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# Espiritualidade e qualidade de vida em médicos que convivem com a finitude da vida

Spirituality and quality of life of physicians who work with the finitude of life

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## ABSTRACT

Introduction: In the medical field there are still gaps regarding the concept of death and the finitude of life, very often understood as a failure of Medicine and not as an integral part of existence. In this context, the view of death as an error, the failure of a treatment, generates anxiety and demands by doctors themselves, which can affect their physical, mental and spiritual health.

Objective: To analyze the relationship between spirituality, religious practices, and quality of life of medical professionals in the field of oncology and palliative care who deal with the finitude of life on a daily basis in a reference hospital in northeastern Brazil.

Method: Cross-sectional, analytical and guantitative study with an intentional and convenience sample. Questionnaires were applied to describe the sociodemographic profile, quality of life (WHOQOL – bref) and spirituality using the Brief Religious/Spiritual Coping Scale (Brief RCOPE) and the Spirituality Self Rating Scale (SSRS). Data analysis used the Statistical Package for the Social Sciences (SPSS), version 13.0 for Windows. The study was approved by the REC of IMIP under Opinion 2,890,118.

Result: Twenty oncologists and palliative care physicians participated in the study; most were women (55%), of white ethnicity (60%), Catholic (80%) and married (70%). The SSRS scale identified an average score of 21.75. In the Brief RCOPE, the positive aspect scored 2.64, the negative aspect 1.47, and the total aspect 2.04. There was a significant positive association between the SSRS and RCOP results (p=0.0). When associating WHOQOL - bref with Brief RCOPE, a direct relationship with statistical significance of the psychological domain was obtained with total RCOP (p-value: 0.01) and with negative RCOP (p-value: 0.03).

Conclusion: The study showed a relationship between spirituality and quality of life, as well as positive aspects of faith for coping with everyday stress, corroborating the discussion of the importance of including spirituality as a protective factor in health.

Key words: Spirituality; Quality of life; Palliative care; Mental health.

## RESUMO

Introdução: Na área médica, ainda existem lacunas no que tange à concepção de morte e à finitude da vida, muitas vezes entendida como falha da medicina e não como parte integrante da existência. Nesse contexto, a visão da morte como um erro, um insucesso de um tratamento, gera ansiedade e cobrança por parte dos próprios médicos, podendo afetar sua saúde física, mental e espiritual.

Objetivo: Este estudo teve como objetivo analisar a relação entre espiritualidade, práticas religiosas e qualidade de vida de profissionais médicos da área de oncologia e cuidados paliativos que convivem diariamente com a finitude da vida em hospital de referência do Nordeste brasileiro.

Método: Trata-se de um estudo transversal, analítico e quantitativo com amostra intencional e por conveniência. A coleta de dados foi realizada por meio de um questionário sociodemográfico, e adotaram-se os seguintes instrumentos: World Health Organization Quality of Life-bref (WHOQOLbref), Escala de Coping (Enfrentamento) Religioso-Espiritual Abreviada (CRE-Breve) e Spirituality Self Rating Scale (SSRS). A análise dos dados utilizou o Statistical Package for the Social Sciences (SPSS) 13.0 para Windows. O estudo foi aprovado pelo CEP do IMIP sob o Parecer nº 2.890.118.

Resultado: Participaram do estudo 20 médicos oncologistas e paliativistas: a maioria sendo mulheres (55%), brancos (60%), católicos (80%) e casados (70%). A SSRS identificou um escore médio de 21,75. Na Escala CRE-Breve, o aspecto positivo ficou com pontuação de 2,64, o aspecto negativo em 1,47 e o aspecto total com 2,04. Houve associação positiva significativa entre os resultados da SSRS e CRE (p = 0,0). Quando se associou a WHOQOL-bref com a CRE-Breve, foi obtida relação direta com significância estatística do domínio psicológico com CRE total (p-valor: 0,01) e com o CRE negativo (p-valor: 0,03).

Conclusão: O estudo apontou uma relação entre a espiritualidade e a qualidade de vida, assim como aspectos positivos da fé para o enfrentamento do estresse cotidiano, corroborando com a discussão da importância de incluir a espiritualidade como fator protetor na saúde.

Palavras-chave: Espiritualidade; Qualidade de Vida; Cuidados Paliativos; Saúde Mental.

