Università Campus Bio-Medico di Roma

Corso di dottorato di ricerca in
Scienze Biomediche Integrate e Bioetica
XXXVIII ciclo a.a. 2022-2023

Role of malnutrition on clinical outcomes of patients with hypercapnic respiratory failure treated with non-invasive mechanical ventilation

Sonia Zotti

Coordinatore e Tutore
Prof. Raffaele Antonelli Incalzi

28 Febbraio 2026

Acknowledgements

My deepest gratitude goes to my family and to Dino, without whom I would not have been able to achieve this further milestone. They have always believed in me more than I believed in myself. They supported me throughout the pursuit of this PhD and stood by me during the most demanding and intense periods of work.

I would also like to thank those who did not believe in me, as they pushed me to strive harder and continuously improve. They are the ones who challenge you, who encourage you to question yourself, to study, and to grow every single day.

I am sincerely grateful to the colleagues and Professors of my School of Specialization, who contributed to my training and allowed me to become the physician-researcher I am today.

I also thank the new colleagues who gave me the opportunity to challenge myself in a new professional environment and who continue to support my growth.

Finally, to my son Lorenzo, who has transformed my life. I wish for him to always remain curious and hungry for knowledge, and to never stop believing in research as I have done. Without research, medicine would never have achieved the extraordinary discoveries that shape our present.

Table of Contents

Introduction

Malnutrition is defined as a state of imbalance between nutrient intake or uptake and physiological needs, resulting in altered body composition, reduced physical and mental function, and impaired clinical outcomes.[1] It encompasses both deficiencies (undernutrition), excesses (overnutrition), and imbalances of energy or nutrients.[1] Undernutrition is a specific subtype of malnutrition characterized by insufficient intake or assimilation of energy and nutrients, leading to loss of fat-free mass, muscle wasting, and functional decline.[1] Epidemiological data indicate that the prevalence of malnutrition in hospitalized adults ranges from 20% to 50% at admission, with further nutritional deterioration occurring during hospitalization; hospital-acquired malnutrition affects up to 65% of inpatients, especially when assessed prospectively.[2-4] In older populations, malnutrition prevalence is approximately 3–10% among community-dwelling adults, 20–40% in hospital inpatients, and up to 50% in nursing home or long-term care residents, depending on the diagnostic criteria and care setting.[5]

Undernutrition is associated with increased length of hospital stay and higher mortality in patients with respiratory failure across all age groups.[1] In critically ill adults, including those with acute respiratory failure and community-acquired pneumonia, malnutrition is linked to longer hospital and ICU stays, increased need for mechanical ventilation, and higher odds of in-hospital death.[5-7] For example, severe malnutrition in ICU patients is associated with a median hospital stay more than twice as long and an odds ratio for mortality of 2.78 compared to well-nourished patients.[4]

In older adults, malnutrition—quantified by tools such as the Geriatric Nutritional Risk Index (GNRI) and Mini Nutritional Assessment Short-Form (MNA-SF)—is an independent predictor of prolonged hospitalization and in-hospital mortality, with hazard ratios for death ranging from 1.89 to 2.45 and significant increases in hospital and ICU length of stay.[8-12] The impact is most pronounced in those aged 65–79 years and in patients with fewer comorbidities.[5] Thus, across all age groups, early identification and intervention for malnutrition are essential to mitigate these adverse outcomes.[13-15] Similarly, malnutrition is strongly associated with increased risk and severity of respiratory failure.[16-17] The relationship is multifactorial: malnutrition impairs respiratory muscle strength, particularly the expiratory muscles, which reduces effective ventilation and cough, predisposing to atelectasis and infection.[17] It also leads to structural changes in the lung parenchyma, including reduced surfactant production, decreased elastic fiber content, and increased susceptibility to edema and atelectasis, all of which compromise gas exchange and lung mechanics.[18] Indeed, in chronic respiratory diseases such as COPD, malnutrition correlates with worsened lung function, increased exacerbations, and higher mortality due to an impairment of the immune function and the ability to clear pulmonary infections that further extend the risk of respiratory compromise.[19-21] As a result, the highest-risk groups for developing respiratory failure in consequence of malnutrition are those with advanced age and chronic or neuromuscular respiratory conditions, especially when compounded by an acute illness or hospitalization.[22-25] Age increases susceptibility to malnutrition-induced respiratory failure due to cumulative physiological decline, increased disease burden, and impaired compensatory mechanisms.[1,26] Sarcopenia, reduced appetite, impaired sensory swallowing, and chronic low-grade inflammation are physiological changes that drive catabolic processes and impair nutritional status.[26-27] The so-called “anorexia of aging,” characterized by decreased appetite and early satiety, further contributes to reduced energy intake. Polypharmacy may alter taste perception, gastrointestinal function, and overall nutritional balance. The “inflammaging”, persistent inflammation in advanced age and chronic disease, promotes catabolism and muscle wasting. Additionally, functional impairment and disability can limit access to food and the ability to prepare or consume adequate meals. These factors create a vicious cycle of nutritional decline, reduced muscle mass, and increased vulnerability to acute stressors such as respiratory failure. Indeed, these mechanisms make older adults more susceptible to respiratory failure during acute illness or exacerbations of chronic disease, particularly those in hospitals or nursing homes.[28-29] Therefore, monitoring strategies for early detection of malnutrition in patients with respiratory failure remain a critical issue.

The Global Leadership Initiative on Malnutrition (GLIM) provides a consensus-based diagnostic framework for adult malnutrition requiring at least one phenotypic and one etiologic criterion following nutritional risk screening.[30-31] The three phenotypic criteria are unintentional weight loss, low body-mass index (BMI), and reduced muscle mass (often estimated by calf circumference when advanced body composition tools are unavailable); the two etiologic criteria are decreased food intake or assimilation and high disease burden, indicated by persistent or recurrent inflammation. Severity is graded as moderate or severe based on the extent of phenotypic abnormalities. This approach is validated for prognostic value and is recommended for systematic assessment in hospitalized adults, including those with respiratory failure.[1,31] In patients with respiratory failure, the GLIM criteria are applied after initial risk screening with a sensitive tool. If screening suggests risk, clinicians assess phenotypic and etiologic features. In the context of respiratory failure, this approach is particularly relevant due to the high prevalence of inflammation and catabolic stress in these patients.[32-34] For adults**,** validated screening tools such as the Malnutrition Universal Screening Tool (MUST), Nutritional Risk Screening 2002 (NRS-2002), Simplified Nutrition Assessment Questionnaire (SNAQ), and Malnutrition Screening Tool (MST) are recommended in hospital settings.[1,34] These tools assess recent weight loss, BMI, appetite changes, and disease burden. For older adults**,** the Mini Nutritional Assessment–Short Form (MNA-SF) is the better validated and most widely used tool, demonstrating strong prognostic value for acute respiratory illness and hospitalization.[16,34] The

MNA-SF incorporates questions on food intake, weight loss, mobility, acute illness, neuropsychological problems, and BMI, with scores <12 indicating risk of malnutrition. For patients with chronic respiratory disease (e.g., COPD), combining BMI, fat-free mass index (FFMI), and MNA-SF improves detection of malnutrition, as muscle wasting may be present even with normal BMI.[16,33-34] Therefore, early detection of malnutrition in patients with respiratory failure requires systematic, age-appropriate screening using validated tools, followed by comprehensive assessment with GLIM criteria and a detailed monitoring of dietary intake, functional capacity (e.g., handgrip strength), and body composition analysis.[35-38] This approach is essential to guide timely nutritional intervention and improve clinical outcomes.

Indeed, laboratory markers have a limited role in the early detection of malnutrition in critical illness as respiratory failure.[39] Traditional markers such as serum albumin, prealbumin, transferrin and retinol-binding protein are not reliable due to confounding by inflammation and fluid shifts and do not reliably reflect nutritional status.[39] In older adults and critically ill patients, low concentrations of albumin and prealbumin are frequently observed in malnutrition but are confounded by acute illness and inflammation, limiting their specificity and sensitivity for early detection.[40-41] Serial measurement of short half-life proteins (transthyretin, retinol-binding protein) may help monitor changes in nutritional status over time, but their utility for early detection is limited and should be interpreted cautiously in the setting of inflammation and organ dysfunction.[39,42] The most current consensus is that laboratory markers should be used only as a complement to comprehensive clinical assessment, including history, physical examination, anthropometry, and validated screening tools, rather than as primary diagnostic criteria.[40-41]

Respiratory Sarcopenia

Sarcopenia, defined as the progressive and generalized loss of skeletal muscle mass and strength, represents a key component of frailty and frequently coexists with malnutrition in older adults.[42-44] Beyond its impact on mobility and functional independence, sarcopenia has important respiratory implications. Respiratory muscles, including the diaphragm, are skeletal muscles and may be affected by the same catabolic and inflammatory processes underlying systemic muscle loss.[45] Reduced respiratory muscle strength and endurance may impair ventilatory efficiency and limit the ability to compensate for increased respiratory load. Indeed, diaphragmatic dysfunction may contribute to ineffective ventilation, carbon dioxide retention, and difficulty in weaning from non-invasive respiratory support. Due to this pathophysiological link between nutritional status, muscle dysfunction, and ventilatory failure, sarcopenia should be considered into the clinical evaluation framework.

Indeed, patients with hypercapnic respiratory failure and nutritional impairment, may frequently present loss of fat-free mass and muscle wasting, which may adversely affect respiratory muscle strength and function. These patients are at higher risk of intolerance to non-invasive ventilation and impairment of weaning and should be monitored for sarcopenia at hospital admission.[46] The so-called "respiratory sarcopenia" that involves all respiratory muscles such as the diaphragm, is associated with an accelerated deterioration in functional status and quality of life and can affect patients with any lung disease, although it is best studied and described in association with COPD.[47-49] The prevalence of sarcopenia in COPD patients varies between 14.5% and 25% increasing with age and disease severity.[49] Previous studies have shown that respiratory sarcopenia is an independent predictor of mortality in patients with COPD.[50-51] Moreover, glucocorticoids, which are frequently prescribed for the treatment of acute COPD exacerbations, play a pivotal role by suppressing protein synthesis and promoting protein breakdown despite their usual effect of stimulating appetite.[51] In age-related diaphragmatic sarcopenia, the atrophy of type IIa and/or IIb muscle fibers leads to a decline in forced ventilation and coughing ability, primarily affecting airway clearance. These functional alterations could increase the vulnerability of older adults to respiratory infections and related complications.[51]

As mentioned before, patients affected by respiratory sarcopenia and concomitant mechanical abnormalities, such as airflow limitation in COPD or lung stiffness in pulmonary fibrosis, may be more prone to developing respiratory failure when increased breathing is requested. However, evidence regarding easily measurable indicators of respiratory sarcopenia, which may be helpful for risk stratification of patients with chronic lung diseases, is still scarce. Recently, sonographic assessment of the diaphragm has provided a non-invasive measurement of respiratory efficiency through its thickness and excursion to quickly evaluate patients with acute illness at the bedside.[52] Deniz et al. have demonstrated that individuals diagnosed with sarcopenia exhibit a thinner ultrasound (US)-assessed diaphragm thickness as compared to the non-sarcopenic ones.[53] In addition, muscle mass and strength positively correlated with respiratory function measured through peak expiratory flow.[53] However, no studies have investigated the association between US-assessed diaphragmatic excursion (DE) and thickening fraction (TF) with sarcopenia in patients with pulmonary diseases during an acute respiratory failure (ARF).

Considering these perspectives, establishing at admission patients with malnutrition and diaphragmatic dysfunction related to respiratory sarcopenia under non-invasive respiratory support, through nutritional screening tools and a practical and low-cost bedside thoracic ultrasound, may help to stratify those at increased risk of mortality who require additional interventions. Early intervention in patients with respiratory disease and respiratory failure, as nutritional support could improve outcomes, including muscle strength and ventilator weaning.

