk' or 'malnourished' by MNA-SF scores had normal BMI and depleted/borderline BIA measurements of fat free mass (FFM) / fat mass (FM) and specifically indices (FFMI and FMI, in kg/m^2). Potential reasons for the observed MUST-MNA-SF discordance include: the MUST uses World Health Organization (WHO) BMI grading criteria, and there maybe difficulty in obtaining accurate weight loss information in this patient group. Further, the MNA-SF has additional screening questions on 'mobility' and 'neuropsychological problems' which would create a tendency to score worse in a frail older patient group.

An important area to address which overlaps malnutrition is 'cachexia'/'cachexia-risk', as acute and chronic illness has a typical effect upon food intake (anorexia) and metabolism (e.g. hypermetabolism and raised protein breakdown), principally through actions of circulating proinflammatory cytokines[11,12]. Other measurable domains of nutritional status which are sensitive to malnutrition and inflammation include important blood markers such as albumin, which is utilised in the GNRI[9], and is a well known prognostic marker[13-16]. C-reactive protein (CRP) is another routine blood marker indicating inflammatory status and has known prognostic potential[17,18]. Recently, the CRP/albumin ratio has been used to better predict mortality risk in septic patients[19].

A better understanding of the relationship between malnutrition risk screening, body composition assessment and blood markers in heterogeneous groups of frail older hospital patients on clinical outcomes may improve coordinated hospital nutritional care in the UK.

This study was undertaken in a heterogeneous group of frail older adults admitted to wards specialising in elder care in the UK. We examined outcome of hospital admission, length of stay (LOS), time to medical fitness to discharge (TMFFD) and mortality at 12 months post admission and related them to inpatient measurements of MUST, MNA-SF and BIA. Further, examination was made of routine blood markers, urea, albumin, CRP, and the CRP/albumin ratio to investigate their importance in relation to malnutrition risk and outcomes.

(497 words)

Methods

Participants and study design

This cohort study was undertaken between September 2012 and May 2013 and recruits were from a purposive sampling from admissions to two hospital wards in Lincoln, UK specializing in care of frail older patients[10]. Full ethical approval was obtained from NHS Leicester, East Midlands Research Ethics Committee (ref: 12/EM/0186) prior to study commencement, ethical guidelines followed and informed consent sought from all patients. Exclusion criteria from the study were: patients unable or unwilling to give informed consent and patients who were nil by mouth or tube fed. BIA measures were contraindicated in patients with defibrillation or cardiac pacemaker devices. The aim was to recruit 100-150 patients in-line with other similar studies; however the exclusion criterion of ability to consent and designated study time restraints dictated the current number. Patients were followed from admission to 12 months post admission with outcomes recorded including: TMFFD, LOS in

hospital (days), and deaths at 12 months. Blood measurements were also recorded where available.

Nutritional assessment

MUST tool and MNA-SF® screening

MUST and MNA-SF® screening was performed as described previously[10], whereby screening scores were converted into categories for nutritional status using MUST and MNA-SF® scoring criteria either 'low risk'/'normal'(0 points-MUST, 12-14 MNA-SF), 'medium risk/at risk' (1 point-MUST, 8-11 MNA-SF) and 'high risk'/'malnourished' (≥2 points-MUST, 0-7 MNA-SF).

Anthropometric measurements

Height (m) and weight (kg) measurements were performed as described previously[10.]

Bioelectrical impedance measurements

BIA measurements were performed as described previously[10], using the Kyle et al[20] equation for estimation of FFM (kg) and FM (kg) and index values, FFMI (kg/m^2) and FMI (kg/m^2), and compared to reference values[21].

Blood markers

Routine blood markers were collected and measured in-line with normal patient care in hospital. Ethical clearance was obtained to utilise these as part of the research study. Markers utilised and analysed included; urea, albumin, C-reactive protein (CRP) and the CRP-albumin ratio. Patients were also classified according to albumin

level and ‘malnutrition severity’, using an adapted method from paper by Bouillanne et al[9], i.e. <30 g/l: severe; 30-34.9 g/l: moderate; and >35 g/l low+absent combined.