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#### INTRODUCTION

The search for religiousness and/or spirituality (R/S) has always existed in human history, but only recently has medical science shown interest in investigating the topic. There are still gaps regarding the concept of death, especially when health professionals are in continuous contact with this sphere. In this sense, the progress of research has indicated the need to reconstruct the interrelationships between science and R/S in the face of several situations of physical and psychological vulnerability of the human being, including finitude and its consequences<sup>1,2</sup>.

In conditions of illness, spirituality and religiousness are relevant terms for both the individuals who go through this process and the physicians and family members. Because they are terms commonly used as synonyms, it is necessary to understand their distinction. While spirituality can be understood as the set of all emotions and convictions of a nonmaterial nature, with the assumption that there is more in living than can be perceived or fully understood, related to issues such as the meaning of life without being limited to any specific type of belief or religious practice<sup>3</sup>, religiousness can be understood as the most basic level of religion, regarding how much the individual believes, follows and practices a certain religion<sup>4</sup>.

Spirituality transcends the everyday world and is based on personal questionings of existential questions of meanings and purposes<sup>5</sup>. Spiritual and religious beliefs and practices are commonly used by patients and physicians to deal with illness and other stressful changes. In the literature, it is evident that more spiritualized people have better mental health and adapt more quickly to problems compared to those who are less spiritualized. These possible benefits for mental health and well-being have physiological consequences that affect physical health, the risk of developing diseases and responses to treatment<sup>6</sup>.

Regarding the finitude of life, death presents itself as a subject that faces relevant difficulties, even for physicians who have it not only as an element of their own lives, but also inherent to their daily work. It is also noteworthy that, although current Medicine is quite effective in the search for the healing of the body, it still needs training to address the global suffering that accompanies the process of illness and death<sup>7</sup>. Thus, a significant percentage of physicians, throughout their training, are not prepared to deal with death as an inherent factor of the human condition and, for that reason, in the quest to defeat it, they often forget that it is a fight against the invincible<sup>8</sup>.

The death that medical students learn to deal with is a dead, soulless death. When they actually face death, with body and soul, conflicts and paradoxes emerge between the desired conceptions for this confrontation, and the assimilated assumptions gain expression in the experienced intersubjective interactions<sup>9</sup>. Professionals who are not adequately prepared to deal with these situations may experience a range of reactive feelings that may negatively impact them<sup>10</sup>.

The influence of spirituality in mitigating these harmful physical and mental impacts on the lives of these professionals, and the growing interest in issues that address this correlation between quality of life, spirituality and religiousness indicate a need for studies in the area. In this sense, the present study analyzed the relationship between spirituality, religious practices and quality of life of medical professionals working in the field of oncology and palliative care who have to deal with the finitude of life on a daily basis in a referral hospital in northeastern Brazil.

#### **METHOD**

This is an observational, analytical, cross-sectional and quantitative study that analyzed oncologists and palliative care physicians who deal with the finitude of life on a daily basis in the oncology sector in a referral hospital in northeastern Brazil. Data collection was carried out between May and July 2019. Professionals who were away from the service due to leave of absence or vacation during the data collection period did not participate. This was an intentional and convenience sample, totaling 20 oncologists and palliative care physicians who agreed to participate in the study. Data collection was performed using a sociodemographic questionnaire and the WHOQOL – bref scale, the Brief Religious/Spiritual Coping Scale (Brief RCOPE) and the Spirituality Self Rating Scale (SSRS).

The Sociodemographic Questionnaire involved the following variables: gender, age, ethnicity, family income, marital status, religion. The WHOQOL - bref, from the World Health Organization, is an instrument containing 26 questions to assess guality of life. Questions 1 and 2 that address general quality of life are answered using the Likert scale that ranges from 1 to 5, and the higher the score, the better the quality of life. In addition to questions 1 and 2, the instrument also has another 24 questions, which are aspects that comprise the 4 domains: physical, psychological, social relationships and environment. To obtain data through this scale, the scores of the interview are added for each aspect and for each domain and divided by the number of participants, thus obtaining an average. The averages, which also range from 1 to 5, represent the results obtained for the domains and the aspects. Therefore, based on the results, quality of life is classified as: needs improvement (when it is 1 to 2.9); regular (3 to 3.9); good (4 to 4.9) and very good (5)<sup>11</sup>.

