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HEALTH: CHALLENGES AND SOLUTIONS

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PRESENTATION

The book *Health: Challenges and Solutions* is an essential work for anyone seeking a comprehensive and up-to-date understanding of the challenges and solutions in the field of health. With an interdisciplinary approach, the book explores fundamental topics that involve public health, health policies, the evolution of diseases, and the impact of new technologies on treatment and prevention.

The reading is highly recommended for students and professors in fields such as Medicine, Nursing, Public Health, Nutrition, Psychology, and Physical Education, as it offers a solid theoretical foundation, along with case studies and practical examples that facilitate the understanding of topics discussed in the classroom. At the same time, the book presents recent data and up-to-date discussions that can help prepare future professionals for the real challenges they will face in their careers.

For health professionals, such as doctors, nurses, nutritionists, and public policy managers, *Health: Challenges and Solutions* serves as a valuable resource for making informed decisions. The book analyzes emerging issues, such as the impact of climate change on global health, antimicrobial resistance, pandemic management, and the inclusion of digital technologies in clinical practice, topics that are directly related to the daily lives of these professionals.

Additionally, the book is accessible to the general public who seek to better understand how health systems work and what the main threats and solutions to health in the 21st century are. With clear language and didactic explanations, it allows any reader, even without technical training, to understand global challenges and viable alternatives for a healthier and more sustainable future.

Health: Challenges and Solutions is, therefore, a recommended read for anyone who desires a comprehensive and critical view of the healthcare system, covering both global issues and innovative solutions.

SUMÁRIO

CHAPTER 1

BOTULINUM TOXIN TYPE-A IN THE MANAGEMENT OF CHRONIC PAIN: A LITERATURE REVIEW

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ABSTRACT: There is increasing evidence suggesting the efficacy of botulinum toxin type A (BoNT-A) in treating chronic pain of various etiologies. In addition to being studied for migraines and trigeminal neuralgia, this substance has been evaluated for conditions such as tension headaches, cervicalgia, myofascial pain, neuropathy, among others. This variety of applications reflects the multifunctional capacity of BoNT-A to influence neurophysiological processes associated with pain perception and transmission. BoNT-A has various mechanisms of action in pain treatment, including its ability to modulate pain transmission at both peripheral and central levels. These findings suggest that the substance has promising potential to treat a variety of chronic pain conditions. Given the relevance of the topic, the objective of this review was to address the use of botulinum toxin type A in treating different types of chronic pain. For the research, searches were conducted in databases, initially selecting 26 articles, of which 12 were deemed relevant. Thus, the importance of conducting further research to fully understand the role of BoNT-A in pain treatment is emphasized. These studies are essential to provide additional evidence on the efficacy and safety of BoNT-A in various painful conditions, allowing for more precise and personalized clinical guidance on its use.

KEYWORDS: Botulinum toxin, Chronic pain, Pain.

RESUMO: Há cada vez mais evidências que sugerem a eficácia da toxina botulínica tipo A (BoNT-A) no tratamento da dor crônica de várias etiologias. Além de ser estudada para enxaquecas e neuralgia trigeminal, essa substância tem sido avaliada em condições como cefaleias tensionais, cervicalgia, dor miofascial, neuropatia, entre outras. Essa variedade de aplicações reflete a capacidade multifuncional da BoNT-A em influenciar os processos neurofisiológicos associados à percepção e transmissão da dor. A BoNT-A possui diversos mecanismos de ação no tratamento da dor, incluindo sua capacidade de modular a transmissão da dor tanto a nível periférico quanto a nível central. Essas descobertas sugerem que a substância possui um potencial promissor para tratar uma variedade de condições de dor crônica. Levando-se em consideração a relevância do assunto em questão nos dias atuais, o objetivo da presente revisão foi abordar o uso da toxina botulínica tipo A no tratamento dos diferentes tipos de dor crônica. Para a elaboração da pesquisa, foram feitas buscas em bases de dados, selecionando-se inicialmente 26 artigos, dos quais 12 se enquadraram para a relevância do estudo. Destaca-se assim, a importância de realizar mais pesquisas para entender completamente o papel da BoNT-A no tratamento da dor. Esses estudos são fundamentais para oferecer evidências adicionais sobre a eficácia e segurança da BoNT-A em várias condições dolorosas, permitindo uma orientação mais precisa e personalizada do seu uso clínico.