Data analysis

Data is presented as mean average measurements ± standard deviation (SD) with a range (minimum-maximum) and [median] values. Data has been grouped into ‘alive’ and ‘deceased’ at 12 months post admission and where relevant into nutritional screening categories by albumin. Statistical analysis was performed using IBM SPSS Statistics, version 21, New York, USA. T-tests and Pearson correlations were used for normally distributed data and Mann-Whitney-U and Spearman correlations test for nonparametric data. ANOVA and Bonferronni post-hoc test were performed on more than two groups of data. Categorical differences were analysed using Chi-squared testing. Receiver-operator characteristic (ROC) curve analysis methods were performed on raw data of variables to evaluate their predictive performance on the prediction of mortality outcome in patients[22]. A P value of $< 0{\cdot}05$ was considered statistically significant.

Results

Data was recorded for 78 patients and followed up 12 months post admission. Within patient medical notes, blood markers were available for the following: albumin (n=66 patients), urea (n=76), CRP (n=73), and CRP/albumin ratio (n=65). Patients were grouped according to mortality status at 12 months and data is presented in Table 1. LOS and urea measurements were significantly higher in the deceased group; and

BMI and MNA-SF score significantly lower. Patients had BIA measured (n=66) as completed previously[10] and grouped by mortality status (Table 2). FM and FMI by BIA were found to be significantly lower in patients who died.

Table 1. Table to show differences in patients grouped by mortality status, 12 months after hospital admission. Mean ± SD is presented with (minimum-maximum) and [median] values for comparison.

	Alive	**Deceased**
N	54 (69%)	24 (31%)
Males/females	30/24 (56%/44%)	19/5 (79%/21%)
Age, y	81.7±7.4 (65-93) [83]	83.0±8.8 (62-96) [84]
TMFFD, d	8.5±7.6 (0-37) [7]	10.4±13.8 (0-66) [6]
LOS, d	15.4±12.7 (2-68) [10]	25.0±22.9 (6-102) [19]*
BMI, kg/m^2	26.4±5.5 (17.2-45.1) [26.3]	23.8±4.9 (16.6-37.2) [23.3]*
MUST score	0.4±0.8 (0-4) [0]	0.6±1.1 (0-4) [0]
MUST – 'Low risk'	43 (80%)	17 (71%)
MUST – 'Medium risk'	5 (9%)	2 (8%)
MUST – 'High risk'	6 (11%)	5 (21%)
MNA-SF score	8.6±2.7 (3-14) [8.5]	6.6±2.4 (2-11) [7]*
MNA-SF – 'Normal'	7 (13%)	0 (0%)
MNA-SF – 'At risk'	26 (50%)	9 (46%)
MNA-SF – 'Malnourished'	21 (37%)	15 (54%)
Urea (mmols/l)	8.9±4.3 (3.1-21.1) [7.8]	11.4±8.7 (1.7-43.9) [10]*
CRP (mg/l)	56.1±67.4 (0.6-287) [25]	78.6±73.6 (2.1-221) [44.5]
Albumin (g/l)	31.0±6.1 (15-43) [31]	29.4±5.2 (20-39) [29]
CRP-albumin ratio	2.1±2.6 (0.05-11.04) [1]	3.1±2.7 (0.06-9.39) [2.4]

*significantly different compared to patients alive at 12 months: LOS, (P=0.018); BMI, (P=0.018); MNA-SF, (P=0.001); Urea, (P=0.05).

Table 2. Comparison of BIA data for FFM and FM and index values (FFMI and FMI in kg/m^2) for patient mortality status, 12 months after hospital admission. Mean ± SD is presented with (minimum-maximum) and [median] values for comparison.

