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The Impact Of Muscular Atrophy On Functional Outcomes In Pediatric Critical Care: A Cross-Sectional Observational Study

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Trabalho de Conclusão de Curso de Fisioterapia, da Universidade Federal de Ciências da Saúde de Porto Alegre, como requisito parcial para obtenção do título de Bacharel em Fisioterapia

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Tornar-se fisioterapeuta é um processo. Por isso, dedico esse trabalho a todos os pacientes que cruzaram meu caminho e me proporcionaram aprendizados que moldaram a profissional que eu serei.

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RESUMO

OBJETIVOS: Investigar a associação entre a ocorrência de atrofia muscular durante a internação em Unidade de Terapia Intensiva Pediátrica (UTIP) e o desenvolvimento de novas morbidades nos momentos de alta da UTIP e hospitalar. **DESENHO:** Estudo unicêntrico, transversal observacional, com pacientes recrutados entre dezembro de 2021 e abril de 2023. **CENÁRIO:** Unidade de Terapia Intensiva Pediátrica em um hospital público terciário no sul do Brasil. **PACIENTES:** Foram incluídas crianças de 1 mês até 12 anos de idade incompletos, que estivessem em ventilação mecânica invasiva por pelo menos 24h. Foi coletada uma amostra de 101 pacientes, com uma mediana de idade de 19 meses, e sendo a maioria do sexo masculino (63,4%). **INTERVENÇÕES:** Nenhuma. **PRINCIPAIS VARIÁVEIS DE INTERESSE:** Atrofia muscular, definida como redução de 10% ou mais da espessura muscular, em comparação com a primeira imagem ultrassonográfica obtida; desenvolvimento de nova morbidade, definida como aumento de dois pontos ou mais e um único domínio, comparado com a pontuação na Escala FSS prévia à internação. **RESULTADOS:** A atrofia muscular ocorreu em 39,6% dos pacientes. O desenvolvimento de nova morbidade foi presente em 77,2% dos pacientes na alta da UTIP, e em 22,8% dos pacientes na alta hospitalar. **CONCLUSÕES:** A associação entre a atrofia muscular e o desenvolvimento de nova morbidade na alta da UTIP foi demonstrada somente em crianças sem diagnóstico respiratório (P = 0,05). Adicionalmente, nós observamos uma alta prevalência de atrofia muscular e de desenvolvimento de nova morbidade após a admissão na UTIP.

Palavras-chave: Atrofia muscular; Escala FSS; Nova Morbidade; Unidade de Terapia Intensiva Pediátrica (UTIP).

ABSTRACT

OBJECTIVE: To investigate the association between the occurrence of muscular atrophy during critical care admission and the development of new morbidity at PICU and hospital discharge. **DESIGN:** Unicenter, cross-sectional observational study, with patients recruited between December 2021 and April 2023. **SETTING:** Pediatric Intensive Care Unit (PICU) on a tertiary public hospital in southern Brazil. **PATIENTS OR PARTICIPANTS:** We included children aged one month to incomplete 12 years who had undergone mechanical ventilation for at least 24 hours. A random sample of 101 patients were included, with a mean age of 19 months, being the majority of male sex (63.4%). **INTERVENTIONS:** None. **MAIN VARIABLES OF INTEREST:** Muscular atrophy, defined as a reduction of 10% or more in muscle thickness compared to the first obtained ultrasonographic image; development of new morbidity, defined as an increase of 2 points or more in a single domain compared to the pre-hospitalization FSS score. **RESULTS:** Muscle atrophy occurred in 39.6% of the patients. The development of new morbidity was present on 77.2% of the patients at PICU discharge and on 22.8% at hospital discharge. **CONCLUSIONS:** The association between muscle atrophy and the development of new morbidity at PICU discharge was shown only in children without respiratory diagnoses ($p = 0.05$). Additionally, we observed a high prevalence of muscle atrophy and the development of new morbidities after PICU admission.

Keywords: Muscular atrophy; FSS Scale; New Morbidity; Pediatric Critical Care

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ICU: Intensive Care Unit

PICU: Pediatric Intensive Care Unit

MRC: Medical Research Council

US: Ultrasound

FSS: Functional Status Scale

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ARTIGO

THE IMPACT OF MUSCULAR ATROPHY ON FUNCTIONAL OUTCOMES IN PEDIATRIC CRITICAL CARE: A CROSS-SECTIONAL OBSERVATIONAL STUDY

(A ser submetido ao periódico: Medicina Intensiva)

(Fator de Impacto: 3)

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The authors declare that there is no conflict of interests.

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ABSTRACT

Objective: To investigate the association between the occurrence of muscular atrophy during critical care admission and the development of new morbidity at PICU and hospital discharge.

Design: Unicenter, cross-sectional observational study, with patients recruited between December 2021 and April 2023.

Setting: Pediatric Intensive Care Unit (PICU) on a tertiary public hospital in southern Brazil.

Patients or participants: We included children aged one month to incomplete 12 years who had undergone mechanical ventilation for at least 24 hours. A random sample of 101 patients were included, with a mean age of 19 months, being the majority of male sex (63.4%).

