



## Original article

# Malnutrition and its impact on cost of hospitalization, length of stay, readmission and 3-year mortality<sup>☆</sup>

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## ARTICLE INFO

## Article history:

Received 15 August 2011

Accepted 3 November 2011

## Keywords:

Malnutrition

Hospitalization outcomes

Mortality

Cost

Subjective Global Assessment

Prevalence

## SUMMARY

**Background & aims:** The confounding effect of disease on the outcomes of malnutrition using diagnosis-related groups (DRG) has never been studied in a multidisciplinary setting. This study aims to determine the prevalence of malnutrition in a tertiary hospital in Singapore and its impact on hospitalization outcomes and costs, controlling for DRG.

**Methods:** This prospective cohort study included a matched case control study. Subjective Global Assessment was used to assess the nutritional status on admission of 818 adults. Hospitalization outcomes over 3 years were adjusted for gender, age, ethnicity, and matched for DRG.

**Results:** Malnourished patients (29%) had longer hospital stays ( $6.9 \pm 7.3$  days vs.  $4.6 \pm 5.6$  days,  $p < 0.001$ ) and were more likely to be readmitted within 15 days (adjusted relative risk = 1.9, 95% CI 1.1–3.2,  $p = 0.025$ ). Within a DRG, the mean difference between actual cost of hospitalization and the average cost for malnourished patients was greater than well-nourished patients ( $p = 0.014$ ). Mortality was higher in malnourished patients at 1 year (34% vs. 4.1%), 2 years (42.6% vs. 6.7%) and 3 years (48.5% vs. 9.9%);  $p < 0.001$  for all. Overall, malnutrition was a significant predictor of mortality (adjusted hazard ratio = 4.4, 95% CI 3.3–6.0,  $p < 0.001$ ).

**Conclusions:** Malnutrition was evident in up to one third of the inpatients and led to poor hospitalization outcomes and survival as well as increased costs of care, even after matching for DRG. Strategies to prevent and treat malnutrition in the hospital and post-discharge are needed.

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**Abbreviations:** DRG, Diagnosis-related groups; LOS, Length of hospital stay; NUH, National University Hospital; SGA, Subjective Global Assessment.

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## 1. Introduction

Malnutrition is prevalent in the hospital setting with 20–50% of patients identified as malnourished at admission.<sup>1,2</sup> Poor nutrition has been adversely associated with a range of clinical, functional and economic outcomes.<sup>1,3,4</sup> Malnourished patients have been shown to have a length of hospital stay 1.5–1.7 times longer than well-nourished patients.<sup>3,4</sup> They have also been shown to have a three-fold increase in mortality over a 12-month period post discharge.<sup>3</sup>

The prevalence of inpatient malnutrition and its related outcomes are likely to vary with different populations and health care settings. Yet there are few studies reporting prevalence of malnutrition in Asian hospitals and these have largely focused on older adults.<sup>5–7</sup> The true prevalence of malnutrition in a Singapore

acute-care hospital setting has not been clearly established. A previous study done in a large acute-care hospital in Singapore, found the “prevalence” to be 15% using Subjective Global Assessment (SGA).<sup>8</sup> However, this figure is likely to be an underestimate as only patients screened to be at risk of malnutrition using the Malnutrition Screening Tool<sup>9</sup> were assessed using SGA. Furthermore, patients were selected from four discipline-specific wards and hence may not be representative of all hospital patients.

Few studies have prospectively examined the long term clinical outcomes of malnutrition<sup>3</sup> and consideration of the confounding effect of disease or diagnosis-related groups (DRG) is rare.<sup>10</sup> Even fewer studies have investigated mortality outcomes using data from national death registers.<sup>3</sup> Furthermore, most studies evaluating the prognostic significance of malnutrition have focused on Caucasian populations, whilst studies in Asian populations are scarce.<sup>1,3,4</sup>

The aim of this study was to comprehensively determine the prevalence of malnutrition and its impact on length of hospital stay, readmission, 3-year mortality and cost of hospitalization in patients newly admitted to an acute-care tertiary hospital in Singapore, across different DRG.