	Alive (n = 48)	**Deceased (n = 18)**
Males/Females	27/21 (56%/44%)	15/3 (83%/17%)
FFM, kg	49.4±9.2 (31.7-72.0) [49.6]	51.5±9.7 (37.5-72.7) [50.7]
FFMI, kg/m^2	17.5±2.5 (13.2-23.5) [17.5]	17.9±2.4 (13.5-22.2) [17.8]
FM, kg	25.5±10.5 (3.4-50.6) [22.5]	17.2±9.9 (3.1-42) [18.1]*
FMI, kg/m^2	9.3±4.1 (1.1-22.5) [8.1]	6.1±3.8 (1.3-16.8) [6.4]*

*significantly different compared to patient group alive at 12 months: FM, (P=0.005); FMI, (P=0.006).

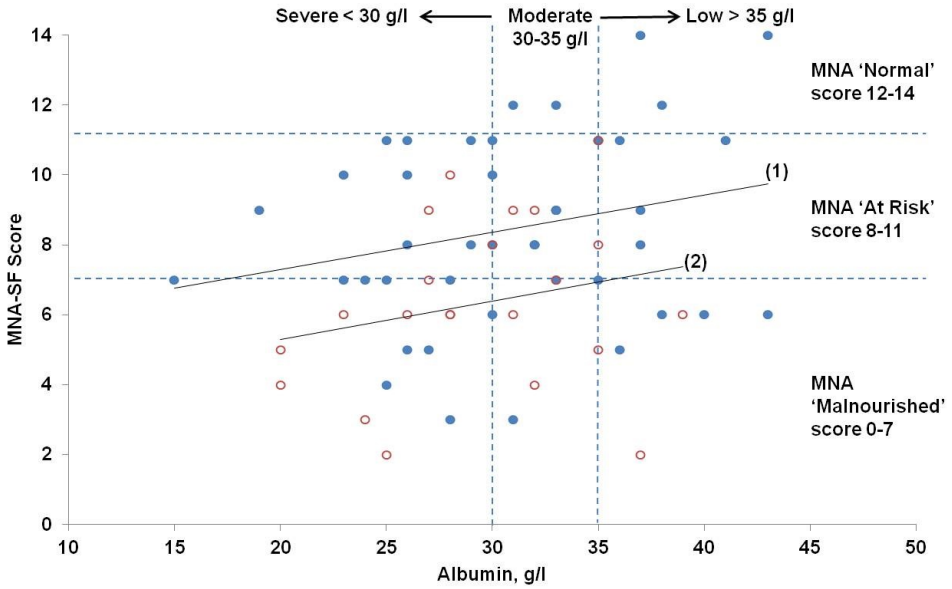
Classification by albumin level

Grouping patients by albumin level as a potential indicator of nutritional status is shown in Table 3. The relationship of albumin level against MNA-SF score is depicted in Figure 1 with cut-off points shown. The nonparametric correlation between albumin and MNA-SF was statistical significant (r=0.025, P=0.046).

Table 3. Patients grouped by albumin classification of malnutrition status. Mean ± SD is presented with (minimum-maximum) and [median] values for comparison.