Diaphragmatic Ultrasound

Methodology and reproducibility

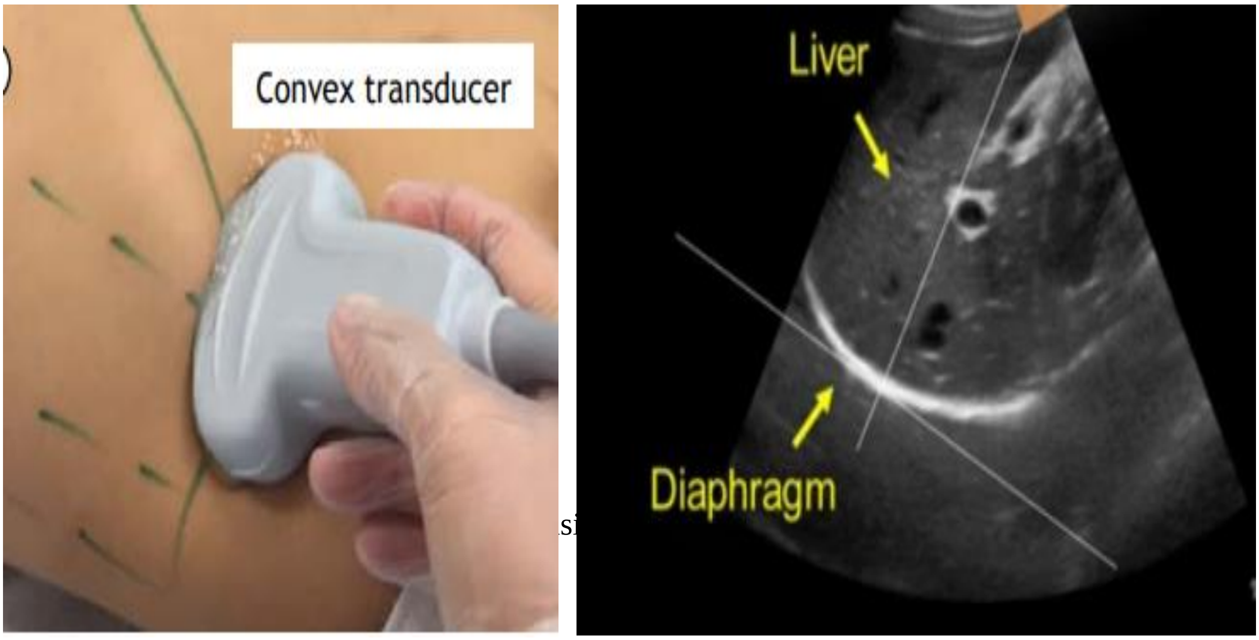
Diaphragmatic US is a non-invasive portable and quick tool presenting a linear relationship between diaphragmatic movement and inspired volume, which allows quantitative and qualitative assessment of diaphragmatic movement.[54]

Considering previous works, it has been suggested as the technique of choice for defining diaphragmatic function.[55-57] Indeed, following the appropriate standards, it is a reproducible technique with good inter and intra-observer reliability and good reproducibility.[58-59]

Ultrasound measurement of diaphragmatic motion

As shown in Figure 1, the cranio-caudal movement of the dome of the diaphragm during quiet breathing can be monitored using curvilinear ultrasound probes.

Figure 1: A convex transducer uses a lower frequency, allowing a deep penetration and a wide field of view.



2.5 and 3.5 mHz convex transducers should be used during subjects' quiet breathing (QB) or forced maneuvers.[59] Right and anterior to the midclavicular line subcostal scans need to be performed to visualize the gallbladder and the inferior cave vein that are considered as the anatomical landmarks for obtaining a conventional transverse section in B-mode scans and to ensure consistent procedure execution.[59] The M-mode technique pattern for diaphragm motion is used to achieve a more accurate measurement compared to B-mode images. As shown in Figure 2, with M-mode ultrasonography, the diaphragm appears as a single thick echogenic line. During inhalation, the contracting diaphragm moves towards the ultrasound probe.[59]

Figure 2. M-Mode Ultrasound Imaging of the diaphragmatic excursion.

Reference values for diaphragmatic motion obtained using M-mode ultrasound were previously established by Boussuges et al. (Figure 3).[60]

Figure 3. Normal and pathologic values for diaphragm US. [60]

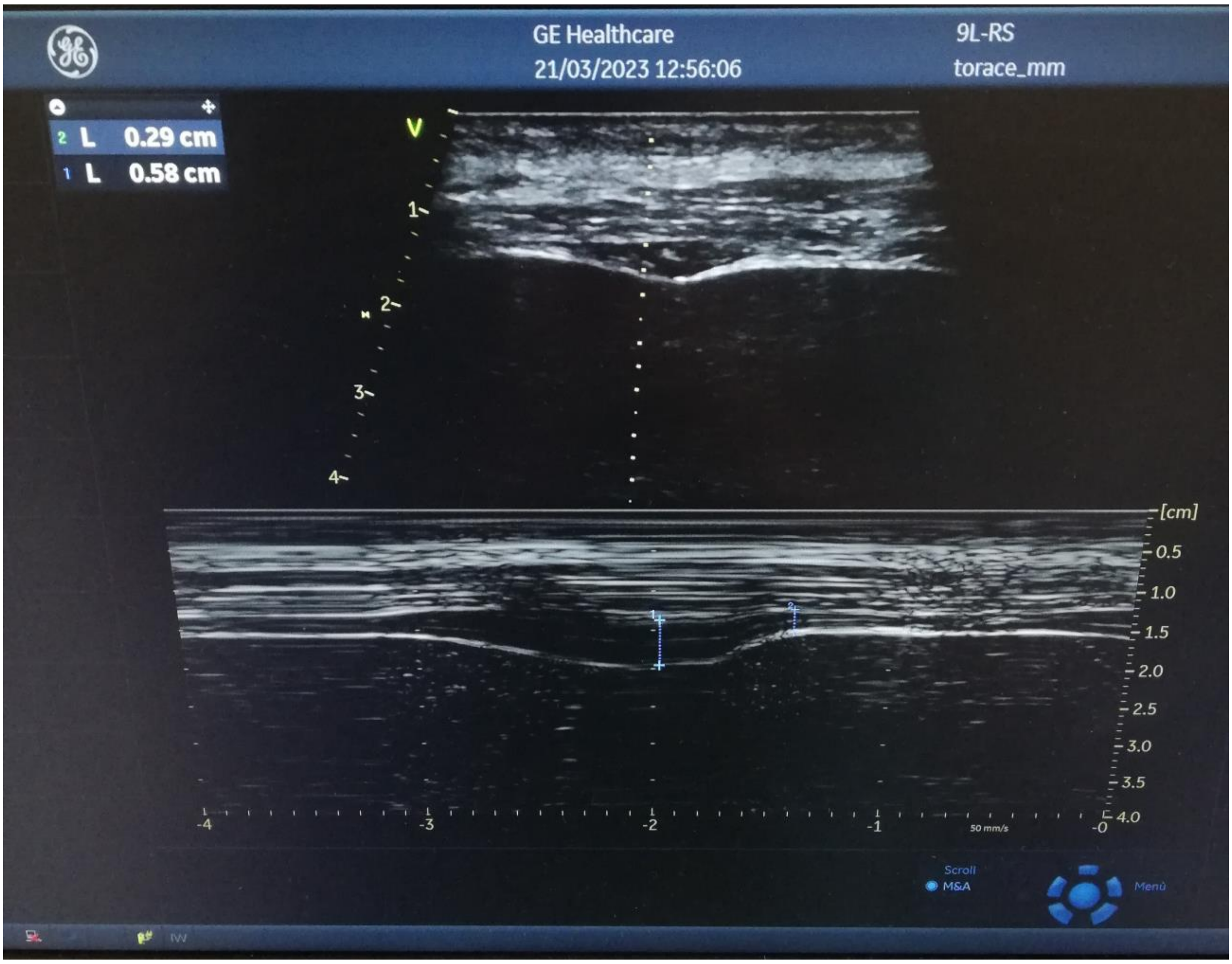
Diaphragmatic area	Parameter and test	Mean normal values ± SD	Pathologic values	Reference
Zone of apposition	diaphragmatic thickness	2.7±0.5 mm	<2 mm	Gottesman et al. [26], 1997
	thickening fraction[a]	37±9%	<20%	
Dome	diaphragmatic tidal excursion	women: 16±3 mm men: 18±3 mm	women: <9 mm men: <10 mm	Boussuges et al. [22], 2009
	sniff test	women: 26±5 mm men: 29±6 mm	women: <16 mm men: <18 mm	
	deep breath	women: 57±10 mm men: 70±11 mm	women: <37 mm men: <47 mm	

Ultrasound measurement of diaphragmatic thickening

The thickening of the diaphragm indicates a shortening of the diaphragm. Its absence during inspiration confirms diaphragmatic paralysis. If there is muscle atrophy, thickness decreases, and the diaphragm does not contract during inspiration.[61-62] Operators use linear ultrasound probes with high-frequency ultrasound waves (7–18 Hz) to create high-resolution images of diaphragm thickness.

To measure diaphragm thickness, operators place the ultrasound probe longitudinally parallel to the long axis of the body, usually between the eighth to tenth intercostal space, at the anterior axillary line or midway between the anterior- and mid-axillary lines.[60] The costo-phrenic sinus is identified as the transition between lung and liver (right). The zone of apposition, where the diaphragm is opposed to the rib cage, is located caudal to the costo-phrenic sinus. While operators select B-mode imaging, the diaphragm is identified as a three-layer structure (two echogenic layers of peritoneum and pleura sandwiching a more hypoechoic layer of the muscle itself) underneath the intercostal muscles that reappear as lung artifact recedes (Figure 4).

Figure 4. M-Mode Ultrasound Imaging of the diaphragmatic thickening.



The lower limit of normal diaphragmatic thickness at rest (at the end of an unforced expiration) in most patients is 1.5 mm. As shown in Figure 3, the two indexes usually used for the diagnosis of diaphragmatic paralysis include a diaphragmatic thickness' value < 2 mm and a diaphragmatic

TF value < 20% (TF: thickness at the end of the inspiration – thickness at the end of expiration in %).[60]

Background and Rationale

As mentioned before, several nutritional screening tools have been developed to identify older adults at risk of malnutrition. However, their applicability in an emergency setting as during acute respiratory failure remains uncertain. Among available instruments, the NRS-2002 is most frequently used in acutely ill and hospitalized patients, as it incorporates both nutritional impairment and disease severity.[63] Nevertheless, evidence supporting its use in patients undergoing non-invasive mechanical ventilation is limited and derives primarily from small observational studies conducted in patients with acute exacerbations of COPD or acute hypercapnic respiratory failure using this single screening tool.[63] Other instruments, such as the SNAQ, MNA, MST and MUST, have been validated mainly in stable geriatric or general inpatient populations and have not been specifically evaluated in patients with acute hypercapnic respiratory failure treated with NIMV.[24,26] Cui J et al. showed that in patients with COPD-related respiratory failure treated with ward-based non-invasive ventilation, nutritional risk identified by NRS-2002 was independently associated with higher mortality, increased NIV failure, and prolonged hospitalization.[64] Chen et al. showed that in COPD patients with respiratory failure, NRS-2002 independently predicted hospital readmission, further supporting the prognostic relevance of this nutritional screening in this population.[65] To date, the assessment of nutritional status in patients with acute hypercapnic respiratory failure treated with a respiratory support such as HFNC or NIMV has been largely limited to the use of single nutritional screening instruments, most commonly the NRS 2002. Importantly, comparative validation studies of nutritional screening tools have been conducted mainly in heterogeneous medical inpatients, geriatric wards, or community-dwelling populations, rather than in respiratory patients admitted to a sub-intensive care unit.[16] As shown in Table 1, none of them was targeted to patients with acute hypercapnic respiratory failure requiring ventilatory support.

Table 1. Nutritional screening tools and available evidence in acute respiratory failure and NIMV settings

Screening tool	Originally designed for	Evidence in acute illness	Evidence in acute respiratory failure / COPD exacerbation	Evidence specifically in NIMV patients	Use of disease severity	Head-to-head comparisons in NIMV
NRS-2002	Hospitalized, acutely ill patients	✔ Extensive	✔ Limited (small observational studies)	◐ Used in small cohorts	✔ Yes	✕ No
MNA / MNA-SF	Geriatric, stable populations	✔ Moderate	✕ Very limited	✕ None	✕ No	✕ No
MUST	General hospital & community	✔ Moderate	✕ Limited	✕ None	✕ No	✕ No
SNAQ	Community & long-term care	✔ Limited	✕ None	✕ None	✕ No	✕ No
MST	Hospitalized & oncology patients	✔ Moderate	✕ Very limited	✕ None	✕ No	✕ No

Legend:
✔ evidence available ◐ limited/indirect evidence ✕ no evidence

Consequently, the relative diagnostic and prognostic performance of these tools in this selective population remains unclear, particularly within the emergency department setting, where clinical instability, time constraints, and limited resources significantly influence the feasibility of nutritional assessment. In this context, advanced body-composition techniques, although accurate, are often impractical or unreliable during the acute phase of respiratory failure. Consequently, nutritional evaluation in real-world emergency care relies predominantly on rapid, bedside screening instruments.

Therefore, this doctoral project was novel in providing a systematic, head-to-head evaluation of six commonly used nutritional screening tools (NRS-2002, MNA, MNA-SF, MUST, SNAQ, MST) and their ability to predict intra-hospital mortality, length of hospital stays

(LOS) and respiratory support duration in a distinct population of hypercapnic patients treated in sub-intensive care units.

Aims of the Research Project

Primary Objectives

The aim of this research's project was to evaluate the association of malnutrition on clinical outcomes of patients with hypercapnic respiratory failure treated with respiratory support as HFNC or NIMV.

The specific objectives are:

1. Evaluation of the performance of six screening tools (MNA and its short form, NRS 2002, MUST, SNAQ, MST) in detecting malnutrition in hypercapnic patients treated with HFNC or NIMV.
2. Using the screening tool with the greater diagnostic performance together with metabolic surrogates (total serum protein and albumin) to identify the better predictor of in-hospital mortality, length of hospital stay (LOS), duration of the respiratory support during an ARF, and 3-month mortality.