Interventions: None.

Main variables of interest: Muscular atrophy, defined as a reduction of 10% or more in muscle thickness compared to the first obtained ultrasonographic image; development of new morbidity, defined as an increase of 2 points or more in a single domain compared to the pre-hospitalization FSS score.

Results: Muscle atrophy occurred in 39.6% of the patients. The development of new morbidity was present on 77.2% of the patients at PICU discharge and on 22.8% at hospital discharge.

Conclusions: The association between muscle atrophy and the development of new morbidity at PICU discharge was shown only in children without respiratory diagnoses ($p = 0.05$). Additionally, we observed a high prevalence of muscle atrophy and the development of new morbidities after PICU admission.

Keywords: Muscular atrophy; FSS Scale; new morbidity; Pediatric Critical Care.

RESUMEN

Objetivo: Investigar la asociación entre la aparición de atrofia muscular durante la admisión a cuidados críticos y el desarrollo de nuevas morbilidades en la UCI pediátrica y al momento del alta hospitalaria.

Diseño: Estudio observacional unicéntrico y transversal.

Ámbito: Unidad de Cuidados Intensivos Pediátricos (UCIP).

Pacientes: Se incluyeron niños de uno a once meses de edad, en ventilación mecánica durante al menos 24 horas. Se incluyó una muestra de 101 pacientes.

Intervenciones: Ninguna.

Variables de interés principales: Atrofia muscular, definida como una reducción del 10% o más en el grosor muscular; desarrollo de nuevas morbilidades, definido como un aumento de 2 puntos o más en un solo dominio en comparación con la FSS pre hospitalización.

Resultados: La atrofia muscular ocurrió en el 39,6% de los pacientes. El desarrollo de nuevas morbilidades, en el 77,2% de los pacientes al momento del alta de la UCIP y en el 22,8% al momento del alta hospis morbilidades al momento del alta de la UCIP solo se mostró en niños sin diagnósticos respiratorios (p = 0,05). Además, observamos una alta prevalencia de atrofia muscular y el desarrollo de nuevas morbilidades después de la admisión a la UCIP.

Conclusiones: La asociación entre la atrofia muscular y el desarrollo de nuevas morbilidades al momento del alta de la UCIP solo se mostró en niños sin diagnósticos respiratorios (p = 0,05). Además, observamos una alta prevalencia de atrofia muscular y el desarrollo de nuevas morbilidades después de la admisión a la UCIP.

Palabras clave: Atrofia muscular; Escala FSS; Nueva morbilidade; Cuidados Críticos Pediátricos.

INTRODUCTION

The acquired muscular weakness in the ICU corresponds to a potentially reversible acquired neuromuscular disease with multifactorial characteristics[1]. In adults, it is known that diaphragmatic and skeletal muscle atrophy and weakness are associated with difficulties in weaning from mechanical ventilation, prolonged ICU stay, poorer functional outcomes, and increased mortality[2]. This process involves both myopathic and inflammatory characteristics and disuse atrophy in patients under sedation or neuromuscular blockade[1]. In pediatrics, Johnson et al. demonstrated that approximately half of the children admitted to the ICU experienced a reduction of over 10% in diaphragmatic and quadriceps femoris muscle thickness during their hospitalization[2].

In pediatrics, acquired muscular weakness is still understudied due to the challenge of using validated tools and practices with this population during hospital routines. Currently, the most used instruments in adults to assess

weakness in the hospital context are the Medical Research Council (MRC) Scale and the evaluation of handgrip strength through manual dynamometry[3]. However, these measures are limited to conscious and cooperative patients. In children, factors such as younger age, poorer cognitive status, sedation, and lack of cooperation hinder using these tools[3]. Recent studies employing bedside muscular ultrasound (US) have shown that muscle atrophy is prevalent in pediatric critical patients. Additionally, they concluded that muscular US has proven to be a reliable and replicable method in clinical practice[1].

Muscular atrophy in pediatric critical patients may impact their functional recovery; however, this relationship remains understudied. In adults, studies indicate that a significant number of patients develop long-lasting morbidities following ICU admission[4]. The Functional Status Scale (FSS) was specifically developed for hospitalized pediatric patients and assess cognitive and motor domains rapidly and objectively. It can also be used to track the onset of new morbidity, defined as an increase of two or more points in a single domain compared to pre-admission scores[5]. Pereira et al. study demonstrated that most patients exhibited some degree of dysfunction, assessed by the FSS at the time of pediatric intensive care unit (PICU) discharge. Furthermore, patients with poorer outcomes in the FSS showed a higher readmission rate to the PICU[6].

Children with poorer medium to long-term functional outcomes are more likely to require mechanical ventilation, use vasoactive drugs, experience prolonged ventilation, and prolonged PICU stay[7], thereby placing greater demand on public health resources. Such outcomes may be associated with factors such as acquired muscular weakness in the PICU. However, the literature on the factors contributing to a worsened functional state remains

scarce. Therefore, the primary aim of this study was to assess the association between the occurrence of muscular atrophy during critical care admission and the development of new morbidity at PICU and hospital discharge. Secondary outcomes were assessing the prevalence of atrophy and the degrees of dysfunction observed using the FSS scale.