	Plasma albumin & malnutrition status		
	<30 g/l – severe	**30-34.9 g/l - moderate**	**>35 g/l – low/absent**
Albumin, g/l	25±3.3 (15-29) [26]*	31.6±1.2 (30-33) [32]	37.5±2.6 (35-43) [37]
N (%)	28 (42%)	19 (29%)	19 (29%)
Deaths, N (%)	11 (39%)	6 (32%)	5 (26%)
TMFFD, d	12.4±13.7 (0-66) [8]*†	8.3±6.2 (1-22) [6.5]	6.5±6.6 (0-26) [4]
LOS, d	25±21.6 (4-102) [19]*†	17.6±15.4 (2-68) [16]	14.1±9.5 (2-33) [12]
BMI, kg/m^2	24.8±5.2 (17-35.2) [23.2]	27.1±6.2 (18.6-45.1) [26.1]	25.4±5.2 (16.6-33.3) [25.6]
MUST- 'Low risk'	23 (82%)	16 (84%)	14 (74%)
MUST – 'Medium risk'	2 (7%)	2 (11%)	1 (5%)
MUST – 'High risk'	3 (11%)	1 (5%)	4 (21%)
MNA-SF score	7.0±2.5 (2-11) [7]	8.2±2.4 (3-12) [8]	8.6±3.3 (2-14) [8]
MNA-SF – 'Normal'	0 (0%)	2 (10%)	3 (16%)
MNA-SF – 'At risk'	11 (39%)	11 (58%)	8 (42%)
MNA-SF – 'Malnourished'	17 (61%)	6 (32%)	8 (42%)
Urea, mmols/l	10.7±8.6 (1.7-43.9) [8.0]	9.8±4.4 (3.1-18.5) [9.4]	8.7±4.6 (3.2-19.1) [7.6]
CRP, mg/l	96.7±80.6 (4-287) [86]*	65.6±71.8 (1.6-232) [45]	29.2±38.1 (2.5-172) [17]

*†: raw uncorrected data significantly different to >35 g/l albumin group (P<0.05), although after Bonferroni correction no statistical significance remained. *: Bonferroni corrected data <30 g/l albumin significantly different to >35 g/l albumin group (P=0.005); and CRP significantly different between all groups (P<0.001).



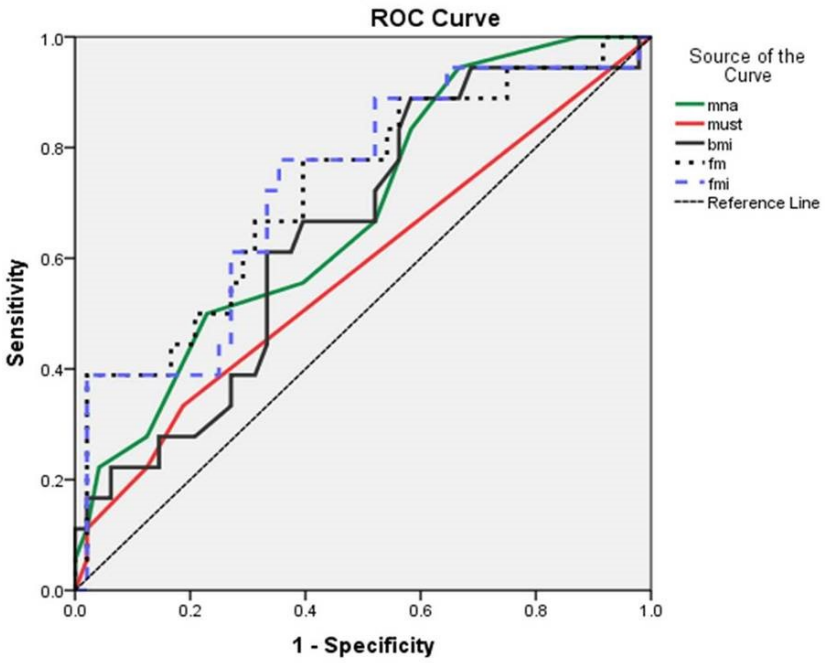
194

195 **Figure 1.** The relationship between plasma albumin (g/l) and MNA-SF score in
196 patients where albumin data was available (n=66). Relevant cut-points indicating
197 malnutrition are shown for both MNA-SF and albumin. Patients alive at 12 months
198 depicted with closed circles (n=44) and deceased open circles (n=22). Note overall
199 group correlation was statistically significant (Spearmans, r = 0.25, P=0.046). In
200 addition, trend-lines are visible for (1): patients alive and (2): deceased.

