RESEARCH ARTICLE

Productivity Loss and Musculoskeletal Symptoms in Brazilian Presenteeism: A Cross-sectional Study

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Abstract:
Background:
The work has been brought to nursing professionals, denoting an increase in illness and consequent decrease in productivity.

Objective:
This study aims to verify the relationship between productivity and the presence of musculoskeletal symptoms in presenteeism.

Methods:
This is a cross-sectional and analytical study conducted with 305 Nursing workers from an emergency hospital in the Brazilian Midwest region. For data collection, four self-applied instruments were used, namely: the Sociodemographic Work and Health Conditions Questionnaire (QSCTS), the Stanford Presenteeism Scale (SPS-6), the Work Limitations Questionnaire (WLQ), and the Brazilian version of the Nordic Musculoskeletal Questionnaire (NMQ), Nordic Musculoskeletal Symptom Questionnaire (QNSO). The “presenteeism” and “presenteeism degree” dependent variables were related to the independent variables using the logistic regression model.

Results:
Presenteeism was identified in 134 (43.8%) workers. Overall productivity loss was 8.8%. Regarding the relationship between presenteeism and the occurrence of musculoskeletal symptoms, workers with problems in the upper back, knees, and neck in the last year were 6.5, 2.7, and 2.2 more likely to be presenteeism, respectively.

Conclusion:
The study confirmed the relationship between greater productivity losses and the incidence of musculoskeletal symptoms with presenteeism events in the Nursing team.

Keywords: Nursing, Presenteeism, Productivity loss, Musculoskeletal, Symptoms, Workers.

1. INTRODUCTION

The Nursing teamwork routine imposes different workloads on these professionals and requires high concentration, dexterity, and responsibility levels from them. In turn, these characteristics are responsible for generating physical and mental wear out, with a consequent work-related productivity loss [1 - 4].

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Among the main repercussions of productivity loss are limitations caused by physical and mental impairments. Physical impairments affect Nursing workers’ bodies to the detriment of the physical efforts required for the development of their care activities, and mental impairments are characterized by problems with the performance of cognitive tasks and also with interpersonal interactions. Workers affected by the aforementioned conditions are more prone to errors, resulting in harm to their health and impairing the quality of the assistance provided [5, 6]. Additionally, the higher sickness...
absence rates associated with long shifts could result in additional costs or loss of productivity for hospitals [6, 7].

The impact on productivity loss in Health and Nursing workers has been pointed out in the literature. A study carried out with 211 Nursing workers from a hospital in the metropolitan region of southern Brazil indicated a mean of 6.38% of lost productivity, with 75% of the nursing technicians having 9.57% of lost productivity, followed by nurses (8.75%) and nursing assistants (8.50%). The Units that presented the greatest productivity losses were Surgical Clinic (8.81%) and Medical Clinic (8.58%). The productivity loss index presented a significant association with chemical (p=0.044) and mechanical (p=0.041) loads, evidencing the type of exposure faced by these professionals in their work practice, with the work-related physical aspects standing out [8].

A number of others studies have evidenced the strong relationship between lost productivity for individuals, musculoskeletal symptoms, and worsening quality of care in health services. The impacts of lost productivity for individuals and health services also include medical errors, physical impairments with musculoskeletal disorders and work limitations, future absenteeism, and increased costs for the institutions [8 - 12].

In this context, with respect to presenteeism, this can be defined as the professional's attendance at their workplace, even if they feel sick, either physically or psychologically. In this way, even affected by this phenomenon, the worker can continue to develop his activities, with greater or lesser impairment of his performance and providing long-term damage to his health [12, 13].

This phenomenon has been mentioned in the literature as a problem nowadays, and recent studies have demonstrated its impact on the finished work, causing a decrease in the productivity of this worker, with consequent losses for organizations, as well as negative repercussions on the quality of care that will reflect in the patient [5 - 8].

Taking note of the aforementioned impacts and the need for actions to mitigate this panorama, there are international recommendations based on Sustainable Development Goals (SDGs) 3 (Good health), 8 (Decent work and economic growth), and 16 (Peace and Justice) focused on workers' health [14], in addition to national recommendations in the Brazilian National Agenda for Health Research Priorities guide that guide the conduction of research studies related to the working conditions for health professionals, the work-related risks for health (chemical, physical, biological, psychosocial, and ergonomic), work-related diseases, the effects of precarious work on workers' health, the economic impact on the Unified Health System (Sistema Único de Saúde, SUS) and, finally, data that confirm the relationship between productivity and the health professionals' employment contracts in the SUS [15].

