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Original article

Performance of CT-based low skeletal muscle index, low mean muscle attenuation, and bioelectric impedance derived low phase angle in the detection of an increased risk of nutrition related mortality

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SUMMARY

Background & aims: The aim of this study was to evaluate in a head to head comparison the performance of bioimpedance derived low phase angle (PA), CT-based low skeletal muscle index (SMI) and low mean muscle attenuation (MA), and Pandora Score (PS) to detect an increased nutrition related mortality in hospitalized patients.

Methods: A total of 7736 patients were hospitalized in Dessau community hospital (Nov 11, 2016–Feb 05, 2017). In 227/7736 patients an abdominal CT scan was obtained and low values (below threshold) of skeletal muscle index (SMI) and mean muscle attenuation (MA) were obtained at L3 level using Slice-O-Matic. In 180/227 patients, malnutrition screening (NRS-2002 $\geq$ 3), determination of low PA (<5th percentile) and calculation of 30-day mortality risk (PS $\geq$ 5%) were done within 6 days after the CT scan.

Results: PA was low in 116 (64%), SMI was low in 95 (53%), and MA was below threshold in 137 (77%) patients. Using hospital mortality (8.3%) as a gold standard, low SMI, low MA, or low PA showed high sensitivity (SMI 93.3%; MA 86.7%; PA 86.7%) and high negative predictive (NPV) values (SMI 98.9%; MA 95.3%; PA 96.9%) and improved specificity (NRS + SMI 65.5%; NRS + MA 50.3%; NRS + PA 50.3%) when combined with the criterion NRS $\geq$ 3. Using hospital mortality as a gold standard, a PS $\geq$ 36 (predicted mortality $\geq$ 5%) showed a sensitivity of 73.3%, a specificity of 62.2% and an NPV of 96.4%. PS predicted mortality was $\geq$5% in 70 (39%) patients and was higher (median 5.2%; IQR: 2.8; 11.8 vs 1.7%; IQR: 1.0; 2.8; $p < 0.001$) in patients with a low PA and this was also observed for low vs normal SMI (median 5.7%; IQR: 2.6; 11.1 vs 2.7%; IQR:1.4;5.5; $p < 0.001$) but not for low vs normal MA (median 3.9%; IQR: 2.1; 8.8 vs 3.4%; IQR: 2.0; 8.1; ns).

Conclusion: Determination of phase angle < 5th percentile is a convenient non-invasive and inexpensive bedside method with high sensitivity and a high negative predictive value to detect patients at risk of nutrition related mortality with a performance comparable to CT derived skeletal muscle index or mean muscle attenuation.

1. Introduction

Malnutrition has been characterized as a subacute or chronic state of nutrition in which a combination of varying degrees of over- or undernutrition and inflammatory activity have led to a change in body composition and diminished function [1]. The extent of changes in body composition cannot reliably be assessed by clinical examination and requires appropriate technical methods, particularly in overweight or obese subjects [2]. Loss of muscle mass can occur in the course of diseases such as malignancy, inflammatory diseases, endocrine disorders and is associated with functional impairment [3,4], an increased risk of fractures and falls [3], prolonged hospital stay [5], nosocomial infections [6] and increased mortality [2,7–9].

The use of CT images to objectively measure skeletal muscle mass and an increased proportion of inter- and intramuscular fat [2,8,10] has triggered an increasing interest in muscle depletion,

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also termed sarcopenia, not only in the geriatric community, but also in the field of oncology [2], intensive care medicine [9] or hepatology and transplantation [7,11,12], to mention only a few. The acquisition of CT images, however, involves the use of ionizing radiation and high cost precluding its widespread use as a primary tool to determine skeletal muscle mass and muscle quality [8].

Bioimpedance analysis (BIA) is a validated diagnostic tool for the determination of body cell mass [13] and BIA based determination of phase angle (PA) has been shown a useful tool to identify patients with a poor survival [14,15]. PA as determined by BIA can be viewed as an integral measure of (muscle) cell mass and function and serves as a general marker of health [16,17]. A low PA is indicative of an increased mortality risk [14,15].

