

# Physiotherapeutic approach and profile of patients treated in the emergency room surgical unit of a tertiary care hospital in the Federal District

*Abordagem fisioterapêutica e perfil dos pacientes assistidos na unidade cirúrgica do pronto-socorro de um hospital terciário do Distrito Federal*

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**Date of first submission:** May 15, 2021

**Last received:** May 19, 2022

**Accepted:** July 8, 2022

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## Abstract

**Introduction:** The emergency room (ER) is the main entry door for the care of critically ill patients. The inclusion of physiotherapists in these sectors is being consolidated in Brazil. **Objective:** To characterize the physiotherapeutic approach and the clinical-functional profile of patients in the ER surgical unit of a tertiary hospital. **Methods:** This was a retrospective cross-sectional study conducted from August to December of 2020. Clinical and functional data, and the main physiotherapeutic procedures performed, were collected. Analyses were conducted by means of the Friedman and Pearson Correlation tests, using SPSS software v.23. **Results:** The sample included 98 patients, 68% male, mean age of  $52 \pm 19$  years. The most common (64%) physiotherapeutic diagnosis was central nervous system (CNS) deficiency with mechanical ventilation (MV) dependence. The mean time of MV use was  $4 \pm 5$  days. Association ( $p < 0.05$ ) between MV time and admission in the emergency department ( $r = 0.972$ ) and between MV time and age ( $r = 0.330$ ) was identified. The most used physiotherapeutic actions were: suction (69%), lung re-expansion therapy (51%), and bed kinesiotherapy (37%). **Conclusion:** Adult men with CNS-related disabilities were the principal patient profile. The physiotherapeutic action in the surgical emergency unit was diverse, with application of motor and respiratory techniques, and the predominant activity was the management and maintenance of MV.

**Keywords:** Emergency treatment. Physical therapy specialty. Rehabilitation.

## Resumo

**Introdução:** O pronto-socorro (PS) tornou-se a principal porta para o início da assistência a pacientes graves. A inserção do fisioterapeuta nesses setores está em processo de consolidação no Brasil. **Objetivo:** Caracterizar a abordagem fisioterapêutica e o perfil clínico-funcional dos pacientes na unidade cirúrgica PS de um hospital terciário. **Métodos:** Trata-se de um estudo transversal retrospectivo realizado no período de agosto a dezembro de 2020. Coletaram-se dados clínicos, funcionais e as principais condutas fisioterapêuticas utilizadas. As análises foram conduzidas por meio dos testes de Friedman e Correlação de Pearson, utilizando o software Statistical Package for the Social Sciences v.23. **Resultados:** Ao todo, a amostra foi de 98 pacientes, dos quais 68% eram homens, com idade média de  $52 \pm 19$  anos. O principal (64%) diagnóstico fisioterapêutico foi deficiência do sistema nervoso central (SNC) com dependência de ventilação mecânica (VM). O tempo médio de uso de VM foi de  $4 \pm 5$  dias. Houve associação ( $p < 0,05$ ) entre tempo de VM e internação no PS ( $r = 0,972$ ) e entre tempo de VM e idade ( $r = 0,330$ ). As condutas fisioterapêuticas mais utilizadas foram a aspiração (69%), terapia de reexpansão pulmonar (51%) e cinesioterapia no leito (37%). **Conclusão:** Os homens em faixa etária adulta e com deficiências relacionadas ao SNC constituíram o principal perfil dos usuários. A atuação fisioterapêutica na unidade de emergência cirúrgica foi ampla, com emprego de técnicas motoras e respiratórias, das quais a atuação predominante ocorreu no manejo e condução da VM.

**Palavras-chave:** Emergência. Fisioterapia. Reabilitação.

## Introduction

Urgent and emergency services offered in the Brazilian emergency room (ER), have become the main gateway for care of critically ill or potentially critically ill patients requiring immediate care due to acute life-threatening dysfunctions.<sup>1-4</sup> The sudden onset of acute morbid or traumatic events, or decompensation in chronic disease, are the primary reasons for individuals to visit the ER.<sup>3,4</sup>

Arriving at this sector may occur in situations of urgency, in which the patient presents injuries that require quick resolution and intervention to prevent them from becoming more severe, or in case of emergency, when there is an imminent risk of death or impairment of vital organs, requiring immediate care or surgery.<sup>4</sup> The emergency room is composed of clinical

and surgical emergency services; in the latter, the focus of care is directed to non-traumatic and traumatic injuries caused by physical injury, resulting from harmful or violent external actions, with high impact on morbidity and mortality rates.<sup>5</sup>