Secondary Objectives

We hypothesized that hypercapnic patients with a pre-existing condition of muscle weakness, such as respiratory sarcopenia, in addition to systemic inflammation due to respiratory diseases, may present a diaphragmatic dysfunction.

The secondary purposes of this study were:

1. To compare US-assessed DE and TF between sarcopenic and non-sarcopenic inpatients admitted with ARF requiring respiratory support.
2. To evaluate if diaphragmatic parameters may have a prognostic role regarding the 3-month mortality and the other in-hospital outcomes.

Materials and Methods

Study Population

This multicenter observational study enrolled 127 patients affected by ARF requiring HFNC or NIMV consecutively admitted to the sub-intensive care unit of Fondazione Policlinico Universitario Campus Bio-Medico in Rome, Azienda Ospedaliera dei Colli in Naples, and Azienda Ospedaliero-Universitaria in Ferrara from January 2023 to September 2025. All participating centers followed the European Respiratory Society/American Thoracic Society recommendations for the clinical application of NIMV or HCNC on the clinical scenarios included in the study.[66]

The study adhered to the principles of the Helsinki Declaration and obtained approval from the Ethical Committee in January 2023 (Protocol Code 101.22 OSS). All subjects provided written informed consent to participate in the enrollment.

Inclusion criteria were adults being hospitalized for ARF due to any respiratory diseases requiring NIMV or HCNC (e.g. any Global Initiative for Chronic Obstructive Lung Disease – GOLD stage, congestive heart failure leading to pulmonary edema, interstitial lung disease, and oncological disorders with lung involvement).

Patients with exclusion criteria as history of unilateral diaphragmatic palsy, recent cardiopulmonary surgery or subcostal laparotomy surgery (< 2 weeks), neurodegenerative or neuromuscular diseases, and severe dementia at higher risk of having dysphagia, were identified during the initial history taking in the Emergency Department and were therefore not included in the study.

Data collection

Patients’ enrollment and evaluation were performed by physicians skilled in geriatric medicine, who received specific training in medical ultrasonography and achieved the certification by the Italian Society of Ultrasonography in Medicine and Biology (SIUMB).

Body Mass Index (BMI), which is calculated as weight (kg) divided by height (m^2), and clinical information about smoking habits and the severity of respiratory failure (paO_2/FiO_2) were recorded from medical charts. Functional capacity (Katz Index of Activities of Daily Living- ADLs and Lawton–Brody Instrumental Activities of Daily Living- IADLs), comorbidity status (measured through the Charlson Comorbidity Index), and ventilation parameters (pressure support and positive end-expiratory pressure at the beginning of NIMV) were also collected during patients’ hospitalization.

Malnutrition Assessment

Malnutrition risk was assessed using six validated screening tools: Nutritional Risk Screening 2002 (NRS-2002), Mini Nutritional Assessment – Short Form (MNA-SF), Mini Nutritional Assessment Full Form (MNA-FF), Malnutrition Universal Screening Tool (MUST), Simplified Nutrition Assessment Questionnaire (SNAQ), and Malnutrition Screening Tool (MST).

NRS-2002 evaluates nutritional risk based on impaired nutritional status (BMI, recent weight loss, and reduced food intake) and disease severity.[63] An additional point is added for patients aged ≥70 years. A total NRS-2002 score ≥3 was considered indicative of nutritional risk, as recommended by international guidelines.

The MNA-SF consists of six items assessing decline in food intake over the previous three months, unintentional weight loss during the last three months, mobility, psychological stress or acute disease in the past three months, neuropsychological problems (dementia or depression), BMI or, when unavailable, calf circumference.[67]

The total score ranges from 0 to 14 points. Patients with a score of 12–14 will be considered having a normal nutritional status, those with a score of 8–11or 0–7 will be classified as at risk of malnutrition or malnourished, respectively.

The MNA-FF is composed of 18 items, grouped into four domains[16]:

1. Anthropometric assessment
    - Body mass index (BMI)
    - Recent weight loss
    - Mid-arm circumference
    - Calf circumference
2. General assessment
    - Lifestyle
    - Medication use
    - Mobility
    - Presence of psychological stress or acute disease
    - Neuropsychological problems
    - Living situation
3. Dietary assessment
    - Number of meals per day
    - Food and fluid intake
    - Protein consumption
    - Mode of feeding

- Appetite

4. Subjective assessment

- Self-perception of nutritional status
- Self-perception of health status

The total MNA-FF score ranges from 0 to 30 points. Patients with a score ≥24 are considered well-nourished, those with 17–23.5 or <17 are at risk of malnutrition or malnourished, respectively.

The MUST score is derived from three components: body mass index (BMI), unintentional weight loss in the previous 3–6 months, and the presence of an acute disease effect associated with little or no nutritional intake for more than five days.[68] Patients with a score of 0 were classified as low risk while a score of 1 and ≥ 2 was considered as medium and high risk, respectively. For analysis, patients with a MUST score ≥1 were considered at increased risk of malnutrition.[68]

SNAQ is an appetite-based screening tool consisting of four items assessing appetite, early satiety, food taste, and meal frequency. Each item is scored from 1 to 5, yielding a total score ranging from 4 to 20. A SNAQ score <14 was considered indicative of high risk of clinically significant (≥5%) weight loss within 6 months.[69]

The MST includes two questions addressing recent unintentional weight loss and reduced appetite.[67] An MST score ≥2 was used to define risk of malnutrition, in accordance with the original validation studies.

All tools were administered at sub-intensive care unit admission through patient interview and clinical assessment. All cut-off values were applied according to validated scoring systems and existing literature.

Biochemical nutritional indicators (albumin, total protein level) were measured at hospital admission.

The final diagnosis of malnutrition was based on the presence of at least one phenotype and one etiologic criterion according to according to GLIM criteria.[30-33]

Sarcopenia Assessment

We applied the EWGSOP2 diagnostic algorithm to define confirmed sarcopenia based on the combination of low muscle strength and low muscle mass.[70] Low muscle strength was assessed by handgrip strength measured at baseline with a hand-held dynamometer and expressed in kg. Handgrip cut-offs of <16 kg (for women) and <27 kg (for men) were considered to define low muscle mass.[71]

The presence of a calf circumference <31 cm was used to detect reduced muscle mass.[70] Calf circumference was used as a proxy for muscle mass in accordance with EWGSOP2 recommendations, as this measure has been consistently validated against reference body-composition techniques.[70] Prior studies have demonstrated moderate correlations between calf circumference and appendicular lean mass assessed by DEXA and BIA, as well as muscle area measured by CT.[72-75]

Because measurements were obtained in an acute emergency setting, where DEXA or BIA could not be performed due to clinical instability and time constraints, calf circumference represented the most practical and operationally feasible method for estimating muscle mass in this cohort. The criteria used to determine sarcopenia (calf circumference and handgrip strength) were obtained in a second step, once the patient's acute condition had stabilized sufficiently to allow safe assessment.

Diaphragmatic motility assessment

DE and TF measurements were taken in a semi-recumbent position and spontaneous breathing before starting the respiratory support, using the US-based imaging system Venue (GE Healthcare, Italy). Standard anatomical landmarks were achieved to ensure consistent procedure execution for repeated measurements in all participants.[58-60]

Ultrasound operators were blinded to sarcopenia status. Absolute and percent intraobserver variability was calculated by the deviation value from the mean on the three measurements.

The lower limit of normal DE during quiet breathing was defined as 10 mm, consistent with the reference values reported by Boussuges et al. and supported by additional studies demonstrating that excursions below this threshold lie outside the expected physiological range in healthy adults.[60] A diaphragmatic TF <20% was used to define reduced diaphragmatic contractility. This threshold is supported by physiological data with normal values in healthy individuals typically ranging between 30–50% and by prior studies that have adopted <20% as an indicator of impaired diaphragmatic function.[60,76-77]

Clinical outcomes

The in-hospital outcomes such as in-hospital mortality, LOS and HFNC/NIMV duration were obtained from patient's medical documentation. Three-month mortality was ascertained during the scheduled post-discharge outpatient follow-up visit.

Statistical Analysis

Continuous variables were reported as mean and standard deviation, while categorical variables are expressed as counts and percentages. For primary study outcomes, statistical analyses were performed comparing well-nourished vs malnourished groups according to GLIM criteria. Between-group differences in nutritional screening scores (MNA®, MNA®-SF, NRS-2002, MUST, SNAQ, and MST) and, duration of ventilatory support (NIMV/HFNC) and LOS were assessed using independent-samples t-tests. When the assumption of homogeneity of variances was violated, as assessed by Levene's test, a Welch's t-test was applied. Categorical outcomes (in-hospital mortality and 3-month mortality) were compared using χ^2 tests or Fisher's exact test when appropriate.

To evaluate the diagnostic performance of nutritional screening tools (Total MNA score, NRS-2002, MUST, SNAQ, and MST) for identifying malnutrition according to GLIM criteria, receiver operating characteristic (ROC) curve analyses were performed. The area under the curve (AUC) with corresponding cut-off values, sensitivity, specificity, and Youden's index were calculated for each tool.

Associations between nutritional indicators and clinical outcomes were evaluated using multivariable regression models. Three nutritional predictors were entered simultaneously in each model: MNA-SF score, serum total proteins (g/dL), and serum albumin (g/dL).
For the 3-month outcome, a multivariable logistic regression model was fitted with death at 3 months as the dependent variable. Results were reported as odds ratios (ORs) with corresponding *p* values.

For continuous outcomes, multivariable linear regression models were applied to estimate the association between the nutritional predictors and: (i) hospital length of stay (LOS) and (ii) duration of non-invasive respiratory support (NIV and/or HFNC), in days. Linear regression results were reported as unstandardized β coefficients (estimate), standard errors, *t* statistics, and *p* values. Overall model significance was assessed using the F-test, and model fit was summarized with R^2.

The association between nutritional status and diaphragmatic ultrasound parameters was explored using Pearson's correlation coefficient (r). Correlation analyses were restricted to quantitative variables.

For the secondary objectives of the study, binary logistic regression was used to assess the relationship between pathological DE and TF with the probability of presenting sarcopenia. Cox regression analysis was applied to assess the association between diaphragmatic dysfunction and 3-month mortality. In addition, multinomial regression models were used to evaluate potential associations of diaphragmatic parameters with length of hospital stay and duration of non-invasive ventilation/high-flow nasal cannula support, taking into consideration their median of 13 and 4 days respectively. In these analyses, intrahospital death was considered as an alternative outcome.

The strength of the above associations was expressed as odds ratios (OR) and 95% Confidence Intervals (95%CIs). Analyses were adjusted for potential confounders, namely age, sex, CCI, and severity of respiratory failure. Normality of continuous variables was assessed by graphical inspection and Kolmogorov–Smirnov testing. Multicollinearity among covariates was assessed using the variance inflation factor, with values >5 considered indicative of significant collinearity.

A two-sided p value < 0.05 was considered statistically significant.

All statistical analyses were performed using R software (version 4.0.2).

Sample size calculation section

Based on previous evidence, we estimated that approximately half of the study population would be affected by malnutrition. Accordingly, with a sample size of 127 patients, the study had more than 80% statistical power to detect a statistically significant area under the receiver operating characteristic curve (AUC) as small as 0.65.

A similar level of power was expected for identifying the nutritional screening tool with the best prognostic performance for mortality, assuming approximately 50 outcome events during follow-up, corresponding to an overall mortality rate of about 40%.

For the secondary objectives of the study, a post hoc power analysis was performed based on the observed differences in diaphragmatic excursion and thickening fraction between sarcopenic and non-sarcopenic patients. Assuming a two-sided alpha level of 0.05, the estimated statistical power was 0.89 for diaphragmatic excursion and 0.58 for thickening fraction.

Ethical Approval

The study protocol was approved by the Campus Bio-Medico University Ethical Committee, as the Coordinating Center, in December 2022 (Protocol Code 101/22 OSS). All participants were given a detailed description of the protocol and signed informed consent was collected from all participants.

Results

Patients' characteristics

A total of 127 patients were included in the analysis, of whom 74 (58.3%) met GLIM criteria for malnutrition (Table 2). Patients with malnutrition were older (76.9 vs 70.2) and presented with a higher comorbidity burden compared with non-malnourished patients (5.9 vs 4.9). Functional status, assessed by activities of daily living (ADLs) and instrumental ADLs (IADLs), was significantly lower in malnourished patients (2.9 vs 4.6 and 2.5 vs 4.9, respectively).

Accordingly, malnourished patients showed lower BMI (24.0 vs 34.1), lower total protein levels and serum albumin (5.7 vs 6.9 and 3.2 vs 3.5, respectively). Indeed, they presented a more severe respiratory failure (PaO2/FiO2: 183.7 vs 212.9) and those requiring NIMV needed minor levels of pressure support (PS: 10.8 vs 13.0) and positive end-expiratory pressure (PEEP: 5.9 vs 6.5).