In a prospective study, we sought to evaluate the diagnostic value of sarcopenia assessed by CT derived skeletal muscle index (SMI), mean muscle attenuation (MA), and BIA derived PA in the identification of malnourished patients carrying the risk of an increased hospital mortality in a head to head comparison. Furthermore, we sought to evaluate the agreement in risk prediction between SMI, MA, or PA on the one hand and nutrition related predicted 30-day mortality risk using the Pandora Score (PS) [18]. PS is a patient- and nutrition derived simple, robust scoring system for a general population of hospitalized patients to be used for risk stratification and is based on 7 indicators with 31 item classes on a scale from 0 to 75 points. The indicators are age (0–17 points), nutrient intake (0–12 points), mobility (0–11 points), hydration status (0–10 points), BMI (0–9 points), cancer (9 points) and main disease group (0–7 points) [18].

2. Materials and methods

In the period from 11.11.2016 to 05.02.2017, 227 consecutive patients underwent abdominal computer tomography (CT) for clinical and diagnostic indications independent from the present study. Three of the 227 eligible patients withdrew consent and the remaining 224 were entered in a prospective study evaluating SMI, MA, PA and PS mortality risk using hospital mortality as a gold standard. In this period, a total of 7736 patients were hospitalized at Dessau Community Hospital.

In 180/224 patients, nutrition risk screening by NRS-2002 [19], BIA measurement [13] and an interview to obtain the information relevant for the calculation of PS mortality risk were done within 6 days after the CT. At the time of the CT 145 patients were on a general ward, 20 were in casualty department and 15 were on ICU. Informed consent was obtained from all patients. 44 patients were excluded from the analysis for the following reasons: 7 patients had a cardiac pacemaker or an implanted defibrillator; 4 patients had limb amputations or severe ulcers of the extremities; 3 patients died within 6 days after the CT, and 30 patients because they were discharged before data acquisition could completed. In order to characterize the patient sample, all patients were categorized as to ICD-10 disease group on the basis of their main diagnosis at discharge (Table 1).

A list of all patients in whom an abdominal CT was done was provided on a daily basis. Nutrition risk score NRS-2002 and the interview for collection of data relevant for the calculation of PS mortality risk [18] were obtained by a single experienced person (MV). All BIA measurements were done by the same person (MV) in a standardized fashion, placing electrodes on the dominant side [13] using a phase sensitive device NutriBox (Data Input GmbH, Darmstadt, Germany) and BIANOSTIC AT-electrodes (Data Input GmbH, Darmstadt, Germany). Coefficient of variation was 1.3%. From these measurements PA was obtained and categorized as low PA when found to be below the 5th percentile using age, gender, and BMI matched reference values of Bosy-Westphal et al. [17] based on a Central European database comprising 214732 adults. All data was entered into the electronic patient file immediately after it was obtained. Patients with a PS in the range of the 9th and 10th deciles were considered to have an increased PS mortality risk of $\geq$5% [18].

CT-based determination of the muscle mass was done using Slice-O-Matic® (Version 5.0, TomoVision, Montreal, Canada) on images at mid-L3-level. For this purpose, the appropriate slice was selected (MV, CB) and saved for later evaluation. The evaluation software Slice-O-Matic identifies muscle tissue by setting the Hounsfield units (HU) to a range of −29 to +150 [2] also providing the mean muscle attenuation (MA) given in HU. The coefficients of variation for skeletal muscle area were 5.0% and for muscle attenuation 4.8%. For further evaluation, the skeletal muscle area was normalized to the patient's stature by calculation of the skeletal muscle index (SMI, cm^2/m^2). Gender and BMI matched cut-off values for low SMI and low MA were used as proposed by Martin et al [8].

Statistical analysis was done using SPSS Statistics 22 (IBM, Armonk, USA), Excel 2007 (Microsoft, Redmond, USA) and the Excel Add-In XLStat (Addinsoft, New York, USA). Mean values and standard deviations as well as medians and interquartile ranges were calculated. In addition, levels of significance were determined by means of the Mann-Whitney-U-test. Furthermore, sensitivity and specificity as well as positive and negative predictive values were calculated using hospital mortality as the reference. Kappa statistics were used to analyze agreement between low PA (<5th percentile), low SMI (below cutoff according to Martin et al. [8], or low MA (below cutoff according to Martin et al. [8]) and PS.