This high complexity requires a qualified and effective care model.<sup>3</sup> This model was traditionally provided only by physicians and nurses prepared to manage acute diseases and traumas. In recent decades, however, overcrowding of these sectors and growing costs resulted in changes in health care, with the emergence of new interprofessional models that allowed the inclusion of physiotherapists in these teams.<sup>6</sup>

In clinical practice, however, it has been observed that inclusion of physiotherapists in the ER depends on the country and the jurisdiction's professional regulation.<sup>6,7</sup> International care management models have been undergoing restructuring, aiming to ensure comprehensive and more humanized health care. Countries such as Austrália,<sup>8</sup> the United Kingdom,<sup>9</sup> the United States<sup>10</sup> e Canada<sup>11</sup> are currently adopting physiotherapy services in their emergency departments for the management of musculoskeletal and cardiovascular disorders. Recently, a systematic review involving international studies showed that physiotherapy in the ER was able to provide effective care in pain control and reduction, minimize disability and functional loss, significantly reduce the waiting time in ERs, and provide patients with an experience of greater satisfaction with the care received.<sup>6</sup>

Meanwhile, in the organizational models of Brazilian management, the role of the physiotherapist in the ER is still not well regulated. The first practices of physiotherapist in multidisciplinary teams in Brazilian ERs date to the 2000s, in the State Hospital of Grajaú (São Paulo), and in 2005, when the Paulista School of Medicine of the Federal University of São Paulo (UNIFESP) identified the need for including physiotherapist in the ER of the São Paulo Hospital, which motivated the establishment of the specialty of physiotherapist in the ER, and the qualification of this first group that worked in this institution, in 2007.<sup>12,13</sup> Only in 2018, however, did the Federal Council of Physiotherapist and Occupational Therapy (COFFITO)<sup>14</sup> recognize the role of the physiotherapist in health care in urgent and emergency units, and included the physiotherapist in urgent and emergency sectors in the country, which is still in consolidation. The national scientific evidence in ERs with burn<sup>1</sup> and pediatric<sup>15</sup> patients has already shown that physiotherapy in the ER has promising results

in attenuating respiratory clinical signs and symptoms, by using several care techniques, resulting in management of invasive mechanical ventilation, oxygen therapy, and kinesiotherapy practices

Evidence in the literature on the role and performance of physiotherapists in urgent and emergency surgery are scarce within this context, in which the ER is structurally subdivided according to the purpose of care. Inclusion of physiotherapists in multidisciplinary teams is not yet a reality in all Brazilian ERs. Therefore, this study aimed to characterize the physiotherapeutic approach and the clinical-functional profile of patients in the surgical ER unit of a tertiary care hospital in the Federal District.

## Methods

### Study design and ethical aspects

This study was approved by the Research Ethics Committee of the Institute for Strategic Management in Health of the Federal District (opinion number 4.115.125).<sup>16</sup> The data collection period occurred from August to December of 2020, by analyzing hospital admission records from November and December of 2018, conducted once a week by a single evaluator who reviewed the sources used.

### Study site

This study was conducted in the surgical unit of the emergency department of the Base Hospital of the Federal District, a reference in trauma in the region. The unit has a total of 13 beds, distributed into four stabilization beds and nine intermediate care beds, which have the provision of multidisciplinary care, including the physiotherapy service, which is provided for a period of 12 hours a day (including morning and evening shifts).

### Eligibility criteria and sample exclusion

The sample was recruited by convenience. Volunteers admitted to the surgical ER unit (stabilization or intermediate care), of both sexes, over 18 years of age, and with a physiotherapist record were eligible. Those who were hospitalized for clinical emergencies, with incomplete records, or with impossibility of locating the medical record were excluded. For those who had duplicate records (more than one hospitalization in the

sector during the study period), only the first record of hospitalization was considered for analysis.

### Study protocol

Data collected for sample characterization included sociodemographic data, such as age, sex, comorbidities, and lifestyle habits (smoking and alcoholism), and clinical data, such as: admission clinical diagnosis, length of stay in the ER, medications (time using vasoactive medications, corticosteroids, sedatives, and neuromuscular blocker during hospitalization in the ER), predicted weight of the patient from the predictive equations of the research network of Acute Respiratory Distress Syndrome (ARDSNet),<sup>17</sup> body mass index (BMI), length of mechanical ventilation, cause of orotracheal intubation (OI), and the clinical outcome at the time of discharge from the ER.