PATIENTS AND METHODS

This prospective cohort study was conducted with patients discharged from the PICU of one tertiary public hospital in southern Brazil. Participants were recruited between December 2021 and April 2023. We included children aged one month to incomplete 12 years, accompanied by one of their parents or legal guardians, who had undergone mechanical ventilation for at least 24 hours. Patients were excluded if they were dependent on ventilatory technology before admission to the PICU, readmitted to the PICU within less than 24 hours after discharge, and with a diagnosis of neuromuscular disease, cerebral palsy, stroke, or any other neurological and/or genetic diagnosis associated with muscle weakness and/or muscle tone alteration. All patients admitted to the PICU who met the established inclusion criteria were invited to participate in the study. The Ethics Committee of the Institution (2021-0119) approved this protocol, and written consent for participation in the study from each child's parents or relatives was obtained. After signing the consent form, clinical and demographic information were collected from the electronic medical records, including the following data: sex, age (months), diagnosis, duration of

mechanical ventilation use, length of stay in the PICU, and total length of hospital stay.

Muscle Thickness Measurement

Ultrasonography was performed using a portable ultrasound imaging device, Sonosite M-turbo (FUJIFILM Sonosite, WA, USA), equipped with a 6-13MHz linear probe. Measurements were conducted following previously published protocols from our group[8]. Two muscles were examined, whenever possible, for each child: the brachial biceps and femoral quadriceps. The contralateral side was evaluated if the right upper and lower limbs could not be visualized due to any underlying structure (e.g., peripheral venous access, external fixator). Muscles were assessed supine, with arms and legs extended and muscles relaxed. The upper limb was supinated, and the lower limb was positioned with extended knees and ankles in a neutral position.

Transverse ultrasonographic images of the muscles in anatomical locations corresponding to the maximum diameter within the muscle belly were obtained at the following points: brachial biceps: ⅔ from the acromion to the antecubital fold; femoral quadriceps: ½ from the anterior-superior iliac spine to the upper edge of the patella. A surgical pen was used to mark the location for transducer placement on the skin. The transducer was positioned perpendicular to the skin with a generous amount of contact gel, and minimal transducer pressure was applied to ensure no muscle compression. Measurements were taken at the following moments: up to 24 hours on the first day of admission, after 72 hours, and weekly until discharge from the PICU, as long as it did not exceed a period longer than 28 days in the unit. An experienced

ultrasonographer trained evaluators and the reliability was assessed as described in the study by Oliveira et al[8]. Muscle atrophy was defined as a reduction of 10% or more in muscle thickness compared to the first obtained ultrasonographic image, similar to previous studies[2].

Functional Assessment

For the functional assessment, the FSS-Brazil, validated for the Brazilian pediatric population[9,10], was applied at the bedside to all participants. Patients were assessed for up to 24 hours on the first day of admission, at PICU discharge, and at hospital discharge by a trained evaluator. Additionally, pre-hospitalization scores were retrospectively obtained through information from parents and legal guardians.

The scale consists of six domains, including mental status, sensory, communication, motor function, feeding, and respiratory function, each of which is categorized from normal (1) to very severe dysfunction (5)[10]. By summing the values obtained in this categorization, a global FSS score is established, ranging from six to 30 and classified as follows: 6-7, adequate function; 8-9, mild dysfunction; 10-15, moderate dysfunction; 16-21, severe dysfunction; > 21, very severe dysfunction[10]. The emergence of new morbidity was considered an increase of 2 points or more in a single domain compared to the pre-hospitalization score[5].

Statistical Analysis

For qualitative variables, we described the absolute and relative frequencies. For quantitative variables, we calculate the mean and standard

deviation for data with a symmetric distribution and the median and interquartile range with an asymmetric distribution. The normality of the data was assessed using the Shapiro-Wilk or Kolmogorov-Smirnov test. The association between categorical variables was verified using the Fisher's Exact Test. Statistical analysis of the obtained data was carried out using the Statistical Package for Social Science (SPSS) v.26.0 for Windows, with a significance level of 5% ($p<0.05$).

RESULTS

A total of 101 patients were included in this study, the majority being from the male sex. The mean age was 19 months. The main reason for admission to the PICU was acute respiratory failure. Clinical and demographic data is summarized in **Table 1.**

The variation between the first and last measurements was used to analyze the muscle mass loss. Muscle atrophy occurred when the child exhibited a reduction equal to or greater than 10% in the quadriceps and/or biceps brachialis during hospitalization. There were three losses due to the presence of venous access or other medical devices that hindered the performance of the muscle ultrasound in one of the evaluated muscle groups. Upon discharge from the PICU, 39.6% of children presented muscle atrophy.

Table 1. Sample demographic and clinical characteristics.