Table 2. Baseline characteristics of the study sample

	All **n=127**	**Well-nourished** **n=53**	**Malnourished** **n=74**
Age (years) (mean; SD)	74.0 (10.9)	70.2 (10.0)	76.9 (10.7)
Sex (female) (n; %)	68 (53.5)	23.0 (43.4)	45 (60.8)
BMI (Kg/m^2) (mean; SD)	28.7 (8.1)	34.1 (7.7)	24.0 (5.1)
CCI (mean; SD)	5.5 (2.4)	4.9 (2.0)	5.9 (2.6)
Smokers (n, %)	26 (20.5)	10 (18.9)	19 (25.7)

ADLs (mean; SD)	3.6 (2.2)	4.6 (1.9)	2.9 (2.0)
IADLs (mean; SD)	3.5 (2.9)	4.9 (2.8)	2.5 (2.5)
Respiratory diseases (n; %)			
COPD	57 (45)	22 (41.5)	35 (47.3)
Acute PE	10 (7.9)	4 (7.5)	6 (8.1)
Lung cancer	45 (35.4)	21 (39.6)	24 (32.4)
Pneumonia	2 (1.6)	1 (1.9)	1 (1.3)
Restrictive disorders	13 (10.2)	4 (7.5)	6 (8.1)
PaO2/FiO2 (%) (mean; SD)	195.9 (77.0)	212.9 (72.3)	183.7 (78.4)
PEEP (cmH2O) (mean; SD)	6.2 (1.6)	6.5 (1.8)	5.9 (1.4)
Pressure support (cmH2O) (mean; SD)	11.7 (3.6)	13.0 (3.8)	10.8 (3.1)
NIMV (n; %)	75 (59.0)	32 (60.3)	43 (58.1)
Hb (g/dL)	12.1 (2.5)	12.6 (2.4)	11.8 (2.5)
Creatinine (mg/dL)	1.2 (0.7)	1.2 (0.6)	1.2 (0.8)
Total serum protein (g/dL) (mean; SD)	5.9 (0.8)	6.9 (0.8)	5.7 (0.8)
Albumine g/dL (mean; SD)	3.3 (0.7)	3.5 (0.7)	3.2 (0.6)

Abbreviations: BMI, Body mass index; CCI, Charlson Comorbidity Index; ADLs, Activities of Daily Living; IADLs, Instrumental Activities of Daily Living; COPD, Chronic obstructive pulmonary disease; PE, Pulmonary edema, pO2/FIO2, arterial oxygen partial pressure to fractional inspired oxygen; PEEP, positive end-expiratory pressure; NIMV, Non-Invasive Mechanical Ventilation; Hb, Hemoglobin.

Diagnostic performance of nutritional screening tools

As shown in Table 3, malnourished patients showed worse nutritional screening scores across all evaluated tools.

Table 3. Primary outcomes of the study sample

	All n=127	**Well-nourished n=53**	**Malnourished n=74**	**p-value**
MNA®	17.2 (5.7)	20.3 (4.1)	14.9 (5.6)	<0.001
MNA®-SF	7.3 (3.5)	9.1 (3.1)	6.0 (3.1)	<0.001
NRS-2002	2.5 (1.4)	1.8 (1.4)	3.0 (1.1)	<0.001
MUST	2.5 (1.5)	1.7 (1.3)	3.1 (1.4)	<0.001
SNAQ	13.6 (2.7)	14.5 (2.0)	13.0 (3.0)	<0.001
MST	2.0 (1.8)	1.4 (1.5)	2.4 (1.9)	0.002

Abbreviations: MNA, Mini Nutritional Assessment; MNA-SF, Mini Nutritional Assessment Short-Form; NRS-2002, Nutritional Risk Screening 2002; MUST, Malnutrition Universal Screening Tool; SNAQ, Simplified Nutrition Assessment Questionnaire; MST, Malnutrition Screening Tool.

Independent samples t-tests demonstrated statistically significant differences between malnourished and non-malnourished patients for all nutritional screening tools ($p < 0.05$). The largest difference in mean values between groups was observed for the Total MNA score (20.3, SD 4.1 vs 14.9, SD 5.6; $p < 0.001$), followed by MUST (1.7, SD 1.3 vs 3.1, SD 1.4; $p < 0.001$), MNA-SF (9.1, SD 3.1 vs 6.0, SD 3.1; $p < 0.001$) and NRS-2002 (1.8, SD 1.4 vs 3.0, SD 1.1; $p < 0.001$).

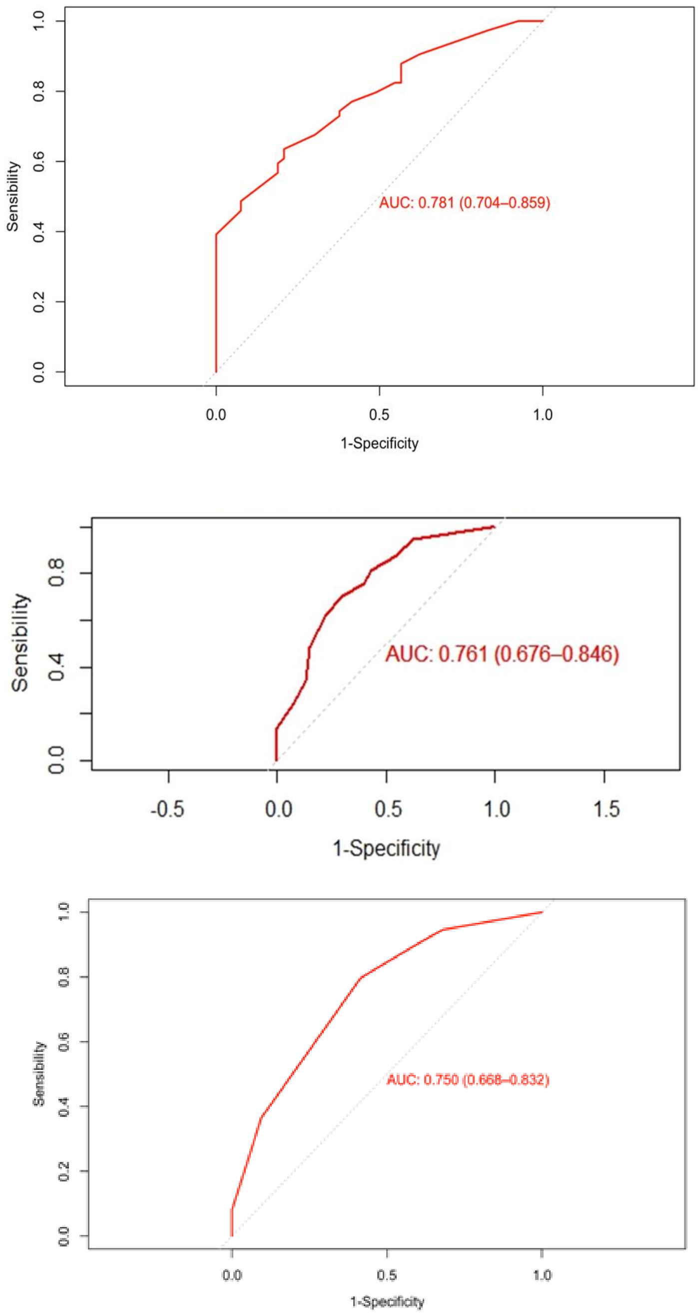
ROC curve analyses showed that the Total MNA score had the highest discriminative ability for identifying malnutrition according to GLIM criteria, with an AUC of 0.781, indicating good diagnostic performance (Figure 5).

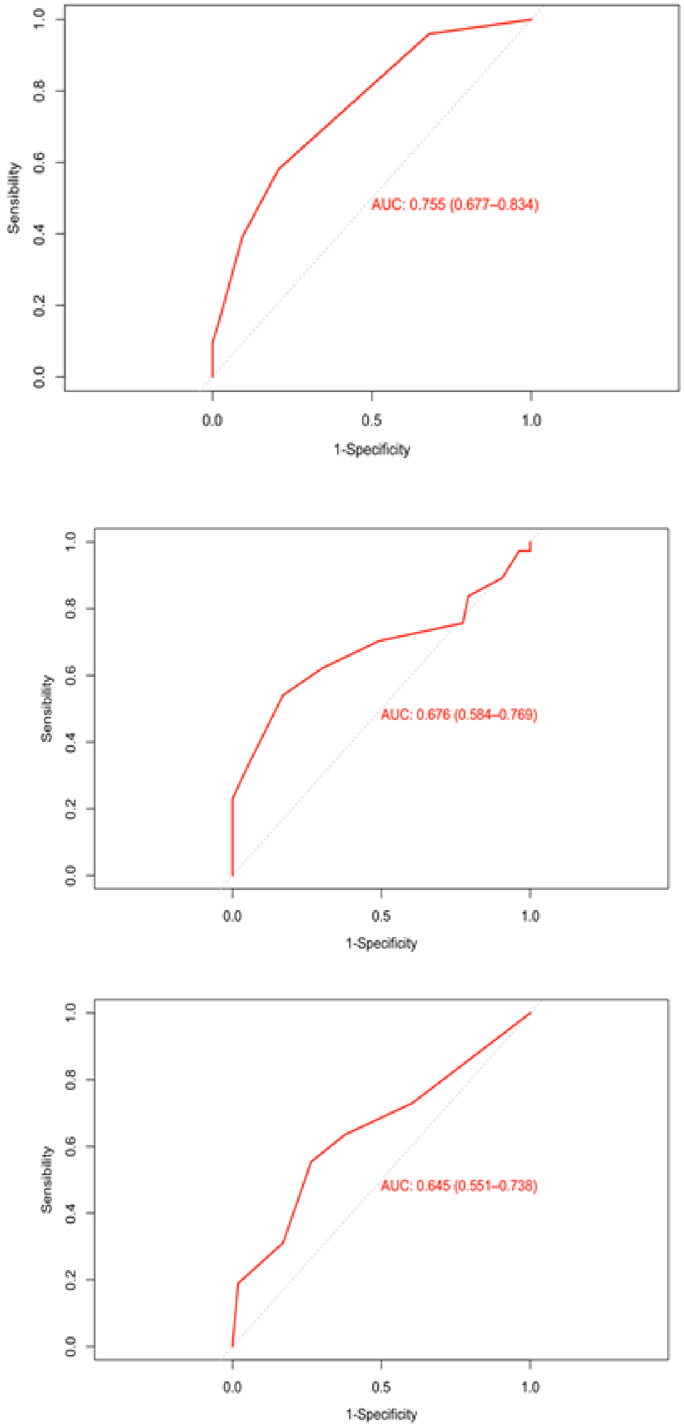
At the optimal cut-of value (≤ 16.75), Total MNA score demonstrated a sensitivity of 63.5% and a specificity of 79.2%.

Among the remaining tools:

- MNA-SF (AUC = 0.76), MUST (AUC = 0.75) and NRS-2002 (AUC = 0.75) showed good discriminative performance,
- SNAQ (AUC = 0.68) and MST (AUC = 0.64) demonstrated only moderate accuracy.

Figure 5. ROC curves for diagnostic performance of nutritional screening tools





Receiver Operating Characteristic (ROC) curves comparing the diagnostic performance of MNA, MNA-SF, MUST, NRS-2002, SNAQ, and MST in predicting 3-month mortality.

Association between nutritional indicators and primary outcomes

As presented in Table 4, in the overall population, the mean of respiratory support duration was 4.9 days (SD: 3.2) and of LOS was 16.3 days (SD: 10.7). Indeed, 16 (12.6%) and 33 patients (25.9%) had intra-hospital and 3-month mortality, respectively.

Table 4. Clinical outcomes of the study sample

	All n=127	Well-nourished n=53	Malnourished n=74	p-value
NIMV/HFNC Duration (days) (mean; SD)	4.9 (3.2)	4.5 (3.0)	5.2 (3.4)	0.256
Hospital LOS (Days) (mean; SD)	16.3 (10.7)	14.0 (11.2)	17.9 (10.2)	0.047
In-hospital Death (n; %)	16 (12.6)	4 (7.5)	12 (16.2)	0.146
3-month Death (n; %)	33 (25.9)	5 (9.4)	28 (37.8)	<0.01

Abbreviations: NIMV, Non-Invasive Mechanical Ventilation; HFNC, High-flow nasal cannula; LOS, Length of hospital stay.

Hospital length of stay was significantly longer in malnourished patients (17.9, SD 10.2 days) compared with well-nourished individuals (14.0, SD 11.2 days; p = 0.047). On the contrary, no significant difference was observed in the duration of ventilatory support between groups (4.5, SD 3.0 vs 5.2, SD 3.4 days; p = 0.256) and in-hospital mortality (7.5% vs 16.2% p = 0.146). Indeed, three-month mortality was significantly higher in malnourished patients compared with well-nourished individuals (37.8% vs 9.4%; p < 0.001).