In light of the above and considering the repercussions that work has brought about for Nursing professionals, denoting an increase in illness and a consequent reduction in the productivity of these workers, the following question arises: Is there a relationship between the occurrence of presenteeism in Nursing workers with productivity loss and musculoskeletal symptoms? To such end, the study objective was to verify the relationship between productivity and the presence of musculoskeletal symptoms in presenteeism.

2. MATERIALS AND METHODS

This is a cross-sectional and analytical study conducted with Nursing workers from an emergency hospital in the Brazilian Midwest region. The aforementioned hospital is a health institution of a legal nature, public administration, and municipal management, with the Municipal Health Secretariat as its main sustainer.

In 2019, the institution had 458 workers that comprised the local Nursing team, of which 305 participated in this study. Consequently, all the respective professionals were invited to participate in the study, with the inclusion of all those who had been working for at least 6 months in the institution.

After individual contacts to explain the study and acceptance to participate, the workers were invited to sign the Free and Informed Consent Form (FICF), which was signed in two copies, one for the participant and the other for the researchers. Along with the aforementioned document, they were also handed in the entire data collection material, as it consisted of self-applicable instruments. It is noted that all the instruments were duly validated and that previous authorization from the people responsible was granted for their use in the current study.

Each participant received an opaque and sealed envelope containing the study instruments that should be filled in individually and delivered to the researchers within a period corresponding to their next shift after receipt. In order not to impair the participants' work routine, as well as to reduce the possibility of biases due to institutional interests, the participants were allowed to use a reserved room provided by the permanent education sector of the service to answer the data collection instruments. After this phase, this material was returned by 306 workers, who comprised the final sample of the study.

For data collection, four self-applied instruments validated for Brazilian Portuguese were used, namely: the Sociodemographic Work and Health Conditions Questionnaire (Questionário Sociodemográfico de Condições de Trabalho e Saúde, QSCTS), the Stanford Presenteeism Scale (SPS-6), the Work Limitations Questionnaire (WLQ) and the Brazilian version of the Nordic Musculoskeletal Questionnaire (NMQ), Questionário Nórdico de Sintomas Osteomusculares (QNSO).

QSCTS was developed by the researchers and its objective was to determine the participants' sociodemographic profile with information relevant to the social and economic conditions, professional training, as well as to working and health conditions. It is a semi-structured questionnaire with 64 nominal and 8 numerical variables. It was validated in terms of face and content by a panel comprised of six expert judges on workers' health, mental health, and Nursing administration, as well as by two professionals who had worked for at least two years in Nursing care, represented by a nurse and a nursing technician. The agreement index achieved by the expert judges in the validation process was 0.90.
SPS-6 was developed by a number of researchers at the Stanford School of Medicine and the American Health Association and is indicated for studies that assess health and productivity conditions. It is a Likert-type ordinal scale (1-5), with answer options that vary as follows: from 1 (strongly disagree) to 5 (strongly agree), consisting of 2 dimensions with 3 items each, the first being associated with the “finished work” construct, and the second referring to “maintained concentration”, totaling 6 questions [16].

According to the aforementioned source, to obtain the overall SPS-6 score, the points answered are added up, which can vary from 6 to 30. The authors of the original version determine that scores classified as low (from 6 to 18 points) indicate reduced performance and that high scores (from 19 to 30 points) correspond to greater ability of the worker to concentrate and perform all the work duties, despite presenting some health problem. The scale was adapted to Brazilian Portuguese in 2012, showing good psychometric properties [17].

WLQ is a self-applied questionnaire with 25 items, whose purpose is to measure the interference degree that health problems impose on individuals’ ability to perform their tasks at work, as well as the impact they exert on workers’ productivity. The instrument consists of 25 items, that are distributed in 4 domains, namely: Time Management; Physical Demands; Mental-Interpersonal Demands; and the Output Demands domain [18].