Variable	n = 101
Age (months)	19 (0.93 - 132)
Sex (male)	63.4%
Time on mechanical ventilation (days)	5.39 (1 - 30)
Length of stay on PICU (days)	10.41 (3 - 82)
Total length of stay (days)	35.99 (6 - 222)
Atrophy	40 (39.6%)
New morbidity at PICU discharge	78 (77.2%)
New morbidity at hospital discharge	23 (22.8%)
Diagnosis:	
Respiratory	71 (70.3%)
Gastrointestinal/hepatic	12 (11.9%)
Oncological	10 (9.9%)
Metabolic	2 (2%)
Genetic Syndrome	2 (2%)
Cardiovascular	1 (1%)
Renal	1 (1%)
Others	2 (2%)

PICU: Pediatric Intensive Care Unit. Results are expressed as median (interquartile range) or n (%).

The Functional Status Scale (FSS) score at the time of hospital discharge was collected from 90 patients through data from electronic medical records. There were ten losses due to in-hospital mortality and one loss due to hospital transfer and subsequent information loss. Patients diagnosed with other conditions exhibited a low level of dysfunction at hospital discharge, whereas those with respiratory diagnoses returned to no dysfunction. The

median total FSS scores were comparable between patients with and without atrophy, as established in **Table 2**.

Table 2. Association between the total FSS score and muscular atrophy.

Group	Atrophy		P value
	Yes (n=34)	No (n=56)	
At PICU discharge:			
All patients	11 (10 - 13)	11 (10 - 12)	0.497
Patients with respiratory diagnostic	11.5 (10 - 13.25)	11 (10 - 12)	0.345
Patients with others diagnoses	11 (10 - 11.75)	11 (8 - 13)	0.974
At hospital discharge:			
All patients	7 (6 - 9)	6 (6 - 8)	0.351
Patients with respiratory diagnostic	6 (6 - 9)	6 (6 - 7.25)	0.345
Patients with others diagnoses	8 (6 - 11)	8 (7.5 - 10.5)	0.656

PICU: Pediatric Intensive Care Unit. Results expressed as median (interquartile range).

At the time of PICU discharge, the prevalence of new morbidity was 77.2%, and at hospital discharge, this persisted in 22.8% of the patients. **Figure 1** illustrates the occurrence of atrophy in patients who developed new morbidity. We consider that the prevalence of new morbidity was significantly higher in patients with atrophy compared to those without atrophy among the group with other diagnoses at the time of PICU discharge. There was no significant association between the emergence of new morbidity and the presence of muscle atrophy in patients diagnosed with respiratory conditions.

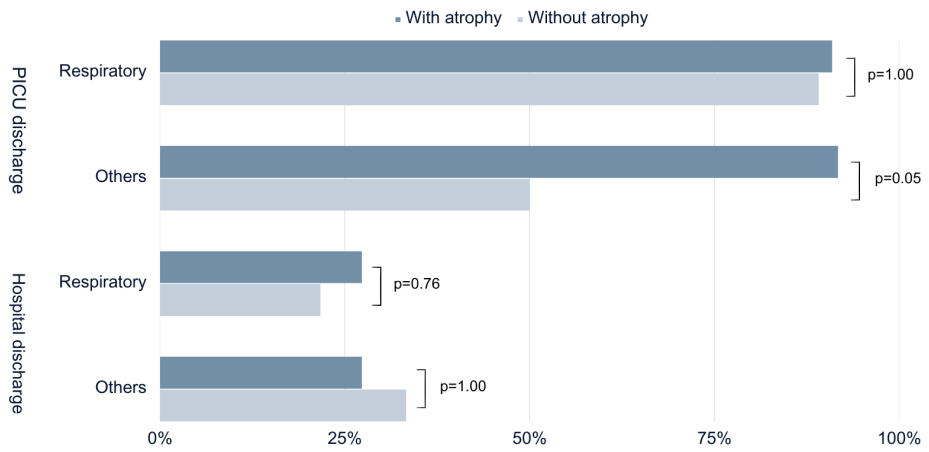

Figure 1. Association between atrophy and new morbidity.

DISCUSSION

Studies indicate that muscular ultrasound is capable of detecting the presence of atrophy, which is common and occurs early in pediatrics[2]. However, its association with functional outcomes is still unclear in this population. In our study, we observed that in the majority of patients, there was no association between the occurrence of muscle atrophy and the development of new morbidity. Secondarily, we identified a high prevalence of muscle atrophy and the presence of moderate dysfunction at PICU discharge.

Studies by Johnson et al. and Delia Valverde Montoro et al. demonstrated an average reduction of 1.5% per day in the femoral quadriceps thickness in critically ill children[2,11], similar to findings in the adult population[12]. In the study by Valla et al., the analysis of the last ultrasound measurement obtained from the quadriceps compared to the first showed a 13.3% reduction

in muscle thickness[1]. Furthermore, the prevalence of atrophy (defined as a reduction in thickness equal to or greater than 10%) in one or more muscle groups occurred in 83% of the analyzed patients[2]. In our study, muscular atrophy (in femoral quadriceps or brachial biceps) occurred in 39.6% of patients during the PICU admission period.