The Brief RCOPE has questions that are in line with the five key objectives of religion, which are: search for meaning,

control, spiritual comfort, intimacy with God and with other members of society, life transformation<sup>12,13</sup>.

The Brief RCOPE identifies how religiousness and spirituality can influence the coping with adversity. The scale consists of 49 items divided into two dimensions: The positive religious coping subscale (PRC) with 34 items and 7 factors and the negative religious coping subscale (NRC) with 15 items and 4 factors; it also has 4 general indices and 11 factorials by the average of the items. The results vary from 1 to 5 for the use of the religious/spiritual Coping strategy, meaning: none or negligible (1.00 to 1.50); low (1.51 to 2.50); medium (2.51 to 3.50); high (3.51 to 4.50); very high (4.51 to 5.00). It includes a descriptive question about the greatest stress situation that occurred in the last three years, from which the participant answers the scale. Two questions were added: attribution of value to the degree of perceived stress and classification of the experienced stress situation. In relation to the NRC/PRC ratio, this is an inversely proportional index, as it is expected that the person mobilizes more the positive Religious Coping (RCOP) in relation to the negative RCOP<sup>14</sup>.

The following are identified as positive methods of RCOP: 1. Benevolent Religious Reappraisal, which is outlined as the ability to redefine the stressor through religion as benevolent and potentially beneficial; 2. Collaborative Religious Coping, would be described as the attempt to control and solve problems in partnership with God; 3. Religious focus, understood as seeking relief from a stressful situation by focusing on religion; 4. Help through religion, understood as the effort to provide comfort and spiritual support to others; 5. Spiritual support, consists in seeking renewed comfort and security through God's love and care; 6. Support from members and/or patrons of the religious institution, encompasses the search for comfort and renewal of trust through the love and care of members and patrons of the religious institution; 7. Religious forgiveness encompasses seeking help from religion to change feelings of anger, hurt and fear associated with an offense into peace; 8. Spiritual connection, which is described as the search for a connection with transcendental forces<sup>15,16</sup>.

The negative methods are identified through: 1. **Reappraisal of God as punitive**, described as redefining the stressor as divine punishment for individual sins; 2. **Demonic or malevolent reappraisal**, encompasses redefining the stressor as evil phenomena or acts of the devil; 3 **Reappraisal of God's powers**, described as the Redefining of Divine powers to influence the stressful situation; 4. **Religious delegation coping**, consists of passively waiting for God to solve problems; 5. **Spiritual discontent**, is the expression of confusion and discontent with God; 6, **Interpersonal religious discontent**, is understood as an expression of confusion and discontent with members and patrons of the religious institution; 8. **Divine intervention**, is the supplication for direct divine intervention<sup>15,16</sup>.

The SSRS instrument consists of the patient's spirituality aspects, presenting 6 items on a Likert scale ranging from 1 (strongly agree) to 5 (strongly disagree), assessing the importance of spirituality for the interviewee, their effort and level of faith. The answers must be given according to the individual's perception at the time of answering the questions. To obtain the results, it is necessary to add the scores, which varies from 6 to 30. Regarding the items that must be recoded, inversions are carried out in which the score of 5 becomes 1; 2 becomes 4; and so on. The recoded answers are added to produce the total score, which in turn represents the level of spiritual orientation. This scale was validated in Brazil and the reliability test showed a Cronbach's alpha coefficient of 0.78, a value considered acceptable, which validates the use of the instrument<sup>17</sup>.

Its items are related to spiritual orientation and analyzes whether the individual values issues related to the spiritual dimension, whether they consider them important and apply them in their life. Each item on the scale addresses issues pertaining to the spiritual dimension and its application in life. The first item concerns the importance of spending time with private spiritual thoughts and meditations; the second asks about the effort to live according to religious beliefs; the third seeks to make a comparison between the relevance of spiritual thoughts they have when they are alone and in religious or spiritual meetings; the fourth addresses the interest in reading about matters related to spirituality or religion; the fifth asks whether spirituality helps to maintain one's stability and balance in life; and finally, the sixth item assesses how much spirituality is the basis of an individual's life<sup>17</sup>.