Each of the domains has a scale from 0 to 100 (limited none of the time - limited all the time), whose score indicates the time percentage that the workers were limited to perform their work tasks in the last two weeks. After calculating the scores for each domain, the WLQ global score is defined, which is calculated by applying a specific validated formula [19].

Thus, to calculate the score for each WLQ domain, the arithmetic means were calculated, followed by the recommended formula (WLQ Scale Score=25*(average item score-1)). After applying this calculation, the WLQ Index was estimated using the formula (WLQ Index=(β1 X WLQ Time management + β2 X WLQ Physical Demands + β3 X WLQ Mental-Interpersonal Demands + β4 X WLQ Output Demands)), where β1=0.00048, β2=0.00036, β3=0.00096, and β4=0.00106. With the WLQ index value, calculation of the Global At-Work Productivity Loss Index was performed with the following formula: [WLQ At-Work Productivity Loss Index=(1-exp (-WLQ Index))].

The aforementioned instrument had its version translated and adapted to Brazilian Portuguese and was considered satisfactory, easy to apply, with preserved reliability and validity, and with the recommendation to be used in the Brazilian population [18]. It is noted that its copyright is under the responsibility of Mapi Research Trust, Lyon, France, accessible via the following virtual link: https://eprovide.mapi-trust.org.

QNSO had its first version published in 1987 under the name of Nordic Musculoskeletal Questionnaire (NMQ), with the proposal to standardize the measurement of reports of musculoskeletal symptoms to facilitate comparisons of results between studies that seek to assess this important construct [19]. It was translated into Brazilian Portuguese in 2002, presenting satisfactory concurrent validity and reliability indices [20].

This instrument basically constitutes an anatomical map, presenting in a topographical form, different regions of the human body, with multiple or binary choices regarding the occurrence of musculoskeletal symptoms in the different regions, distributed in 36 questions. The participants must report the occurrence of possible symptoms referring to two different moments, considering the last 12 months and the last 7 days, respectively, both preceding the data collection date. In addition to that, they should also inform of any distancing from the work activities in the last year [19, 20].

The data were organized in spreadsheets and later exported to the R Core Team (2021) statistical program. The numerical variables were presented using descriptive statistics and the mean, median, and standard deviation were calculated; and the categorical variables were presented through the distribution of relative and absolute frequencies.

The “presenteeism” and “presenteeism degree” dependent variables were related to the independent variables using the logistic regression model. The independent variables were selected through the Stepwise method, and they were maintained if their significance level was below 10%.

After estimating the regression coefficients, the likelihood ratio test statistic was calculated, which evaluates the significance of the model, the rate of correct answers, the Nagelkerke $R^2$ statistic, and the Hosmer and Lemeshow test for goodness of fit and odds ratios, with 95% confidence intervals.

The dependent variables referring to the WLQ instrument were related to the NMQ items and the “presenteeism” and “presenteeism degree” variables using Mann-Whitney's nonparametric test. The non-normality of the dependent variables was verified by using the Shapiro-Wilk test.

The individuals that did not answer at least one of the independent variables were discarded from the logistic regression analysis.

3. RESULTS

The study participants were 305 Nursing workers, which represents a 66.8% response rate. They were 220 nursing technicians (71.9%) and 86 nurses (28.1%). Regarding the sociodemographic characterization, 260 (85.0%) workers were female and the male gender was represented by 46 individuals (15%). In relation to marital status, 138 (45.0%) workers stated being single, 123 (40.1%) answered that they were married, whereas 44 (14.9%) professionals reported being widowed, separated, or divorced. As for having children, 215 (70.3%) mentioned having at least one.

As for the performance sectors in which these workers, 177 (58.0%) worked in an inpatient unit (medical/surgical), 93 (30.3%) in Intensive Care Units (ICUs), and 36 (11.7%) in the hospital emergency service. In turn, regarding the work shifts, 106 (34.6%) worked during the day on a 12/36-hour shift.
regime, 87 (33.0%) worked full-time during the day between six and eight hours a day, and 70 (23.0%), on night shifts with 12/36-hour schedules, while 41 (13.3%) were on 12/60-hour night shifts. The aforementioned variation in the workers’ hour load was related to the type of employment contract they had in the locus.