The functional profile of patients, the physiotherapy diagnosis adopted at the time of admission to the ER was used to categorize the functional profile of the patients. Patient mobility (baseline before admission, on admission, and at discharge from the ER), was obtained from the ICU Mobility Scale (IMS),<sup>18</sup> which consists of an ordinal scale with 11 points, in which 0 characterizes the patient who does nothing (no activity, lying in bed) and 10 is attributed to those who walk independently, without a gait aid. All assessments were performed by the unit's physiotherapist. For those patients under sedation/analgesia with ventilatory drive suppression, the institutional protocol was followed, which consisted of using the volume controlled ventilation mode, with a tidal volume of 8 ml per kilo of predicted weight, with square flow wave, respiratory rate of 10 breaths per minute and inspiratory pause of 10 seconds. At the end the measurement of peak pressure, plateau, and positive end expiratory pressure (PEEP) were recorded in the patient's chart, which were later used to evaluate lung mechanics (compliance, resistance, driving pressure, and compliance ratio). All the patients were ventilated using Puritan Bennett™ equipment (model 840, Covidien - United States).

The gas exchange index was obtained from the ratio of partial pressure of oxygen ( $\text{PaO}_2$ ) by fraction of inspired oxygen ( $\text{FiO}_2$ ), collected by the nurse for arterial blood gas analysis, performed with the patient in dorsal decubitus position with the head at 30°, one hour after the initial ventilatory adjustments instituted by the physiotherapist. The  $\text{FiO}_2$  was initially 100% for all patients.

The primary early motor physiotherapist techniques used during the care were collected (kinesiotherapy in bed, sedation, orthostasis, and walking) to characterize the profile of the physiotherapeutic approach in the ER. In addition, the main respiratory physiotherapy techniques used were collected, such as: oxygen therapy (and the interfaces); involvement of the physiotherapist assisting the multiprofessional team during the OI of patients who required MV; the ventilatory mode on admission (controlled pressure, controlled volume, or pressure support); use of optimal PEEP titration; pulmonary re-expansion; progression of ventilatory weaning; and extubation. The use of noninvasive ventilation (and its indication for use), and the bronchial hygiene therapy techniques that were applied to the patients during their stay in the ER were recorded.

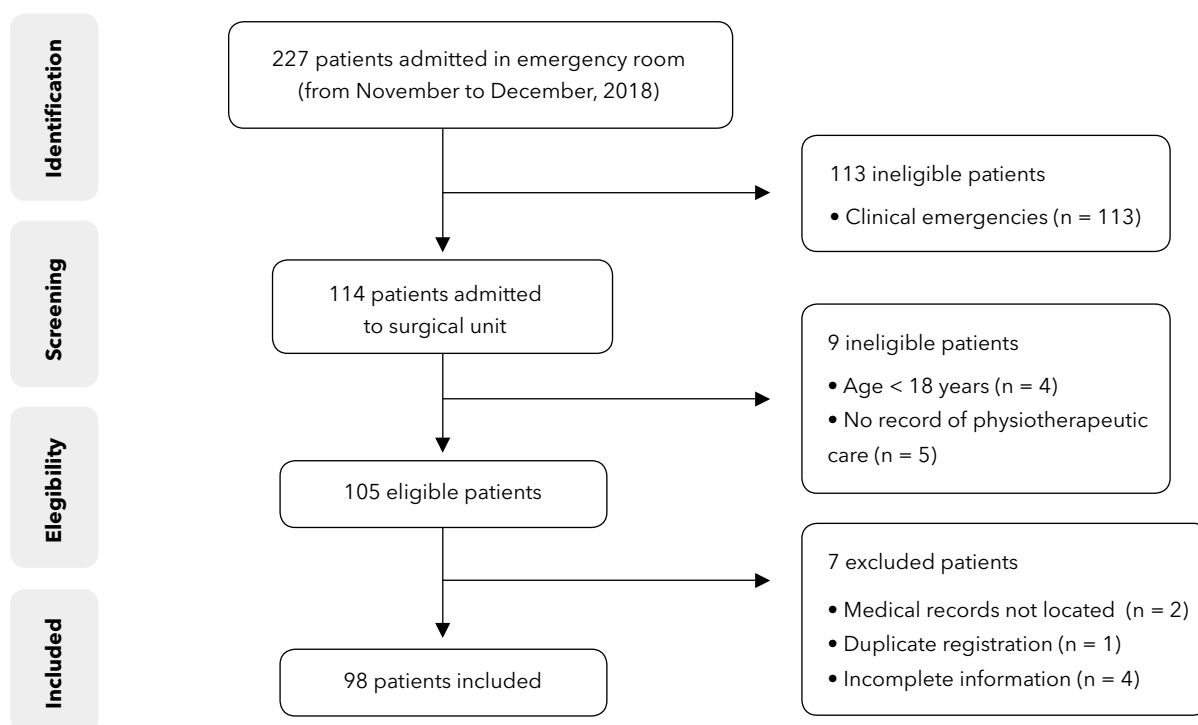
### Statistical analysis

A descriptive statistical analysis was performed. From the analysis of normal distribution, assessed by means of the Komolgorov-Smirnov test (KS), the numerical variables are presented using mean and standard deviation (SD), or median and interquartile range (IIQ); and the categorical data is represented using absolute