PALAVRAS-CHAVE: Toxina botulínica, Dor crônica, Dor.

1. INTRODUCTION

The prevalence of moderate to severe chronic pain in Europe is about 20%, with primary headache disorders affecting approximately 2.6% of the German population, including 1.1% diagnosed with chronic migraine. Medication overuse headache has a global prevalence estimated between 0.5% and 7.2%, while about 7% of the general population suffers from some form of chronic neuropathic pain (Sandrini *et al*., 2017).

Chronic pain represents a significant social and economic burden, affecting daily activities, productivity, personal relationships, and contributing to depressive symptoms. In the U.S., annual costs for medical treatment and pain relief for migraine, low back pain, and fibromyalgia amount to thousands of dollars. Although less than the cost of cancer pain treatment, persistent pain and primary headache have a significant impact due to their chronic nature. With the limitations of current pharmacological approaches and the risk of opioid abuse, alternative treatments need to be considered (Sandrini *et al*., 2017).

Botulinum toxin type A (BoNT-A) therapy has emerged as a promising approach in the treatment of chronic pain disorders, which represent a significant challenge for patients and healthcare professionals, often involving a complex interaction of physical and psychosocial factors. However, the growing understanding of BoNT-A's mechanisms of action and its efficacy in reducing pain has sparked interest within the medical community (Lang, 2003; Colhado; Boeing; Ortega, 2009).

Botulinum toxin (BoNT), a potent natural toxin produced by the anaerobic bacterium *Clostridium botulinum*, blocks the release of acetylcholine at the neuromuscular junction by inhibiting the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex. Since the pioneering use of BoNT for treating strabismus over 40 years ago, therapeutic indications for BoNT type A (BoNT-A) and, more recently, type B for treating excessive and/or unwanted muscle tone have progressively expanded (Sandrini *et al*., 2017; Matak *et al*., 2019).

In light of the above, the aim of this review is to address the use of botulinum toxin type A (BoNT-A) in the treatment of various types of chronic pain.

2. METHODOLOGY

This study is a descriptive research that constitutes an integrative literature review. Searches were conducted in the databases "US National Library of Medicine" (PubMed), Lilacs, and Google Scholar, using the following health science descriptors: “botulinum toxin,” “chronic pain,” and “pain,” as well as their English equivalents.

The inclusion criteria for the preparation of the study were: publications in English or Portuguese, with thematic relevance to the review, with preference given to publications in the aforementioned databases from the last 10 years, and clinical trial articles.

From the searches in the mentioned databases, 26 articles were selected for the authors' analysis, of which 12 met the previously established criteria and were included in the reference base for this study.

Thus, the aim of the review was to address the use of botulinum toxin type A (BoNT-A) in the treatment of different types of chronic pain.

3. RESULTS AND DISCUSSION

There is growing evidence supporting the use of BoNT-A in the treatment of chronic pain from various etiologies. In addition to migraine and trigeminal neuralgia, the substance has been investigated for conditions such as tension-type headaches, cervical pain, myofascial pain, and neuropathic pain, among others. This range of indications reflects the multifaceted ability of BoNT-A to modulate neurophysiological processes involved in pain perception and transmission. (Sandrini *et al*., 2017).

Some studies have investigated the different mechanisms by which BoNT-A interferes with pain transmission. One of the well-known mechanisms is the selective inhibition of nociceptive neurotransmitter release and pro-inflammatory substances responsible for pain transmission, such as substance P, glutamate, and CGRP (calcitonin gene-related peptide). This neurochemical action contributes to reduced neuronal sensitivity and attenuation of the inflammatory response associated with migraine, thereby reducing the sensation of pain. (Durham; Cady; Cady, 2004; DO; Hvedstrup; Schytz, 2018; Matak *et al*., 2019).

Additionally, the role of BoNT-A in modulating pain receptor sensitivity has been explored. The substance may interact with specific receptors on nerve endings, altering

their sensitivity to painful stimulation. This results in a decreased receptor response to pain, contributing to symptom relief. (Matak *et al*., 2019).