Regarding the health conditions of these participants, 35 (11.4%) indicated a mean consumption of 4 cigarettes a day. In relation to the consumption of alcoholic beverages, 89 (29.1%) mentioned drinking at least twice a week, and 64 (21.0%) stated periodic/continuous medication use. When asked about the practice of physical activity, 76 (24.8%) stated they practiced some activity, with a frequency of at least once a week indicated by 17 (21.0%) workers, while 32 (42.1%) practiced some physical activity 2 times a week and 27 (35.5%), at least 3 times a week.

Presenteeism was identified in 134 (43.8%) workers. When analyzing the presenteeism degree in that group, 51 (42.5%) had a low score (6-18 points), which denotes a reduction in work performance, while 69 (57.5%) obtained higher scores (19-30 points), which corresponds to greater ability of the workers to concentrate and perform all the work duties, even with some health problem and, therefore, being considered a presenteeism.

Overall productivity loss was 8.8% according to the WLQ At-Work Productivity Loss Index, with a global score of WLQ index=0.08. The most affected domain was Physical Demands, represented by a score of 40.6, which corresponds to a limitation of more than 40% of the time that these workers had to perform their work tasks in the last two weeks, mainly related to less ability to perform tasks that require bodily strength, endurance, movement, coordination, and flexibility. Output Demands was the second most affected domain, with a limitation estimated at 30.5%, followed by Time Management and Mental-Interpersonal Demands, represented by 30.3% and 29.6%, respectively.

When assigning the variables of the logistic regression model to presenteeism, where 0 is an absence of presenteeism and 1 is presenteeism, the Stepwise method was considered, with the variable remaining in the model if its significance was less than 10%. A total of 291 full answers were considered for the estimation of the model, as shown in Table 1.

This model is significant by the likelihood ratio test ($X^2(11) = 76.3866, p<0.001$) and was able to adequately predict 73.54% of the answers, with 52.25% for presenteeism and 86.67% for the absence of presenteeism. The Nagelkerke R² measure is 0.3139 and the Hosmer and Lemeshow statistical value is 3.2897, with $p=0.9149$, indicating adequate model fit.

According to Table 1, the data allow inferring those female workers and those with children presented 2.4 and 3.3 more chances of being presenteeism, respectively. Likewise, professionals aged at least 50 years old and those who were away from work due to medical leaves in the last year presented 3.6 and 2.7 more chances of being presenteeism, respectively. Regarding the relationship between presenteeism and the occurrence of musculoskeletal symptoms, workers with problems in the upper back, knees, and neck in the last year were 6.5, 2.7, and 2.2 more likely to be presenteeisms, respectively.

Table 1. Estimates of the coefficients of the logistic regression model for presenteeism with sociodemographic variables and musculoskeletal symptoms in Nursing workers at a municipal hospital and emergency service, Midwest, Brazil, 2019-2020 (n=291).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds Ratio</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥50 years old</td>
<td>3.6</td>
<td>1.2 - 12.7</td>
</tr>
<tr>
<td>Female gender</td>
<td>2.4</td>
<td>1.2 - 4.9</td>
</tr>
<tr>
<td>Having children</td>
<td>3.3</td>
<td>1.3 - 8.6</td>
</tr>
<tr>
<td>Away from work due to medical leave in the last year</td>
<td>2.7</td>
<td>1.2 - 6.0</td>
</tr>
<tr>
<td>Weekly frequency of physical activity</td>
<td>1.0</td>
<td>1.0 - 1.0</td>
</tr>
<tr>
<td>Problem in the upper back in the last year</td>
<td>6.5</td>
<td>1.7 - 32.5</td>
</tr>
<tr>
<td>Problem in the lower back in the last year</td>
<td>1.3</td>
<td>1.0 - 1.6</td>
</tr>
<tr>
<td>Problem in the knees in the last year</td>
<td>2.7</td>
<td>1.1 - 7.0</td>
</tr>
<tr>
<td>Problem in the neck in the last year</td>
<td>2.2</td>
<td>1.0 - 5.3</td>
</tr>
</tbody>
</table>

The analysis of the association of presenteeism with WLQ and its domains and musculoskeletal symptoms is represented in Table 2. The results obtained showed that presenteeisms had greater global productivity losses at work and in the overall WLQ score ($p<0.04$), as well as greater productivity loss in the Physical Demands domain ($p<0.001$). Likewise, presenteeisms had a significantly higher incidence of musculoskeletal symptoms in the neck and knee regions.

