ORIGINAL ARTICLE

Malnutrition: muscle wasting, inflammation, RDW, and their relation with adverse outcomes

Desnutrición durante la estancia hospitalaria: desgaste muscular, inflamación, ancho de distribución eritrocitaria y su relación con resultados adversos

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Abstract

Objective: *The objective of the study was to explore red cell distribution width (RDW) as a surrogate marker of inflammation, alone and in conjunction with muscle wasting to predict malnutrition-related adverse outcomes.* **Methods:** *This was a single-center observational study including adult hospitalized patients. Demographic variables, malnutrition criteria, and RDW were captured within 24 hours of hospital admission. Correlation tests and regression models were performed between these variables (RDW and muscle wasting) and adverse outcomes (in-hospital mortality and unplanned transfer to critical care areas (CCA).* **Results:** *Five hundred and forty-five patients were included in the final analysis. Muscle wasting showed an independent association with adverse outcomes in every regression model tested. RDW alone showed fair predictive performance for both outcomes' significance and the adjusted model with muscle wasting showed association only for unplanned transfer to CCA.* **Conclusion:** *RDW did not improve the prediction of adverse outcomes compared to muscle wasting assessed by physical examination and simple indexes for acute and chronic inflammation. Malnourished patients presented higher RDW values showing a possible metabolic profile (higher inflammation and lower muscle). It is still unknown whether nutrition support can influence RDW value over time as a response marker or if RDW can predict who may benefit the most from nutritional support.*

Keywords: *Malnutrition. Inflammation. Muscle. Red cell distribution width. Adult*

Resumen

Objetivo: *Explorar el ancho de distribución eritrocitaria (ADE) como un marcador subrogado de inflamación, individualmente y en conjunto con el desgaste muscular, para predecir resultados adversos asociados a la desnutrición.* **Método:** *Estudio unicéntrico, observacional, incluyendo pacientes adultos hospitalizados. Se capturaron variables demográficas, criterios de desnutrición y el ADE en las primeras 24 horas de ingreso. Se realizaron pruebas de correlación y modelos de regresión entre dichas variables (ADE y desgaste) y resultados adversos (mortalidad hospitalaria y traslado no planeado a áreas críticas).* **Resultados:** *Se incluyeron 545 pacientes. El desgaste muscular mostró asociación independiente con los resultados adversos en cada modelo. El ADE individualmente mostró un desempeño aceptable para la predicción de ambos resultados, y en modelos ajustados con desgaste muscular mostró asociación únicamente con traslado no planeado a áreas críticas.*

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Conclusiones: *El ADE no mejoró la predicción de resultados adversos comparado con el desgaste muscular por exploración física e índices simples de inflamación. Los pacientes con desnutrición presentaron mayores valores de ADE, mostrando un posible perfil metabólico (mayor inflamación y menos músculo). Aún se desconoce si el soporte nutricional puede influenciar el ADE como un marcador de respuesta o si puede predecir una respuesta favorable al soporte nutricional.*

Palabras clave: *Desnutrición. Inflamación. Músculo. Ancho de distribución eritrocitaria. Adulto.*

Introduction

Malnutrition is known as a risk factor for a large number of adverse outcomes in hospitalized adult patients[1,2]. Malnutrition diagnosis has been recently proposed using the Global Leadership Initiative on Malnutrition (GLIM, core leadership: ASPEN: American Society for Parenteral and Enteral Nutrition, ESPEN: European Society for Parenteral and Enteral Nutrition, FELANPE; Federación Latino Americana de Terapia Nutricional, Nutrición Clínca y Metabolismo and PENSA: The Parenteral and Enteral Nutrition Society of Asia) criteria. The presence of at least one phenotypic criterion (unplanned weight loss, low body mass index [BMI], and decreased muscle mass) and one etiologic criterion (reduced nutrient intake, altered nutrient assimilation or absorption, acute and chronic inflammation) is required to diagnose malnutrition. Once diagnosed the severity of malnutrition will be determined by specific thresholds based on phenotypic criteria[3].