frequency (f) and percentage (%). For comparative purposes, mobility (baseline, on admission, and at discharge from the ER) was analyzed using the Friedman test for repeated measures, with post-hoc paired Wilcoxon and Bonferroni correction ( $\alpha^* = \alpha/3 = 0.016$ ).<sup>19</sup> The association between MV time with age, length of stay and driving pressure, and the age and length of stay in the ER, was obtained using Pearson's correlation test, considering: null ( $|r| < 0.25$ ), weak ( $0.25 \leq |r| < 0.50$ ), moderate ( $0.50 < |r| \leq 0.75$ ) or strong ( $0.75 < |r| < 1.00$ ).<sup>20</sup> All analyses were performed using the SPSS software, version 23.

### Results

Initially, 227 patients admitted in all ERs of the Federal District, Brasilia, during the time of the study were assessed. Of these, only 114 were admitted to the surgical unit, and 98 were eligible to comprise the sample, as shown in Figure 1. The studied sample had a mean age of  $52 \pm 19$  years, and was predominantly male (68%). The most common cause of admission was traumatic brain injury (TBI), in 31% of the sample. The mean length of stay in the surgical ER unit was  $4 \pm 5$  days (Table 1).



**Figure 1** - Flow chart of the observational study.

**Table 1** - Clinical characteristics of the sample (n = 98)

<b>Variables</b>	<b>Descriptive easures</b>
<b>Male</b> , n (%)	68 (69)
<b>Age</b> (years), mean (SD)	52 (19)
<b>Body mass index</b> , median (IQR)	25 (6)
<b>Comorbidities</b> , n (%)	
Diabetes Mellitus	11 (11)
Chronic obstructive pulmonary disease	4 (4)
High blood pressure	27 (27)
Smoking	11 (11)
Alcoholic	11 (11)
<b>Emergency room admission diagnosis</b> , n (%)	
Hemorrhagic stroke	23 (24)
Peripheral arterial disease	5 (5)
Bone fracture	7 (7)
Hemopneumothorax	3 (3)
Cancer	11 (11)
Firearm shooting	3 (3)
Polytrauma	6 (6)
Postoperative	4 (4)
Traumatic brain injury	30 (31)
Other causes	6 (6)
<b>Medications</b> , median (IQR)	
Corticosteroids (days)	0 (0)
Vasoactive agents (days)	2 (3)
Sedatives (days)	2 (2)
Neuromuscular blockers (days)	0 (0)
<b>Mechanical ventilation</b>	
Use of mechanical ventilation, n (%)	88 (90)
Mechanical ventilation time (days), mean (SD)	3 (5)
<b>Causes of orotracheal intubation</b> , n (%)	
Glottis edema	1 (1)
Acute respiratory failure	16 (18)
Reduced consciousness/Upper airway protection	69 (79)
Cardiorespiratory arrest	2 (2)
<b>Length of stay</b> , mean (SD)	
In emergency room (days)	4 (5)
In hospital (days)	17 (16)
<b>Outcome discharge from emergency room</b> , n (%)	
Surgery center	22 (21)
Nursing care	8 (8)
Death	36 (37)
Other emergency room units	14 (15)
Intensive Care Unit surgical/traumatic	13 (14)
Transfer to other hospitals	5 (5)

Note: Data shown in means and standard deviation (SD), medians and interquartile range (IQR), absolute frequencies (n) and percentage (%).

The major physiotherapeutic diagnosis at the admission to the ER was for disabilities related to central nervous system dysfunctions, with MV dependence in 64% of the sample. The functional assessment of the patients identified a significant mobility decline ( $p < 0.001$ ) at admission and discharge, both with a median (IQR) of 0 (0) points when compared to the baseline score (prior

to hospitalization), which was 10 (9) points. Regarding pulmonary findings, the mean driving pressure at initial adjustments was  $10 \pm 3$  cmH<sub>2</sub>O. The most frequent motor physiotherapy intervention was kinesiotherapy in bed (37%), while respiratory physiotherapy and bronchial hygiene therapy were, respectively, lung re-expansion therapy (52%) and orotracheal suctioning (69%) (Table 2).