3. Results

All 180 patients were classified according to the ICD-10 on the basis of their main diagnosis at discharge (Table 1) and three diagnosis groups emerged dominant: malignancies (C00-D48)

Table 1
Main discharge diagnoses of 180 patients according to ICD-10 diagnostic group.

Classification of diseases	ICD-10	Number of cases (n = 180)	Proportion of cases [%]
Infectious and parasitic diseases	A00 - B99	1	0.6
Neoplasms	C00 - D48	65	36.1
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50 - D89	2	1.1
Endocrine, nutritional and metabolic diseases	E00 - E90	4	2.2
Mental and behavioural disorders	F00 - F99	1	0.6
Diseases of the circulatory system	I00 - I99	12	6.7
Diseases of the respiratory system	J00 - J99	2	1.1
Diseases of the digestive system	K00 - K93	50	27.8
Diseases of the skin and subcutaneous tissue	L00 - L99	1	0.6
Diseases of the musculoskeletal system and connective tissue	M00 - M99	4	2.2
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	R00 - R99	8	4.4
Injury, poisoning and certain other consequences of external causes	S00 - T98	30	16.7

amounting to 36%, diseases of the digestive system (K00-K93, 28%) ranking second, and injuries, poisoning and certain other consequences of external causes (S00-T98, 17%) ranking third. Demographic, predicted mortality and body composition data are given in Table 2 for men and women separately. In 116 (64%) patients PA was low (<5th percentile). SMI was in the sarcopenic range in 95 (53%) patients whereas muscle attenuation was below normal in 138 (77%) patients. NRS-2002 was ≥3 in 105 (58%) of patients.

Hospital mortality of our cohort was 8.3% which is three times higher than overall mortality (2.7%) in our hospital. Median PS mortality risk (PS median 33 points; IQR: 26; 42) amounted to 3.8% (IQR: 1.9; 9.3). Low SMI showed a high sensitivity (93.3%) and a high negative predictive value (98.9%) (Table 3) in identifying patients with a higher mortality. Low MA showed a similar performance with a high sensitivity (86.7%) and a high negative predictive value (95.3%) (Table 3). Likewise, low PA (<5th percentile) exhibited a high sensitivity (86.7%) and a high negative predictive value (96.9%) in identifying patients with a higher mortality (Table 3).

We were interested to explore whether the performance in predicting mortality could be improved when a single criterion low PA (<5^{th} percentile), or low SMI, or low MA was combined with NRS 2002 ≥ 3 as a second mandatory criterion. We observed a higher specificity of 65.5% and 50.3% (data not shown) for the combination of low SMI and NRS ≥ 3 and low MA and NRS ≥ 3, respectively. Also, specificity was improved to 50.3% (data not shown) for the combination of low PA and NRS ≥ 3.

Using hospital mortality as a gold standard, a PS cutoff ≥36 points (predicted mortality ≥ 5%) showed a sensitivity of 73.3%, a specificity of 62.2% and a negative predictive value of 96.4% (Table 3). There was moderate agreement (kappa 0.43) between PS mortality risk and the combined criteria PA < 5th percentile and NRS ≥ 3. Agreement was weak between PS mortality risk and PA< 5th percentile alone (kappa 0.33), or low SMI (kappa 0.33), or low SMI combined with NRS ≥ 3 (kappa 0.38), or low MA (kappa 0.19), or low MA combined with NRS ≥ 3 (kappa 0.39).