A previous study has shown a correlation between malnutrition and its severity, according to the GLIM criteria, with adverse outcomes such as mortality or worsening of the clinical condition requiring unplanned transfer to critical care areas (CCA). Muscle wasting and inflammation were found to be independent risk factors for such outcomes, as previously shown these are malnutrition characteristics. However, muscle wasting was assessed by physical examination and inflammation was determined using simple indexes related to chronic and acute illness inflammation such as the Charlson comorbidity index (CCI) and the NRS2002 illness severity accordingly (Fig. 1, upper panel)[1].

The inclusion of more objective markers related to muscle mass and inflammation in the nutritional assessment could improve its precision and performance to detect adverse outcomes in adult hospitalized patients.

Red cell distribution width (RDW) shows the discrepancy between red cell volume, represented as a percentage of dispersion or coefficient of variance, representing ineffective erythropoiesis. Previous studies have shown a correlation between higher RDW values and mortality in adult critically ill patients, mainly during sepsis[4-9]. One study showed a correlation between higher RDW and sarcopenia measured with dual-energy X-ray absorptiometry (DEXA), especially in patients with overweight and obesity[10]. It has been theorized that the RDW can be a marker of chronic inflammatory states, given red cells' life span (approximately 120 days) directly affecting erythropoiesis by chronic inflammation and concomitant oxidative stress[11,12].

RDW can be considered a routine test in hospitalized patients, and its use usually does not increase workload and costs of attention, highlighting the relevance of exploring this laboratory test as an inflammatory marker. Given the correlation of muscle wasting and inflammation with adverse outcomes in adult inpatients, we included RDW as a biomarker related to inflammation alone and adjusted for muscle wasting by physical exploration to explore its utility in predicting adverse outcomes (Fig. 1, lower panel).

Methods

Study design and center

This was a single-center observational study carried out in a private (78 beds) teaching hospital. This center has a wide span of capacity for attention to different medical and surgical specialties (orthopedic surgery, general surgery, neurology, neurosurgery, cardiology, geriatrics, internal medicine, gynecology, oncology, etc.).

Inclusion of patients started on the April 21 and ended on the July 31, 2021 (102 days), follow-up ended at hospital discharge.

Inclusion criteria

Every non-pregnant adult patient (≥18 years old) was admitted to regular hospital wards, with RDW processed at the hospital's laboratory within the first 24 h of admission to the ward.

Patients discharged from CCA to the regular ward were included; the assessment was performed at the moment they arrived in the regular ward. Patients admitted from other hospitals for continuity of care were included (as "Other hospital"). Programmed admission (elective) was considered for every patient coming from home to receive previously planned treatment. Previous hospitalization within 6 months before current admission was captured as a binary variable (yes/no).

Exclusion criteria

Patients admitted for bariatric and/or esthetic surgery, previous neuromuscular disease (because muscle mass physical assessment could be biased), admitted for palliative care, or with do not resuscitate order. Patients with hematological malignancies as a history or recent diagnosis (within actual hospitalization), patients admitted for chronic anemia, or with RDW processed after 24 h of admission or in another center were excluded from the study.

Elimination criteria

If information was not provided due to denial of the routine evaluation or inability to communicate and without any family or caregiver to provide the requested information. Patients transferred to another hospital for continuity of care were also eliminated.

Screening and assessment

Nutritional assessment was carried out by the nutrition department by direct interview with the patient or caregiver if communication with the patient was not possible. During the routine evaluation, the clinician searches for phenotypic criteria, such as unplanned weight loss, low BMI (according to age), and muscle wasting; along with etiologic criteria such as low intake and gastrointestinal conditions impairing nutritional intake[3]. Physical assessment was performed searching for reduced muscle mass (as one phenotypic criterion) following the recommendations of the Subjective Global Assessment and Fischer et al. (searching for signs of decreased muscle at the triceps, chest, quadriceps, deltoids, trapezius, temporalis, hands, mild axillary line, etc.). Decreased muscle mass was rated as 0: none, 1+: mild deficit, 2+: moderate deficit, 3+: severe deficit[13,14].

Chronic inflammation was determined by the CCI given that considers only chronic conditions (present if ≥ 1 point), and acute inflammation was determined by the injury score of the NRS 2002 (present if ≥ 1 point), both considered independent etiologic criteria.

Biochemical markers

Hemoglobin (g/dL) and RDW (%) as determined by the local laboratory. Hemoglobin normal value: 12.0-16.0g/dL, RDW normal value: 11.5-15.0%.

