Morphomic Malnutrition Score: A Standardized Screening Tool for Severe Malnutrition in Adults

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Financial Disclosure: none declared.

Conflict of Interest: Stewart C Wang is listed as an inventor on US Patent #US 20140064583 A1. All other authors have none to declare.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jpen.1175.

Abstract:

Background: Granular diagnostic criteria for adult malnutrition are lacking. *Objective:* This study uses analytic morphomics to define the Morphomic Malnutrition Score (MMS), a robust screening tool for severe malnutrition. *Methods:* The study population (n=643) consisted of 2 cohorts: 1) 124 emergency department patients diagnosed with severe malnutrition by a registered dietitian (RD) and an available computed tomography (CT) scan within 2 days of RD evaluation, and 2) 519 adult kidney donor candidates to represent a healthy cohort. Body composition markers of muscle area and abdominal adiposity were measured from patient CT scans using analytic morphomic assessment, and then converted to sex- and age-adjusted percentiles using the Reference Analytic Morphomics Population (RAMP). RAMP consists of 6000 patients chosen to be representative of the general population. The combined cohort was then randomly divided into training (n=453) and validation (n=190) sets. MMS was derived using logistic regression. The model coefficients were transformed into a score, normalized from 0 to 10 (10 = most severe). *Results:* Severely-malnourished patients had lower amounts of muscle and fat than kidney donors, specifically for dorsal muscle group area at T12 ($p<0.001$), psoas muscle area at L4 ($p<0.001$), and subcutaneous fat area at L3 ($p<0.001$) – all parameters in MMS. MMS for severely-malnourished patients was higher than kidney donors (7.7±2.2 vs. 3.8±2.0, respectively; p-value<0.001). An MMS>6.1 was accurate in determining nutrition diagnosis (82.1% sensitivity; 88.3% specificity; 85.2% balanced accuracy). *Conclusions:* MMS provides an evidence-based, granular assessment to distinguish severely-malnourished adults from a healthy population.

Clinical Relevancy Statement

A malnutrition score using patient specific measures of body composition measured from CT scans provides a standardized screening criterion for severe malnutrition in adults. This novel screening tool utilizes robust surrogates for fat and muscle loss to produce a highly sensitive and specific test for detecting severe malnutrition. This work is clinically relevant for clinicians who recognize malnutrition as a risk factor for poor clinical outcomes and are aiming for a more efficient and reproducible method to screen for patients at true risk.

Introduction

Malnutrition is "an acute, subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition or undernutrition with or without inflammatory activity have led to a change in body composition and diminished function."[1] Malnutrition contributes to increased morbidity and mortality in hospitalized adult patients, including increased risk for developing nosocomial infection, pressure injury, and other complications.[2] Additionally, malnutrition is associated with longer hospital length of stay, increased hospital readmission, and increased healthcare costs.[2]

The incidence and prevalence of malnutrition differ between patient populations and healthcare institutions and vary based on the assessment tools used to identify malnutrition across care settings.[3-5] The incidence and prevalence of malnutrition are somewhat difficult to determine due to a lack of objective tests that can be used to definitively define and substantiate the malnutrition diagnosis.[3-5] Traditional malnutrition indices often fail to consider the extent to which inflammation and illness contribute to the development and progression of malnutrition.[3-5]

In 2012, the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Academy of Nutrition and Dietetics (Academy) jointly published consensus recommendations for the identification and documentation of adult malnutrition (undernutrition).[4] The consensus statement

established standardized criteria for severe and non-severe (moderate) malnutrition within six domains: energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid that may mask weight loss, and diminished functional status measured by handgrip strength. The recommendations outlined etiology-based definitions for malnutrition based on acute illness/injury, chronic disease, and starvation.[6]

The consensus statement aimed to alleviate compliance challenges in diagnosing and documenting adult malnutrition, using a standardized set of characteristics to generate consistent and reproducible results. These recommendations differ from traditional and historic definitions of malnutrition in identifying malnutrition based on etiology, considering multiple manifestations of undernutrition, and discriminating between non-severe and severe malnutrition.[4-5]

Differentiating between mild, moderate, and severe changes in body composition, as outlined in this paper, can be challenging and subject to interobserver bias. The accuracy and reliability of using muscle loss, fat loss, fluid accumulation, and handgrip strength to diagnose malnutrition may be confounded by other variables specific to a patient's case, condition, or overall treatment plan. Definitions of mild malnutrition were not included in this paper. Discrepancy remains between evidence-based best practice recommendations for malnutrition identification.[7] Overall, rigorous validation of the ASPEN/Academy consensus recommendations have not been published, and opportunities exist to develop methods that can objectively measure and quantify changes in body composition over time.