## 2. Methods

### 2.1. Study participants and study design

The study participants were patients newly admitted to National University Hospital (NUH), which is a 987-bed acute tertiary hospital, with a comprehensive range of medical and surgical specialties. Its catchment includes the western region of Singapore as well as complicated clinical cases that require specialist tertiary care from all over the country. To ensure that study subjects were as representative of the institution's patient profile as possible, consecutive patients newly admitted to a pre-determined sequence of 16 wards were screened for eligibility from February to November 2006. Patients were included in the study if they were aged 18–74 years old and had not been enrolled in the study during previous admissions. Pediatric patients were excluded because nutrition assessment methods differ between adults and children. Psychiatric, Intensive Care Unit and maternity patients were excluded at the hospital's request. Based on a pre-determined fixed sequence of wards, we assessed all newly admitted eligible patients to a maximum of six patients per day. Once all 16 wards had been covered, the sequence was repeated. This recruitment strategy enabled consecutive sampling within a feasible target of five to six consents and assessments per day. Demographics of the study sample were compared with all patients admitted over the period of the study, except those in the excluded categories. Data on hospital population were retrieved from the hospital's Management Information Services.

### 2.2. Nutritional assessment

To avoid inter-rater variability, a single dietitian assessed the nutritional status using SGA within 48 h of admission.<sup>11</sup> Subjective Global Assessment is a validated and widely used nutrition assessment tool which involves evaluation of weight and dietary intake changes, gastrointestinal symptoms, functional capacity and physical examination for evidence of fat depletion, muscle wasting and nutrition-related edema.<sup>11</sup> The SGA classifies patients into three categories; well nourished, moderately malnourished and severely malnourished.<sup>11</sup> It was chosen as the assessment tool for this study because of its good prognostic value for a range of clinical outcomes, including mortality.<sup>3,4,12</sup>

### 2.3. Hospitalization outcomes and mortality data

Each patient was prospectively tracked for the length of hospital stay (LOS), cost of hospital stay before government subsidy, inpatient mortality and unplanned readmission within 15 days, 90 days and 6 months from the discharge date of the index admission. Index admission refers to the admission in which the participants were recruited for this study. Patients' LOS were tracked via the hospital's electronic medical records (Computerized Patient Support System). Patients' readmission to the hospital, inpatient mortality and actual cost of hospital stay for each study subject were tracked from the hospital's System Application Product (SAP) system. Actual hospitalization cost for each participant was the cost incurred before government subsidy and includes hospital stay, professional fees, medications, tests and ward consumables. Patient mortality at 1, 2 and 3 years from the index admission were retrospectively tracked from the Singapore Death Registry through the Singapore Ministry of Health. The National Healthcare Group Domain Specific Review Board approved this study and a member of the Singapore Ministry of Health staff had permission to access the Singapore Death Registry for this study. The Ministry of Health staff was provided with a password-protected complete study dataset. The mortality data for each patient was added and returned as a de-identified dataset to the principal investigator.

To ascertain the effect of malnutrition on LOS and cost compared to well-nourished patients who had similar disease type and severity, participants' DRG were obtained retrospectively from the hospital's Casemix Department.<sup>13</sup> Each DRG has a specific numerical code as assigned by the Australian National Diagnosis Related Groups.<sup>13</sup> The DRG is a system widely used by many countries to cluster patients with a variety of diagnoses and procedures into diagnostic groups on the basis that cases within a group will have a similar level of complexity and their treatment is expected to utilise a similar level of hospital resources and hence incur similar costs.<sup>14</sup> They are used as a basis for hospital funding allocation.<sup>14</sup> Participants who had been classified with a malnutrition sub-component in the DRG were reclassified with the corresponding DRG without malnutrition so that matching between similar codes of DRG can be performed in the statistical analysis.<sup>13</sup> The length of hospital stay and cost of hospitalization for each participant were compared with the Singapore public hospital and study hospital expected average LOS and cost specific to the DRG.<sup>15</sup> These two approaches effectively control for the potential confounding effects of the type and severity of illness on the hospitalization outcomes and cost.

### 2.4. Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (version 18.0, SPSS Inc., Chicago, IL, USA). Descriptive data for quantitative variables (LOS and cost) were presented as median and mean  $\pm$  standard deviation (SD), and categorical variables (readmission and mortality) were presented as n (%). Differences in LOS and hospitalization costs between well-nourished and malnourished groups were evaluated using mixed model analysis with DRG as a random effect to handle correlated effects, adjusted for age, gender and race. Conditional logistic regression matching by DRG (matched case–control design) was carried out to evaluate the association between nutritional status and outcomes variables (mortality and readmission), adjusting for gender, age and race, presenting relative risk with 95% confidence interval.