Finally, the diagnosis of malnutrition (at least one phenotypic and one etiologic criterion present) and its severity were determined according to the GLIM criteria (3), and a nutritional therapy plan was proposed.

Data collection

The study team collected the variables (including demographic ones) after every screening/assessment (or at the end of the shift).

Outcomes

Mortality and unplanned transfer to CCA were obtained using the information provided by the Rapid Response Team monthly report and the Clinical file service.

Statistical analysis

For the statistical analysis, the Shapiro–Wilk test was used to determine the type of distribution of the quantitative variables, presenting them as mean (standard deviation) or median (interquartile range) if presented normal or non-normal distribution, respectively. Qualitative variables are presented as frequency (percentage).

Receiver operating characteristics (ROC) curves were used to explore the performance of RDW to predict adverse outcomes, showing its Area Under the Curve (AUC).

Finally, binary logistic regression was modeled using different pre-planned models:

Model 1: Muscle wasting, acute inflammation (as NRS2002 injury score), and chronic inflammation (CCI) versus mortality.

Table 1. General characteristics

Variables	Malnutrition		
	No (n = 408)	Yes (n = 137)	Total
Age (years)	46 (35-66)[$]	70 (48-82)[$]	52 (36-71)
Gender			
Male	203 (49.8)[$]	54 (39.4)[$]	257 (47.2)
Female	205 (50.2)[$]	83 (60.6)[$]	288 (52.8)
CCI	0 (0-1)[$]	1 (0-3)[$]	0 (0-2)
BMI	26.63 (24.33-29.74)[$]	23.39 (20.82-26.37)[$]	26.03 (23.44-29.28)
Previous hospitalization*	49 (12.0)[$]	41 (29.9)[$]	90 (16.5)
Source of admission			
Emergency room	326 (79.9)	116 (84.7)	442 (81.1)
Programmed (elective)	58 (14.2)	10 (7.3)	68 (12.5)
Critical areas	18 (4.4)	9 (6.6)	27 (5.0)
Other hospital	6 (1.5)	2 (1.5)	8 (1.5)
Total NRS2002 (points)	1 (0-2)[$]	4 (3-5)[$]	1 (1-3)
Hemoglobin (g/dL)	14.7 (13.3)[$]	13.4 (11.5-14.7)[$]	14.4 (12.9-15.7)
RDW (%)[#]	13.0 (12.5-13.9)[$]	14.3 (13.0-15.8)[$]	13.1 (12.5-14.3)
Mortality	2 (0.5)[$]	11 (8.0)[$]	13 (2.4)
Unplanned transfer to CCA	5 (1.2)[$]	16 (11.7)[$]	21 (3.9)

RDW: red cell distribution width; CCA: Critical care area; CCI: Charlson comorbidity index; BMI: body mass index;
*within the last 6 months; [#]Red cell distribution width; [$]the difference between groups ($p < 0.05$).
Hemoglobin normal value: 12.0-16.0 g/dL; RDW normal value: 11.5-15.0%.

Model 2: Muscle wasting, acute inflammation (as NRS2002 injury score), and chronic inflammation (CCI) versus unplanned transfer to CCA.

Model 3: Muscle wasting and inflammation (RDW) versus mortality.

Model 4: Muscle wasting and inflammation (RDW) versus unplanned transfer to CCA.

Every model was adjusted for possible confounding variables observed during the initial analysis.

The Local Ethics Committee approval was obtained previously.

R studio cloud ® and SPSS 24.0 (BMI) were used for statistical analysis considered significant every $p < 0.05$.

Results

A total of 545 patients were included in the final analysis, with a malnutrition prevalence of 25.14%. General characteristics are presented in Table 1.

Malnourished patients showed a higher age, illness severity, CCI, and RDW, but lower hemoglobin and BMI. A higher proportion of malnourished patients was female and showed adverse events (mortality and unplanned transfer to CCA) and previous hospitalization (within 6 months).

Malnutrition using the GLIM criteria was correlated with mortality (Odds Ratio [OR] 17.72, 95% Confidence interval [95%CI] 3.88-81.02) and unplanned transfer to CCA (OR 10.66, 95%CI 3.83-26.69).

Given the differences in age and gender, every model was adjusted for such variables, showing no correlation with adverse events in all of them.