As shown in Table 5, in the multivariable logistic regression model including MNA-SF, total proteins, and albumin, MNA-SF was independently associated with 3-month mortality (OR

1.235, *p* = 0.0016), with higher MNA-SF scores being associated with 23.5% higher odds of survival at 3 months. Serum albumin and total protein levels were not independently associated with 3-month mortality.

Table 5. Multivariable logistic regression analysis for 3-month mortality

Variable	Odds ratio	Std. Error	z	p-value
Intercept	2.363	1.542	0.558	0.577
MNA SCREEN sf	**1.235**	0.067	**3.149**	**0.0016**
Serum Total Proteins (g/dL)	0.631	0.451	-1.022	0.307
Albumine (g/dL)	1.552	0.567	0.775	0.438

The model showed modest explanatory capacity, with a Nagelkerke R^2 of 0.141, indicating that approximately 14% of the variability in 3-month mortality was explained by the included predictors.

In the multivariable logistic regression model for in-hospital mortality (Table 6), none of the evaluated nutritional variables (MNA-SF, serum total proteins, and albumin) were independently associated with the outcome. The overall explanatory capacity of the model was limited, with a Nagelkerke R^2 of 0.056.

Table 6. Multivariable logistic regression analysis for in-hospital mortality

Variable	Odds ratio	Std. Error	z	p-value
Intercept	0.213	2.036	-0.758	0.449
MNA SCREEN sf	0.987	0.083	-0.155	0.877
Serum Total Proteins (g/dL)	1.683	0.654	0.796	0.426
Albumine (g/dL)	1.199	0.784	0.232	0.817

In the multivariable linear regression model for LOS (Table 7), the overall model was statistically significant (F = 3.098, p = 0.029) but explained a limited proportion of LOS variability (R^2 = 0.071).

Table 7. Multivariable linear regression analysis for hospital length of stay

Variable	Estimate	Std. Error	t	p-value
Intercept	13.480	7.023	1.920	0.057
MNA SCREEN sf	-0.328	0.279	-1.174	0.243
Serum Total Proteins (g/dL)	**4.698**	2.069	**2.271**	**0.025**
Albumine (g/dL)	**-6.727**	2.555	**-2.633**	**0.010**

Overall, higher serum albumin levels were independently associated with shorter hospitalization, with an estimated reduction of approximately 6.7 days per 1 g/dL increase, whereas higher total protein levels were associated with a longer hospital length of stay, corresponding to an increase of approximately 4.7 days per 1 g/dL, within this multivariable framework.

In the multivariable linear regression model for duration of non-invasive respiratory support (Table 8), the overall model was not significant (F = 0.818, p = 0.486) and had minimal explanatory capacity (R^2 = 0.020).

Table 8. Multivariable linear regression analysis for duration of ventilatory support

Variable	Estimate	Std. Error	t	p-value
Intercept	4.334	2.156	2.010	0.047
MNA SCREEN sf	-0.115	0.086	-1.342	0.182
Serum Total Proteins (g/dL)	-0.081	0.635	-0.127	0.899
Albumine (g/dL)	0.567	0.784	0.723	0.471

Sarcopenia and diaphragmatic measurements

Considering the measure of muscle strength, HGS had a mean of 19.7 Kg, and 81 patients (64%) had a pathological value. Regarding the surrogate marker of muscle mass, the mean of calf circumference was 31.1 cm and 77 patients (60%) had a reduced measurement (Table 9).

Concerning respiratory parameters, no differences were found according to severity of ARF, but a significantly higher pressure support was used in non-sarcopenic compared with sarcopenic patients (12.74 vs 10.64 cmH_2O, $p=0.012$).

Indeed, in the overall study population, mean diaphragmatic excursion was 2.3 cm (SD 0.9) and mean diaphragmatic thickening fraction was 22.2 % (SD 10.1). These values are within the ranges previously reported in the literature for patients with respiratory disease and in mixed populations including stable and acutely ill subjects.[60-62,76-77]

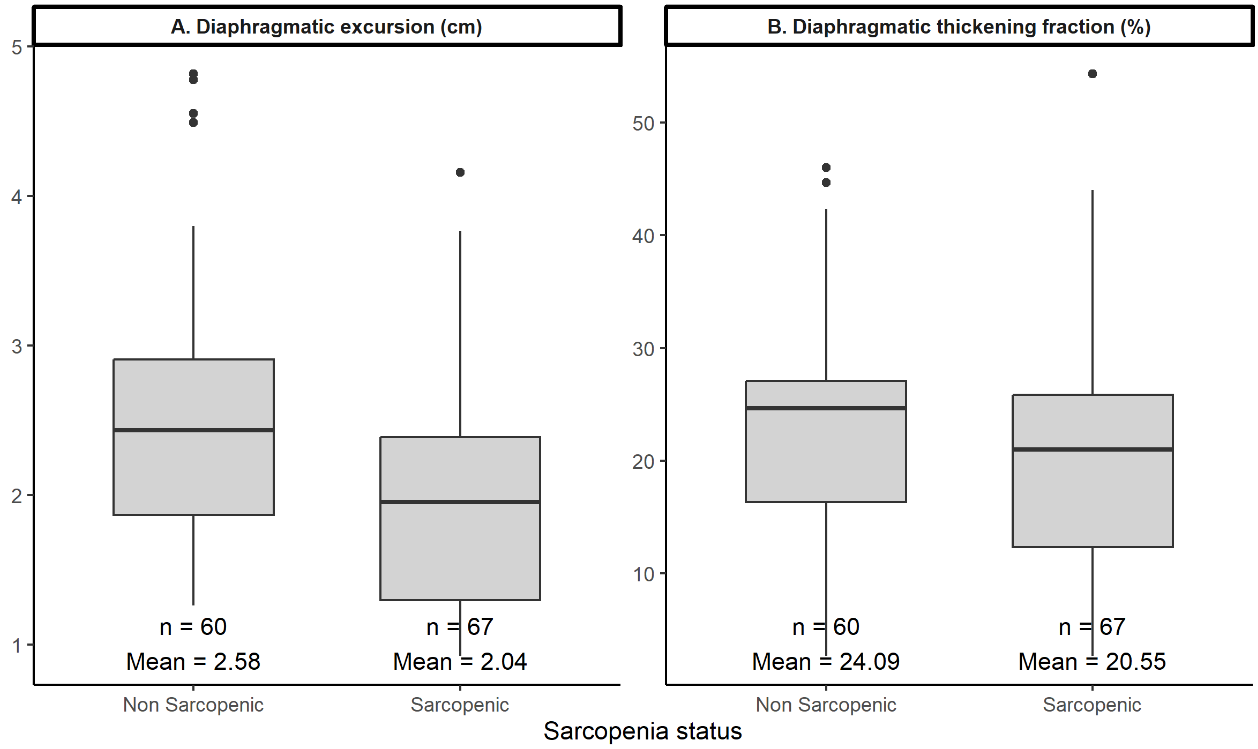
Table 9. Sarcopenia and diaphragmatic US-parameters

	All n=127	**Non-Sarcopenic n=60**	**Sarcopenic n=67**
Handgrip (Kg) (mean; SD)	19.7 (8.8)	25.8 (7.6)	14.4 (5.9)
Calf circumference (mean; SD)	31.1 (5.5)	35 (5.4)	27.6 (2.3)
Baseline respiratory characteristics			
PaO2/FiO2 (%) (mean; SD)	195.8 (77.6)	204.7 (82.6)	187.5 (72.2)
PEEP (cmH2O) (mean; SD)	6.2 (1.6)	6.5 (1.8)	5.9 (1.4)
Pressure support (cmH2O) (mean; SD)	11.7 (3.6)	12.74 (3.7)	10.64 (3.2)
DE (cm)	2.3 (0.9)	2.7 (0.9)	2.0 (0.7)
TF (%)	22.2 (10.1)	25.5 (10.0)	19.9 (9.6)

Abbreviations: DE, Diaphragmatic excursion; TF, Thickening fraction.

When comparing patients by the presence of sarcopenia (Figure 6), we found that sarcopenic patients had a significantly lower DE (mean value 2.04 [SD 0.8] vs 2.58 [SD 0.9] centimeters, p=0.001) and TF (20.5 [SD 10] vs 24.0 [SD 9.9] %, p=0.03) than non-sarcopenic patients. The intraobserver variability results of DE and TF measurements were less than 15 % (5% and 7.1% respectively).

Figure 6. Boxplots showing diaphragmatic function in sarcopenic and non-sarcopenic participants.



(A) Diaphragmatic excursion and (B) diaphragmatic thickening fraction.

Logistic regression analysis (Table 10) showed an inverse association between DE and sarcopenia at admission (OR 0.46, 95%CI 0.28-0.71, p=0.001), which remained statistically significant after adjusting for age, sex, BMI, CCI and paO2/FiO2 (OR 0.28, 95%CI 0.11-0.59, p=0.002). An inverse significant association was also observed between TF and sarcopenia in the unadjusted (OR 0.96, 95%CI 0.92-0.99, p=0.03), but not in the adjusted model.

Table 10. Logistic regression for the association of diaphragmatic excursion and thickening fraction with sarcopenia

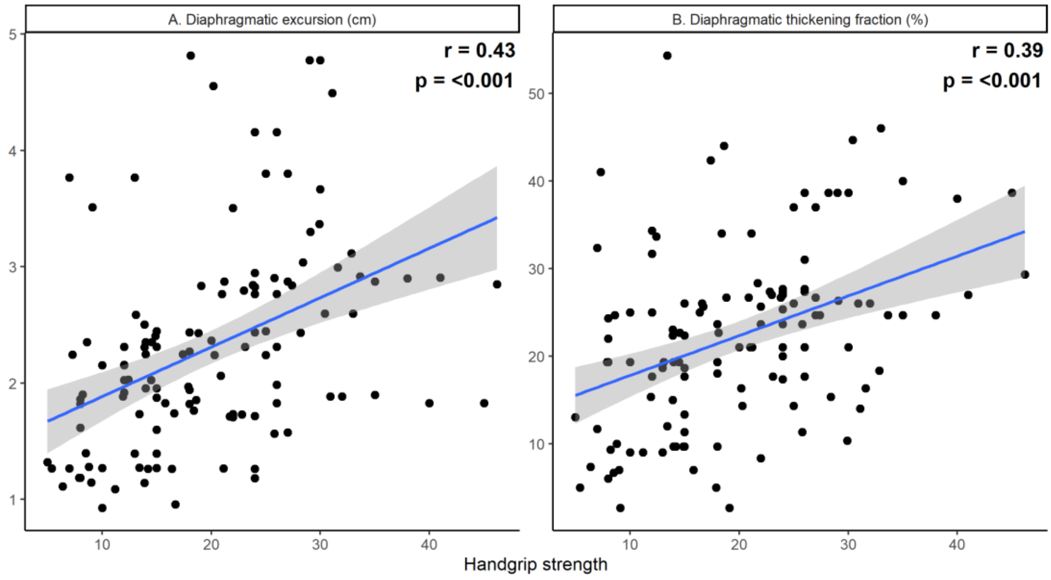
	Odds ratio (95% Confidence Interval) for sarcopenia p-value	
	Model 1	**Model 2**
DE	0.46 (0.28-0.71)	0.28 (0.11-0.59)
	p=0.001	p=0.002
TF	0.96 (0.92-0.99)	1.01 (0.94-1.09)
	p= 0.03	p=0.7

Model 1 is unadjusted. Model 2 is adjusted for age, sex, Body Mass Index, Charlson Comorbidity Index, paO_2/FiO_2.

In addition, due to the heterogeneity of underlying respiratory conditions in our cohort, exploratory subgroup analyses were performed for the COPD (n=57) and oncological (n=45) groups, limited to the two diagnostic categories with sufficiently large sample sizes. The association between reduced diaphragmatic excursion and sarcopenia remained significant in the COPD subgroup ($p < 0.005$), whereas no significant association was found in the oncological subgroup ($p = 0.5$).

Moreover, as presented in Figure 7, a positive relation was found between HGS and diaphragmatic parameters, showing a correlation coefficient of 0.43 and 0.39 for excursion and thickness ($p<0.05$), respectively.

Figure 7. Scatter plots of handgrip strength and diaphragmatic function. (A) Diaphragmatic excursion and (B) diaphragmatic thickening fraction.



As shown in Table 11, after adjustment for age, sex, comorbidity burden, and respiratory failure severity, pathological DE was not associated with 3-month mortality (HR 0.96, 95% CI 0.63–1.42), prolonged hospital stay (OR 0.72, 95% CI 0.46–1.13) or prolonged NIMV/HFNC duration (OR 0.86, 95% CI 0.54–1.36).

Similarly, after adjustment for the same confounding factors, pathological TF showed no association with 3-month mortality (HR 1.05, 95% CI 0.68–1.62), prolonged hospital stay (OR 0.97, 95% CI 0.93–1.02) or prolonged NIMV/HFNC duration (OR 1.01, 95% CI 0.96–1.05).