Analytic morphomics utilizes computed tomography (CT) scans to provide patient-specific body composition markers and may provide the standardization that is lacking in conventional diagnostics. Previous investigators have associated morphomic measurements of muscle and fat with mortality and complications across varying clinical populations.[8-13] We used analytic morphomics measures of muscle and fat to develop a Morphomic Malnutrition Score (MMS). We

hypothesize that the novel score can serve as a robust screening tool for severe malnutrition in adults.

Methods

Study Population

MMS is a regression coefficient-based score that was trained and validated on a retrospectively collected study population that consisted of both severely malnourished and normal patient populations (Figure 1).

The severely-malnourished cohort (n=124) included adult patients admitted from the Michigan Medicine emergency department (ED) between 2014 and 2016, who i) were administered a nutrition assessment by a registered dietitian (RD) during their encounter; ii) had an RD note with a nutrition diagnosis of severe malnutrition; and iii) had a CT scan within 2 days of RD evaluation that included complete T10 to L4 imaging. Prior to being included in the analysis, each patient's medical record was reviewed retrospectively by a Michigan Medicine RD to confirm that the clinical diagnosis of severe malnutrition satisfied current Michigan Medicine criteria. Malnutrition at Michigan Medicine was identified using a standard set of criteria. The criteria include characteristics for severe and non-severe (moderate) malnutrition in specific domains: weight loss over time, BMI, dietary inadequacies, and physical signs and symptoms (muscle loss and fat loss). Patients were classified as severely malnourished based on the identification of two or more characteristics from two different domains (Table 1). Patient age, sex, body mass index (BMI), and serum albumin were retrospectively collected from electronic medical records. BMI at the time of nutrition assessment was recorded by the RD; albumin was obtained proximal to RD evaluation date.

The normal cohort of adult kidney donor candidates (n=519) with an appropriate CT scan between 2000 and 2010 was selected to represent a clinically healthy population. Despite these

patients not having undergone an RD evaluation, the selection criteria for donor candidates[16-17] substantiated a nutrition diagnosis of “normal”. Patient age, sex, BMI, and serum albumin were retrospectively collected from electronic medical records closest to patient scan date; inclusion criteria were the same as well. Both cohorts were combined to form our study population (n=643).

Analytic Morphomics

In this study, cross-sectional areas of dorsal muscle group (DMA), total psoas muscle (TPA), and subcutaneous fat (SFA) were measured between the T10 through L4 vertebral levels to observe trends along the torso. The in-depth methodology on how these morphomic parameters were measured has been covered extensively in our previous works.[8-13] The CT image processing was performed with semi-automated algorithms in MATLAB 13.0 (MathWorks, Natick, MA).[14] Initially, scans were labeled at each vertebral level to provide anatomical landmarks for subsequent measurements. Cross-sectional area of L3 SFA, T12 DMA, and L4 TPA were selected from available measurements (Figure 2). The selection of these measures was based on previous works demonstrating the clinical relevance of these CT measures of fat and muscle in clinical populations. The area measures were then converted into sex- and age-matched percentiles based on Reference Analytic Morphomic Population (RAMP) growth curves.[15]

Reference Analytic Morphomic Population (RAMP)

RAMP consists of approximately 6,000 patients chosen to be representative of the general population and includes both healthy and unhealthy individuals. Chest, abdomen, and pelvis CT scans were collected from patients aged 1 to 91 years, at Michigan Medicine, who were scanned primarily for trauma indications. Quantile regression was performed on each morphomic factor versus age separately for males and females to generate growth curves corresponding to the 5th,

25th, 50th, 75th, and 95th percentiles (Figure 3). This detailed approach to body composition enables the conversion of individual CT body composition measures into age- and sex-matched percentiles. Any individual with a value above the 95th or below the 5th percentile was assigned to the 95th or 5th, respectively.