Models 1 and 2:

To compare and assess the correlation of RDW with adverse outcomes, these initial models do not include RDW. Instead, the inclusion of CCI and NRS2002 illness severity were used as inflammatory markers and the only variable that remained was muscle wasting.

Muscle wasting severity and acute inflammation (NRS2002 illness severity) correlated with adverse outcomes, but chronic inflammation (CCI) did not reach significance in both models (Fig. 2).

ROC curves are shown in Fig. 3 and their analysis is in Table 2.

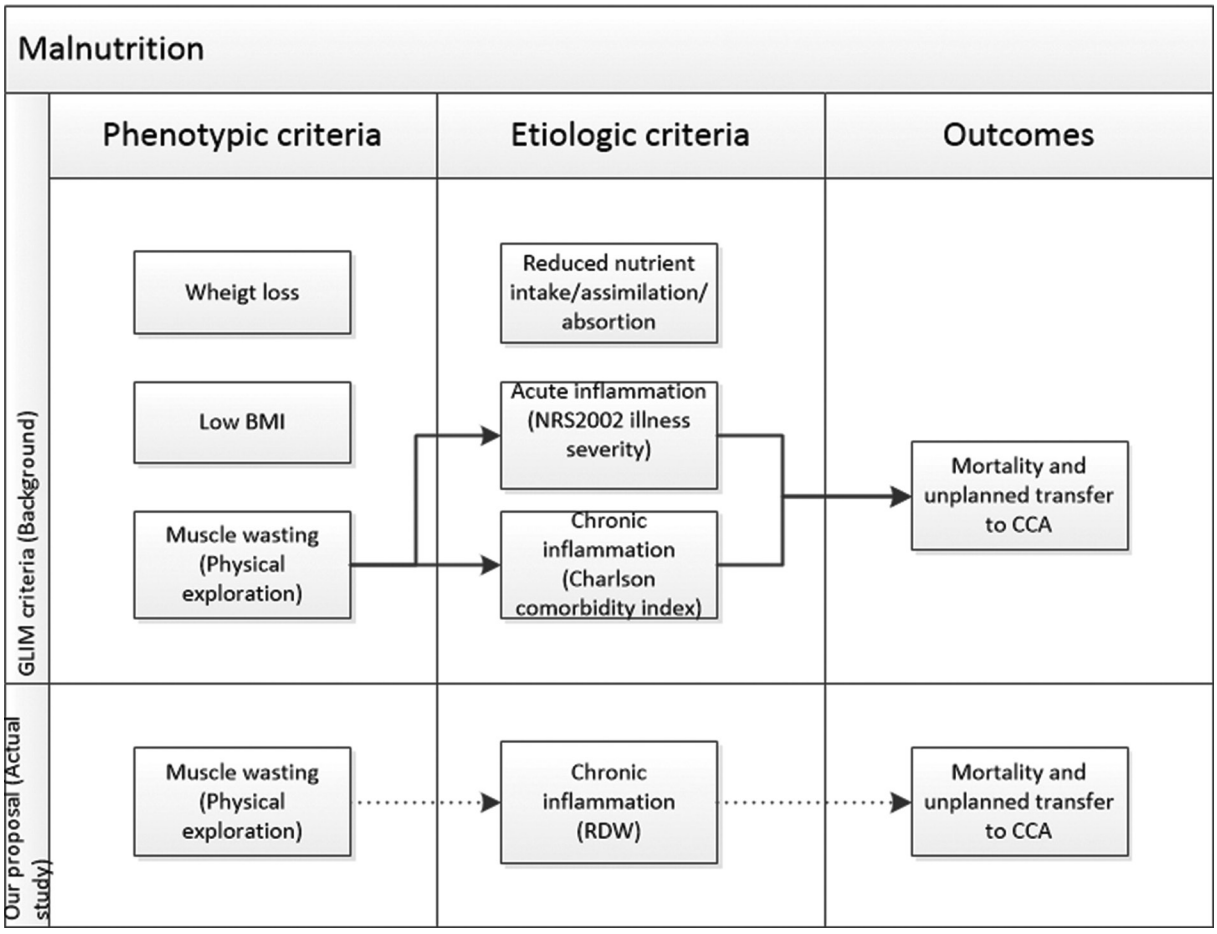

Figure 1. *Previous findings and actual hypothesis. RDW: red cell distribution width; CCA: critical care areas. Continuous line: findings of a previous study (1); Dotted line: actual study hypothesis.*

Table 2. ROC curve analysis

Variable	AUC	p	95% confidence interval	
			Inferior limit	Superior limit
Mortality				
RDW	0.76	0.002	0.67	0.86
Unplanned transfer to critical care areas				
RDW	0.79	< 0.001	0.72	0.87

ROC: receiver operating characteristics; RDW: red cell distribution width; AUC: area under the curve.