The mean age of patients analyzed in the study by Johnson et al. was five years[2], while in our study, the median age was 1 year and 7 months. Children above 1 year show a significantly greater reduction compared to those under 1 year[11], demonstrating a strong correlation with muscle mass loss. In the study by Banwell et al., this correlation was also found, showing that the majority of patients with muscle weakness were over 10 years old, while no child was younger than 18 months[13]. However, we found that muscle mass loss occurs early and significantly, even in younger children.

A cross-sectional study showed that qualitative aspects, such as pennation angle and echogenicity, were considered better predictors of muscle weakness than thickness measurement in adults[14]. In the pediatric population, quadriceps fat thickness and echogenicity did not show significant changes during the PICU and hospitalization period[15], indicating a possible sensitivity difference of these factors between the adult and pediatric populations. We assessed changes in skeletal muscle only quantitatively; however, this measurement demonstrates good intra and inter-rater reliability[8] and lower technical complexity, facilitating its applicability in clinical practice.

The association between muscle atrophy and functional outcomes remains unclear in the pediatric population. A study collected electronic medical record data from a large database and demonstrated that pediatric patients who

developed acquired muscle weakness in the ICU exhibited worse clinical outcomes, such as prolonged mechanical ventilation and a higher need for increased care levels after PICU discharge[16]. The study by Ong et al. found no association between muscle thickness reduction and changes in FSS scores, but the initial ultrasound measurement was obtained late (within 48 hours of admission), and the functional parameter used was an increase of three or more points in the total scale[15].

In our study, we conducted the initial ultrasound measurement within the first 24 hours after intubation, facilitating the early detection of muscular atrophy. Additionally, this is the first study to analyze the association between the occurrence of muscle atrophy and the development of new morbidity in the pediatric population, while also examining the difference in this association in children with respiratory diagnoses compared to others.

Our study found that in children with respiratory diagnoses, the loss of muscle mass was not associated with worse functional outcomes. However, in patients with others diagnoses, the onset of new morbidity at PICU discharge was associated with the occurrence of muscle atrophy. One hypothesis is that patients with respiratory diseases are typically previously healthy and manifest an acute critical condition but experience rapid recovery. On the other hand, the majority of patients in the other group had gastrointestinal, hepatic, and oncological diagnoses as reasons for admission, representing a profile of more chronic diseases and prolonged treatments.

Secondarily, we observed a high prevalence of new morbidity development at the time of PICU discharge among all patients (77.2%). Previous studies[17,18,19] found significantly lower prevalence than those in our

study (3.56%, 5.3%, 4.8%). However, the concept of new morbidity was defined as an increase of 3 points or more in the total score. We used the concept of an increase of 2 points or more in a single domain to ensure that the decline in functional status was clinically substantial[5], which may justify the difference in the prevalence found.

The prevalence of new morbidity decreased to less than half at the time of hospital discharge (22.8%), indicating the recovery of children after the intensive care unit (ICU) stay. However, this remains a significant finding of new morbidity development and may be related to worse long-term clinical and functional outcomes. In the study by Pollack et al., among patients who had new morbidity at hospital discharge, 29% either died or worsened their functional classification during long-term follow-up[5].

Regarding functional classification, both groups exhibited moderate dysfunction at the time of PICU discharge. At hospital discharge, patients with respiratory diagnoses returned to adequate function, while others remained with mild dysfunction. The presence of dysfunction was also not associated with the occurrence of muscle atrophy.

In the adult population, many studies use the Medical Research Council (MRC) scale to assess the presence of weakness in relation to muscle loss[20]. Additionally, the prevention of atrophy has a well-established association with better short- and long-term clinical and functional outcomes. In the pediatric population, factors such as the lack of cooperation from younger children for the application of this assessment model hinder the establishment of an early detection method for acquired muscle weakness in the PICU. The scarcity of

studies addressing this relationship in pediatrics reinforces the lack of screening for acquired muscle weakness, contributing to worse functional outcomes.

Our study has some limitations, such as being a single-center collection with a small and more limited clinical and demographic profile sample, reducing the generalizability to other populations. Additionally, the number of patients with diagnoses other than respiratory disease (29.7%) was small compared to respiratory disease diagnoses (70.3%), making it challenging to analyze outcome differences in patients with acute and chronic conditions. Another limitation is that patients were not analyzed separately by age groups (infants and non-infants). Furthermore, differences in age and motor development (such as walking or non-walking) could impact the relationship between muscle mass loss and functionality and need further investigation. Finally, we excluded children who had prior mechanical ventilation and those with neurological, neuromuscular, or genetic conditions, limiting the applicability of our results to such populations.

CONCLUSION

Our study showed an association between muscle atrophy and the development of new morbidity at PICU discharge only in children without respiratory diagnoses. Additionally, we observed a high prevalence of muscle atrophy and the development of new morbidities after PICU admission. The data highlight the need to develop effective strategies for early detection of muscle weakness in the pediatric population to prevent long-term functional impairments. Finally, future studies examining functional correlations across

different age groups and clinical conditions are necessary to establish the use of muscular ultrasound as a routine tool in clinical practice.