Table 11. Association of diaphragmatic parameters with mortality, length of stay, and duration of respiratory support

Outcome	Predictor	Model 1 HR/OR (95% CI)	Model 2 HR/OR (95% CI)
3-month mortality (Cox)	Pat. DE	0.97 (0.66–1.42)	0.96 (0.63–1.42)
	Pat. TF	1.08 (0.74–1.59)	1.05 (0.68–1.62)
LOS >13 days (vs ≤13)	DE	0.69 (0.45–1.08)	0.72 (0.46–1.13)
	TF	0.97 (0.93–1.01)	0.97 (0.93–1.02)
NIMV/HFNC duration >4 days (vs ≤4)	DE	0.91 (0.59–1.39)	0.86 (0.54–1.36)
	TF	1.01 (0.98–1.05)	1.01 (0.96–1.05)

Model 1: unadjusted
Model 2: adjusted for age, sex, Charlson Comorbidity Index, PaO_2/FiO_2
Abbreviations: DE, Diaphragmatic Excursion; TF, Thickening Fraction; LOS, Length of Stay; NIMV, Non-Invasive Mechanical Ventilation; HFNC, High-Flow Nasal Cannula.

Finally, considering the MNA as the nutritional screening tool with higher diagnostic performance, a Pearson correlation analysis was assessed between Total MNA score and mean DE and TF. This investigation observed a weak but statistically significant positive correlation with DE ($r = 0.189$, $p = 0.033$) and no significant association with TF ($r = -0.109$, $p = 0.221$).

Discussion

In this PhD research project, it was evaluated the performance of commonly used nutritional screening tools in patients with acute hypercapnic respiratory failure treated with non-invasive respiratory support and explored their association with clinical and functional outcomes. The main findings of this study suggest a high prevalence of malnutrition in these respiratory patients and a stronger association between Total MNA score and malnutrition, as defined by GLIM criteria.

To date, no study has directly compared the diagnostic performance of different screening tools in hypercapnic respiratory patients. This comprehensive head-to-head comparison demonstrated that all evaluated nutritional screening instruments had a malnutrition discriminatory capability, however in this peculiar population, their diagnostic performance varied substantially.

Among the tools assessed, the MNA showed the highest distinguishing ability, achieving good overall diagnostic accuracy. This finding is consistent with previous evidence from geriatric and hospitalized populations, in which MNA-based tools outperformed shorter or disease-focused screening instruments.[16] The superior performance of the Total MNA likely reflects its multidimensional structure, which integrates dietary intake, recent weight loss, functional status, mobility, and anthropometric parameters. Such a comprehensive approach may be particularly relevant in patients with acute respiratory failure, in whom malnutrition is often multifactorial and closely intertwined with functional decline and comorbidity burden.[78]

The MNA-SF, MUST, and NRS-2002 also demonstrated good diagnostic performance, although slightly inferior to the Total MNA. NRS-2002 is widely recommended in hospitalized patients due to its incorporation of disease severity[63]; however, our findings suggest that, in this specific respiratory population, the inclusion of functional and geriatric domains, as provided by MNA-based tools, may offer additional diagnostic value. Conversely, SNAQ and MST showed only moderate accuracy, which is in line with their original validation in community-dwelling or general inpatient populations rather than in acutely ill respiratory patients requiring ventilatory support.[32]

In COPD cohorts receiving NIV, most evidence has relied on single-tool approaches, particularly NRS-2002. In a ward-based NIV setting for COPD with type II respiratory failure, Cui et al. reported that NRS-2002 identifies nutritional risk and relates to clinically relevant outcomes during NIV care.[64] Similarly, Chen et al. supported NRS-2002 as a prognostic tool in hospitalized COPD patients with respiratory failure, including readmission-related outcomes.[65] Taken together, prior literature supports the prognostic relevance of NRS-2002, but does not establish it as the better diagnostic tool against GLIM, nor does it compare it directly with other tools in a hypercapnic acute-care population.

Therefore, our findings extend the field by suggesting that when the target is GLIM-defined malnutrition, the full MNA may be more discriminative than tools primarily designed for rapid risk screening in mixed medical inpatients. Indeed, from an emergency hospitalization perspective, new data also supports the value of MNA-based screening in respiratory admissions.

A recent study in older patients urgently hospitalized for respiratory diseases found MNA-SF to be a significant predictor of mortality risk, reinforcing that MNA-derived scores may capture clinically meaningful vulnerability in acute respiratory presentations.[10] This aligns with our observation that MNA-based tools continue to be robust even in acute settings, where feasibility can be challenging but the clinical payoff of early risk stratification remains high.

In addition, the present results confirm that malnourished patients experienced longer hospital stays, prolonged duration of non-invasive respiratory support, and substantially higher in-hospital and three-month mortality rates compared with well-nourished patients. As mentioned before, prior observational studies conducted in patients with COPD exacerbations or acute respiratory failure have consistently demonstrated that nutritional risk or malnutrition is associated with increased mortality, longer hospitalizations, and higher rates of treatment failure or complications in this clinical population.[64-65,78-79]

In line with these reports, our findings reinforce the concept that malnutrition represents not only a marker of baseline vulnerability, but also a determinant of delayed recovery, increased healthcare resource utilization and adverse prognosis during acute respiratory illness.

When evaluating the independent association between nutritional indicators and clinical outcomes, the MNA-SF score emerged as the only variable independently associated with three-month mortality, whereas serum albumin and total protein levels did not retain prognostic significance.

This result aligns with current evidence and international consensus, which recognizes that biochemical markers are strongly influenced by inflammation, fluid shifts, and acute illness, thereby limiting their reliability as indicators of nutritional status or prognosis in critically ill patients.[41]

In contrast, screening tools that incorporate clinical, functional, and nutritional dimensions seem to better capture the complexity of malnutrition and its prognostic implications. Interestingly, although serum albumin was not associated with mortality, higher albumin levels were independently associated with a shorter length of hospital stay. This finding may reflect the role of albumin as a marker of illness severity and systemic inflammation rather than a direct surrogate of nutritional status.[39-40]

Conversely, the positive association between total serum proteins and length of stay likely reflects residual confounding related to inflammation, acute-phase response, or underlying disease burden, highlighting the difficulty of interpreting isolated laboratory parameters in acute care settings. No independent association was observed between nutritional indicators and the duration of non-invasive respiratory support. This may suggest that ventilatory support duration is influenced by multiple factors beyond nutritional status alone, including disease etiology that may lead to differences in weaning or escalation of care.

Finally, in the present study, we found no significant association between nutritional status and diaphragmatic thickening fraction, while only a weak positive correlation was observed between Total MNA score and diaphragmatic excursion. These findings suggest that, during acute respiratory failure, diaphragmatic dysfunction may be influenced by multiple factors beyond nutritional status alone, including acute inflammation, hypercapnia, mechanical loading, and patient–ventilator interaction. In fact, while chronic malnutrition has been associated with respiratory muscle weakness in stable respiratory diseases, in acute setting it's likely that respiratory sarcopenia and not the sole malnutrition may prevail and influence the ultrasound-derived diaphragmatic parameters.

Our secondary objectives of the study demonstrated that sarcopenic patients presented a reduced diaphragmatic motility when compared to non-sarcopenic patients and a positive correlation between HGS and DE resulted in all patients.

Indeed, a statistically significant inverse association was found between DE and sarcopenia, even when adjusting for possible confounding factors as age, sex, body mass index, comorbidity burden and severity of respiratory failure. The persistence of the association between DE and sarcopenia could support the hypothesis that reduced diaphragmatic mobility may be related to intrinsic respiratory dysfunction rather than being solely driven by frailty, illness severity, or anthropometric factors.

Our results confirm the study by Deniz et al. demonstrating that sarcopenic older patients have thinner diaphragmatic thickness compared to non-sarcopenic subjects.[53]

However, patients with chronic pulmonary diseases, heart failure or pulmonary malignancies were excluded from that study.[53]

Similarly, Lee et al. showed that diaphragm thickness correlates closely with established markers of sarcopenia, and that both inspiratory and expiratory muscle strength are strongly linked to diaphragmatic thickness even after adjustment for confounders.[83]

These findings support the use of diaphragm thickness and respiratory muscle strength as practical indicators of sarcopenia in older adults.[83] To our knowledge, this is the first study analyzing sarcopenia and diaphragmatic thickness and excursion derived from US-based assessment in patients with ARF under NIMV or HFNC.

In line with present literature, our results confirm that sarcopenic patients admitted to hospital for acute respiratory failure requiring respiratory support have a significantly lower DE at quiet breathing and TF. In addition, a recent work of Cerundolo et al has suggested a novel combination of lung, diaphragm and right vastus lateralis muscle thickness ultrasound in old, frail patients with acute respiratory illness.[84] They linked the Primary Care Frailty Index to ultrasound measurements to have clinically relevant information on frailty and worse outcomes and improve the management of geriatric patients with respiratory illness.[84]

Our rationale for exploring respiratory sarcopenia during acute hypercapnic respiratory failure derives from the well-established link between malnutrition, muscle loss, and impaired respiratory mechanics. Malnutrition is a primary driver of skeletal muscle catabolism, including diaphragmatic and accessory respiratory muscles.[85-87] In this context, diminished diaphragmatic mass and contractile capacity can impair CO_2 clearance, increase the work of breathing, and predispose patients to noninvasive ventilation failure and worse clinical outcomes.

Thus, integrating nutritional vulnerability and respiratory sarcopenia into our analysis provides a physiologically coherent framework for understanding heterogeneity in outcomes in hypercapnic respiratory failure. Interestingly, pressure support was higher in non-sarcopenic patients, suggesting that ventilatory assistance did not confound the observed poorer diaphragmatic performance in the sarcopenic group. Individuals with sarcopenia generally exhibit impaired inspiratory pressure generation, as consistently described in studies linking sarcopenia to weaker maximal inspiratory and expiratory pressures and thinner diaphragmatic musculature.[82] Such patients may poorly tolerate higher levels of pressure support that can provoke patient–ventilator desynchrony and could be ventilated by clinicians with more cautious support settings. This aspect may support the interpretation that the reduced diaphragmatic motility observed in these patients reflects an intrinsic respiratory muscle impairment rather than an effect of ventilatory assistance.

Considering these perspectives, establishing at admission patients with pathological diaphragmatic motility related to sarcopenia under respiratory support, through a practical and low-cost tool as the bedside thoracic ultrasound, may help to stratify those at increased risk of mortality who require additional interventions.

In this context, our results showed a significant inverse relationship between diaphragmatic motility and sarcopenia. During a systemic inflammation induced by an exacerbation of a respiratory disease, patients with sarcopenia at admission may be more predisposed to develop respiratory muscle weakness and diaphragmatic dysfunction as well. However, when considering the association between diaphragmatic parameters and adverse outcomes such as three-month mortality, hospital stay duration, and total ventilation time, we did not find substantial results. Recent studies on COPD have demonstrated that a reduced diaphragm TF could be useful to predict NIV failure, longer hospital stay, and higher mortality rate.[52, 88-89] Marchioni et al. found that COPD patients with a diaphragmatic TF <20%, and requiring non-invasive ventilation, were 4.4-times more likely to require intubation.[80] Additionally, they more frequently underwent tracheostomies and experienced higher rates of in-hospital and 90-day mortality, but no longer hospital stays.[80]

In our population we did not find any significant differences in adverse outcomes between patients with impaired or preserved diaphragmatic functions. Possible explanations for these results may be the different causes of ARF included in the study. In fact, our study sample enrolled older people hospitalized for any respiratory disease, including end-stage chronic interstitial lung disease and any grade of lung cancer, which *per se* have a poor prognosis. For the same reason, our hospital LOS and respiratory support duration were much longer than in previous studies in COPD, considering that some of our patients were discharged home with HFNC or died without the possibility of NIMV weaning. Indeed, the heterogeneity of respiratory conditions in our cohort may have influenced diaphragmatic function and clinical outcomes, as different diseases affect respiratory mechanics and systemic inflammation in distinct ways.

Our exploration analyses on the sole COPD and oncological patients suggest that the relationship between sarcopenia and diaphragmatic dysfunction may be attributable to underlying disease and larger, disease-specific studies are needed to further clarify these patterns. Moreover, Mercurio et al. demonstrated that a TF lower than 36.3% could predict NIV failure in hypoxemic patients, unlike our study, which considered a cut-off of 20% in accordance with other published studies.[60,82]

Finally, it could be hypothesized that other factors that were not considered in our analysis might have influenced the length of hospital stay in our study, such as intra-hospital infections or lack of family support at discharge.

Clinical implications

The results of this PhD project have relevant clinical implications. First, they highlight the high burden of malnutrition in patients treated with non-invasive respiratory support and its association with clinically meaningful outcomes. Second, they suggest that reliance on a single screening tool—often chosen for convenience rather than validated performance—may be suboptimal in this setting. The superior diagnostic accuracy of the Total MNA score supports its use as a valuable screening instrument even in acute care, if patient cooperation allows its administration. Indeed, this research's project findings highlight the applicability and relevance of US techniques in the examination of diaphragm in patients during an acute respiratory event.

Beyond its diagnostic value, early diaphragmatic ultrasound may have several relevant clinical applications in the management of ARF.