RDW alone showed fair performance to predict mortality and unplanned transfer to CCA.

Final models (3 and 4) were constructed as follows (Fig. 4).

Using RDW as an inflammatory marker showed significance in model 4 as an independent risk factor but did not increase the percentage of correct classification in both models compared with the initial models (Fig. 2). Again, muscle wasting was correlated with adverse outcomes in both models (3 and 4).

Discussion

In the present study, muscle wasting and inflammation showed to be independently correlated with adverse outcomes. Using RDW as an inflammatory biomarker showed statistical performance in the ROC curves predicting unplanned transfer to CCA and in-hospital mortality. RDW did not add classification performance in the regression analysis adjusted with muscle wasting, searching for correlations with adverse outcomes, and compared more simplistic models using the CCI and the NRS2002 illness severity score. However, RDW remained an independent risk factor for clinical deterioration requiring transfer to CCA.

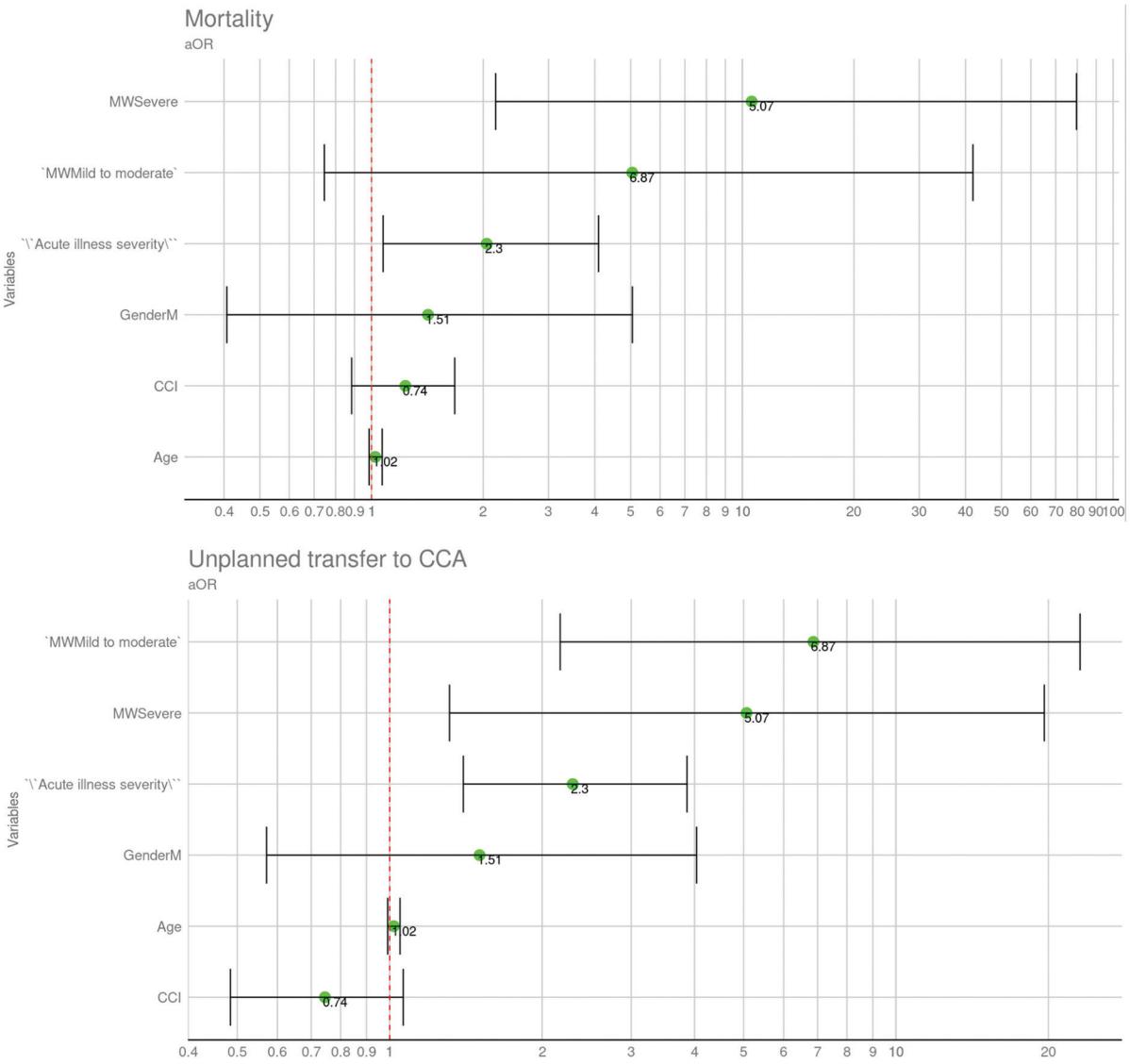

Figure 2. *Initial regression analysis. Mortality, Hosmer Lemeshow test p > 0.05, percentage of correct 97.6%. Unplanned transfer to critical care areas. Hosmer Lemeshow test p > 0.05, percentage of correct 96.0%. Acute inflammation according to NRS2002 illness severity (0-3 points), and chronic inflammation according to the Charlson comorbidity index. CCI: Charlson comorbidity index; MW: muscle wasting; GenderM: gender male; aOR: adjusted odds ratio; Error bars: 95% confidence interval.*

It is worth to mention the significant difference in RWD between both groups (well-nourished and malnourished), suggesting a profile in malnourished patients with a physiological association such as muscle wasting and inflammation. Being that those patients with malnutrition showed higher RDW values.

RDW has shown a correlation with mortality mainly in critically ill adult patients. Recently, Moreno–Torres et al. observed a group of 203 septic patients admitted to the intensive care unit, showing higher values of RDW in non-survivors, but also RDW remained elevated (during the first 7 days from admission) when compared with non-survivors. Using ROC curves adjusted for CCI, immunosuppression, nosocomial infection, National Early Warning Score 2, Sequential Organ Failure Assessment, Simplified Acute Physiology Score-II, and hemoglobin, RDW at admission presented an AUC of 0.812 for in-hospital mortality. RDW showed an AUC of 0.76 for mortality in our model, but when adjusting for muscle wasting resulted in a small (but significant) correlation with clinical deterioration requiring transfer to CCA and no correlation with mortality, this contrast remarks the importance of muscle mass during inflammatory conditions[8].