The proportion of patients in the various item classes of PS is given in Table 4 showing dehydration in 25 (13.9%), normal fluid status in 91 (50.6%), or overhydration in 64 (35.6%) of our patient sample. In our cohort, 70 (39%) patients were found to have a high PS mortality risk of ≥5% and 110 (61%) patients had a PS mortality risk < 5%. Patients with a low PA (<5^{th} percentile) showed a significantly higher PS mortality risk than those with a PA ≥ 5^{th} percentile (median 5.2; IQR: 2.8; 11.8% vs. median 1.7; IQR: 1.0; 2.8%; p < 0.001). Likewise, PS mortality risk was significantly higher in patients with a low vs. normal SMI (median 5.7; IQR: 2.6; 11.1% vs median 2.7; IQR: 1.4; 5.5%; p < 0.001). Surprisingly, we found no difference in PS mortality risk for patients with a low or a normal MA (median 3.9; IQR: 2.1; 8.8% vs median 3.4 (IQR: 2.0; 8.1%, p = 0.85).

Table 2
Demographic, Pandora Score, PS predicted mortality and body composition data of study population according to gender.

	Women (n = 88)	Men (n = 92)
Age [y]	69 (61–78)	67 (58–76)
Body-Mass-Index [kg/m^2]	24.7 (21.6–30.3)	25.9 (22.4–30.1)
Pandora Point Value	34 (27–44)	31 (24–39)
Predicted Mortality [%]	4.0 (2.1–11.3)	3.0 (1.5–7.0)
PA [°]	4.3 (3.5–5.0)	4.9 (3.6–5.7)
PA in subgroup low PA [°][b]	4.0 (3.0–4.4)	3.9 (3.2–4.4)
SMI [cm^2/m^2]	40.1 (36.8–46.5)	48.8 (44.1–54.6)[a]
SMI in subgroup low SMI [cm^2/m^2][c]	37.1 (33.6–39.0)	45.8 (42.6–50.1)[a]
MA [HU]	26.5 (21.4–33.8)	29.9 (22.3–36.3)
MA in subgroup low MA low [HU][c]	26.2 (21.8–34.1)	29.7 (23.6–35.4)

Values are median (interquartile ranges).
[a] p < 0.001 for women vs. men; all other comparisons not significant.
[b] PA < 5^{th} percentile according to Bosy-Westphal et al. [17] (66 women, 50 men).
[c] SMI low (48 women, 47 men) and MA low (70 women, 68 men) as classified to gender and BMI matched cutoff values according to Martin et al. [8]. MA = mean muscle attenuation, PA = phase angle, SMI = skeletal muscle index.

4. Discussion

In this prospective study, we undertook a head to head comparison of CT derived low skeletal muscle index (SMI), low muscle attenuation (MA) and bioimpedance derived low phase angle (PA < 5^{th} percentile) as objective measures of impaired body composition carrying an increased mortality risk. Our main findings were a high sensitivity and a high negative predictive value for low SMI, low MA, or PA < 5^{th} percentile using hospital mortality as gold standard. When either low SMI, low MA or low PA were combined with NRS ≥3 as a second criterion specificity was improved for low SMI, low MA, or low PA. Also, we found a high sensitivity and a high negative predictive value for PS mortality risk using hospital mortality as gold standard. Agreement was moderate between PS and PA < 5^{th} percentile combined with NRS ≥3 but only fair for low PA, low SMI, low SMI plus NRS ≥3, low MA or low MA plus NRS ≥3.

Our findings reflect the real-world situation in a community hospital serving 30000 in-patients per year. Patients were entered in this study purely on the basis that an abdominal CT scan was done as requested by the caring physicians, none of whom were involved in this study. Therefore, our study cohort was not intended to serve as a representative sample for all patients served by our hospital. Not surprisingly, the availability of an abdominal CT resulted in the selection of more severely ill patients with a mortality three times higher than overall mortality of our hospital. One third of our patients were oncologic with gastrointestinal disorders and injuries ranking second and third. This disease spectrum with gastrointestinal and oncologic patients accounting for 64% of our cohort and the fact that 58% had an NRS-2002 ≥ 3 indicate a high risk for disease related malnutrition in our cohort. All data regarding NRS, BIA measurement and PS was obtained and entered immediately into the electronic patient file by the same person within six days after the CT scan was done. Analyses of CT images and determination of SMI and MA were done only after all nutrition related data had been entered into the electronic patient file.