Statistical Methods

The study population was randomly split into a training set (n=453, 70%) and validation set (n=190, 30%). Univariate tests were performed on the training set to assess statistical significance between patient factors and nutrition diagnosis. T-tests were used to compare means of continuous variables; Fisher's exact test was used to compare proportions of binary variables between severely-malnourished and normal patients. Candidate parameters of the morphomics score were those shown to be associated with patient outcomes in previous studies[8-13] and demonstrated both a significant relationship and good discrimination ability with nutrition diagnosis as measured by p-value and area under the receiver operating characteristic curve (AUROC), respectively. Using the training set, a multivariable logistic regression model with nutrition diagnosis as the dependent variable was generated with the selected parameters using elastic net regularization to mitigate the risks of overfitting and collinearity.[18] To create a more intuitive evaluation metric, the final regression equation was transformed into a score (MMS) normalized to a range of 0.0 to 10.0, rounded to the nearest tenth, with 10.0 being the most severe degree of malnutrition.

The optimal MMS cutoff to distinguish severe malnutrition from a normal diagnosis was selected to maximize balanced accuracy $[(sensitivity + specificity)/2]$. The ability of this method to correctly classify patients as severely-malnourished or normal was assessed by comparing its sensitivity, specificity, and balanced accuracy in the validation set to those achieved by using the

clinical criteria of low BMI (<19 kg/m^2), and low albumin (<3.5 g/dL), using the RD diagnosis as the benchmark classification.

Statistical significance was determined by an alpha level of 0.05 and statistical analysis was performed in R version 3.4.2.[19]

This HIPAA-compliant study was approved by the Medical School Institutional Review Board at the University of Michigan. The requirement for informed consent was waived.

Results

Study Population

T-tests and Fisher's exacts test showed significant differences ($p<0.001$) between normal and severely-malnourished patients in all observed variables (Table 2). Furthermore, univariate AUC values showed better discriminating ability using body composition percentiles when compared against the clinical predictors of low BMI and low albumin. Compared to the normal cohort, the severely-malnourished cohort was older and a greater proportion were male, low BMI, and low albumin. The severely-malnourished cohort had lower percentiles across all measured vertebra levels for dorsal muscle group area, total psoas muscle area, and subcutaneous fat area.

Malnutrition Scoring and Classification

Multivariable logistic regression demonstrated that low muscle and fat area percentiles were associated with severe malnutrition (regression coefficients, L3 $SFA_{centile}$: -0.025; L4 $TPA_{centile}$: -0.020; T12 $DMA_{centile}$: -0.036). After normalization, the final MMS equation was:

$$MMS = 10.55 - (.0343 * SFA_{centile}) - (.0274 * TPA_{centile}) - (.0494 * DMA_{centile})$$

Patients with severe malnutrition had higher MMS than normal patients (7.7±2.2 vs. 3.8±2.0 respectively; p-value < 0.001). MMS had an AUROC of 0.89 in the training set and 0.94 in the validation set (Figure 4a). A cutoff score of MMS > 6.1 maximized balanced accuracy in the training set and was selected to distinguish between a nutrition diagnosis of severe and normal (Figure 4b). The distribution of scores in the training set and validation set were similar, however, the improved AUC was attributed to the paucity of low scores in the severely-malnourished cohort in the validation set (Figure 4c). In the validation set, low BMI had a sensitivity of 41.7%, specificity of 100%, and balanced accuracy of 70.8%; low albumin had a sensitivity of 63%, specificity of 100%, and balanced accuracy of 81.5%; MMS > 6.1 produced sensitivity of 82.1%, specificity of 88.3%, and balanced accuracy of 85.2% (Table 3).

Discussion

In this study, we present a novel standardized screening tool for severe malnutrition which utilizes sex- and age-adjusted reference percentiles of muscle area and abdominal adiposity incidentally imaged by CT performed for unrelated clinical indications. Lower percentiles of total psoas area, dorsal muscle group area, and subcutaneous fat area demonstrated a strong association with a severe malnutrition diagnosis. The multivariate model from which MMS was derived was internally validated and demonstrated improved accuracy in classifying severely-malnourished versus normal patients when compared to low BMI or low albumin alone. Scores for severely

malnourished patients were significantly higher than patients diagnosed as normal. Furthermore, the cutoff value for severe malnutrition generated a highly sensitive diagnostic test. Internal validation of the score cutoff generated the highest sensitivity when compared against indicators for low BMI and low serum albumin. Within this context, high sensitivity is most useful for MMS to avoid incorrectly refuting the presence of a potentially treatable risk factor like malnutrition.