BoNT-A also has the capacity to modulate the activity of ion channels on neuronal membranes. By interfering with the function of these channels, the substance can regulate nerve impulse transmission and reduce neuronal excitability, leading to decreased pain perception. (Matak *et al*., 2019).

Beyond peripheral mechanisms, there is also evidence regarding BoNT-A's effects on the central nervous system. It has been found that the substance can modulate neuronal activity at central levels, affecting brain regions involved in pain processing. This suggests that BoNT-A may have analgesic effects not only locally but also in brain areas responsible for pain perception. This ability to influence neuronal plasticity and modulate central pain pathways is crucial for pain relief in patients with chronic migraine, where central sensitization plays a significant role in maintaining symptoms. (DO; Hvedstrup; Schytz, 2018; Matak *et al*., 2019).

Chen and Meng (2020) addressed a crucial issue regarding the use of BoNT-A in the context of chronic pelvic pain (CPP) in women, characterized by persistent pain in the pelvic organs for more than six months and encompassing a variety of symptoms such as pelvic pain, dyspareunia, irritable bowel syndrome, and dysuria. Within this framework is chronic pelvic pain syndrome (CPPS), which may affect a single organ or multiple organs in the pelvic region. Due to a lack of understanding of its specific cause, there is no established standard treatment for CPPS. However, botulinum toxin type A (BoNT-A) emerges as a potential therapeutic option. Application of BoNT-A in the bladder has been shown to reduce pain in patients with interstitial cystitis/bladder pain syndrome. Additionally, injection of BoNT-A into pelvic floor muscles has been associated with improvements in chronic pain syndrome. Although BoNT-A may alleviate symptoms, its effectiveness often requires repeated injections due to its reversible nature. It is also important to consider the potential adverse effects of BoNT-A, which may exacerbate pre-existing conditions such as constipation, stress urinary incontinence, and fecal incontinence.

Tugnoli *et al*. (2007) investigated the effects of BoNT-A on capsaicin-induced pain and neurogenic vasodilation in human skin. This study involved applying capsaicin to the skin of volunteers to induce pain and neurogenic vasodilation. Subsequently, botulinum toxin type A was administered to the same skin area, and the effects were evaluated compared to a control group that received placebo or no treatment. Pain and vasodilation

parameters were monitored and recorded over time to assess the efficacy of botulinum toxin in reducing symptoms. The results demonstrated a significant reduction in capsaicin-induced pain following BoNT-A application, as well as a decrease in neurogenic vasodilation, suggesting a direct analgesic effect of the substance.

In turn, the clinical trial by Ranoux *et al*. (2008) examined the direct analgesic effects of BoNT-A in patients with chronic neuropathic pain, revealing a significant reduction in pain intensity following BoNT-A application compared to the control group, indicating a direct analgesic effect of the substance in patients with chronic neuropathic pain.

In the randomized, double-blind clinical trial conducted by De La Torre Canales *et al*. (2024), patients with refractory masticatory myofascial pain were treated with BoNT-A or placebo. The results revealed a significant reduction in pain intensity in patients treated with BoNT-A compared to the control group that received placebo. These findings suggest that BoNT-A may be effective in relieving pain in patients with refractory masticatory myofascial pain, offering a promising therapeutic option for this debilitating condition. In addition to pain reduction, the study also examined the effects of BoNT-A on the somatosensory and psychosocial aspects of patients. The results showed significant improvements in pressure sensitivity and pain threshold, as well as in mental health-related quality of life, in individuals treated with BoNT-A compared to those receiving placebo. These findings suggest that BoNT-A not only alleviates pain but may also modulate sensory and psychosocial aspects associated with refractory masticatory myofascial pain, thereby improving patients' quality of life.

Buonocore *et al*. (2017) reported a case of a patient with chronic neuropathic pain refractory to conventional treatment. The patient, diagnosed with phantom limb syndrome after traumatic amputation, experienced a significant reduction in pain intensity following the administration of botulinum toxin type A (BoNT-A). This singular case suggests a promising new therapeutic approach for managing neuropathic pain, particularly in patients with inadequate responses to conventional treatments. The administration of BoNT-A in this specific case demonstrated efficacy in reducing debilitating neuropathic pain, providing relief to the patient and improving their quality of life. These results highlight the potential of botulinum toxin as a viable therapeutic option for individuals suffering from refractory neuropathic pain, particularly those with post-amputation phantom limb syndrome.