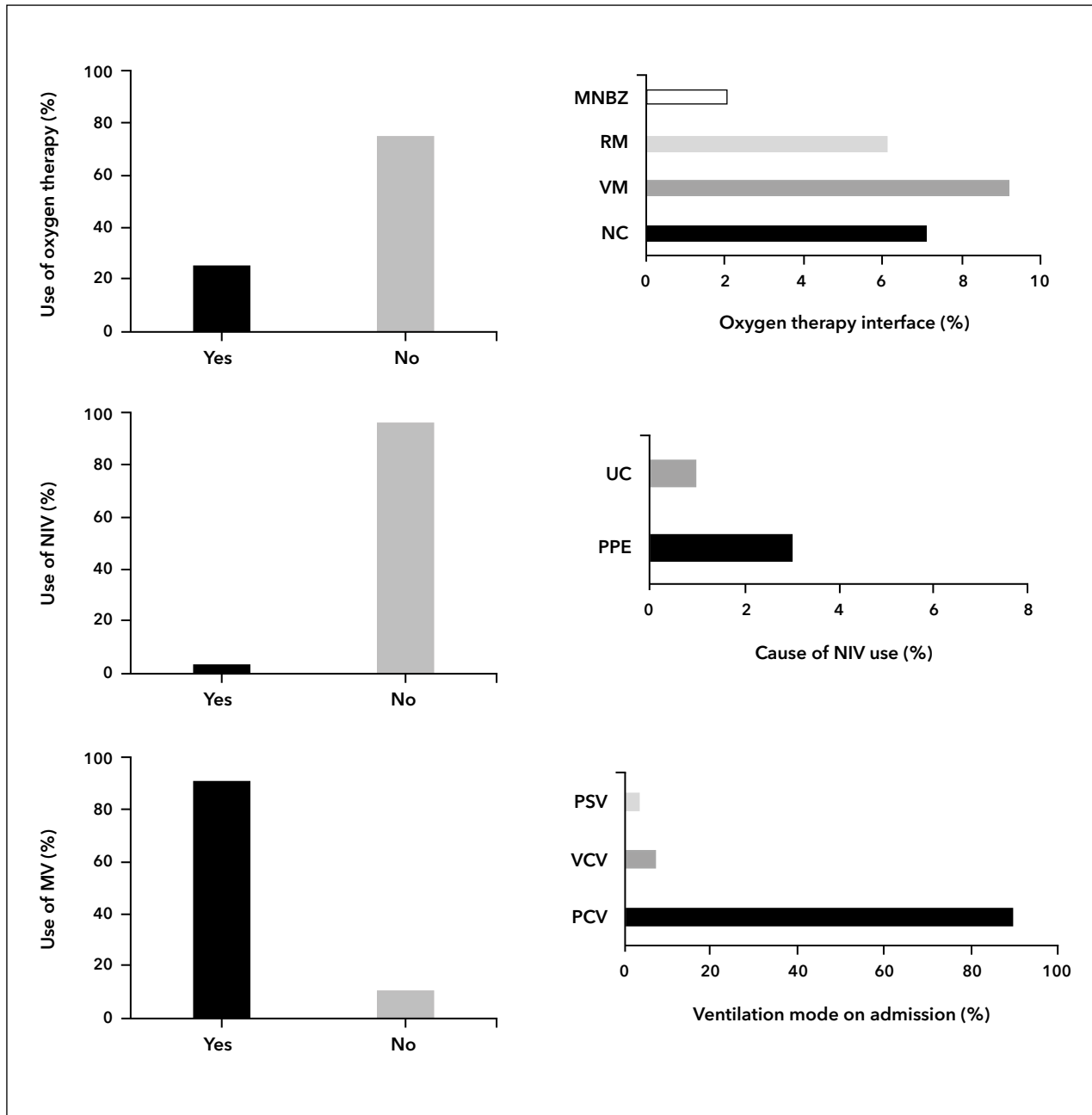
**Table 2** - Functional sample profile (n = 98) and the main physiotherapeutic intervention during hospitalization in the ER