The recent consensus statement from ASPEN and the Academy proposed a set of characteristics to improve malnutrition identification. Their criteria included intake, weight loss, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid, and diminished functional status to provide an etiology-based approach to make malnutrition diagnostics more reproducible and easier to define. BMI was among the parameters in the Michigan RD nutrition assessment. BMI is recognized as a widely used indicator for obesity and nutrition status; however, previous studies have shown that it is unable to discern lean mass content from body fat mass.[20] Albumin is another common diagnostic criteria that previous investigators – including ASPEN and the Academy – have demonstrated to be an insensitive and non-specific indicator of nutrition status.[4] Neither BMI nor albumin alone are reasonable screening criteria for severe malnutrition, however, they were the available criteria that were retrospectively available for all study patients. Because low BMI is included in the existing RD diagnosis, we would expect it to perform reasonably well. However, albumin is not included in the RD diagnosis and was only included due to its previous use by other investigators.[21,22] Like those investigators, we do not recommend using low albumin as an indicator of malnutrition in hospitalized patients as albumin is an acute phase reactant and plasma levels are decreased in a number of disease states unrelated to nutrition status such as injury, inflammation, sepsis, fluid shifts and anasarca, and synthetic liver dysfunction. MMS aims to inform the development of an objective screening protocol by providing a quantitative assessment of muscle and fat, independent of factors like BMI and albumin, to better characterize body changes caused by malnutrition.

There are limitations to this study. First, this is a retrospective study and is subject to biases of such methodology. Our study population was also from a single institution. While we cannot argue that it is representative of a general ED patient population, the opportunity to produce a novel diagnostic criterion for severe malnutrition using reproducible methods was deemed worthwhile to work within the shortcomings of our data. Our nutrition diagnosis of kidney donor candidates as "normal" has not been validated by clinicians or health centers outside of this work. Evaluation for kidney donation at Michigan Medicine is available to those who are genuinely willing to donate, physically fit, in good general health, and free from diabetes, cancer, kidney disease, and heart disease. The pre-donation evaluation includes assessment by a nephrologist, transplant surgeon, and a social worker, and candidates only receive a CT if they have completed their evaluation and were deemed an excellent candidate to donate a kidney. Classifying these successful candidates as nutritionally "normal" was a clinically-based decision that involved both the RD and the physicians. The exclusion of all other ED patients with a non-severe (e.g., moderate, none) nutrition diagnosis presents bias. However, the characteristics of severe malnutrition had the most objective criteria to substantiate the diagnosis. Furthermore, it was our objective to first assess whether our novel markers of muscle and fat could quantitatively distinguish a healthy patient from the severely-malnourished population.

Future works will focus on investigating clinical populations where malnutrition is prevalent and CT imaging is part of the treatment protocol. Calculating other populations' MMS and associating it with clinical outcomes can inform the link between malnutrition and poor outcomes. Patient claims data is also desirable in order to determine whether an MMS screen positive for severe malnutrition is associated with higher episode costs. MMS serves as a robust indicator of a widely–recognized risk factor that is not clearly defined, yet likely modifiable if administered the appropriate regimen. Furthermore, MMS utilizes patient-specific data measured from CT scans performed for other

medical indications, making implementation simple and scalable for screening to identify patients who would benefit from RD assessment and intervention for malnutrition.

Acknowledgments:

The authors would like to thank Caryn Boyd for her assistance in procuring Emergency Department raw data elements.

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Table 1
Michigan Medicine adult malnutrition diagnosis guidelines

		Malnutrition (Moderate)	Malnutrition (Severe, Protein-Calorie)
	ICD 10 Code	**E44.0**	**E43**
Domain	**Weight Loss**	Significant weight loss: 1-2% in 1 week 5% in 1 month 7.5% in 3 months 10% in 6 months 20% in 12 months	Severe weight loss: > 2% in 1 week > 5% in 1 month > 7.5% in 3 months > 10% in 6 months > 20% in 12 months
	BMI		BMI <18.5
	Dietary Inadequacies	>7 days with a nutrient intake of ≤ 75% of total estimated energy requirements *or* >7 days with a nutrient intake of ≤ 75% of baseline/usual intake	≥ 1 month with intake of ≤ 50% of total estimated energy requirement *or* ≥ 1 month with intake of ≤ 50% of baseline/usual intake
	Physical Findings	Mild loss of muscle mass Mild loss of subcutaneous fat	Moderate or severe loss of muscle mass Moderate or severe loss of subcutaneous fat Delayed wound healing
	Functional Status	N/A	Markedly reduced hand grip strength (>2 standard deviations below mean)

A minimum of 2 characteristics from 2 different domains is required for the diagnosis of malnutrition.

Clinical judgement should be used when using this table for the identification of malnutrition.

Table 2

Summary statistics comparing severely-malnourished and normal cohorts. Variables used in the malnutrition score in bold.