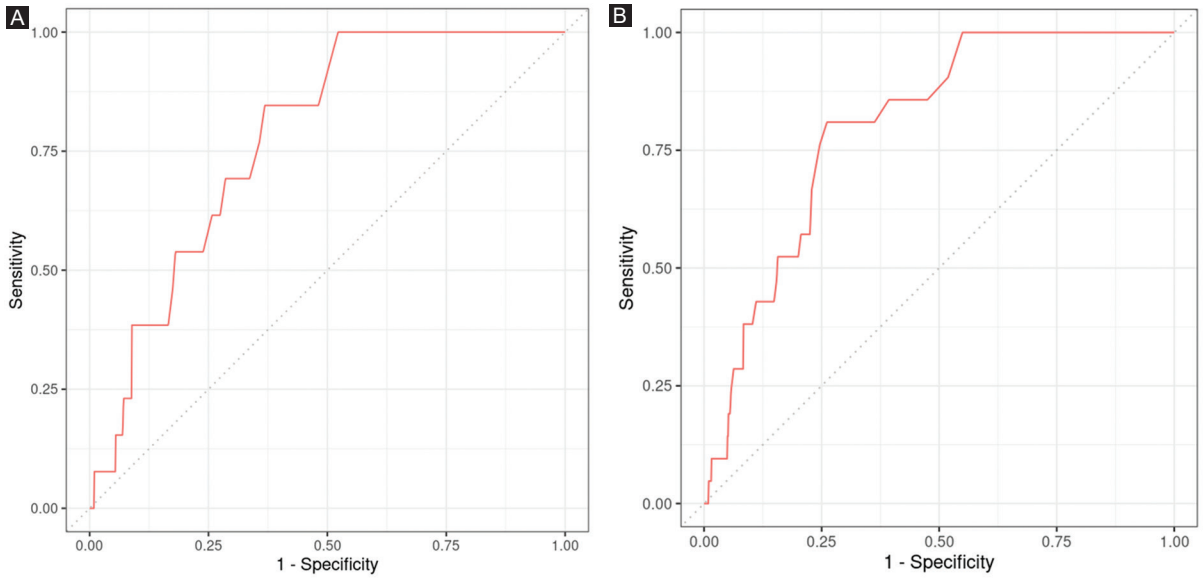

Figure 3. *Receiver operating characteristics curves.* **A:** *RDW versus mortality.* **B:** *RDW versus unplanned transfer to critical care areas. RDW: red cell distribution width.*

Zhang et al. conducted a meta-analysis to explore the role of RDW as a prognostic marker in critically ill patients with sepsis. Including 11 studies with a total of 17,961 patients a hazard ratio of 1.14 (1.09-1.20) for mortality was found for elevated RDW values[5].

Kim et al. evaluated the relation between RDW and muscle mass measured by DEXA in participants of the National Health and Nutrition Examination Survey (NHANES) 1999-2006. Low muscle mass was defined by skeletal muscle index or ASM (appendicular skeletal muscle [kg]/body weight [kg] × 100) using a cutoff point estimated from the mean ASM and its standard deviations (11,761 patients) and then adding low gait speed (< 0.8 m/s in a 20ft walk test) to define sarcopenia (2825 patients). Higher RDW was significantly associated with a higher risk for low muscle mass and sarcopenia, and when adjusting for BMI the relation was significant only in overweight and obese patients, showing the poor utility of BMI for nutritional status assessment[10]. The physiological explanation for these results remains to be elucidated, but if RDW really can be translated as a marker of inflammation (and perhaps as a chronic inflammation marker), and conditions such as obesity are considered proinflammatory[15], the loss of muscle mass, and function associated with inflammation could be the explanation for such results.

Inflammation has an influence in protein metabolism and muscle wasting, given that during the inflammatory process, gluconeogenesis and production of acute phase reactants as repair measures need amino acid mobilization from muscles, resulting in muscle wasting, a cardinal sign of malnutrition[16].

A recent secondary analysis of the study by Merker et al. was nutritional support in high nutritional risk patients (total NRS2002 ≥ 3 points) correlated with lower 30-day mortality, compared to standard of care. This correlation disappeared when analyzing the results between patients presenting high inflammation (C reactive protein > 100 mg/L) with patients with low-to-moderate inflammation (C reactive protein < 100 mg/L). Furthermore, nutritional support did not influence C reactive protein levels during the intervention[17]. These results underline the influence of inflammation with malnutrition, being that both conditions correlate with worse outcomes when they are present at the same time.

Limitations of the present study are its observational nature increasing the risk for residual confounders and being a single-center study reduces the external validity. Furthermore, there is a high risk for an impression when there is a low prevalence of the outcomes, 2.38% (13/545) for mortality and 3.85% (21/545) for unplanned transfer to CCA, showing that the population observed was at an overall lower risk for adverse events. The use of physical examination searching for muscle wasting introduced a wide confidence interval given the lack of precision. Finally, patient-centered outcomes were not considered.

