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Title page

Full title

Risk of malnutrition is an independent predictor of mortality, length of hospital stay and hospitalization costs in stroke patients

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Running title: Malnutrition and outcomes after stroke

Abstract

Background

Malnutrition is associated with poor outcomes after stroke. Nutrition screening tools are used to identify patients at risk of malnutrition but so far no nutrition screening tool has been validated for use with patients who have had a stroke. This study aimed to determine the ability of the Malnutrition Universal Screening Tool to predict poor outcomes in stroke patients, including mortality, cumulative length of hospital stay and hospitalisation costs.

Methods and Results

Patients were recruited from consecutive admissions at two hyper-acute stroke units in London and were screened for risk of malnutrition (low, medium and high) according to MUST. Six-month outcomes were obtained for each patient through a national database.

Of 543 recruited patients, 51% were males, mean age was 75 years and 87% had an ischaemic stroke. Results showed a highly significant increase in mortality with increasing risk of malnutrition ($p < 0.001$). This association remained significant after adjusting for age, severity of stroke and a range of stroke risk factors ($p < 0.001$). For those patients who survived, length of hospital stay and hospitalisation costs increased with increasing risk of malnutrition ($p < 0.001$ and $p = 0.049$, respectively). This association remained significant in the adjusted model ($p < 0.001$ and $p = 0.001$, respectively).

Conclusions

Risk of malnutrition is an independent predictor of mortality, length of hospital stay and hospitalisation costs at 6 months post stroke. Research is needed to determine if nutritional support for medium or high risk patients results in better outcomes. The routine screening of stroke patients for risk of malnutrition is recommended.

INTRODUCTION

Malnutrition has been identified as a common problem that affects stroke patients and is associated with poor outcomes, including increased mortality and morbidity(1-4). Moreover, malnutrition poses a significant burden on healthcare resources (5) and it has been suggested that disease-related malnutrition is an important determinant of hospitalization costs (6) but, to date, this association has not been tested in patients who have had a stroke.

Furthermore, it has been shown that malnutrition is often an under-recognised and undertreated problem and, in this context, the wide use of simple strategies to quickly identify patients at risk of malnutrition is advocated (7-9). One way of identifying patients with nutritional problems who may benefit from nutritional intervention is to use a validated nutrition screening tool (NST). Current guidelines recommend all stroke patients to be screened for risk of malnutrition at the time of admission to hospital and regularly thereafter (10). Patients who are identified as at risk of malnutrition should be referred for further assessment and have an appropriate nutritional care plan implemented. However, no published studies have validated a NST for use in stroke patients (11-13) and this is an area that lacks a strong evidence base (13).

The Malnutrition Universal Screening Tool (MUST) is a NST, launched in 2003, which involves assessment of BMI, % weight loss over the previous 3-6 months and the effect of acute illness on dietary intake (9). It was designed for use in any patient group in any healthcare setting and has been suggested as an appropriate tool for patients who have had a stroke (10). A different NST was designed for use in stroke patients in the acute phase (14), but neither of these NSTs has been specifically validated in this patient group.

The present study was designed to determine the ability of MUST to independently predict negative outcomes in acute stroke patients, more specifically mortality, length of hospital

stay and hospitalization costs during the first six months post stroke. If patients who are at risk of malnutrition are correctly and promptly identified, they should be more likely to benefit from nutritional support and, ultimately, this could have a positive impact on their recovery.

A preliminary report of these results has been presented in abstract form (15).

SUBJECTS AND METHODS

Study sample

In this prospective observational study, patients were recruited from consecutive admissions at two hyper-acute stroke units in south London between June 2011 and May 2012. Patients were considered eligible for the study if they were 18 years or older, not pregnant, with a diagnosis of stroke (confirmed by a computerised tomography scan, a magnetic resonance imaging scan or the consultant's clinical judgment) and with a National Health Service (NHS) number (which was a requirement to assess each patient's outcomes six months subsequent to recruitment). Ethical approval was obtained from the Yorkshire and the Humber – Leeds West Research Ethics Committee (reference: 11/YH/0054) and written, informed consent to participate in the study was obtained from patients or, if they lacked capacity, a consultee.