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ANEXOS

ANEXO A

Revista Medicina Intensiva

Endereço: https://www.medintensiva.org/en-guia-autores

MEDICINA INTENSIVA will consider for publication those works based on topics related to the practice of intensive medicine, medical emergencies, and critical care medicine in coronary units. Manuscripts will be evaluated for publication if they meet the following requirements: the material is original, presentation is clear, the methodology of the study is appropriate, the results are valid, the conclusions are reasonable, and the information is relevant. MEDICINA INTENSIVA complies with the guidelines of the International Committee of Medical Journal Editors: Uniform requirements for manuscripts submitted to biomedical journals. If the authors have further questions that are not answered within these instructions, they should refer to http://www.icmje.org.

Types of articles, sections

The MEDICINA INTENSIVA journal is comprised of the following sections:

Original Articles. This category includes randomised clinical trials, cohort studies, studies on screening or diagnostic tests, cost-effective analyses, meta-analyses, systematic reviews, decision-making evaluation studies, other interventionist studies, and case-control studies. Meta-analyses and systematic reviews must be registered in PROSPERO. This section will include clinical articles as well as animal research or experimental studies. The maximum length of the text must not exceed 3,000 words (excluding the Resumen/Abstract, Tables and References). The information that cannot be included in the manuscript due to this word count limit can be published as

electronic supplementary material (ESM), which has no length limitations, with addition of the tables and figures considered opportune. The maximum allowed literature references is 40. Up to 6 Tables and Figures will be admitted (e.g. 4 Tables and 2 Figures). In multicentre studies, the number of authors will be limited to 12; the rest will appear at the end of the article. The total number of Tables and Figures will not exceed 6. The length of the structured Resumen/ Abstract will be 250 words.

Review Articles. These articles present updates on a specific topic in the field of intensive care medicine. Reviews will preferably be commissioned by the Editorial Committee, although those proposed by collaborators may be accepted. Thus, before submitting the manuscript, the authors should always contact the Editorial Committee in order to propose the review article in question, at which time it will be determined whether the journal would be interested in its publication. The maximum length of the text will not exceed 4,000 words (excluding the Resumen/Abstract, Tables and References). The maximum number of literature references permitted is 80. Authors may also make use of the ESM for more extensive information that cannot be included in the print edition due to the Word count limitations, with addition of the tables and figures considered opportune. Up to 6 Tables and Figures will be allowed (e.g. 4 Tables and 2 Figures). It is recommended to include one or several figures in this type of manuscripts. The number of authors will be limited to 4. The Resumen/Abstract will not be structured, but it must provide information on its content, with a length limit of 150 words.

Special Articles. This section includes articles written by scientific societies, workgroups or groups of experts (clinical practice guidelines, consensus conferences, systematic reviews, etc.) that review a topic of current interest in intensive care medicine. Other publications include articles sent by renowned experts that analyse current social aspects or those of special interest for our specialty. The maximum length must not exceed 4,000 words (excluding the Resumen/Abstract, Tables and References). The maximum number of references permitted is 80. Up to 4 Tables and Figures will be allowed (e.g. 3

Tables and a Figure). It must include an unstructured Abstract in English (and a Resumen in Spanish) of approximately 150 words.

Updates. Reviews commissioned by the Editorial Committee of MEDICINA INTENSIVA are included in this section and will be part of a series that will review in detail current topics in intensive care medicine in successive issues of the journal. The maximum length must not exceed 4,000 words (excluding the Resumen/Abstract, Tables and References). The maximum number of literature references permitted is 80. The ESM may be used for information that cannot be included in the print edition due to the word count limit, with addition of the tables and figures considered opportune. Up to include always 6 Tables and 6 Figures will be allowed. It is recommended to include always one or several figures in this type of manuscripts. The number of authors is limited to 4. It must include an unstructured Abstract in English (and a Resumen in Spanish) of approximately 150 words.

Points of View. The articles included in this section are those in which an opinion is expressed about a controversial topic in the field of intensive care medicine. Points of View will preferably be commissioned by the Editorial Committee, although those proposed by collaborators may be accepted. Thus, before submitting the manuscript, the authors should always contact the Editorial Committee in order to propose the Point of View article in question, at which time it will be determined whether the journal would be interested in its publication. The maximum length of the text must not exceed 1,000 words (excluding Tables and References). The information that cannot be included in the manuscript due to this word count limit can be published as electronic supplementary material (ESM), which has no length limitations, with addition of the tables and figures considered opportune. The maximum number of references allowed will be 10, and up to 2 Tables and one Figure. The number of authors is limited to 2. It will not have a Resumen /Abstract.