201

202 ***ROC curve analysis***

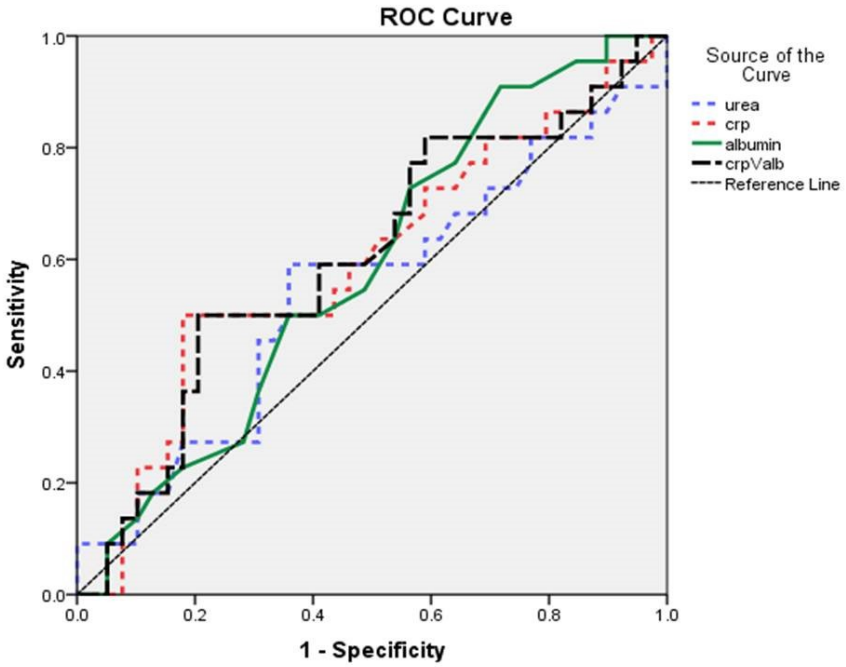
203 ROC curve analysis was performed on data variables evaluating their relative
204 performance as mortality predictors and is presented as follows: MNA-SF and MUST
205 scores, BMI, FM and FMI, Figure 2; and blood markers, urea, CRP, albumin and
206 CRP-albumin ratio, in Figure 3.



Area Under the Curve

Variable	Area	Std. Error	Sig.	95% Confidence Interval	
				Lower	Upper
fm	0.726	0.072	0.005	0.584	0.867
fmi	0.728	0.071	0.005	0.588	0.868
bmi	0.650	0.074	0.062	0.505	0.795
mna	0.679	0.072	0.026	0.539	0.820
must	0.577	0.083	0.338	0.415	0.739

Figure 2. ROC curves for variables: MNA-SF, MUST, BMI, FM and FMI; Statistical data for area under the curve is presented in Table below graph. Standard error is under nonparametric assumption and asymptotic significance and 95% confidence intervals (lower and upper bound) are shown. Null hypothesis: true area = 0.5.



Area Under the Curve

Variable	Area	Std. Error	Sig.	95% Confidence Interval	
				Lower	Upper
urea	0.543	0.080	0.578	0.386	0.700
crp	0.594	0.078	0.224	0.442	0.747
albumin	0.582	0.074	0.290	0.437	0.727
crpValb	0.603	0.077	0.186	0.452	0.753

Figure 3. ROC curves for variables: urea, CRP, albumin and the CRP-albumin ratio (crpValb). Statistical data for area under the curve is presented in Table below graph. Standard error is under nonparametric assumption and asymptotic significance and 95% confidence intervals (lower and upper bound) are shown. Null hypothesis: true area = 0.5.

Variables found to be significantly different from the reference line indicating that they are significant predictors of mortality were MNA-SF score, FM, and FMI. BMI had a trend to significance (P=0.062). MUST was not found to be a significant predictor of mortality outcome. FFM and FFMI were not included in the presentation

of data as there was no statistical significance. Blood markers were analysed and have been presented in Figure 3 as a comparison. None were significantly different to the reference line however, the CRP-albumin ratio performed numerically better. However, note the confidence intervals (lower and upper bound) would suggest for all variables relatively high sampling error which is most likely due to the low patient number and data set, and high variability in the blood markers.