First, bedside assessment of diaphragm excursion could assist in triage by identifying patients with markedly reduced respiratory muscle reserve who need closer monitoring or earlier consideration of alternative support strategies.

Second, diaphragmatic dysfunction may contribute to prognostic stratification, as reduced mobility has been associated with worse outcomes in selected respiratory populations.

Thus incorporating diaphragm assessment into initial evaluation may therefore help identify frail individuals who would benefit from tailored ventilatory strategies.[80,82,88-91]

Finally, detecting impaired diaphragmatic function at admission could support early rehabilitation planning, including respiratory muscle training, optimization of nutritional status, and individualized weaning protocols aimed at preserving muscle activity.

Strengths and limitations

This study has several strengths, including the prospective assessment of multiple nutritional screening tools, the use of GLIM criteria as a reference standard, and the focus on a clinically relevant population treated with non-invasive respiratory support. Nevertheless, some limitations should be acknowledged.

First, the sample size enrolled was rather limited, considering the wider range of pulmonary diseases included in the study. Except for the exploratory subgroup analyses on COPD and oncological groups, the modest sample size did not allow us to stratify the analysis according to the different respiratory causes of ARF, which could have potentially influenced our primary and secondary outcomes. Indeed, the observational nature of the study does not allow causal inferences. Moreover, in the secondary analysis, a priori sample size calculation was not conducted. The post hoc estimation of statistical power showed adequate power for diaphragmatic excursion but lower power for thickening fraction, which may have limited our ability to detect significant associations involving TF.

Second, although M-mode US has resulted in good intra- and interobserver variability in assessing the diaphragm, the lack of data on interobserver variability was a main limitation of the present study.[58-60] Furthermore, diaphragmatic motility by US assessment was performed during spontaneous breathing without any evaluation of lung volumes. Since different volumes correlate with the diaphragm’s ability to contract, the measurement of volumes might have helped us to understand better the overall mechanism leading to progressive diaphragmatic dysfunction. In addition, we could only evaluate the right hemidiaphragm due to the presence of the liver as an appropriate ultrasound window that allowed us to obtain optimal images. However, without diaphragm lesions or paralysis, it is unlikely that the assessment of the left hemidiaphragm might have changed the results of the present study.

Third, we could not perform phrenic nerve stimulation to measure diaphragmatic dysfunction, and this aspect was not reassessed over time, limiting insight into potential spontaneous recovery.

A further limitation is the absence of direct body composition measurements, such as bioelectrical impedance analysis. This prevented a more precise characterization of muscle mass and the use of calf circumference as a surrogate of it in acutely ill patients may introduce misclassification bias. Concomitant conditions such as congestive heart failure could have led to an overestimation of calf circumference, potentially resulting in an underdiagnosis of sarcopenia.

This bias would likely have attenuated the observed associations, suggesting that our findings may be conservative and could be strengthened if more precise body composition methods were available.

Although further validation is required, early identification of malnutrition using an appropriate screening tool may facilitate timely nutritional interventions, potentially improve recovery trajectories and reduce resource utilization in patients with acute respiratory failure.

Importantly, this study could provide a basis for further investigating the use of DE and TF into the routine evaluation and as screening tools in predicting worse outcomes in patients with sarcopenia at admission. Diaphragmatic US being economical and easily accessible, could provide a more evident confirmation of the respiratory efficiency, and be extended, thanks to the possibility of a quick evaluation at bedside, to acutely ill patients undergoing non-invasive mechanical ventilation outside intensive care units.

Conclusions

The relationship between nutritional status and respiratory muscle function remains an area of growing interest. Overall, these findings underscore the clinical relevance of early nutritional screening using validated tools, particularly MNA-based instruments, in patients with acute hypercapnic respiratory failure. In this population malnutrition is highly prevalent and associated with worse clinical outcomes. Among commonly used screening tools, the Total MNA score demonstrated the better diagnostic performance for identifying GLIM-defined malnutrition.

Establishing malnutrition at admission may help stratify patients at higher risk of poor outcomes and prompt timely, individualized nutritional interventions, with potential implications for recovery trajectories and healthcare resource utilization. Future research needs to evaluate the prognostic role of diaphragmatic dysfunction, easily assessed at bedside by US, in predicting adverse events or worse survival in respiratory diseases other than COPD. This would eventually help to stratify those at increased risk of mortality due to the development of respiratory muscle fatigue which may be worsened by the concomitant presence of malnutrition and/or sarcopenia.

Author’s declaration

I declare no conflict of interest.

This research received no external funding.

I am thankful to my colleagues who collaborated in data collection for their valuable contribution, and to all the study participants of this PhD research project.

References

1. Cederholm T, Bosaeus I. Malnutrition in adults. N Engl J Med. 2024;391(2):155–165. doi:10.1056/NEJMra2212159
2. Schuetz P, Seres D, Lobo DN, Gomes F, Kaegi-Braun N, Stanga Z. Management of disease-related malnutrition for patients being treated in hospital. The Lancet. 2021 Nov 20;398(10314):1927-38.
3. Cass AR, Charlton KE. Prevalence of hospital-acquired malnutrition and modifiable determinants of nutritional deterioration during inpatient admissions: a systematic review of the evidence. Journal of Human Nutrition and Dietetics. 2022 Dec;35(6):1043-58.
4. Hiura G, Lebwohl B, Seres DS. Malnutrition diagnosis in critically ill patients using 2012 Academy of Nutrition and Dietetics/American Society for Parenteral and Enteral Nutrition standardized diagnostic characteristics is associated with longer hospital and intensive care unit length of stay and increased in-hospital mortality. JPEN J Parenter Enteral Nutr. 2020;44(2):256–264. doi:10.1002/jpen.1599
5. Wolters M, Volkert D, Streicher M, Kiesswetter E, Torbahn G, O'Connor EM, O'Keeffe M, Kelly M, O'Herlihy E, O'Toole PW, Timmons S. Prevalence of malnutrition using harmonized definitions in older adults from different settings–A MaNuEL study. Clinical Nutrition. 2019 Oct 1;38(5):2389-98.
6. Viasus D, Pérez-Vergara V, Carratalà J. Effect of undernutrition and obesity on clinical outcomes in adults with community-acquired pneumonia. Nutrients. 2022;14(15):3235. doi:10.3390/nu14153235
7. Hegelund MH, Ryrsø CK, Ritz C, et al. Are undernutrition and obesity associated with post-discharge mortality and rehospitalization after hospitalization with community-acquired pneumonia? Nutrients. 2022;14(22):4906. doi:10.3390/nu14224906
8. Shi X, Shen Y, Yang J, Du W, Yang J. Relationship of the geriatric nutritional risk index to mortality and length of stay in elderly patients with acute respiratory failure: a retrospective cohort study. Heart Lung. 2021;50(6):898–905. doi:10.1016/j.hrtlng.2021.07.012
9. Folven KI, Biringer E, Nilsen RM, et al. Increased risk of rehospitalisation and death in older hospital patients at risk of malnutrition: a cohort study. J Nutr Health Aging. 2025;29(2):100455. doi:10.1016/j.jnha.2024.100455
10. Ishiwari M, Kono Y, Togashi Y, et al. Mini Nutritional Assessment Short-Form as a risk factor for mortality in patients with respiratory disease undergoing urgent hospitalization. BMC Geriatr. 2025;25(1):113. doi:10.1186/s12877-025-05767-2
11. Feng M, Liu Y, Li Q, et al. Association between geriatric nutritional risk index and adverse outcomes in critically ill patients with chronic obstructive pulmonary disease: a cohort study of 2824 older adults. BMC Pulm Med. 2024;24(1):634. doi:10.1186/s12890-024-03454-3

12. Tseng HK, Cheng YJ, Yu HK, et al. Malnutrition and frailty are associated with a higher risk of prolonged hospitalization and mortality in hospitalized older adults. Nutrients. 2025;17(2):221. doi:10.3390/nu17020221
13. Orlandoni P, Peladic NJ, Di Rosa M, Venturini C, Lattanzio F. Undernourished and undertreated: the role of nutritional care in geriatric hospital outcomes. Nutrients. 2025;17(18):3021. doi:10.3390/nu17183021
14. Baumgartner A, Hasenboehler F, Cantone J, et al. Effect of nutritional support in patients with lower respiratory tract infection: secondary analysis of a randomized clinical trial. Clin Nutr. 2021;40(4):1843–1850. doi:10.1016/j.clnu.2020.10.009
15. Silva-García J, García-Grimaldo A, Rodríguez-Moguel NC, et al. Malnutrition is associated with clinical outcomes in mechanically ventilated patients with pneumonia and other lung manifestations: a retrospective cohort study. Nutr Clin Pract. 2025;40(4):870–879. doi:10.1002/ncp.11269
16. Cereda E, Pedrolli C, Klersy C, et al. Nutritional status in older persons according to healthcare setting: A systematic review and meta-analysis of prevalence data using MNA ®. Clinical Nutrition. 2016;35(6):1282-1290. doi:10.1016/j.clnu.2016.03.008
17. Lunardi AC, Miranda CS, Silva KM, Cecconello I, Carvalho CR. Weakness of expiratory muscles and pulmonary complications in malnourished patients undergoing upper abdominal surgery. Respirology. 2012;17(1):108–113. doi:10.1111/j.1440-1843.2011.02049.x
18. Dias CM, Pássaro CP, Cagido VR, et al. Effects of undernutrition on respiratory mechanics and lung parenchyma remodeling. J Appl Physiol (1985). 2004;97(5):1888–1896. doi:10.1152/japplphysiol.00091.2004
19. Kobayashi S, Ono M, Ishida M, et al. Malnutrition in Japanese patients with chronic obstructive pulmonary disease: a prospective cohort study. Medicine (Baltimore). 2025;104(41):e45203. doi:10.1097/MD.0000000000045203
20. Keogh E, Williams EM. Managing malnutrition in COPD: a review. Respir Med. 2021;176:106248. doi:10.1016/j.rmed.2020.106248
21. Budweiser S, Meyer K, Jörres RA, et al. Nutritional depletion and its relationship to respiratory impairment in patients with chronic respiratory failure due to COPD or restrictive thoracic diseases. Eur J Clin Nutr. 2008;62(3):436–443. doi:10.1038/sj.ejcn.1602708
22. Cano NJ, Roth H, Court-Ortuné I, et al. Nutritional depletion in patients on long-term oxygen therapy and/or home mechanical ventilation. Eur Respir J. 2002;20(1):30–37. doi:10.1183/09031936.02.01812001
23. Eraslan Doganay G, Cirik MO. Determinants of prognosis in geriatric patients followed in respiratory ICU: either infection or malnutrition. Medicine (Baltimore). 2021;100(36):e27159. doi:10.1097/MD.0000000000027159
24. Dent E, Wright ORL, Woo J, Hoogendijk EO. Malnutrition in older adults. Lancet. 2023;401(10380):951–966. doi:10.1016/S0140-6736(22)02612-5
25. Janssens JP, Krause KH. Pneumonia in the very old. Lancet Infect Dis. 2004;4(2):112–124. doi:10.1016/S1473-3099(04)00931-4

26. Cruz-Jentoft AJ, Volkert D. Malnutrition in older adults. N Engl J Med. 2025;392(22):2244–2255. doi:10.1056/NEJMra2412275

27. Norman K, Haß U, Pirlich M. Malnutrition in older adults—recent advances and remaining challenges. Nutrients. 2021;13(8):2764. doi:10.3390/nu13082764

28. Gea J, Sancho-Muñoz A, Chalela R. Nutritional status and muscle dysfunction in chronic respiratory diseases: stable phase versus acute exacerbations. J Thorac Dis. 2018;10(Suppl 12):S1332–S1354. doi:10.21037/jtd.2018.02.66

29. Battaglia S, Spatafora M, Paglino G, et al. Ageing and COPD affect different domains of nutritional status: the ECCE study. Eur Respir J. 2011;37(6):1340–1345. doi:10.1183/09031936.00032310

30. Cederholm T, Jensen GL, Correia MITD, et al. GLIM criteria for the diagnosis of malnutrition: a consensus report from the Global Clinical Nutrition Community. Clin Nutr. 2019;38(1):1–9. doi:10.1016/j.clnu.2018.08.002

31. Cederholm T, Jensen GL, Correia MITD, et al. The GLIM consensus approach to diagnosis of malnutrition: a 5-year update. Clin Nutr. 2025;49:11–20. doi:10.1016/j.clnu.2025.03.018

32. Cederholm T, Bosaeus I, Barazzoni R, et al. Diagnostic criteria for malnutrition – An ESPEN Consensus Statement. *Clinical Nutrition*. 2015;34(3):335-340. doi:10.1016/j.clnu.2015.03.001

33. Jensen GL, Cederholm T, Correia MITD, et al. GLIM consensus approach to diagnosis of malnutrition: a 5-year update. JPEN J Parenter Enteral Nutr. 2025;49(4):414–427. doi:10.1002/jpen.2756

34. Schuetz P, Seres D, Lobo DN, et al. Management of disease-related malnutrition for patients being treated in hospital. Lancet. 2021;398(10314):1927–1938. doi:10.1016/S0140-6736(21)01451-3

35. Ishiwari M, Kono Y, Togashi Y, et al. Comparison of three nutritional screening tools in older patients with urgent hospitalization for various respiratory diseases. Intern Med (Tokyo). 2025. doi:10.2169/internalmedicine.6034-25

36. Kaluźniak-Szymanowska A, Krzymińska-Siemaszko R, Wieczorowska-Tobis K, Deskur-Śmielecka E. Optimal assessment of nutritional status in older subjects with chronic obstructive pulmonary disease: comparison of three screening tools used in the GLIM diagnostic algorithm. Int J Environ Res Public Health. 2022;19(3):1025. doi:10.3390/ijerph19031025

37. Stephenson H, Roberts M, Klimkeit E, Smith T. Uncovering undernutrition in chronic obstructive pulmonary disease: beyond body mass index. Respir Med. 2022;205:107026. doi:10.1016/j.rmed.2022.107026

38. Serón-Arbeloa C, Labarta-Monzón L, Puzo-Foncillas J, et al. Malnutrition screening and assessment. Nutrients. 2022;14(12):2392. doi:10.3390/nu14122392

39. Ostermann M. Laboratory assessment of nutritional status in ICU patients. Curr Opin Clin Nutr Metab Care. 2025;28(6):509-514. doi: 10.1097/MCO.0000000000001165.