**Table 1**  
Demographics (frequency or mean  $\pm$  standard deviation) of study participants and hospital population.<sup>a</sup>

		Study sample (n = 818)	Hospital population <sup>a</sup> (n = 21,348)	p-Value
Gender	Male	59%	56%	0.24
	Female	41%	44%	
Race	Chinese	62%	60%	0.05
	Malay	20%	18%	
	Indian	11%	13%	
	Others	7%	9%	
Age	Mean age (years)	51.9 $\pm$ 15.4	49.3 $\pm$ 15.9	<0.001

<sup>a</sup> Profile of inpatient admissions from National University Hospital's Management Information Services, matched for study data collection period (February–November 2006) and study selection criteria (i.e. 18–74 years old not admitted to pediatrics, psychiatry, intensive care and maternity units).

### 3. Results

#### 3.1. Demographics of participants

A total of 1079 patients fulfilled the inclusion criteria and were eligible to participate in the study. From these, 818 (76%) patients participated in the study, 11 declined to participate and 250 were discharged within 48 hours of admission before SGA could be completed. The demographic profiles of the participants and of the hospital population are described in Table 1. The study sample was older than the hospital population (difference = 2.6 years, CI 1.48–3.58) but there was no difference in gender or race.

#### 3.2. Prevalence of malnutrition

Using SGA, 71% (583) patients were classified as well nourished, 25% (205) as moderately malnourished and 4% (30) as severely malnourished. The moderately and severely malnourished categories have been combined for subsequent analysis. The highest prevalence of malnutrition was found in patients from oncology (71%), endocrinology (48%) and respiratory medicine (47%) (Fig. 1).

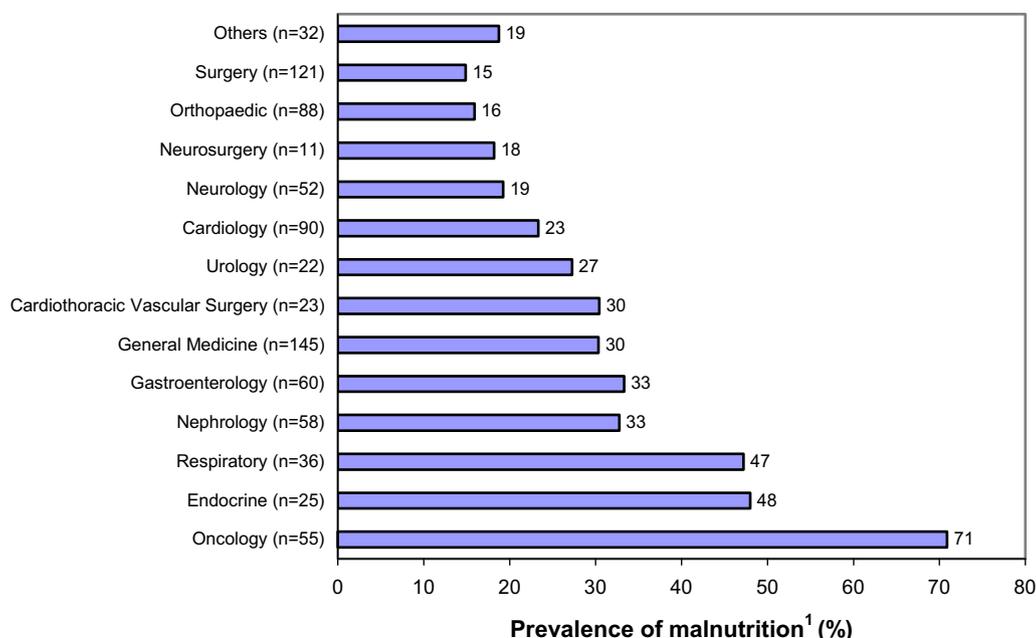


Fig. 1. Prevalence of malnutrition by specialties (n = 818). <sup>1</sup>Malnutrition was determined with Subjective Global Assessment within 48 h of hospital admission.