Baseline data collection

The following data were collected on admission to hospital: date of admission, date of stroke, gender, ethnic group, type of stroke, living conditions prior to stroke, medical history (as identified by the medical team, potentially relevant as stroke risk factors and chronic conditions likely to affect nutritional status prior to admission), record of previous stroke,

the result of a routinely applied scale that measures the severity of stroke (the National Institutes of Health Stroke Scale (NIHSS) score), the result of the swallow screening test. Current weight was measured with either chair or hoist clinical scales (Seca, Leicester, UK), with patients wearing light clothing and without shoes. Height was measured using a portable stadiometer (Seca, Leicester, UK), according to standard methodology, for patients able to stand; in patients who were unable to stand, recalled height (if judged to be reliable and realistic) or a surrogate measure, i.e. height estimated using ulna length, was used (16). Usual (pre-illness) weight was obtained from the patient, a relative or carer and medical notes, and the current and usual weight were used to calculate percentage of unintentional weight loss in the previous 3 to 6 months (<5%, 5-10% or > 10%). Measured weight and height were used to calculate BMI (weight/height²). The effect of acute disease and the inability to eat or “nil by mouth” for more than 5 days was assessed by reference to the patient’s medical notes. The same researcher (FG) collected all the information and completed the MUST, as described in the explanatory MUST booklet (http://www.bapen.org.uk/pdfs/must/must_explan.pdf). Thus, the sum of scores obtained for each question related to BMI, unintentional weight loss, the effect of acute disease and the inability to eat for more than 5 days results into an overall risk of malnutrition score, which categorises patients into low (score = 0), medium (score = 1) or high risk (score ≥ 2).

Follow-up procedure

Mortality data for each patient for a follow-up period of 6 months after the stroke were obtained from Summary Care Records, an electronic patient record that stores a defined set of key patient data for every patient in England. Information on hospital admissions was obtained as a tailor-made report from the Hospital Episode Statistics (HES) databases. HES is a data warehouse containing details of all admissions, outpatient appointments and emergency attendances at NHS hospitals in England (17). Diagnosis codes for inpatients

were grouped into Healthcare Resource Groups (HRG) in the HES report. The cost analysis was based on the hospital payment system in place in England. The Department of Health “Payment by Results tariff information spreadsheet for 2012 to 2013” for payment of healthcare providers (18) was used to transform the HRG into the tariffs paid by commissioners. Analyses on cumulative length of hospital stay (LOS) and hospitalization costs relate to the total number of days spent in hospital, anywhere in England, during the follow-up period, and were conducted on patients who survived at 6 months post stroke.

Statistical analysis and sample size calculation

Statistical analyses were conducted to determine the association between risk of malnutrition on admission to hospital (exposure) and mortality, length of hospital stay and hospitalization costs at 6 months post-stroke (outcomes). The multivariable analyses included the following potential confounders and effect modifiers: ethnicity, age, gender, type of stroke, severity of stroke and stroke risk factors (hypertension, diabetes, dyslipidemia, smoking, ischemic heart disease, heart failure, atrial fibrillation, previous transient ischemic attack and heavy alcohol consumption).

Baseline characteristics of the three nutrition risk categories (low, medium and high) were compared using the Chi-square test for categorical variables and ANOVA for continuous variables. The Chi-square test was conducted to compare the differences in categorical outcomes (e.g. mortality rates) across the three nutrition risk categories, and the Kruskal-Wallis test or ANOVA was used for continuous outcomes (e.g. LOS and costs) depending on whether these data were normally distributed. Since the distribution of both LOS and hospitalization costs was skewed, univariate analysis of variance was conducted on ranked data to assess the effect of possible confounders on these outcomes. Cox Proportional Hazards Models were used to compare risk of mortality (crude and adjusted HRs, with 95%

CI) between risk of malnutrition categories, with the low risk group as the reference category. Sensitivity analyses were conducted as needed, e.g. to handle missing data. Statistical analyses were carried out using SPSS software version 19.0 for Windows (Chicago, Illinois, USA). Any differences were considered significant when $p < 0.05$.

Sample size calculation

Assuming 20% patients are malnourished on admission to a Stroke Unit(1) and that 35% of malnourished patients and 20% in the adequately nourished die during the first 6 months after a stroke (data from the Feed Or Ordinary Diet Trial Collaboration(2)), a total sample size of 539 subjects was required to achieve a power of 95%, to detect a difference in mortality between malnourished and adequately nourished patients, with a significance level of 0.05 in a two-tailed Chi-squared test. The G-Power Software(19) was used to perform this calculation.

RESULTS

During the recruitment period, 925 patients were admitted and screened in the stroke units of both hospitals, from which 543 were recruited and included in the study. The remaining patients were not recruited mainly because they were individuals who had not had a stroke (n=289), did not have a NHS number or went back to their home country which prevented the follow-up process (n=21), were receiving end of life care (n=21) or had been recruited before (n=12). The proportion of eligible patients who could not be recruited was only 6%.

There were no missing data from variables collected at baseline and follow-up, except for the MUST score in 6 patients for whom it was impossible to quantify weight loss, because

information regarding usual weight could not be obtained from any source (patient, relative or medical records).

Baseline characteristics

The 537 patients included in the analysis had a mean age of 74.7 years, 51% were men, 87% had an ischemic stroke, 81% were white, 22% had had a previous stroke and 34% were diagnosed with inadequate swallow following the bedside screening test by nurses on admission to hospital. There were 342 patients (64%) at low risk, 39 (7%) at medium risk and 156 (29%) at high risk of malnutrition and the baseline characteristics stratified by risk of malnutrition are presented in **Table 1**.