Discussion

Previously, we showed a potential discordance between MUST and MNA-SF scoring in frail older hospital patients[10]. In this report, we show that 12 months after hospital admission a total of 31% of the participants had died. Those patients who died had a significantly longer hospital LOS (P=0.018) and a trend for an increase in TMFFD (Table 1). The mortality group had a significantly lower MNA-SF score (P=0.001) and there was a visible discordance in relative balance of MUST, MNA-SF categorisation between the alive and deceased patients. ROC curve analysis (Figure 2) found that the MNA-SF was a significant predictor of mortality outcome, whereas MUST was not. Rasheed and Woods also found that the MNA-SF categorised more people admitted to hospital as malnourished/at risk of malnutrition than MUST[23]. They noted that both tools have relative ability to predict mortality, but MNA-SF was better at predicting LOS. Van Bokhorst-de van der Schueren et al discussed in a recent systematic review of current nutrition screening tools for the hospital setting, that the MNA generally fairs better in older patients compared to the MUST, and that MUST is a not a good predictor of outcome in older patients[4]. Further, Soderstrom et al, showed in a large cohort of older people (n=1767) that the MNA is predictive of

mortality (a 50 month follow-up period) after taking into account confounding factors[3]. However, Vischer et al, failed to show a predictive effect of MNA-SF in hospitalised older patients with a heavy disease burden[24]. This is interesting as the patient group studied here also had a high disease burden (although this was not recorded as a 'comorbidity/severity index'). The Vischer et al study was performed in a larger patient group (n=444), over a longer 4 year period[24]. They also observed that BMI was a significant predictor of mortality. In the data presented here BMI was found to be significantly lower in the mortality group, despite still being within a 'normal weight' BMI category (by WHO and MUST). Estimation of FM and FMI by BIA was found to be significantly lower, whilst FFMI was similar (17 kg/m^2). ROC curve analysis (Figure 2) found that both FM and FMI were significant predictors of mortality outcome (P=0.005), whereas BMI had a trend towards significance (P=0.062). This data may be supportive of a potential BMI or obesity paradox[25], and is in-line with a study by Bouillanne et al, which showed a protective effect of FM as opposed to FFM with mortality in older hospital patients[26]. This may be viewed as unexpected as it has been assumed that FFM has a more important role. For example, the breakdown of FFM body protein tissue to fuel the acute phase stress response to illness and infection and the concomitant production of circulating acute phase proteins and glucose etc. We previously showed that high proportions of male patients had low/depleted FFMI values (and also skeletal muscle index-unpublished data), whilst having a normal BMI (e.g. 20-24.9 kg/m^2)[10]. The low FFMI values may be due to the effects of complicated overlapping malnutrition, sarcopenia and cachexia states common in the frail older hospitalised patient. This is important to adequately address in clinical practice, however, the relationship of FM with clinical outcomes and mortality in this group requires further study and may relate to other

274 factors. Possible reasons for the observed phenomena may relate to the diverse
275 function of the FM/adipose tissue organ, for example, acting as an energy resource
276 during illness and potentially acting in a protein sparring manner; and/or due to other
277 endocrine and immune functions of the tissue.
278 Routine blood markers have been previously shown to indicate changes in relative
279 nutritional status, inflammation and have prognostic abilities. In this study, albumin,
280 CRP, the CRP-albumin ratio and urea were measured and related to clinical
281 outcomes in patients. Albumin levels were found to be typically low across all
282 patients (30.5±5.9 g/l), potentially indicating a combination of malnutrition and
283 inflammation burden. However, there was no significant difference with patients
284 grouped by mortality at 12 months (Table 1), or significant predictive ability by ROC
285 curve analysis (Figure 3). Grouping patients by albumin classification of malnutrition
286 (Table 3) showed that there were a greater proportion of people who died with lower
287 albumin scores, with a trend for TMFFD and LOS to be higher and a highly
288 significant relationship with CRP (lower albumin, higher CRP). There was also a
289 significant correlation relationship between albumin and MNA-SF score (Figure 1).
290 Furthermore, there were 7 patient deaths in hospital of which 6 had albumin data
291 available (24.5±3.7 g/l), and was found to be significantly lower ($P<0.05$) than the
292 patients who were alive at 12 months or those that died post hospital discharge. This
293 is in-line with other observations that albumin is a known predictor of mortality[14-16].
294 Albumin may be an important measurable nutritional domain which should be
295 considered in relation to inflammation burden and weight loss, despite recently being
296 observed to not be related to body composition-related nutritional status[27]. Albumin
297 levels are also utilised within clinically determining cachexia presence (along with
298 weight loss, BMI, presence of inflammation etc.), and is a key component of the