Malnourished patients were older (58 years vs. 49 years,  $p < 0.001$ , 95% CI 7–11) and more likely to be male (32% vs. 26%,  $p = 0.016$ ). On this basis, both age and gender were included in all statistical models. There was no difference in the prevalence of malnutrition among different races (Chinese 32%, Malay 25%, Indian 22%, Other ethnic 20%;  $p = 0.08$ ).

#### 3.3. Hospitalization outcomes, cost and mortality

Table 2 compares hospitalization outcomes, costs and mortality between well-nourished and malnourished patients. Independent of gender, age, race and matching for DRG, malnourished patients stayed in the hospital significantly longer, were more likely to be readmitted within 15 days, and had higher mortality up to three years post discharge. Table 2 also shows the length of stay and cost of hospitalization and comparison of these variables with the average for NUH and Singapore. Forty-five percent of malnourished patients were hospitalized longer than that recommended under the DRG for public hospitals compared to 21% for well-nourished patients. Malnutrition was a significant predictor of overall mortality with adjusted hazard ratio (HR) of 4.4, (95% CI 3.3–6.0),  $p < 0.001$  (Fig. 2). Out of the 235 patients that were identified as malnourished in this study, only three had been classified under the DRG co-morbidity as malnourished.

There were 530 patients (343 well nourished and 187 malnourished) that could be matched for 95 DRG, with each DRG having at least a well nourished and a malnourished case (range of  $n$  values within each DRG = 2–22). Conditional logistic regression was used to effectively average out the association between nutritional status and outcomes variables within each DRG cluster across the whole cohort, and the results presented in Table 2.

### 4. Discussion

This study is amongst the first to examine the impact of malnutrition on length of hospital stay, readmission, hospitalization cost and mortality in a large sample representative of patients admitted to a major Singaporean tertiary hospital. In addition, few

**Table 2**  
Comparison of hospitalization outcomes, costs and mortality between well-nourished and malnourished patients ( $n = 818$ ).

Outcome variables	Well-nourished ( $n = 583$ )	Malnourished <sup>a</sup> ( $n = 235$ )	Results, unadjusted	Results, adjusted <sup>b</sup>	Results, DRG matched <sup>c</sup>	Results, DRG matched, adjusted <sup>c,d</sup>
Length of hospital stay (days), mean $\pm$ sd	4.6 $\pm$ 5.6	6.9 $\pm$ 7.3	$P < 0.001$	$P = 0.001$	$P < 0.001$	$P = 0.001$
Length of hospital stay (days), median (range)	3 (1–63)	4 (1–59)				
Readmission within 15 days of index admission, $n$ (%)	61 (10.5)	40 (17.0)	RR: 1.6 (CI: 1.1, 2.3) $P = 0.013$	RR: 1.6 (CI: 1.0, 2.4) $P = 0.040$	RR: 1.8 (CI: 1.0, 3.0) $P = 0.035$	RR: 1.9 (CI: 1.1, 3.2) $P = 0.025$
Readmission within 90 days of index admission, $n$ (%)	133 (22.8)	87 (37.0)	RR: 1.6 (CI: 1.3, 2.0) $P < 0.001$	RR: 1.5 (CI: 1.1, 1.9) $P = 0.010$	RR: 1.4 (CI: 1.0, 1.9) $P = 0.081$	RR: 1.4 (CI: 0.9, 2.0) $P = 0.101$
Readmission within 6 months of index admission, $n$ (%)	187 (32.1)	113 (48.1)	RR: 1.5 (CI: 1.2, 1.9) $P < 0.001$	RR: 1.3 (CI: 1.0–1.7) $P = 0.036$	RR: 1.3 (CI: 1.0, 1.8) $P = 0.067$	RR: 1.3 (CI: 1.0, 1.8) $P = 0.097$
Inpatient mortality, $n$ (%)	2 (0.3)	10 (4.3)	RR: 12.3 (CI: 2.7, 55.5) $P < 0.001$	RR: 12.0 (CI: 2.5–59.0) $P = 0.002$	RR: 7.0 (CI: 0.8, 62.7) $P = 0.081$	RR: 3.9 (CI: 0.3, 45.5) $P = 0.271$
1-year mortality, cumulative, $n$ (%)	24 (4.1)	80 (34.0)	RR: 8.3 (CI: 5.4, 12.6) $P < 0.001$	RR: 7.4 (CI: 4.6–11.9) $P < 0.001$	RR: 4.2 (CI: 2.3, 7.6) $P < 0.001$	RR: 4.4 (CI: 2.3, 8.3) $P < 0.001$
2-year mortality, cumulative, $n$ (%)	39 (6.7)	100 (42.6)	RR: 6.3 (CI: 4.5, 8.9) $P < 0.001$	RR: 5.2 (CI: 3.6–7.7) $P < 0.001$	RR: 3.3 (CI: 2.1, 5.3) $P < 0.001$	RR: 3.2 (CI: 1.9, 5.3) $P < 0.001$
3-year mortality, cumulative, $n$ (%)	58 (9.9)	114 (48.5)	RR: 4.8 (CI: 3.7, 6.5) $P < 0.001$	RR: 3.9 (CI: 2.8–5.4) $P < 0.001$	RR: 2.9 (CI: 1.9, 4.3) $P < 0.001$	RR: 2.8 (CI: 1.8, 4.4) $P < 0.001$
Cost of hospitalization for individual patient (S\$), mean $\pm$ sd	3707 $\pm$ 5541	4606 $\pm$ 6665	$P = 0.049$	$P = 0.085$	$P = 0.037$	$P = 0.070$
Cost of hospitalization for individual patient (S\$), median (range)	1897 (179–70,472)	2534 (297–50,215)				
Difference between study subjects length of hospital stay and NUH's similar diagnosis-related group (DRG) average length of stay (days), mean difference $\pm$ sd	0.1 $\pm$ 4.3	1.5 $\pm$ 6.9	$P = 0.001$	$P = 0.002$	$P < 0.001$	$P = 0.001$
Difference between study participant length of hospital stay and all Singapore public hospitals' similar diagnosis-related group (DRG) average length of stay (days), mean difference $\pm$ sd	–0.5 $\pm$ 4.5	0.7 $\pm$ 7.0	$P = 0.004$	$P = 0.006$	$P = 0.001$	$P = 0.003$
Difference between study participants actual cost of hospitalization and NUH's similar diagnosis-related group (DRG) average cost of hospitalization (S\$), mean difference $\pm$ sd	488 $\pm$ 3494	1392 $\pm$ 6150	$P = 0.008$	$P = 0.013$	$P = 0.009$	$P = 0.014$