Another study analyzing the use of BoNT-A in managing refractory or debilitating chronic pain was conducted by Schwarzer, Mäcken, and Enax-Krumova (2023), who explored its potential in emerging areas of pain medicine, such as complex regional pain syndrome (CRPS) and post-traumatic chronic pain. They reviewed recent clinical studies and scientific evidence to evaluate the efficacy and safety of BoNT-A in these contexts, highlighting its promising role as an additional therapeutic option for patients with debilitating chronic pain.

BoNT-A may be considered as a therapeutic option for patients with chronic pain refractory to other treatment modalities. The favorable safety profile and long-lasting effects of BoNT-A make it an attractive alternative for individuals who do not respond adequately to conventional analgesics or who experience significant side effects with other therapeutic approaches. (Sandrini *et al*., 2017).

4. CONCLUSION

A BoNT-A possui uma abrangente gama de mecanismos de ação no tratamento da dor, destacando sua capacidade de modular a transmissão da dor em níveis periféricos e centrais. Nesse sentido observou-se que a substância possuir uma capacidade promissora no tratamento de diversas condições de dor crônica.

Esses achados são fundamentais para o desenvolvimento de estratégias terapêuticas mais eficazes no manejo da dor crônica e aguda, no entanto, devemos acrescentar que, embora os resultados sejam promissores, o nível de qualidade da evidência ainda não é alto o suficiente para fornecer diretrizes explícitas para médicos da dor.

Ressalta-se portanto a necessidade de mais pesquisas para elucidar completamente o papel da BoNT-A no manejo da dor, incluindo estudos clínicos randomizados e controlados em diferentes populações de pacientes. Esses estudos são essenciais para fornecer evidências adicionais sobre a eficácia e segurança da BoNT-A em diversas condições dolorosas, ajudando a orientar sua utilização clínica de forma mais precisa e individualizada.

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CHAPTER 2

CANNABIDIOL IN THE TREATMENT AND MANAGEMENT OF PAIN

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ABSTRACT: *Cannabidiol*, a compound known for thousands of years, has been extensively studied recently for the management of various health conditions, including pain. Considering the relevance of the subject to date, the aim of this review was to analyze the use of cannabidiol for the treatment and management of pain, taking into account its action in the human body and its potential benefits and harms. For the study, searches were conducted in databases, initially selecting 58 articles, of which 23 were relevant to the research. Although researchers still do not fully understand the exact mechanisms of action of the compound for pain management and relief, studies have shown positive results in patients, especially when used with other medications. However, society still needs more research on the topic for a better approach and understanding of the subject.

KEYWORDS: *Cannabidiol*, *Cannabis*, pain.

RESUMO: O *cannabidiol*, composto já conhecido por milhares de anos, tem sido amplamente estudado atualmente para o manejo de diversas condições de saúde, dentre elas a dor. Considerando-se a relevância do assunto em questão até os dias atuais, o objetivo da presente revisão foi analisar uso de *cannabidiol* para o tratamento e manejo da dor, levando em consideração sua ação no corpo humano e seus potenciais benefícios e malefícios. Para a elaboração do estudo, foram feitas pesquisas em bases de dados, selecionando-se inicialmente 58 artigos, dos quais 23 se enquadraram para a relevância da pesquisa. Apesar de os pesquisadores ainda não compreenderem completamente os exatos mecanismos de ação do composto para o manejo e alívio da dor, pesquisas tem mostrado resultados positivos nos pacientes, principalmente quando utilizadas com outros medicamentos, no entanto, a sociedade ainda necessita de mais pesquisas acerca do tema para uma melhor forma de abordagem e melhor entendimento do assunto.

PALAVRAS-CHAVE: *Cannabidiol*, *Cannabis*, dor.