Editorials. Included in this section are works in which the author/s discuss and analyse an Original published in the Journal. The Editorials will always be commissioned by the Editorial Committee. Also included in this section will be

articles that summarise the view of a current topic by the Editorial Committee of MEDICINA INTENSIVA or the Board of Directors of Sociedad Española de Medicina Intensiva , Crítica y Unidades Coronarias (SEMICYUC). The maximum length of the text must not exceed 1,000 words (excluding the bibliography). The maximum number of references allowed is 10 and one Table or Figure will be admitted. The number of authors will be limited to 2. It will not include a Resumen or Abstract.

Scientific letters. A description of several clinical cases in which are described new aspects or important added value on the pathophysiology of the disease, its diagnosis or treatment. Studies based on questionnaires that have received a high response rate are also considered in this section. The maximum length of the text must not exceed 1,000 words, and the text will not be structured into sections. Up to 2 Figures or Tables will be allowed. The supplementary information that cannot be included in the manuscript due to this word count limit can be published as electronic supplementary material (ESM), which has no length limitations, with addition of the tables and figures considered opportune. The number of signatories must not be greater than 6, and the number of literature references is limited to 10. Scientific Letters will not have a Resumen/Abstract.

Letters to the editor. In this open section, objections or comments related to articles recently published in the Journal, and possibly on relevant articles published in other journals of special interest for intensive medicine, or comments on topics of importance associated with the speciality. Letters to the Editor sent to Medicina Intensiva must refer to articles published within the two previous months at most. The maximum length of the text must not exceed 500 words, and up to 5 literature references will be allowed. There must be no more than four signing authors. Those Letters to the Editor that deal with articles previously published in the Journal will have the right to reply. They will be submitted to the author of the original work, who will be able to reply in a letter of the same length within a period of one month. The Editorial Committee will try to publish the Letter to the Editor and the reply together.

Images in Intensive Medicine. This section will publish all types of images that are demonstrative and contain a teaching message by themselves. The maximum number of figures is 3. They must be accompanied by a text of less than10 lines. Whenever possible, the image should include graphic aids (arrows, asterisks). The number of signing authors will be limited to 3, and the image must be of sufficient graphical quality (minimum resolution of 300 dots per inch (dpi). No abstract, figure captions or references are allowed.

Language

This journal is published in Spanish and in English language.

Essential title page information

Title. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible.
Author names and affiliations. Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled. You can add your name between parentheses in your own script behind the English transliteration. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials.
Ensure that the e-mail address is given and that contact details are kept up to date by the corresponding author.
Present/permanent address. If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.
Word count. It is important to include the word count, indicate the number of

words in the abstract in Spanish and English and the number of words in the main text (excluding the abstract, references, tables, and figure legends).

Summary of a manuscript structure (Original Article)

1. Title
2. Abstract: a) Objective, b) Design, c) Setting, d) Patients or participants, e) Interventions, f) Main variables of interest, g) Results, h) Conclusions
3. Text: a) Introduction, b) Patients and Methods, c) Results, d) Discussion
4. Contribution of the Authors
5. Funding
6. Conflict of Interest
7. Acknowledgements
8. References
9. Tables
10. Figures

Introduction

The introduction should be clear and concise while establishing the purpose of the study and reasonably summarising the current situation of the topic to be discussed. The introduction should prepare the reader to comprehend the text that follows. It should not be a review of the topic itself, nor a hurried discussion. It should finish with a clear and specific description of the study objectives.

Patients and methods

This section should provide sufficient details so that a specific experience can be reproduced based on the information given. It should indicate the hospital where the experiment or research has been conducted, its duration, characteristics of the series studied, selection criteria used, variables of interest (primary and secondary) and the techniques used (devices used with name and city of manufacturer in parentheses), drugs used with generic name, dose and means of administration). If the methods or procedures are widely used and well known, the corresponding bibliographic reference should be provided to

avoid a detailed description. In the case of clinical trials with randomised distribution, randomisation methods should be explained and it should be stated whether the random assignation was blinded. The statistical methods used should be appropriately described.

Results

The findings should be quantified and presented with the appropriate indicators for error or uncertainty (such as confidence intervals). This section should state, but not discuss, the observations made of the patients and the method used, in logical sequence. The results can be expressed in detail in the text or rather in the form of tables and figures, but unnecessary repetitions should be avoided of the results shown in the tables and figures. Manuscripts that present results of a clinical trial of parallel groups with random distribution should include the CONSORT flowchart (http://www.consort-statement.org/), which illustrates the distribution and patient progress throughout the study. Manuscripts that present reports about systematic reviews or meta-analyses will follow the guidelines from the PRISMA declaration (http://www.prisma-statement.org). The manuscripts that assess the utility of diagnostic tests should follow the STARD format (http://www.consort-statement.org/stardstatement.htm).

Discussion

The authors should expand on their own opinion about the topic without repeating data provided in the Introduction or Results. This section should include the following aspects: a) the most relevant findings; b) the practical application of the results; c) the possible methodological limitations and the reasons for which the results are valid; d) the correlation with similar publications and the analysis of the similarities and differences with the findings of other authors; and e) the indications and suggestions for further research, providing new hypotheses when justified, and clearly stating them as such. It is not necessary to include conclusions; these should be exclusively derived from the study.