Variables	Descriptive measures
<b>Physiotherapeutic diagnosis, n (%)</b>	
Decreased alertness associated with reduced consciousness	5 (5)
Central nervous system deficiency with mechanical ventilation dependence	63 (64)
Deficiency of the osteomioarticular system due to fracture/soft tissue	16 (16)
Deficiency of the musculoskeletal system due to surgery/amputation	6 (6)
Systemic deficiency associated with bloodstream infection	4 (4)
Ventilatory deficiency associated with ARF and mechanical ventilation dependence	4 (4)
Total physiotherapist sessions (days), median (IQR)	3 (4)
<b>Main techniques of motor physiotherapist, n (%)</b>	
Exercise in the bed	36 (37)
Bedside sitting	9 (9)
Orthostatism	6 (6)
Ambulation	6 (6)
<b>Main respiratory physiotherapy techniques, n (%)</b>	
Mechanical ventilator weaning	24 (25)
Extubation	8 (8)
Participation in orotracheal intubation	16 (16)
Lung re-expansion therapy	51 (52)
Positive end-expiratory pressure titration	0 (0)
<b>Main bronchial hygiene techniques, n (%)</b>	
Orotacheal suction	67 (69)
Flow bias maneuver in mechanical ventilation	12 (12)
Assisted cough	2 (2)
<b>Mobility assessment, median (IQR)</b>	
IMS baseline	10 (9)
IMS at ER admission	0 (0)*
IMS at ER discharge	0 (0)**
<b>Pulmonary function assessment at admission, mean (SD)</b>	
Lung compliance	50 (13)
Pulmonary resistance	14 (5)
Driving pressure	10 (3)
Oxygenation index	238 (108)
Compliance/predicted weight ratio	0,80 (0,2)

Note: ER = emergency room; ARF = acute respiratory failure; IMS = ICU Mobility Scale. Data shown using mean and standard deviation (SD), median and interquartile range (IQR), absolute frequencies (n) and percentage (%). Friedman test ( $p = < 0.001$ ), with Paired Wilcoxon post-hoc and Bonferroni correction with a significance level of  $p \leq 0.016$ . \*Baseline vs. admission  $p < 0.001$ ; \*\*Baseline vs. discharge  $p < 0.001$ .

The majority of the sample (90%) required MV, and the main reason was reduced level of consciousness and the need for airway protection, in 70% of the sample. The predominant ventilatory mode of initial adjustments

instituted by the physiotherapist was pressure-controlled ventilation (90%). In addition, the use of oxygen therapy and non-invasive mechanical ventilation (NIV) were 20% and 4%, respectively (Figure 2).