Table 2. Association of presenteeism with the Work Limitations Questionnaire (WLQ) and its domains and musculoskeletal symptoms in Nursing workers from a municipal emergency hospital, Midwest region, Brazil, 2019-2020 (n=306).

<table>
<thead>
<tr>
<th>Presenteeism</th>
<th>Domains</th>
<th>n</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>WLQ score</td>
<td>116</td>
<td>10.0</td>
<td>8.7</td>
<td>6.7</td>
<td>0.04</td>
</tr>
<tr>
<td>No</td>
<td>WLQ Index</td>
<td>184</td>
<td>8.4</td>
<td>6.6</td>
<td>6.7</td>
<td>-</td>
</tr>
<tr>
<td>Physical Demands</td>
<td>Yes</td>
<td>118</td>
<td>49.6</td>
<td>45.8</td>
<td>30.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>185</td>
<td>35.3</td>
<td>33.3</td>
<td>27.9</td>
<td>-</td>
</tr>
<tr>
<td>WLQ Index</td>
<td>Yes</td>
<td>116</td>
<td>9.3</td>
<td>8.3</td>
<td>6.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>
4. DISCUSSION

In this study, we confirmed the relationship between greater productivity losses and the incidence of musculoskeletal symptoms with presenteeism events in the Nursing team [6, 21], as already reported in other work contexts [22, 23]. Understanding this phenomenon is extremely important for Nursing, especially in planning its activities in health services.

The first aspect to be noted is the large contingent of female nurses, as well as middle-aged or older (≥50 years old), who had a high odds ratio (OR) and should be considered in the evaluation of presenteeism. In this scope of women and their hegemony in the Nursing area, mainly due to the cultural and historical aspects attributed to the profession, physical and mental burden is still infused for this group because of their functions. Such factors can be strongly linked to the work activities and to the quality of care provided by them, as well as to their decision-making and to the high rates of disturbances and stress among the workers [4, 24].

Some situations can be surveyed to try to explain that relationship, such as the social burden of being a woman and a mother, the need to have formal jobs in addition to the household chores that impose a double shift on them, as well as being a working woman and a mother, the marital status when it comes to married women and the required subservience of male chauvinist society and, for those who are single mothers, the challenge of raising their children amidst the division of work, maternal and household tasks [25].

However, the 21st century women have played a role in society that has brought about a break with these paradigms of submission and restriction to household and maternal activities, to the detriment of their space in the job market, in the search for training and professional qualification, as well as their recognition as a workforce that must be equalized mainly in terms of wages, regardless of gender, with labor guarantees, daycare centers and schools for their children [25].

Regarding the age factor, it was noticed that the workers aged at least 50 years old presented 4 times more chances of being presenteeism. Such findings can be explained by the Nursing work characteristics, which require high attention, concentration, dexterity, and responsibility levels from these workers in the performance of their duties. However, the literature has shown that older workers, specifically from 40 years of age, seek to present greater engagement with work, even with greater or lesser impairment of their performance [4, 26], which must be well understood by managers who must offer resources and strategies that value their physical and cognitive capabilities and limits, to the point of remaining active and recognized in the job market [4, 26].

When observing the high presenteeism rates indicated in the literature and its forms of presentation it is important to reflect on how complex and multifactorial this phenomenon is, which makes it difficult to control and report. Among such consequences, it is worth mentioning those related to direct care to the patients, having increased chances of medical errors, mainly inmedications. For the institutions, in turn, significant economic impacts are observed [27, 28].

A study that sought to quantify the harm rate and level of medication errors reported by the professionals and to determine the stages of the medication process in which the reported errors occurred in Saudi Arabia evidenced that a total of 71,332 medication error events were described in the Pharmaceutical Assistance General Department's database. The physicians were responsible for 63,120 (88.5%) errors reported, and the pharmacists detected the errors more frequently (75.9%). Most of the errors observed occurred in the prescription phase (84.8%), followed by the transcription (5.8%) and dispensation (5.7%) phases. A total of 4,182 (5.8%) errors reached the patients [29].