1. INTRODUCTION

The scientific term for the cannabis plant is *Cannabis sativa*, a plant with both male and female flowers that belongs to the Cannabaceae family. Native to Central and Eastern Asia, it has historically been used by rural communities to treat various ailments due to its psychoactive and hallucinogenic effects, as well as being recognized as a therapeutic resource. It is believed that this plant is not prone to substance abuse and does not cause harm when used for medicinal purposes (Lukhele; Motadi, 2016; Guida *et al*., 2019).

The composition of cannabis includes approximately 540 natural compounds, with Δ9-tetrahydrocannabinol or tetrahydrocannabinol (THC) being the predominant psychotropic component and cannabidiol (CBD) being the second most common and principal non-psychotropic ingredient. THC's action is related to its binding and activation of two specific cannabinoid receptors, CB1 and CB2, which are coupled to G proteins (López-Valero *et al*., 2018; Kenyon; Liu; Dalgleish, 2018; Amin; Ali, 2019; Aparicio-Blanco *et al*., 2019).

The CB1 receptor is primarily found in the central and peripheral nervous systems, while CB2 receptors are predominantly present in the immune system. Endogenous cannabinoids interact with these receptors. CB1 agonists act at various sites along the pain transmission pathways, including the activation of peripheral, spinal, and supraspinal CB1 receptors, each independently reducing nociception (Skrabek *et al*., 2008).

The endocannabinoid system shows several similarities to the opioid system. Both CB1 receptors and opioid receptors are found in similar regions of the nervous system involved in pain control, such as the periaqueductal gray, rostral ventromedial medulla, and spinal cord. Additionally, cannabinoids have been associated with the inhibition of prostaglandin E-2 synthesis, reduced platelet aggregation, and a significantly stronger anti-inflammatory effect compared to hydrocortisone and aspirin (Skrabek *et al*., 2008).

The therapeutic actions of Δ9-THC and CBD include their ability to act as analgesics, antiemetics, anti-inflammatory agents, anticonvulsants, neuroprotective compounds, and they also exhibit antineoplastic activities. For instance, CBD has been shown to induce cell death in human glioma cells U87 and U373, possibly through caspase activation and involvement of reactive oxygen species (Lukhele and Motadi, 2016; Sultan; Marie; Sheweita, 2018; Amin; Ali, 2019; Zhang *et al*., 2019).

Cannabis-based medications, such as nabilone (a compound similar to Δ9-THC), nabiximols, and dronabinol (a synthetic version of Δ9-THC), are prescribed to alleviate nausea and vomiting caused by chemotherapy. Sativex (which contains a mixture of Δ9-THC and CBD) has been used to relieve neuropathic pain (Amin; Ali, 2019).

Therefore, the aim of this review is to study the use of cannabidiol in the treatment and management of pain, considering its action in the human body and its potential benefits and drawbacks.

2. METHODOLOGY

This study is a descriptive research that constitutes an integrative literature review. Searches were conducted in the databases “US National Library of Medicine” (PubMed) and Google Scholar, using the following health science descriptors: “cannabidiol,” “cannabis,” and “pain,” as well as their corresponding terms in English and Spanish.

The inclusion criteria for this study were: publications in English, Portuguese, and Spanish with thematic relevance to the review, with preference given to publications from the aforementioned databases from the last 10 years, as well as some pioneering research on the subject for a better theoretical foundation.

From the searches in the mentioned databases, 58 articles were selected for the authors' analysis, of which 23 met the previously established criteria to compose the reference base for this study.

Thus, the aim of the review was to analyze and elucidate the use of cannabidiol in the treatment of various types of pain.

3. RESULTS AND DISCUSSION

For general understanding, the results and discussion sections initially list cannabis-derived medications approved for medicinal use in some countries:

Plant-derived cannabinoids include tetrahydrocannabinol (THC) and oromucosal CBD (nabiximols; Sativex®) or oral CBD (Epidiolex®). Among synthetic cannabinoids, nabilone (Cesamet® or Canemes®), a synthetic analog of THC, is approved in some countries for the treatment of nausea/emesis refractory to cancer patients, and dronabinol (Marinol® or Syndros®), another synthetic THC used for similar purposes (Petzke *et al*., 2021).