40. Keller U. Nutritional laboratory markers in malnutrition. *J Clin Med*. 2019;8(6):775. doi:10.3390/jcm8060775

41. Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. *Nutrients*. 2017;9(8):829. doi:10.3390/nu9080829

42. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. The Lancet. 2019 Jun 29;393(10191):2636-46.

43. Sayer AA, Cooper R, Arai H, Cawthon PM, Ntsama Essomba MJ, Fielding RA, Grounds MD, Witham MD, Cruz-Jentoft AJ. Sarcopenia. Nature Reviews Disease Primers. 2024 Sep 19;10(1):68.

44. Sayer AA, Cruz-Jentoft A. Sarcopenia definition, diagnosis and treatment: consensus is growing. Age and ageing. 2022 Oct 1;51(10):afac220.

45. Kera T, Kawai H, Hirano H, et al. Definition of Respiratory Sarcopenia With Peak Expiratory Flow Rate. *J Am Med Dir Assoc*. 2019;20(8):1021-1025. doi:10.1016/j.jamda.2018.12.013

46. Schols AMWJ. Pulmonary cachexia. *Int J Cardiol*. 2002;85(1):101-110. doi:10.1016/S0167-5273(02)00238-3

47. Nagano A, Wakabayashi H, Maeda K, et al. Respiratory sarcopenia and sarcopenic respiratory disability: concepts, diagnosis, and treatment. *J Nutr Health Aging*. 2021;25:507–515.

48. Jones SE, Maddocks M, Kon SSC, et al. Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. Thorax. 2015;70(3):213-218. doi:10.1136/thoraxjnl-2014-206440

49. Chailleux E, Laaban JP, Veale D. Prognostic Value of Nutritional Depletion in Patients With COPD Treated by Long-term Oxygen Therapy. *Chest*. 2003;123(5):1460-1466. doi:10.1378/chest.123.5.1460

50. Grosu HB, Lee YI, Lee J, Eden E, Eikermann M, Rose KM. Diaphragm Muscle Thinning in Patients Who Are Mechanically Ventilated. *Chest*. 2012;142(6):1455-1460. doi:10.1378/chest.11-1638

51. Decramer M, Lacquet LM, Fagard R, et al. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med*. 1994;150:11–16.

52. Cao Y, Li P, Wang Y, et al. Diaphragm dysfunction and rehabilitation strategy in patients with chronic obstructive pulmonary disease. *Front Physiol*. 2022;13:872277.

53. Deniz O, Coteli S, Karatoprak NB, et al. Diaphragmatic muscle thickness in older people with and without sarcopenia. *Aging Clin Exp Res*. 2021;33:573–580.

54. Pingleton SK. Enteral nutrition in patients with respiratory disease. Eur Respir J. 1996;9(2):364–370. doi:10.1183/09031936.96.09020364

55. Houston JG, Angus RM, Cowan MD, McMillan NC, Thomson NC. Ultrasound assessment of normal hemidiaphragmatic movement: relation to inspiratory volume. Thorax. 1994;49(5):500-503. doi:10.1136/thx.49.5.500

56. Houston JG, Fleet M, Cowan MD, McMillan NC. Comparison of ultrasound with fluoroscopy in the Assessment of suspected hemidiaphragmatic movement abnormality. Clin Radiol. 1995;50(2):95-98. doi:10.1016/S0009-9260(05)82987-3

57. Sferrazza Papa GF, Pellegrino GM, Di Marco F, et al. A Review of the Ultrasound Assessment of Diaphragmatic Function in Clinical Practice. Respiration. 2016;91(5):403-411. doi:10.1159/000446518

58. Testa A, Soldati G, Giannuzzi R, Berardi S, Portale G, Gentiloni Silveri N. Ultrasound M-Mode Assessment of Diaphragmatic Kinetics by Anterior Transverse Scanning in Healthy Subjects. Ultrasound Med Biol. 2011;37(1):44-52. doi:10.1016/j.ultrasmedbio.2010.10.004

59. Scarlata S, Mancini D, Laudisio A, Benigni A, Antonelli Incalzi R. Reproducibility and Clinical Correlates of Supine Diaphragmatic Motion Measured by M-Mode Ultrasonography in Healthy Volunteers. Respiration. 2018;96(3):259-266. doi:10.1159/000489229

60. Boussuges A, Gole Y, Blanc P. Diaphragmatic Motion Studied by M-Mode Ultrasonography. Chest. 2009;135(2):391-400. doi:10.1378/chest.08-1541

61. Cohn D, Benditt JO, Eveloff S, McCool FD. Diaphragm thickening during inspiration. J Appl Physiol. 1997;83(1):291-296. doi:10.1152/jappl.1997.83.1.291

62. Gottesman E, McCool FD. Ultrasound evaluation of the paralyzed diaphragm. Am J Respir Crit Care Med. 1997;155(5):1570-1574. doi:10.1164/ajrccm.155.5.9154859

63. Kondrup J. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clinical Nutrition. 2003;22(3):321-336. doi:10.1016/S0261-5614(02)00214-5

64. Cui J, et al. Nutritional Risk Screening 2002 as a predictor of outcome during general ward–based noninvasive ventilation in chronic obstructive pulmonary disease with type II respiratory failure. *Clin Respir J.* 2015.

65. Chen R, et al. The use of Nutritional Risk Screening 2002 to predict readmission rate in COPD patients with respiratory failure. *Eur J Intern Med.* 2017.

66. Rochwerg B, Brochard L, Elliott MW, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J*. 2017;50:1700581.

67. Skipper A, Ferguson M, Thompson K, Castellanos VH, Porcari J. Nutrition Screening Tools. *Journal of Parenteral and Enteral Nutrition*. 2012;36(3):292-298. doi:10.1177/0148607111414023

68. Stratton RJ, King CL, Stroud MA, Jackson AA, Elia M. 'Malnutrition Universal Screening Tool' predicts mortality and length of hospital stay in acutely ill elderly. British Journal of Nutrition. 2006;95(2):325-330. doi:10.1079/BJN20051622

69. Wilson MMG, Thomas DR, Rubenstein LZ, et al. Appetite assessment: simple appetite questionnaire predicts weight loss in community-dwelling adults and nursing home residents. Am J Clin Nutr. 2005;82(5):1074–1081

70. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*. 2019;48:16–31.

71. Vaishya R, Misra A, Vaish A, Ursino N, D'Ambrosi R. Hand grip strength as a proposed new vital sign of health: a narrative review of evidences. *J Health Popul Nutr*. 2024;43(1):7. doi:10.1186/s41043-024-00500-y.

72. Rolland Y, Lauwers-Cances V, Cournot M, et al. Sarcopenia, calf circumference, and physical function of elderly women: a cross-sectional study. *J Am Geriatr Soc.* 2003;51:1120–1124.

73. Kim M, Shinkai S, Murayama H. Calf circumference as a surrogate marker of muscle mass for diagnosing sarcopenia in older adults. *Geriatr Gerontol Int.* 2020;20:7–12.

74. Barbosa-Silva TG, Bielemann RM, Gonzalez MC, et al. Prevalence of sarcopenia among community-dwelling elderly in Brazil: a comparison of CC, BIA, and skeletal muscle mass by anthropometry. *Am J Clin Nutr.* 2016;103:1220–1226.

75. Kawakami R, Miyachi M, Sawada SS, Torii S, Midorikawa T, Tanisawa K, Ito T, Usui C, Ishii K, Suzuki K, Sakamoto S, Higuchi M, Muraoka I, Oka K. Cut-offs for calf circumference as a screening tool for low muscle mass: WASEDA'S Health Study. *Geriatr Gerontol Int.* 2020;20(10):943-950. doi:10.1111/ggi.14025.

76. Sarwal A, Parry SM, Berry MJ, et al. Interobserver reliability of quantitative muscle ultrasound in ICU patients. *Chest.* 2015;147:1283–1290.

77. Summerhill EM, El-Sameed YA, Glidden TJ, et al. Monitoring recovery from diaphragm paralysis with ultrasonography. *Chest.* 2008;133:737–743.

78. Guigoz Y. The mini nutritional assessment (MNA®) review of the literature-what does it tell us?. Journal of Nutrition Health and Aging. 2006 Nov 1;10(6):466.

79. Hallin R, Gudmundsson G, Suppli Ulrik C, et al. Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). *Respir Med.* 2007;101(9):1954–1960. doi:10.1016/j.rmed.2007.04.009

80. Marchioni A, Castaniere I, Tonelli R, et al. Ultrasound-assessed diaphragmatic impairment is a predictor of outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease undergoing noninvasive ventilation. *Crit Care.* 2018;22(1):109. doi:10.1186/s13054-018-2033-x

81. Vivier E, Mekontso-Dessap A, Phael A, et al. Diaphragm ultrasonography to estimate the work of breathing during non-invasive ventilation. *Intensive Care Med.* 2012;38:796–803. https://doi.org/10.1007/s00134-012-2547-7

82. Mercurio G, D'Arrigo S, Moroni R, et al. Diaphragm thickening fraction predicts noninvasive ventilation outcome: a preliminary physiological study. *Crit Care*. 2021;25:219.

83. Lee Y, Son S, Kim DK, Park MW. Association of Diaphragm Thickness and Respiratory Muscle Strength With Indices of Sarcopenia. Ann Rehabil Med. 2023;47(4):307-314. doi:10.5535/arm.23081

84. Cerundolo N, Siniscalchi C, Okoye C, Scarlata S, Parise A, Rendo M, Guerra A, Meschi T, Nouvenne A, Ticinesi A. Integrated Lung, Diaphragm and Lower Limb Muscular Ultrasound: Clinical Correlations in Geriatric Patients with Acute Respiratory Illness. *Diagnostics (Basel).* 2025;15(1):87. doi:10.3390/diagnostics15010087.

85. Selçuk KT, Arslan S, Aydın A, Durmaz D. Which screening tool performs best in identifying malnutrition risk among hospitalized older adults with cardiovascular disease? *Eur Geriatr Med*. 2025;16:1493–1505. doi:10.1007/s41999-025-01187-y

86. Arslan S, Dal N, Tari Selçuk K, Şahin N, Atan RM. Identifying malnutrition risk in hospitalized patients: an analysis of five tools in the light of GLIM criteria. *Postgrad Med*. 2024;136(5):504–513. doi:10.1080/00325481.2024.2363169

87. Selçuk KT, Atan RM, Arslan S, Şahin N. Relationship between food insecurity and geriatric syndromes in older adults: a multicenter study in Turkey. *Exp Gerontol*. 2023;172:112054. doi:10.1016/j.exger.2022.112054

88. Numis FG, Morelli L, Bosso G, et al. Diaphragmatic motility assessment in COPD exacerbation, early detection of Non-Invasive Mechanical Ventilation failure: a pilot study. Crit Ultrasound J. 2014;6(S2):A6. doi:10.1186/2036-7902-6-S2-A6

89. Malhotra N, Gothi D, Kumar R, et al. Ultrasound-guided diaphragm evaluation and outcomes in severe acute exacerbation of chronic obstructive pulmonary disease (uDISCO Study): an observational study. *Monaldi Arch Chest Dis.* 2025

90. DiNino E, Gartman EJ, Sethi JM, McCool FD. Diaphragm ultrasound as a predictor of successful extubation from mechanical ventilation. *Chest.* 2014;146:736–741. doi:10.1378/chest.13-2539

91. Santana PV, Aquino Rodriguez R, et al. Ultrasound of diaphragm to monitor diaphragm atrophy and predict outcomes in critically ill patients. Diagnostics. 2023;13:1116. doi:10.3390/diagnostics13061116