DRG, diagnosis-related group; sd, standard deviation;  $n$ , number; RR, relative risk; CI, 95% Confidence Intervals; S\$, Singapore dollars; NUH, National University Hospital.

<sup>a</sup> Malnutrition as defined by Subjective Global Assessment. Moderate and severe malnutrition are combined.

<sup>b</sup> Adjusted for ethnicity, age, gender.

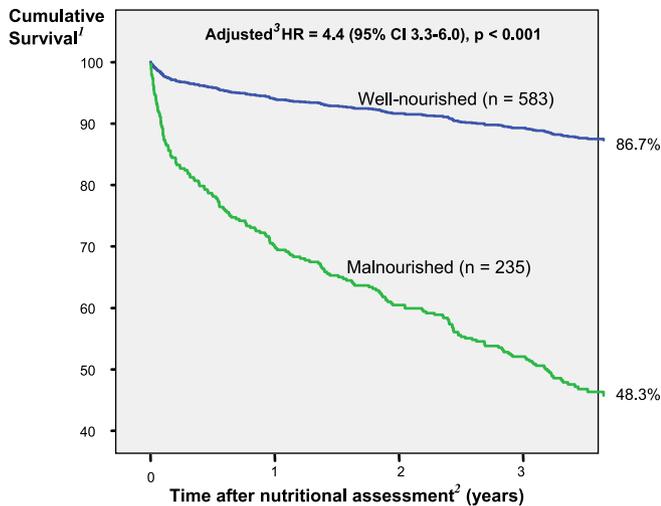
<sup>c</sup> Only 530 subjects could be matched for 95 DRGs.

<sup>d</sup> Adjusted for ethnicity, age, gender and matching for diagnosis-related group (DRG).

studies have controlled for the confounding effect of diagnosis on malnutrition outcomes or used national death register data to determine mortality outcomes. After controlling for the potential confounders of age, gender, ethnicity and DRG, we found that malnourished patients stayed in hospital on average two days longer and were almost twice as likely as well-nourished patients to be readmitted within 15 days of discharge. Malnutrition posed almost a four-fold and three-fold increase in risk of death at 1-year and 3-year follow-up, respectively.