		Severely Malnourished			Normal				
Variable	**Vertebra**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**p-value**	**AUC**
Training Set									
Age (years)		96	62.0	14.3	357	40.8	11.6	<.001	0.87
Female		96	41.7%		357	58.3%		<.004	0.58
Albumin Low (< 3.5 g/dL)		93	52.7%		354	0.6%		<.001	0.76
BMI Low (< 19 kg/m^2)		86	24.4%		351	0.3%		<.001	0.38
Malnutrition Score		96	7.7	2.2	357	3.8	2.0	<.001	0.89
$DMA_{centile}$	T10	96	27.5	23.6	357	59.1	26.6	<.001	0.81
$DMA_{centile}$	T11	96	23.3	22.4	357	61.6	25.2	<.001	0.87
$DMA_{centile}$	***T12***	***96***	***21.9***	***23.7***	***357***	***59.6***	***24.8***	***<.001***	***0.87***
$DMA_{centile}$	L1	96	22.7	22.6	357	54.4	25.9	<.001	0.83
$TPA_{centile}$	***L4***	***96***	***27.3***	***24.1***	***357***	***58.3***	***26.6***	***<.001***	***0.81***
$SFA_{centile}$	T10	96	32.0	29.1	357	59.9	23.6	<.001	0.77
$SFA_{centile}$	T11	96	31.1	29.6	357	61.5	23.1	<.001	0.79
$SFA_{centile}$	T12	96	31.3	30.2	357	62.6	23.0	<.001	0.79
$SFA_{centile}$	L1	96	31.7	30.6	357	63.6	22.9	<.001	0.79
$SFA_{centile}$	L2	96	31.8	30.0	357	62.7	22.7	<.001	0.79
$SFA_{centile}$	***L3***	***96***	***30.7***	***28.8***	***357***	***62.0***	***22.7***	***<.001***	***0.80***
$SFA_{centile}$	L4	96	30.1	28.5	357	60.3	23.0	<.001	0.79
Validation Set									
Age		28	57.1	16.9	162	40.6	11.2	<.001	0.78
Female		28	54%		162	66%		0.208	0.56

Albumin Low (< 3.5 g/dL)		27	63%		157	0%		<.001	0.81
BMI Low (< 19 kg/m^2)		24	42%		159	0%		<.001	0.29
Malnutrition Score		28	8.1	1.9	162	3.5	2.0	<.001	0.94
$DMA_{centile}$	T10	28	26.8	28.2	162	63.5	23.6	<.001	0.84
$DMA_{centile}$	T11	28	22.8	26.7	162	66.0	24.3	<.001	0.88
$DMA_{centile}$	***T12***	***28***	***22.8***	***27.5***	***162***	***63.7***	***24.7***	***<.001***	***0.87***
$DMA_{centile}$	L1	28	25.5	29.9	162	58.1	25.1	<.001	0.81
$TPA_{centile}$	***L4***	***28***	***22.5***	***21.8***	***162***	***63.5***	***24.6***	***<.001***	***0.89***
$SFA_{centile}$	T10	28	21.0	15.3	162	61.4	23.3	<.001	0.91
$SFA_{centile}$	T11	28	20.6	15.7	162	62.1	22.4	<.001	0.92
$SFA_{centile}$	T12	28	21.3	15.9	162	63.5	21.8	<.001	0.93
$SFA_{centile}$	L1	28	21.1	16.2	162	64.1	21.0	<.001	0.94
$SFA_{centile}$	L2	28	20.2	15.3	162	64.3	20.6	<.001	0.95
$SFA_{centile}$	***L3***	***28***	***18.6***	***14.3***	***162***	***63.4***	***21.0***	***<.001***	***0.95***
$SFA_{centile}$	L4	28	18.1	14.3	162	61.4	22.2	<.001	0.94

Table 3

Performance of high malnutrition score, low albumin, and low BMI in classifying patients as severely-malnourished vs. RD diagnosis.

Dataset	Model	Specificity	Sensitivity	Balanced Accuracy
Training	High MMS (> 6.1)	85.7%	80.2%	83.0%
	Low Albumin (< 3.5 g/dL)	99.4%	52.7%	76.1%
	Low BMI (< 19 kg/m2)	99.7%	24.4%	62.1%
Validation	High MMS (> 6.1)	88.3%	82.1%	85.2%
	Low Albumin (< 3.5 g/dL)	100.0%	63.0%	81.5%
	Low BMI (< 19 kg/m2)	100.0%	41.7%	70.8%