Compounded cannabis-derived preparations consist of specific cannabinoids, such as plant-derived THC (Dronabinol®), as well as the cannabis plant itself in its forms of leaves, flowers, resins, and extracts. These preparations may include oils or tinctures containing specific levels of THC and/or CBD, along with other active compounds such as phytocannabinoids, terpenes, and flavonoids. THC and CBD concentrations vary significantly, with THC generally ranging from 3% to 30% and CBD from less than 1% to 13%. Extracts may contain a wide range of THC/CBD combinations, from very low levels to 100% concentration of each compound. Although there is a widespread belief, primarily based on anecdotal reports, that other molecules in the plant, such as terpenes and phenolic compounds, may enhance the therapeutic effects of cannabinoids, this hypothesis still lacks solid scientific evidence (Petzke *et al*., 2021).

The term "dronabinol" is used in distinct ways: as a generic name for synthetic THC in a licensed medical product, such as Marinol® or Syndros® in the United States, and also as a compounded plant-derived preparation in some European countries. It can be administered in various forms, including (a) oromucosally, through sprays such as nabiximols; (b) orally, in capsules (dronabinol, nabilone), oil (CBD), and extracts (dronabinol, herbal cannabis); (c) through smoke or vapor inhalation, using CBD, plant-derived dronabinol, herbal cannabis, and resins; and (d) topically or rectally, with the use of CBD, herbal cannabis, resins, and extracts (Petzke *et al*., 2021).

There are also experimental medications, such as cannabinoid receptor antagonists, negative allosteric modulators, and synthetic THC-11 analogs, which have not yet received approval for pain therapy outside of clinical studies. These include drugs such as rimonabant (SR141716A), fatty acid amide hydrolase inhibitors, and ajulemic acid (AJA, CT-3, IP-751, JBT-101, anabasum). Additionally, there are nutritional supplements based on cannabidiol and cannabis flower extracts, all with THC content of < 0.2%, < 0.3%, or < 1.0%, depending on the country (Petzke *et al*., 2021).

Although cannabis use for pain treatment can be traced back 5000 years, there is still limited information on its mechanisms of action, which include modulation of neuronal activity in the rostral ventromedial medulla, antinociceptive effects in descending pain pathways, and anti-inflammatory properties through inhibition of prostaglandin synthesis. It remains uncertain whether cannabis can alleviate certain types of pain (Amin; Ali, 2019).

The efficacy of cannabis in pain treatment was first evidenced in preclinical studies. It is believed that the endocannabinoid system plays an active role in pain

control, and animal pain models have been used to support this theory. Delta-9-tetrahydrocannabinol (THC) has been shown to produce analgesic effects and reduce hyperalgesia in mice (Hill; Palastro, 2017).

Various forms of medicinal cannabis have mainly provided positive responses for patients with different types of pain: chronic pain, postoperative pain, fibromyalgia-related pain, rheumatoid arthritis, multiple sclerosis, and cancer pain, as well as neuropathic pain, which is a severe form of chronic pain resulting from injuries or diseases affecting the somatosensory system (Borgelt *et al*., 2013; Amin; Ali, 2019).

Studies comparing smoked cannabis to a placebo have shown that participants generally reported effective pain relief, with increased efficacy associated with higher THC content. Overall, pain relief was modest and not as effective as medications specifically prescribed for pain, such as GABA receptor agonists gabapentin and pregabalin (Amin; Ali, 2019).

As a general rule, pain relief tends to be more effective when cannabinoids are taken alongside existing pain medications, rather than on their own. For example, nabiximols, an oromucosal spray with an equal mixture of THC and CBD, is being evaluated in various clinical trials with patients suffering from neuropathic and chronic pain. Each of these studies demonstrated a statistically significant reduction in pain intensity compared to placebo. In most of these trials, patients continued to take their existing analgesic medication in addition to starting the study medication; therefore, the symptom relief obtained with the study drug was beyond the effects achieved with the patients' existing analgesia. Reported adverse events included dizziness, sedation, feelings of intoxication, and nausea. As a limitation, most of these studies had varied definitions for types of pain and included patients who were already using standard analgesics; thus, nabiximols may be more suitable for patients with refractory pain (BLAKE *et al*., 2005; NURMIKKO *et al*., 2007).