Patients at high risk of malnutrition were more likely to be older, to have a more severe stroke, to have a hemorrhagic stroke, to live at home with no support, to have atrial fibrillation, to have gastrointestinal diseases, to have impaired mobility prior to stroke and to have inadequate swallow on admission to hospital.

Outcomes

Table 2 demonstrates that the association between risk of malnutrition and 6-month mortality was statistically significant and graded: the greater the risk of malnutrition, the higher the rate of mortality (Chi-square test, $p < 0.001$), and the higher the unadjusted risk of mortality ($p < 0.001$). At 6 months after stroke, less than 6% of patients at low risk of malnutrition had died while more than 40% had died in the high risk group. After adjusting for a range of confounding factors using a multivariable Cox Proportional Hazards Model (**Table 3**), the association between risk of malnutrition and mortality remained highly significant ($p < 0.001$). Other factors that showed a significant relationship with mortality were age, severity of stroke, hypertension, ischemic heart disease and heart failure, while

gender, ethnicity, type of stroke and other stroke risk factors showed no significant association with mortality. The survival curves related to the multivariable model are illustrated in **Figure 1**. An additional Cox Proportional Hazards Model was conducted including data related to the swallow screening test. The variable 'inadequate swallow' was not an independent predictor of mortality ($p=0.216$) and it did not change the effect of MUST on the outcome ($p<0.001$).

Table 2 also shows the LOS and hospitalization costs for those patients who survived at 6 months post stroke. The distribution of LOS was significantly different across malnutrition risk categories (Kruskal-Wallis test, $p<0.001$), and increased progressively from a median of 14 to 48 days.

When the analysis on hospitalization costs was conducted, it was noted that 2% of the HRG codes provided by HES were not valid or there were no published tariffs for these codes and, therefore, admissions or episodes linked to these codes were excluded (which explains the difference in the number of patients between the results for LOS and for hospitalization costs). Hospitalization costs increased progressively with malnutrition risk category, from a median of less than £5000 in patients at low risk of malnutrition to more than £8000 in patients at high risk of malnutrition, and these differences were statistically significant (Kruskal-Wallis test, $p<0.001$).

The association between risk of malnutrition and LOS and hospitalization costs remained significant after adjusting for potential confounders, using univariate analysis of variance on ranked data ($p<0.001$ for both outcomes), as shown in **Table 4**. Other factors that were significantly associated with LOS and hospitalisation costs were age, severity of stroke, type of stroke, diabetes and heart failure .

A sensitivity analysis was carried out to assess the impact of removing 2% of the admission data, due to lack of information on costs. Analysis was repeated without the 35 patients who had an excluded admission and the associations between risk of malnutrition and hospitalization costs previously observed remained significant and in the same direction (data not shown).

The number of hospital readmissions was also analyzed. Patients who survived and were readmitted to hospital during a period of 6 months post-stroke were identified. The analysis showed that there was no statistically significant difference between rates of hospital readmissions for patients in the three malnutrition risk categories ($p=0.287$), although there was a trend for a higher percentage of hospital readmissions in patients at medium (62%) and high risk of malnutrition (68%) than those at low risk (59%).

DISCUSSION

This study shows that the MUST can be used to predict risk of negative outcomes in stroke patients. The association between risk of malnutrition and the outcomes was statistically significant and graded: the greater the risk of malnutrition, the higher the risk of mortality, the longer the LOS and the greater the hospitalization costs. For those who survived, the median number of days spent in hospital in a period of 6 months was at least 3 times higher for patients who were at high risk of malnutrition. When compared to individuals at low risk, the median cost of hospitalisation was 77% higher for individuals at high risk of malnutrition and 32% higher for those at medium risk.

These results are consistent with previous studies conducted in other populations, e.g. a study conducted in the UK where 150 elderly inpatients with a wide range of conditions

were screened using MUST (20), and a study conducted in Singapore, where 818 patients admitted to 16 different wards had their nutritional status assessed by the Subjective Global Assessment (21). In the Singapore-based study (21), malnutrition was associated with longer hospital stays (6.9 vs. 4.6 days) and a 4-fold increased risk of death at 1-year follow-up, while in the UK-based study¹⁸ high risk of malnutrition was associated with doubling of both mortality and LOS. Both tools were able to identify patients with poor outcomes but it should be noted that the Subjective Global Assessment is a nutritional assessment method which is time-consuming and requires trained personnel, while the present study used a validated nutrition screening method, which is quick and easy to use for non-nutrition specialists, after a short training session.