Continuing with the financial losses arising from presenteeism, the literature shows that the expenses due to the aforementioned condition, specifically with North American Nursing workers, are estimated at nearly US$ 12 billion a year, with a population in that country estimated at more than 329 million inhabitants in the period of the aforementioned study [30]. In the State of Tasmania, AU, the economic burden in 2015 was estimated at approximately 68 million Australian dollars with a substantial impact on productivity loss, as this region had a mean of more than 540,000 inhabitants [31]. It is important to note that, despite the population disparity between the locations, the financial impact is significant in both when looking at the population proportion to the detriment of the financial impact of presenteeism.

Productivity is another important factor to investigate when it comes to the impacts exerted by presenteeism, with loss as a relevant aspect to think about strategies to mitigate this situation, as pointed out by national and international studies [7, 30].

Productivity loss was significant in this study, and the physical aspects were responsible for the main impacts that lead to such findings, especially musculoskeletal disorders. When compared to absenteeism, the productivity losses
associated with presenteeism can be up to 4 times higher [30].

Musculoskeletal disorders are one of the main factors responsible for leading Nursing workers to presenteeism situations, having a reduction in productivity as an outcome, as evidenced in the study. It is believed that such physical symptoms are related to the Nursing work characteristics, reinforcing the increased physical demand required from these professionals in performing their care tasks.

A number of studies have shown that the impacts of musculoskeletal disorders increase the cases of absenteeism among workers and affect the productivity of these professionals due to the disabilities they cause [32, 33]. The findings of the current research denote those problems such as pain/tingling in the back (upper and lower), knees, and neck in the last year significantly increase the chances of presenteeism among the group. The aforementioned results reinforce diverse national and international evidence that imply that Nursing is mainly affected by musculoskeletal problems [34, 35].

Also in relation to the musculoskeletal symptoms, involvement in the neck and knee regions was associated with total productivity loss assessed by the WLQ index score, denoting increased time limitation during work among the presenteeism group. These results warn against the impacts on productivity loss related to the time lost due to these workers’ physical limitations. These numbers are reinforced by the literature regarding their outcomes, the main one being the reduction in working capacity or inability to work, which can lead to a distancing of the professionals from their activities [33, 36].

In the meantime, reflecting on the Nursing working conditions and apprehending their multifaceted aspects are fundamental mechanisms for the elaboration and implementation of policies aimed at workers’ health.

This study contains limitations that must be considered. First, the fact that it was conducted in a single institution, which can impair the external validity of the findings. It also stands out as a limitation of the self-completion of questionnaires by professionals, whose information may not faithfully represent reality, as they are self-reported.

The findings of the current study highlight the significant impact exerted by presenteeism on workers' health and consequently on institutions, with productivity loss as a major associated factor. Thus, strategies aimed at mitigating this situation are important through the creation of programs and policies aimed at workers’ health, as well as through partnerships between teaching, research, and extension institutions with public and private initiatives, in order to guarantee the promotion of actions aimed at workers' health, outlining strategies for professional development, compliance with laws and labor rights and encouraging those involved to have broader and shared discussions on the quality of life at work.

Therefore, it is suggested to carry out multicentric investigations, with stratified and representative samples of different professionals from different levels of health care, which seek to confirm the negative impact of presenteeism related to musculoskeletal disorders on the productivity of workers and institutions.

**LIST OF ABBREVIATIONS**

| SDGs | Sustainable Development Goals |
| SUS | Sistema Único de Saúde |
| FICF | Free and Informed Consent Form |
| QSCTS | Questionário Sociodemográfico de Condições de Trabalho e Saúde |
| SPS | Stanford Presenteeism Scale |
| WLQ | Work Limitations Questionnaire |
| NMQ | Nordic Musculoskeletal Questionnaire |
| QNSO | Questionário Nórdico de Sintomas Osteomusculares |
| OR | Odds Ratio |

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

This study was approved by the Research Ethics Committee of the Federal University of Mato Grosso, under protocol number: 3,217,476.

**HUMAN AND ANIMAL RIGHTS**

No animals were used for studies that are the basis of this research. All the humans were used following the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).
CONSENT FOR PUBLICATION

The written informed consent form was taken from the patients and volunteers.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

Data derived from this research are available on request from the corresponding author.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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