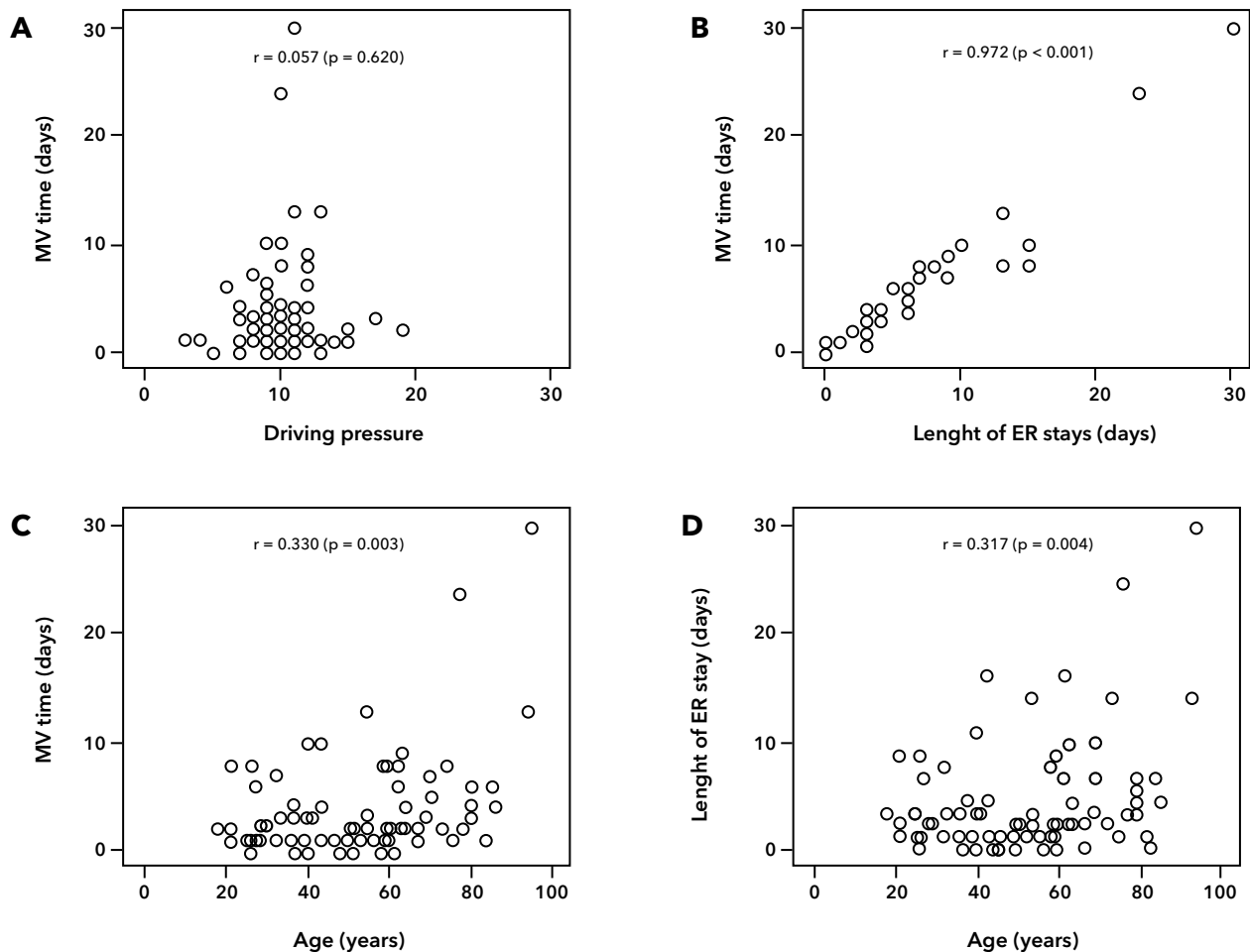


**Figure 2** - Distribution of ventilatory device use, interfaces, and indications for use.

Note: MNBZ = macronebulization; MV = mechanical ventilation; NC = nasal catheter; NIV = noninvasive ventilation; PCV = pressure-controlled ventilation; PPE = preventive post extubation; PSV = pressure support ventilation; RM = rebreather mask; UC = unstable chest; VCV = volume controlled ventilation; VM = venturi mask.

A moderate significant association ( $p < 0.05$ ) was identified between the time of MV utilization and length of stay in the ER ( $r = 0.972$ ). Weak associations between the time on MV with age ( $r = 0.330$ ) and between length of

stay in the ER with age ( $r = 0.317$ ) were also identified. No significant association ( $p = 0.620$ ) between the time on MV and driving pressure was identified in the initial settings, according to Figure 3.



**Figure 3** - Associations between the time of mechanical ventilation (MV) and clinical measures.

Note: Pearson correlation test, significance level  $p < 0.05$ . ER = emergency room.

## Discussion

This study identified the profile of patients in a surgical ER unit, as well as enabled understanding of the major physiotherapeutic procedures that permeated the routine of these professionals during the delivery of care. The patients were predominantly male, in the adult age group, in agreement with studies conducted in other emergency units and TBI victims.<sup>8,21</sup>

It is probable that this profile resulted from the fact that the studied unit is a reference in trauma care in the region. Furthermore, men in an economically active phase may be more exposed to situations and events caused by external causes.<sup>22-24</sup> Although the TBI classification was not controlled (mild, moderate, or severe), most of the causes of orotracheal intubation were related to a reduced level of consciousness, requiring airway protection, which could have been a result of the



TBI. Victims of TBI can develop functional, motor, and respiratory consequences, especially in the acute stages, as they can present irregularities in the ventilatory pattern and dysfunctions in the vital regulatory centers.<sup>25</sup>

The mean length of stay in the ER was four days, exceeding other studies, which identified a mean time of approximately one day.<sup>8,15</sup> The Federal Council of Medicine<sup>26</sup> states that 24 hours after the initial care, the patient admitted to the ER should be discharged or transferred to other units for continuity of treatment. Therefore, the prolonged hospitalization in the ER in this study may infer that the entire local health system was overloaded, as the patients should be reallocated to other units for continuity of treatment, which possibly did not occur due to lack of appropriate beds.

Among the physiotherapeutic diagnoses assigned to the patients at the time of admission, the most common was associated with central nervous system dysfunctions, and MV dependence. No other studies with similar outcomes were identified in the literature. According to the deontological regulations,<sup>27</sup> the physiotherapist is able to act in the prevention, promotion, and treatment of functional kinetic disorders, conferring to them critically a compatible functional diagnosis, and whenever it is considered beneficial, to establish methods, techniques, and/or adjuvant physiotherapeutic resources as a form of therapeutic intervention.<sup>28</sup>

In the aspects related to the patients' functional profile, a reduction of mobility at admission and discharge from the ER were identified, when compared to the baseline. No other studies were found in the literature that assessed the mobility of patients during hospitalization in the ER. Some studies that administered the IMS in critically ill patients in the ICU,<sup>29-31</sup> found a reduction of mobility at the time of admission to the ICU, as at this stage the patients are in an acute phase of the disease. In the ER setting, this acute stage may remain throughout hospitalization and, therefore, it is justifiable that mobility at discharge from the ER also remains lower than the baseline.