In the present study, costs of hospitalization of individuals at high risk of malnutrition were 77% higher than the costs of low risk patients. This is a major contributor, when compared with other factors that have the potential to influence hospitalization costs after stroke. For example, it has been shown that atrial fibrillation increases acute hospitalization costs by 24% (22), depression by 63% (23), hemorrhagic strokes by 65% (vs. ischemic strokes (24)), and younger patients (18-44 years old vs. 45-64 years old) by 6% (25). Other studies that determined the hospitalization costs of nutritionally vulnerable patients report costs 20% (6) or 36% (26) higher, when compared with the costs for well-nourished patients. These different figures are probably related to the methods used to determine the outcomes (e.g. the majority of these studies only analyzed the outcomes related with the first admission, until discharge or death), the tool used to categorise patients as malnourished or at risk of malnutrition and the patient population (e.g. the LOS of stroke patients may be longer than general medical patients, due to the time required for rehabilitation).

Characteristics of patients at high risk of malnutrition

When the characteristics of patients at high risk of malnutrition were examined, it was found that these individuals were more likely to be older and to have a more severe stroke (as demonstrated before, in the stroke and non-stroke population (21, 27)), to have a hemorrhagic stroke (in line with the findings from a study that showed that undernourishment was significantly more prevalent in patients with hemorrhagic strokes than those with ischemic strokes (28)), to live at home with no support, to have impaired mobility (prior to stroke) and to have an inadequate swallow. This group represented 29% of the study population. It should also be noted that, in the present study, the groups of patients categorised as being at medium and high risk of malnutrition included overweight and obese individuals, i.e. the range of BMI values for patients at medium risk was 18.7 to 28.6 Kg/m², and for patients at high risk was 13.2 to 50.5 Kg/m². This shows that underweight patients are not the only ones who are at risk of malnutrition. It also demonstrates that the use of subjective measures to determine nutritional status, such as the “bedside assessment” that has been used in previous clinical trials (2, 29), is unlikely to be a reliable way of identifying patients who are at risk of malnutrition. In this study, approximately 18% of patients had unintentional weight loss prior to stroke. The reasons for the involuntary weight loss (as reported by patients and their carers) were not only associated with a disease/occult pathology or untreated chronic disease such as cancer; in addition, there were psychological and social reasons such as lack of interest in preparing own food, social isolation and depression due to the death of a close relative. In other words, malnutrition has multi-factorial causes, which need to be explored by health and social care professionals so they can provide effective nutritional interventions.

Limitations

The major limitations of this study were the lack of information regarding changes in body weight during follow-up, as well as a lack of information regarding the proportion of

patients who were referred to a dietitian and the type or length of any nutritional intervention the patients may have received. Thus, future studies should assess how many people receive nutritional intervention post stroke, and what impact this has on their outcomes.

Strengths The main merits of this study are the relatively large sample size and the consistency with which the nutritional screening was carried out. Additionally, the follow-up method captured all hospital admissions that occurred anywhere in England. Many studies of the impact of malnutrition only considered the outcomes of the first admission, not being able to report any outcome after the hospital discharge (30, 31). Moreover, to our knowledge, none of the published studies in the area of malnutrition were able to capture hospital readmissions at a national level. Lim et al admit that, because they were not able to monitor the study patients when they were readmitted to other hospitals, an underestimation of the readmission rates may have occurred (21).

The current study included adult inpatients without limitations of age, gender or stroke severity and did not exclude patients who lacked capacity to consent to participate or patients with severe communication problems, which is very common in the acute stage after stroke. In these cases, the researcher contacted the patient's next of kin to obtain assent and information relevant for the study, such as usual weight and unintentional weight loss. This is particularly important to avoid selection bias, which has been reported in national registries of strokes. For example, the Registry of the Canadian Stroke Network reported that the participation rate never exceeded half of the eligible patients (32), while the equivalent participation rates for the present study were 94%.

Conclusion

Being at risk of malnutrition, as identified by MUST, is a significant independent predictor of mortality, LOS and hospitalization costs at 6 months post stroke. These results support the use of MUST to identify stroke patients who are likely to have poor outcomes and may benefit from nutritional support, although the best type and duration of nutritional interventions is yet to be determined.

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Authors' contributions to manuscript: FG, PWE, and CEW designed the research plan; FG conducted research; FG performed statistical analysis in discussion with PWE and CEW; FG, PWE and CEW wrote the paper; FG had primary responsibility for final content. All authors have seen and approved the final manuscript.

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**Risk of
malnutrition**

—■ Low risk
...■ Medium risk
—■ High risk

Figure 1. Survival curves after stroke according to risk of malnutrition (multivariable model adjusted for age, gender, ethnicity, type of stroke, severity of stroke and stroke risk factors (hypertension, diabetes, dyslipidemia, smoking, ischemic heart disease, heart failure, atrial fibrillation, previous transient ischemic attack and heavy alcohol consumption))