Table 3
Performance of skeletal muskel index (SMI), mean muscle attenuation (MA), phase angle (PA) and Pandora Score in identifying patients with a higher mortality.

	Sensitivity [%]	Specificity [%]	Positive predictive value [%]	Negative predictive value [%]
SMI low[a]	93.3	53.3	15.4	98.9
MA low[a]	86.7	24.8	9.4	95.3
PA < 5th percentile[b]	86.7	37.6	11.2	96.9
Pandora Score ≥ 36[c]	73.3	62.2	15.7	96.4

[a] SMI low and MA low as classified by gender and BMI matched cutoff values according to Martin et al. [8].
[b] PA < 5^{th} percentile as classified by gender and BMI matched cutoff values according to Bosy-Westphal et al. [17].
[c] Pandora Score ≥36 cutoff values resulting to predicted mortality ≥5%.

Table 4
Number and frequency of Pandora Score item classes.

Indicator	Study Cohort n = 180	Study Cohort [%]	Pandora Score Validation Sample [%]
1. Age [years]			
<40	8	4.4	12.8
40–50	16	8.9	10.0
50–60	29	16.1	15.7
60–70	50	27.8	19.5
70–80	53	29.4	20.7
80–90	22	12.2	17.1
>90	2	1.1	4.2
2. BMI [kg/m^2]			
<18.5	6	3.3	8.2
18.5–25	77	42.8	42.6
25–30	52	28.9	29.2
30–35	29	16.1	12.7
35–40	10	5.6	4.6
>40	6	3.3	2.7
3. Can you walk?			
without assistance	101	56.1	59.7
only with assistance	54	30.0	27.5
I stay in bed	25	13.9	12.8
4. What did you eat today?			
All	33	18.3	40.2
Half	83	46.1	26.1
Quarter	29	16.1	15.3
Nothing, allowed	2	1.1	9.6
Nothing, not allowed	33	18.3	8.8
5. Speciality of Ward			
Internal	96	53.3	34.8
Surgery	62	34.4	48.6
Geriatrics	1	0.6	8.0
Neurology	0	0.0	1.2
Others	21	11.7	7.4
6. Diseased Organ			
Cancer	64	35.6	17.6
7. Fluid Status			
Dehydrated	25	13.9	8.6
Overhydrated	64	35.6	12.2
Normal	91	50.6	79.2

Number and frequency of the single Pandora Score item classes are given for the study cohort and for comparison from Pandora Score validation sample [18] as published.

As a gold standard we used hospital mortality as the most relevant and clear-cut outcome variable of our patients' hospital stay. In our study we could evaluate the performance of the PS as the world's first nutritional score predicting life expectancy of hospitalized patients over the next 30 days [18]. This tool is of particular interest for clinical practice because it is based on readily available patient data and can be implemented by medical staff without specialty training in nutrition or the need for technical equipment. When compared with the frequency of item classes in the PS validation sample [18] our cohort is characterized by a higher proportion of patients not eating adequately, more patients on internal medicine wards, twice as many cancer patients, and less patients with a normal hydration status. This profile is indicative of a higher nutrition related mortality risk which is borne out by the observed hospital mortality of our cohort. We chose to consider a PS $\geq$ 9th decile of the original publication to identify patients with an increased predicted 30d-mortality and this was equivalent to a PS predicted mortality $\geq$5% [18]. In that approach PS proved to be a helpful and sensitive tool to separate patients with a low from those with a higher mortality. To our knowledge this is the first validation of the PS independent from its original description.

For the CT-based determination of skeletal muscle mass and muscle quality, a specialized software was used to determine skeletal muscle area and skeletal muscle index (SMI) as described by Prado et al. [2]. SMI obtained at the level of L3 has been shown representative of total body muscle mass [10,20–22]. This method has the advantage that already available CT scans can be analyzed retrospectively. The adequate evaluation of the CT images, however, requires expert medical knowledge and can only be carried out by trained staff. The invasive nature due to the use of ionizing radiation and high cost preclude the use of CT-based SMI and MA for the routine assessment of nutritional status. Furthermore, the CT-based SMI is a valid measure of muscle mass only and it should be kept in mind that impaired muscle function also is an important feature of sarcopenia [23] and loss of function may be even more relevant for the patients' prognosis [11,24]. Therefore, the evaluation of MA as a measure of muscle quality has been proposed as a more powerful indicator than muscle mass.