Conclusions

It is not necessary to include conclusions; these should be exclusively derived from the study. The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Appendices

If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Abstract

A concise and factual abstract is required. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

In the **Reviews**, **Special Articles** and **Updates**, the abstracts will not be structured but should be equally informative about the content and should have an approximate length of 150 words.

Structured abstract

Original abstracts will include an Abstract of 250 words of extension, structured in the following sections:

Objective. It will state the reason for the study that will be evaluated or the hypothesis that is established.

Design. The basic design of the study will be described, including the study period and follow-up period. The following terms should be used:
– For *interventionist studies*: clinical trial with randomised distribution; clinical trial with non-randomised distribution; double blind; placebo controlled; crossover design.
– For *studies on diagnostic tests*: reference standard (this is a widely accepted test with which the new or alternative diagnostic test will be compared); this term is preferable to the “gold Standard” or “gold pattern”; blind comparison; validation population.
– For *prognostic studies*: starting cohort (subjects collected at an early stage of the study disease or process that are subsequently followed-up), cohort (subjects observed in a long-term follow-up but do not necessarily have a common starting point); validation cohort or validation sample in clinical prediction model studies.
– For *association or causality studies*: clinical trial with randomised distribution; prospective cohort study; case control studies.
– For the *description of clinical signs and symptoms or diseases*:
case series.
– For *financial evaluation studies*: cost-effectiveness analysis; cost-benefit analysis.

Setting. The setting in which the study has been carried out will be mentioned so that the readers may determine the applicability of the results to their particular work environment.

Patients or participants. The selection criteria must be described, as well as the demographic characteristics of the study subjects, the number of eligible subjects and the number of participating subjects. In case control studies the characteristics used for matching must be specified. In follow-up studies, it must state the proportion of participants that completed the study. In interventionist studies, it must mention the number of patients in whom the intervention was stopped due to the appearance of adverse effects. In prognostic studies, it will mention the percentage losses. The following terms must be employed when

referring to the selection process: random sample; consecutive sample: volunteer sample.

Interventions. The essential aspects of each intervention and its duration will be mentioned.

Main variables of interest. It must mention what were the main variables of interest, as were established before starting collecting the data.

Results. A quantitative estimation of the main study variables must be presented, including the confidence intervals (for example, 95%). In comparative studies, mention must be made of the confidence intervals for the differences between the groups studied. In the event that the main variables of interest are subjective measurements, it must state whether the observers knew the group to which each patient had been assigned. All clinical trials with a random distribution must present the results in accordance with the analysis by intention to treat (the patients are analysed in the group to which they were randomly assigned). All questionnaire-type studies must mention the response rate. Diagnostic tests studies must report the sensitivity, the specificity and the likelihood ratio. If the predictive value is presented, it must also mention the prevalence or pre-test probability.

Conclusions. Conclusions must only be presented that are based directly on the results and the implications for clinical practice, avoiding speculation and excessive generalisation.

Keywords

Immediately after the abstract, provide 3 to 10 keywords, using British spelling, to identify the content of the study for its inclusion in national and international biomedical databases. Terms should be used from the Medical Subject Headings of the Index Medicus, available at: http://www.nlm.nih.gov/mesh/meshhome.html. If no adequate terms are found within the MeSH because if its recent development, commonly used terms can be utilised. Only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes. These keywords will be

used for indexing purposes. Keywords must be included in English and Spanish.

Abbreviations

Only commonly used abbreviations in the field of intensive care medicine will be accepted. The authors should avoid the use of abbreviations in the title and in the abstract of the paper. When an abbreviation first appears in the paper, it should be preceded by the complete defining term, except in the case of common units
of measure. Units of measure should preferably be expressed in accordance with the International System of Units. Chemical, physical, biological and clinical units should always be defined. Ensure consistency of abbreviations throughout the article.

Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Units

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

References

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). These will be presented in Arabic numerals in the order in which they appear in the text with the corresponding correlating number. When authors are mentioned in the text, their names will be included if

there are one or two. When there are more, only the first author will be named, followed by the expression et al., and, in both cases, the corresponding reference citation number.

Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication. The bibliographic citations should be correctly written and the original publication should always be verified.

The names of the journals should be abbreviated in accordance with the style used in the Index Medicus, also available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=journals. The citations will be written by strictly following the Vancouver Citation Style Guide (Med Intensiva. 1998;22:110–8), also available at http://www.icmje.org/. Below are examples of bibliographic citation formats.

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Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

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https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Web references

As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references

This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. This identifier will not appear in your published article.

Preprint references

Where a preprint has subsequently become available as a peer-reviewed publication, the formal publication should be used as the reference. If there are preprints that are central to your work or that cover crucial developments in the topic, but are not yet formally published, these may be referenced. Preprints should be clearly marked as such, for example by including the word preprint, or the name of the preprint server, as part of the reference. The preprint DOI should also be provided.

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Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

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Text: Indicate references by superscript numbers in the text. The actual authors can be referred to, but the reference number(s) must always be given.
List: Number the references in the list in the order in which they appear in the text.