The database was created using Microsoft Excel 2010 and data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 13.0 for Windows. All tests were applied with 95% confidence, the data were identified with their respective absolute and relative frequencies. Numerical variables were represented by measures of central tendency and measures of dispersion. To verify the existence of an association between the categorical variables, the Chi-Square Test and Fisher's Exact Test were used. For guantitative variables, the Kolmogorov-Smirnov Normality Test ( $n \ge 30$ ) was used. In the comparison of two groups, Student's t test (normal distribution) and Mann-Whitney test (non-normal) were used. And in the comparison of more than 2 groups, ANOVA (normal distribution) and Kruskal-Wallis (non-normal) tests were used. The Correlation Coefficient used was Spearman's (non-normal). The present study was started only after approval by the Research Ethics Committee of the Instituto de Medicina Integral Professor Fernando Figueira (IMIP) under Opinion n. 2,890,118 and was carried out following the determinations of resolution 510/16.

#### RESULTS

Twenty professionals participated in the study, whose a mean age was 39.05 years (ranging from 30 to 54 years), most of them women (55%), married (70%), with a monthly income between 10 and 20 minimum wages (75%), with a self-declared white ethnicity (60%) and who practiced the Catholic religion (80%). (Table 1).

As for the data obtained in the quality of life scale, WHOQOL – bref, the average result obtained in the physical domain was the one with the lowest score (3.21), followed by the social relationships domain (3.61) and the environment and psychological domains, with a higher score, with an average of 3.71 in both.

Table 1.Frequencydistributionofsociodemographicvariables of medical oncologists and palliative carephysicians who deal on a daily basis with the finitudeof life at the IMIP. Recife PE. Brazil. 2019.

Variables	N (20)	N (%)	
Gender			
Female	11	55	
Male	9	45	
Marital status			
Single	3	15	
Married	14	70	
Divorced	2	10	
Widower	1	5	
Ethnicity			
White	12	60	
Black	0	0	
Indigenous	1	5	
Brown	7	35	
Income			
Less than 1 minimum wage			
< 10 minimum wages	1	5	
10-20 minimum wages	15	75	
>20 minimum wages	4	20	
Religion			
Spiritist	3	15	
Catholic	16	80	
Without religion	1	5	

Source: Prepared by the authors.

Among the 6 SSRS items, in the assessed sample, it was observed that only one participant completely disagreed with the fact that it is important to spend some time with private spiritual thoughts and meditations. However, it was observed that eight (40%) agreed and five (25%) strongly agreed with this assertion. Regarding the effort to live life according to religious beliefs, five (25%) professionals strongly agreed and seven (35%) agreed that they make a great effort to do that and only one disagreed. Individual prayers or spiritual thoughts were as important as those they would have during religious ceremonies or spiritual meetings for nine (45%) participants. While four (20%) professionals strongly agreed that they enjoy reading about their spirituality and/or religion, six participants (30%) disagreed and three (15%) strongly disagreed with this assertion. Most agreed or strongly agreed that their spirituality helps to maintain a more stable and balanced life. Only two (10%) professionals totally agreed with the fact that their whole life is based on their religion. (Table 2)

The total score of the SSRS total scale, which measures the degree of spirituality, showed an average score of 21.75, with a standard deviation of 4.66.

Regarding religiousness/spirituality (Brief RCOPE), in the positive domain, an average index was identified (2.64), whereas a negligible score (1.43) was identified in the negative domain. The total RCOP (2.04) and the ratio obtained between NRC/PRC (0.55) are considered low indices. These data show that the sample used more the positive coping when compared to negative one.

Regarding the association of variables, no statistical significance was found between gender and the applied scales. When associating the results of SSRS and PRC, there was statistical significance (p=0.00) with a directly proportional correlation of 0.83 and a direct correlation (p=0.0001) between SSRS and total RCOP (0.75).

In the direct correlation between the psychological domain of the WHOQOL – bref, with Total RCOP (0.55) and NRC (0.46), the relationship was significant p=0.01 and p=0.03, respectively.

Still considering the crossings of the WHOQOL – bref, correlating question 26 that deals with negative thoughts and question 9 of the same questionnaire, which addresses the health of the work environment, a p-value of 0.006 was obtained, and showed an inverse relationship of 0.59. There was also statistical significance when question 26 was associated with the domain of social relationships, showing an inverse relationship and a p-value of 0.05.