GNRI[9,12]. In particular, the GNRI has been shown to have good prognostic abilities including within a recent Egyptian study which found that the GNRI had better prognostic ability than the MNA[28].

CRP is another known prognostic indicator and CRP data was collected and assessed in patients (Table 1) as an indicator of inflammatory stress. Levels were clinically significant across the group indicating effects of illness, but there was no significant difference between patients grouped by mortality at 12 months. ROC curve analysis confirmed that neither CRP nor the CRP-albumin albumin were significant predictors of mortality in this group.

Finally, urea was significantly higher in the patients who died at 12 months (Table 1), but was found not to be a significant predictor of mortality outcome by ROC curve analysis. Increases in urea may be predictable in this setting indicating higher whole body protein catabolism, due to illness and associated inflammatory stress, and alterations in kidney function. Blood urea nitrogen has been observed to be an independent predictor of mortality outcome in different patient groups including in cardiovascular diseases and acute coronary syndromes[29]. Pan et al showed recently in older ICU patients that both albumin and urea act as independent and synergistic predictors of mortality[30].

Study limitations include the patient number which may have meant that some analyses were underpowered (e.g. ROC curve analysis of mortality prediction). The lack of significant relationships with the specific blood markers (e.g. ROC curve analysis, Figure 3) is not surprising as circulating concentrations are highly variable (e.g. albumin and CRP) with many factors affecting them[14-18,28]. In addition, this was a single sample collection. The use of BIA and the Kyle equation for FFM estimation is discussed elsewhere as a potential limitation[10]. Furthermore, another criticism may

be the high heterogeneity of frail older people, but this study reflects 'real-world' medicine and chosen screening and assessment tools must be practically effective in this population.

In conclusion, we previously showed discordance between MUST and MNA-SF risk categorisation in frail older hospital patients[10]. This paper suggests that discordance is not only theoretical but may have practical implications for outcome in this group. The MNA-SF is a simple tool and in combination with body composition measurements and blood markers may better categorise frail older patients with respects to their nutritional status and possible clinical outcomes, including mortality risk. Further research is necessary in larger patient cohorts as there are potential healthcare, clinical outcome and economic factors implicated.

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Statement of Authorship

Adrian Slee was the lead author and designated study Chief Investigator, David Stokoe was the designated clinical Principal Investigator; Deborah Birch was a clinical co-investigator involved in data collection and critical input into both the study and manuscript preparation.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Highlights

- The standard routine tool used for malnutrition risk screening in the United Kingdom, the 'MUST', may lack diagnostic accuracy and predictive ability in determining mortality risk in frail older hospital patients.
- The MNA-SF tool appears to be a more accurate tool in determining malnutrition risk and prediction of mortality risk in this patient group.
- A potential BMI paradox is highlighted whereby mortality is greater in patients who have a normal range BMI compared to overweight.
- The fat mass and fat mass index measurements may be predictive of mortality risk in this patient group and requires further study.
- A combination of methods (e.g. the MNA-SF, body composition assessment and blood markers) may be clinically useful in determining nutritional status/malnutrition risk in this patient group and possible clinical outcomes, such as mortality.