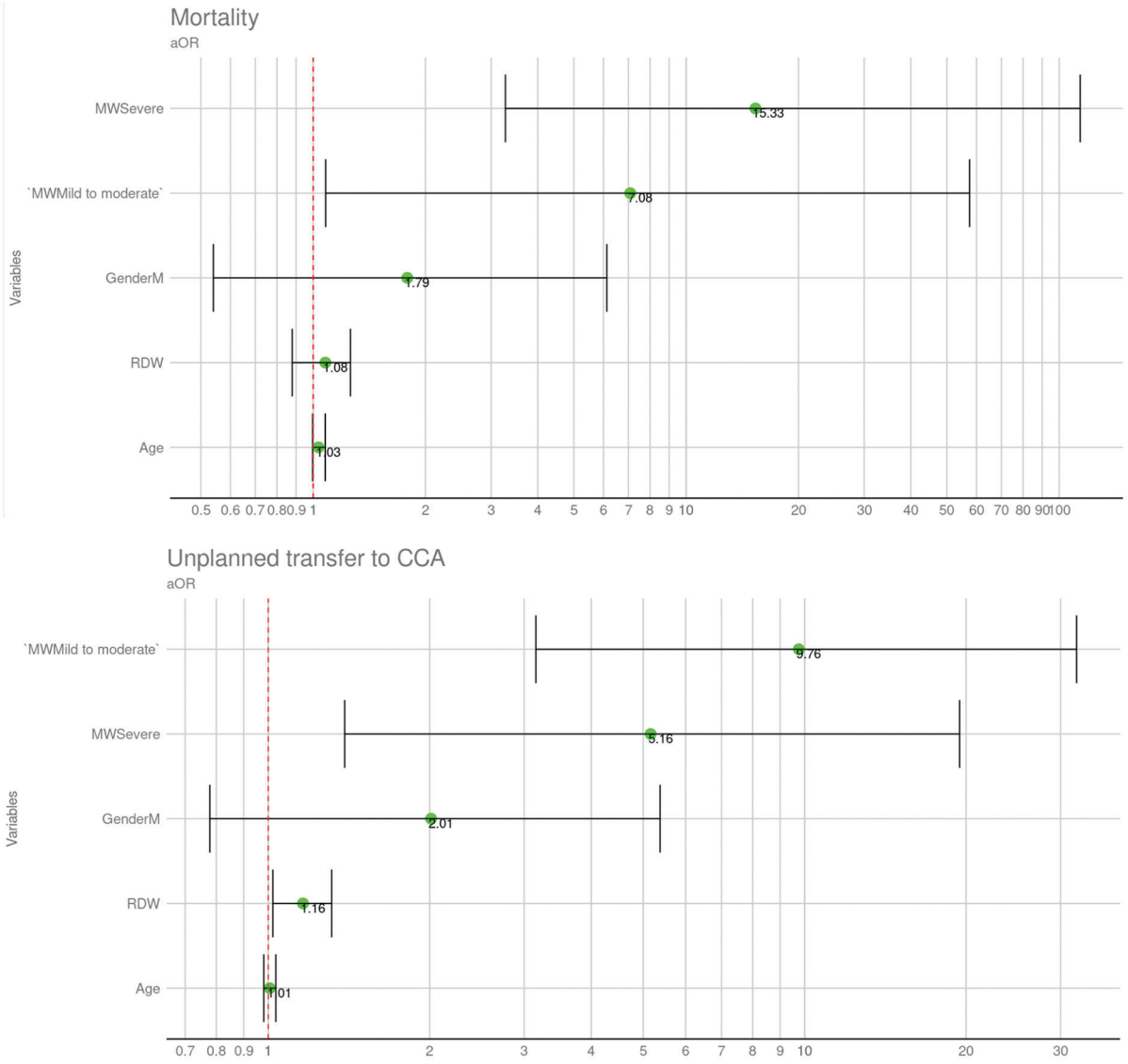

Figure 4. *Final regression analysis. Mortality, Hosmer Lemeshow test p > 0.05, percentage of correct 97.6%, 0% mortality was shown in muscle wasting 1+ subgroup. Unplanned transfer to critical care areas, Hosmer Lemeshow test p > 0.05, percentage of correct 96.0%. Inflammation according to red cell distribution width. RDW: red cell distribution width; MW: muscle wasting; GenderM: gender male; aOR: adjusted odds ratio. Error bars: 95% confidence interval.*

Strengths are the high number of patients observed and a preceding study in our center confirming the greater risk for adverse outcomes related to malnutrition. Furthermore, the observational nature shows a daily practice approach.

Conclusion

Physical examination searching for muscle wasting remains a valid tool to detect patients with malnutrition and the corresponding high risk for adverse outcomes. RDW in conjunction with muscle wasting remained as an independent risk factor for unplanned transfer to CCA (clinical deterioration) but not mortality. It is still unknown whether RDW can detect patients who benefit the most from nutritional support or if RDW changes can be used as a response marker for nutritional support. More studies in different centers, controlling for different nutritional approaches during malnutrition and using biomarker kinetics over time are needed to fully understand the association of RDW, muscle wasting, and clinical outcomes.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of humans and animals. The authors declare that the procedures followed conformed to the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data. The authors declare that they have followed their center's protocols for the publication of patient data.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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