In the present study, 53% of our patients were sarcopenic according to the criteria used by Martin et al. [8] and there was a clear inverse correlation between SMI and mortality risk. This observation is in good agreement with the literature reporting an association between low muscle mass and increased mortality in a variety of conditions [2,7,9,12]. In our cohort, only SMI or low SMI median values differed significantly between women and men but not PA, low PA, MA or low MA values. This lack of gender difference is also evident in the MA threshold values by Martin et al. [8]. Regarding PA one may speculate that the impact of cell function could be more influential than that of cell mass for which a more pronounced gender difference would be expected. Some workers reported that low MA was a more powerful indicator of shorter survival [11,25]. In our cohort, however, looking at survival the performance of low SMI or low MA in terms of excellent sensitivity and negative predictive values were not different.

BIA is a simple, fast, and non-invasive method for body composition analysis providing a measure of body cell mass [13] or a comprehensive assessment of cell mass and cell function using PA as readout [17]. In the present study, PA < 5th percentile of an age, gender, and BMI matched Central European reference population

(214732 adults) was used as diagnostic criterion [17]. The availability of such a reference data base puts PA on solid ground, whereas threshold values for SMI or MA are based on much smaller samples obtained from sick individuals. Low PA has been shown to be a powerful predictor of mortality [17,26]. In good agreement, in our cohort low PA proved to be a highly sensitive tool for identifying patients with a low as opposed to patients with a higher mortality with a negative predictive value of 96.9%. PA is not only a marker of amount and quality of soft tissue mass but also of hydration status [27,28] and, therefore, has been considered a useful indicator of nutritional status [27,29,30]. Disease related malnutrition is associated with an excess in extracellular water and this fact is recognized by including overhydration as a relevant item in tools like Subjective Global Assessment (SGA) [31] or Pandora Score [18]. Moreover, mobilization of overhydration is a reliable indicator of successful nutrition support [32]. Therefore, the presence of overhydration in 36% in our cohort is not surprising considering the fact that 58% had an NRS-2002 $\geq$ 3 and a 30–50% prevalence rate of hospital malnutrition for gastrointestinal and oncologic patients [33] who accounted for 64% of our cohort. In clinical practice, screening would identify a patient at malnutrition risk by an NRS $\geq$3 and thus necessitate a subsequent assessment of nutritional status as proposed by ESPEN [34]. We therefore evaluated the performance of such an approach by combining PA < 5^{th} percentile with NRS $\geq$3 yielding improved specificity for predicting mortality from 24.8% to 50.3%. This combination also showed a good agreement with PS predicted mortality.

There are limitations to our study. In our cohort, the prevalence values of a low PA (64%), low SMI (53%) or low MA (77%) were high and, most likely, this is due to the fact that only patients who were considered so sick that an abdominal CT was requested were included in our study causing a selection bias of more severely ill patients. This selection, however, is unavoidable when the aim of a study is a head to head comparison with CT based SMI or MA. In our view, it would be unethical to expose a cohort of unselected patients to ionizing radiation just for such a head to head comparison. The selection of more severely ill patients is reflected by the mortality of our cohort 3 times higher than contemporary overall hospital mortality. A considerable number of patients had to be excluded from the study mainly due to the fact that they were discharged within 5 days after the CT was done and study staff was not available on German Christmas and New Year holidays.

In conclusion, phase angle <5^{th} percentile is a convenient non-invasive inexpensive bedside method with a high sensitivity and a high negative predictive value to detect patients at risk of nutrition related mortality. The sequential approach screening all hospitalized patients and measuring phase angle in those screened positive appears well suited to focus resources for nutritional intervention on patients with an increased mortality risk.

Conflict of interest

None declared.

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