Although previous studies have shown a prospective association between malnutrition and clinical outcomes, the confounding effect of disease and its complexity have seldom been taken into consideration.<sup>3,16</sup> It is widely agreed that disease and malnutrition are closely linked<sup>17</sup> and that disease may cause secondary malnutrition and vice-versa.<sup>18</sup> However, it is often argued that LOS, mortality and hospitalization costs are primarily determined by the patient's medical condition, and any association with malnutrition

is due to confounding.<sup>19</sup> For example, an oncology case may not live as long as a non-cancer case, regardless of nutritional status. Hence, in this study we accounted for the disease by firstly comparing the LOS and hospitalization cost of our participants with the average LOS and hospitalization cost for patients with similar DRG from within the hospital and with national average; and secondly by matching the DRG in a case–control design. As each DRG describes a cluster of patients with related diagnoses requiring similar investigations and incurring similar treatment costs, by matching by the DRG, we were able to show that malnutrition was indeed an independent predictor of length of hospital stay, readmission, hospitalization cost and mortality. The change in RR for the majority of outcomes seen after matching for DRG indicates that our approach has reduced confounding related to diagnosis and severity of illness. The very substantial changes in RR for mortality after matching confirm that, as is commonly claimed, some of the association between malnutrition and mortality is secondary to the



**Fig. 2.** Cumulative survival in well-nourished and malnourished patients ( $n = 818$ ). HR, Hazard ratio. <sup>1</sup>Survival and mortality data from Singapore Death Registry. <sup>2</sup>Assessment with Subjective Global Assessment within 48 h of hospital admission. <sup>3</sup>Adjusted for ethnicity, age and gender.

underlying effect of disease.<sup>18</sup> However, our results also show that there remains a three to four fold increase in risk, independent of underlying disease, across a wide range of DRG and independent of age and gender. The increase in  $p$  values reflects the smaller sample size available for the matched conditional regression analysis.

The current study found that malnourished patients stayed 1.5 times longer than well-nourished patients. Higher LOS in malnourished patients has been reported elsewhere.<sup>3,4</sup> In an Australian study of 819 patients in two teaching hospitals, malnutrition was also associated with 1.5 times longer LOS compared to well-nourished patients.<sup>3</sup>

The average cost of hospitalization was 24% higher for malnourished patients in this study. The effect of malnutrition on hospitalization cost was statistically significant when DRG was matched in the analysis. However the effect was not sustained when the results were further adjusted for ethnicity, age and gender. When the cost of hospitalization for each participant was compared with the hospital's average cost specific to the individual patient's DRG, the average cost difference for malnourished patients was three times higher than well-nourished patients. This means that malnourished patients incur higher hospital costs over and above those associated with their underlying illness. This echoes previous studies which linked malnutrition with higher hospitalization costs,<sup>16</sup> which are indirectly attributed to longer hospital stay,<sup>4,20</sup> increased use of hospital resources,<sup>4</sup> higher rate of re-admissions,<sup>20</sup> increased infection<sup>21</sup> or pressure ulcer and poor wound healing.<sup>22</sup> In a study by Correia and Waitzberg,<sup>4</sup> a malnourished patient incurred 61% increase in cost of hospitalization after controlling for the risk factors of cancer, infection, age above 60 years old and those undergoing clinical treatment.<sup>4</sup>

Our study found a 60% increase risk in readmissions within 15 days for malnourished patients when compared to well-nourished patients. However at 90 days and six months, even though there was statistical significance when readmissions were controlled for age, gender and ethnicity, the effect disappeared after matching for DRG. Planas et al.<sup>20</sup> showed that malnourished patients were one and half times more likely to be readmitted within 6 months of discharge from the hospital but the results were not controlled for any confounders.<sup>20</sup>

Only 10% of well-nourished patients died in the three years post discharge compared to almost 50% of those who were

malnourished. We found the relative risk of death for malnourished patients to be more than thrice that of well-nourished patients at 1-year and 2-year after being discharged from the hospital even after adjusting for confounders and matching for DRG. To the authors' knowledge, this is the only study that tracked the mortality of hospitalized patients for 3 years post-discharge using national death registry data and matching for DRG. A similar study that used national registry data found that the incidence of mortality in malnourished patients at 1 year was 30%, but did not control for confounders.<sup>3</sup> Other studies that associated malnutrition with long-term mortality have been mainly conducted on elderly participants.<sup>23–25</sup>