When crossing the data obtained in the Brief RCOPE and the negative, positive domains and the total score, a direct relationship can be observed between PRC and NRC

Questions	l strongly agree	l agree	l partially agree	I disagree	l strongly disagree
	N(%)	N(%)	N(%)	N(%)	N(%)
It is important, for me, to spend time with private spiritual thoughts and meditations.	5 (25)	8(40)	6 (30)	1 (5)	-
I try very hard to live my life according to my religious beliefs	5 (25)	7 (35)	7 (35)	1(5)	-
The prayers or spiritual thoughts that I have when I am alone are just as important to me as the ones I would have during religious ceremonies or spiritual gatherings.	9 (45)	5 (25)	5 (25)	1 (5)	-
I like to read about my spirituality and/or my religion	4 (20)	3 (15)	4 (20)	6 (30)	3 (15)
Spirituality helps to keep my life stable and balanced, just as my citizenship, friendships and society do.	7 (35)	9 (45)	3 (15)	1 (5)	-
My life is based on my spirituality	2 (10)	4 (20)	8 (40)	3 (15)	3 (15)

Table 2. Frequency of medical professionals' responses measured by the SSRS scale. Recife PE. Brazil. 2019.

Source: Prepared by the authors.

with a p-value of 0.01 and direct correlation of 0.55. Therefore, the total RCOP has a direct relationship with the PRC with a p-value of 0.00 and direct correspondence of 0.95, which demonstrates a strong correlation. The total RCOP also shows a direct relationship with the NRC, with a p-value of 0.00 and a correlation of 0.78.

#### DISCUSSION

Quality of Life is defined as a person's perception of their position in the context of the culture and system of values in which they live and in relation to their objectives, expectations, standards and concerns<sup>18</sup>. It is a complex concept, as it encompasses physical health, psychological state, level of independence, social relationships, spiritual, religious and personal beliefs, and their relationship with the environment<sup>19</sup>.

The medical profession has stressful aspects, such as the demand for great dedication of one's time, the involvement of a lot of personal responsibility, as well as the constant contact with the suffering of patients and families<sup>20</sup>. There are areas of Medicine in which professionals, despite great difficulty in dealing with death, whether due to failures during medical training, personal difficulties or even the experience of anticipatory grief, often deal with patients in severe conditions of illness, which entails a closer relationship with the dying process, making the process even more complex<sup>21,22</sup>.

In the present study, when assessing the quality of life of these professionals through the WHOQOL-bref, domains that pointed to a regular quality of life were identified. Of these, the physical domain showed the lowest score and is related to pain and discomfort, energy and fatigue, sleep, mobility, activities of daily living, dependence on medication or treatments that can influence our quality of life. These findings are consistent with the literature, which emphasize extreme situations in which an excessive workload and the expectation of high performance prevail, with long work hours and intensification, in remote shifts, for example, multiple employment bonds, taken up to guarantee a minimum income consistent with social expectations, low autonomy, growing difficulties related to infrastructure deficiency, especially when working in public services<sup>23</sup>. In this context, these professionals often resort to the use of medication to attenuate physical and emotional discomfort caused by the working conditions.

On the other hand, the environment domain obtained the highest score. It is related to topics such as physical safety and protection, home environment, financial resources, health and social care, opportunities to acquire new information and skills, opportunities for recreation and leisure, physical environment (pollution/noise/traffic/climate) and transportation. Despite an increasingly more competitive market, even currently, Medicine is seen as a profession with attractive social and financial status, and this circumstance possibly corroborates the fact that this domain has the highest score.

A review study on the health and quality of life of resident physicians showed high incidence rates of stress, fatigue, drowsiness, depression and exhaustion<sup>24</sup>. Specifically in relation to oncology, this is a medical specialty with high indicators of emotional fatigue, thus maintaining a direct correlation with the scores of the domains disclosed in the present study<sup>25</sup>.

The issue of spirituality is very broad and its measurement is quite complex, with spiritual well-being, that is, the subjective perception of the subject's well-being in relation to their beliefs, being one of its aspects that can be evaluated. Instruments aiming to measure spiritual well-being are based on the concept of spirituality that involves a vertical, religious component (a sense of well-being in relation to God), and a horizontal, existential component (a sense of purpose and satisfaction with one's life), with the latter not implying any reference to a specifically religious content<sup>26</sup>.