Early mobilization practices were used in motor physiotherapeutic approaches, and the main technique used was in bed physiotherapist. The study by Tousignant-Laflamme et al.,<sup>32</sup> which proposed to evaluate the inclusion of the physiotherapy service in the emergency room of a university hospital, showed that the presence of this professional was able to prevent the complications of immobility in the elderly.

With regard to respiratory physiotherapeutic practices, the use of different respiratory devices was found, with the main action focused on management and maintenance of invasive mechanical ventilation. The most used ventilatory mode at admission was controlled pressure; in general, the patients presented initial settings for mean driving pressure of 10 cmH<sub>2</sub>O. The time on MV was not associated with the initial driving pressure settings used in this study. The literature has shown that although ventilatory modes have different principles, there is no supremacy between them; however, control of the driving pressure < 15 cmH<sub>2</sub>O is of paramount importance to minimize lung injuries induced by MV.<sup>32-35</sup> Although the ventilatory adjustments and management are shared attributions between physicians and physiotherapists,<sup>36</sup> possibly these protective adjustments were well instituted, especially due to the presence of the physiotherapist in this unit for 12 hours daily.

Associations were also identified between the time on MV, age and length of stay in the ER. These findings may infer that patients with longer MV time, and older patients, may require a longer period of hospitalization - and consequently a transfer to other advanced care settings, such as intensive care units - as the course of acute disease in critically ill or potentially critically ill patients may present variability lasting from a few hours to months, depending on the pathophysiology and responses to treatment.<sup>37</sup>

Among the physiotherapeutic approaches, the use of oxygen therapy was also present in this study, and the main interface used by the physiotherapists was the Venturi mask. This finding corroborates the study of Taquary et al.,<sup>15</sup> conducted in a Brazilian ER with a pediatric population, which indicated the face mask as the most used interface, although the authors did not specify the type of mask (with reservoir or Venturi). The use of NIV was identified in the post-extubation context, and management of unstable chest. The Brazilian recommendation for mechanical ventilation<sup>38</sup> advocates that NIV should be used immediately after extubation, preventively, in patients at risk of reintubation and in chest trauma to improve gas exchange and prevent a new OTI. Finally, the main management of bronchial hygiene therapy was orotracheal suctioning. These findings are in agreement with other studies.<sup>1,15</sup>

This study has limitations regarding its retrospective characteristics; some records were incomplete or had divergent information that made it difficult to locate

some patients, resulting in sampling losses. However, the profile of the patients and the physiotherapy service offered in the ER was established.

International evidence already includes the physiotherapist in collaborative interprofessional practices in the emergency services.<sup>2,3,6,7,30</sup> However, the recognition of the role and expertise of physiotherapy in the Brazilian emergency room is recent<sup>14</sup> and no legislation concerning the compulsory presence of this professional in these sectors exists. Therefore, several Brazilian hospital services do not always offer physiotherapeutic care, which indicates the many challenges to be faced for the inclusion of this professional area. In this context, the findings of this study are relevant for their contribution to the characterization of care, and reinforce the relevance of the broad potential for physiotherapist in sectors of emergency surgical units.

## Conclusion

The patient profile cared for by the physiotherapist service in a surgical ER unit was predominantly composed of males, in the adult age group, with functionally developed disabilities related to central nervous system dysfunctions, and dependence on mechanical ventilation. A significant reduction in mobility was observed during the ER hospitalization in relation to the previous condition. Moreover, the time of mechanical ventilation and age were associated with a longer stay in the ER.

The findings also allowed for identifying that the physiotherapeutic approaches used were broad and involved motor physiotherapy practices, mainly with in bed kinesiotherapy, and respiratory physiotherapy practices, mainly focused on conducting mechanical ventilation with protective initial adjustments, lung re-expansion therapy, and bronchial hygiene techniques, with suctioning being prominent.

## Authors' contribution

GSM participated in the data collection, statistical analysis, data interpretation and writing of the text. RCA collaborated in the interpretation of data and writing of the text. KH and RV reviewed and approved the final version of the manuscript.

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