Given only 3/235 malnourished patients were coded as such in the DRG, it is evident that the majority of malnourished patients in our institution were either not recognized, or not accurately documented and coded for DRG. This scenario was also observed in Australia and Spain whereby only less than 2% of inpatients were coded as malnourished<sup>26,27</sup> in contrast to many studies reporting the prevalence of malnutrition in the hospitals to be more than 30%.<sup>1</sup> Accurate diagnosis and coding for malnutrition could potentially change the patient's DRG to one with a higher weighting and expected LOS, which would then correctly reflect the resources that the hospital spends on these patients, and in some countries would increase the amount of reimbursement the hospital received.<sup>28–30</sup>

The merits of this study are the large sample size recruited from a sequential sample, and the prospective tracking of hospitalization outcomes, including a 3-year national-record based mortality. Although several studies have used DRG data, none has used matching of cases to compare the hospitalization outcomes and cost between malnourished and well-nourished patients.<sup>10,30,31</sup> The study sample was representative of the hospital's admission profile (based on the study selection criteria and period) for gender and race but not for age. However, the difference of 2.6 years in age though statistically significant, is unlikely to be clinically significant or impact on the results. As this study was not able to monitor patients readmitted to other hospitals, readmission rates might be underestimated. However the likelihood of readmission to other hospitals is low because most patients prefer to come back to the hospital in their area, where their medical records are held and they attend post-discharge outpatient clinics. In addition, it is the national policy in Singapore for public ambulance to take emergency patients to the hospitals nearest to their home.

A limitation of this study is that we do not have the data on the number of study patients referred for treatment of malnutrition or the outcome of that treatment. At the time of this study (2006), access to inpatient dietetic services for assessment and treatment of malnutrition was solely through medical referral. Consequently, as was common in many hospitals at that time, it is likely that a substantial proportion of malnutrition risk was unrecognized and untreated.<sup>32,33</sup> In addition, outpatient resources to support malnourished patients were very limited. Indeed, providing an evidence-base to address these issues was a primary motivation for the study. It is possible that in a proportion of patients, nutrition status improved during or subsequent to their admission. However, such improvement is likely to have occurred in a small number of patients and would tend to attenuate associations between nutrition status at admission and clinical outcomes. Subsequent to this study, a comprehensive nutrition screening protocol and on-line dietetic referral system have been successfully implemented.<sup>34</sup>

## 5. Conclusions

Malnutrition is evident in up to one third of the patients admitted to a Singapore tertiary hospital and leads to substantial increases in

length of hospital stay, readmission rate, mortality and hospitalization cost when compared with well-nourished patients of similar diagnosis. As such, this study provides clear evidence that the adverse outcomes of malnutrition are not just a consequence of the disease process. Given the prevalence of malnutrition and its poor short and longer term outcomes, strategies are required to systematically identify and effectively prevent and treat malnutrition in the community, hospital and post-discharge. The effect of nutritional intervention in specialties with high prevalence of malnutrition and continuing care for malnourished patients in the community merits study.

### Statement of authorship

SLL conceptualized, designed and conducted the study, interpreted the data and wrote the manuscript. KCBO, WCL and MF provided significant advice on the design of the study and assisted in writing the manuscript. YHC performed statistical analysis and interpreted the data. LD interpreted the data, provided significant advice on the design of the study and assisted in writing the manuscript. All authors have made substantial contributions and approved the final manuscript.

### Conflict of interest

None of the authors had any conflict of interest related to the authorship of the submitted paper.

### Acknowledgements

The recruitment phase of this study was supported by the National Healthcare Group Small Innovative Grant (NHG-SIG).

We thank Ms Tan Ai Vee (Singapore Ministry of Health), Ms Cherie Tong (National University Hospital) and Ms Serene Wong (National University Hospital) for contributing part of the data collection and Dr Merrillyn Banks (Royal Brisbane & Women's Hospital) for her advice on DRG. We also thank Mr. Dennie Hsu from National University Hospital for his unwavering support for this study.

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