In the current study, it was verified that 45% of the participants agreed or strongly agreed with the fact that it is important to spend time with private spiritual thoughts or meditations, and no one who completely disagreed. This indicator is described as positive, as spiritual practices, such as individual beliefs and activities, have the capacity to help focus on hope, and prayer can be understood as one of the main coping strategies to relieve suffering<sup>27</sup>.

Beliefs regarding spirituality identified in this study were positive, considering that the spiritual orientation score had an average of 21.75 (SD=4.66). This information reflects the individual's spiritual orientation, that is, whether they consider or deem important (more or less) issues relevant to their spiritual dimension and applies them in their life and is in line with that described in an article published in 2018, using the same analysis tool to evaluate health professionals involved in the care of critically-ill patients. In this study, a score of 24.5 was verified, which classifies both results as a relevant degree of spirituality, according to the original scale validation study<sup>28,29</sup>.

When people turn to religion to deal with stress, religious coping occurs<sup>12</sup>. In the literature, coping is described as the way an individual uses their faith to deal with stress and problems in life, emphasizing that faith can include religion, spirituality or personal beliefs. In addition to the association with problemfocused coping strategies, religion can also be correlated with the venting of emotions, which represents a tendency to release these emotions related to stress and negative feelings, which can then show non-adaptive characteristics. Therefore, in relation to the results, the spiritual-religious coping methods can be classified as positive and negative<sup>30-34</sup>.

The present study showed a greater use of positive religious/spiritual coping when facing stressful situations. Therefore, it was demonstrated that the study subjects use the beneficial effects of coping, such as seeking love and protection from God or a greater connection with transcendental forces, seeking comfort in religious literature, seeking to forgive and be forgiven, praying for others' well-being, solving problems in collaboration with God, and redefining the stressor as beneficial. Similarly, they use fewer strategies that generate harmful consequences, such as questioning God's existence, love or acts, delegating problem solving to God, feeling discontentment with God or members of a religious institution, and redefining the stressor as divine punishment or evil forces<sup>34,35</sup>.

It is interesting to compare these data with a study that used the same scale to assess how cancer patients use religious/ spiritual coping strategies in this process of finitude, which obtained a NRC/PRC ratio of 0.54, that is, a very similar index<sup>36</sup>.

It has been described that individuals with higher levels of spirituality have a lower prevalence of depression and anxiety, better quality of life, lower prevalence of heart problems and lower mortality<sup>18</sup>. In a population-based study involving 506 people aged between 16 and 78 years living in the city of Porto Alegre, the protective character of spiritual well-being was demonstrated by its association with the reduction of mental disorders<sup>37</sup>.

It is known that religious involvement seems to have a significant protective effect on physical well-being, since having a biopsychosocial-spiritual view of health implies a more comprehensive view of life, recognizing the relationship of spirituality with other dimensions, while remembering, however, that coping with painful situations is important for improving the quality of life and for the growth of human beings<sup>38</sup>. Therefore, it can be inferred that the positive correlation between the PRC indexes and the SSRS scale of the present study, by pointing to greater spirituality in those involved, as well as the positive association of the WHOQOLbref physical domain with total RCOP, tend to encourage the health professionals in the study to enjoy the described beneficial effects.

#### CONCLUSIONS

Oncologists and palliative care physicians spend a large part of their time with professional activities closely related to the finitude of life, and the view of death can be translated as an error or failure of a treatment, thus generating negative emotional demands that can interfere with the professional performance and these people's lives. Spirituality was related to aspects of quality of life, mainly in the psychological domain. Associations were also identified between the degree of spirituality and the use of positive aspects of faith to face everyday stresses. Thus, the influences of spirituality in the attenuation of these harmful impacts, physical and mental, on these physicians' lives alert to the need to recognize spirituality as an important component for the global health of these professionals.

As limitations, the study has a little representative sample, as it sought information in a single health service, with a cross-sectional design. However, it can be observed that the specificity and demands of care in the field of oncology and palliative care seem to be common in several regions of Brazil and in the world, as evidenced by the literature. It is suggested that follow-up and multicenter studies be carried out aiming to bring to light more information that can contribute to improve the training and quality of life of medical professionals, which can be extended to other specialties.

### **AUTHORS' CONTRIBUTION**

All authors contributed substantially to the study design and planning, data analysis and interpretation, drafting and critical review of the manuscript and approval of the final version of the manuscript.

## **CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

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