Orally administered THC, at doses of 5 to 20 mg (dronabinol), did not show significant improvements in pain reduction in studies with healthy individuals or patients with chronic gastrointestinal pain or post-hysterectomy. However, in cancer patients, only higher doses of THC (15 and 20 mg) demonstrated pain relief comparable to codeine's effect. It is important to note that side effects such as drowsiness, dizziness, and blurred vision may limit cancer pain management with oral THC (Noyes *et al*., 1975; Buggy *et al*., 2003; Naef *et al*., 2003).

Additionally, dronabinol, at doses of 10 mg per day for 3 weeks in patients with multiple sclerosis, resulted in a relative reduction in pain compared to placebo, with no reports of serious adverse events, although patients experienced more dizziness and lightheadedness (Svendsen; Jensen; BACH, 2004).

Nabilone, a synthetic cannabinoid administered orally, was tested for treating pain in fibromyalgia patients in a controlled study with 40 participants. After four weeks of treatment, there was a significant reduction in pain, disease impact, and anxiety, as measured by standardized scales, considering that during the treatment, the medication was titrated from 0.5 mg/day to 1 mg twice daily. The authors stated that the pain relief observed in the treatment group was similar to other treatments used for fibromyalgia, such as fluoxetine, tramadol, and pramipexole. Although patients experienced side effects such as drowsiness and dry mouth, the pain relief was comparable to other commonly used treatments for fibromyalgia. In a separate study, high doses of nabilone showed an increase in pain for patients also receiving morphine after surgery, which was attributed to unexpected effects of cannabinoids at high doses (Beaulieu, 2006; Skrabek *et al*., 2008).

Two meta-analyses examined different cannabis treatments for pain. The first analyzed 18 double-blind clinical studies comparing cannabis preparations with placebo in patients with chronic pain. Cannabis showed a significant reduction in pain intensity, but also adverse effects such as mood disturbances and cognitive changes. The second assessed 14 studies on painful neuropathy associated with HIV, where smoked cannabis, capsaicin patches, and a human nerve growth factor showed efficacy in pain reduction. However, smoked cannabis use may pose health risks, suggesting the need to investigate other forms of administration (Martín-Sánchez *et al*., 2009; Phillips *et al*., 2010).

The efficacy of medicinal cannabis or cannabinoids (Δ9-THC/CBD) in relieving neuropathic pain is still unclear. While THC may be effective, its psychoactive side effects are concerning, whereas CBD appears promising due to its action as a negative allosteric modulator of the CB1 receptor, without inducing psychoactive effects. Cannabinoids may also interact with CB1 and CB2 receptors to alleviate pain, although data on CB1 is inconsistent. Additionally, cannabinoids may act on TRP channels to reduce pain, and their anti-inflammatory effects may contribute to chronic pain relief, as seen in osteoarthritis. However, further research is needed to fully understand the effects of cannabinoids in treating neuropathic pain (Amin; ALI, 2019).

Although physicians might consider recommending cannabis for certain conditions where some evidence of efficacy exists, there are many other considerations before making an official recommendation. In addition to the issue of the legality of recommending cannabis by physicians, there are potential adverse events associated with its use both in the short and long term that need to be weighed. Acute cannabis intoxication can affect memory perception, time, and motor functions. Cannabis may exacerbate existing anxiety or mood disorders and, in some cases, increase the risk of developing such disorders. There is a strong association between cannabis use and the development of psychotic disorders in individuals with a genetic predisposition. Cannabis use during adolescence can cause permanent changes in the developing brain, such as reduced gray matter density in the hippocampus and corpus callosum.

4. CONCLUSION

Patients often seek medical consultations due to unbearable chronic pain. While medications such as NSAIDs or opioids are commonly used to alleviate this pain, their prolonged use can lead to adverse health effects. In this context, studies have investigated the use of cannabis as an alternative for treating chronic pain. Some patients have reported relief from consuming cannabis in various forms, and its use has been legalized in some U.S. states and several countries around the world. Compared to opioids, studies suggest that cannabis use presents fewer adverse effects and may even reduce dependence on these medications.

Overall, these studies show statistically significant improvements in various types of pain when medicinal cannabis is used. Trials indicate that smoked cannabis or cannabis extracts (THC

) are effective for several types of pain, particularly neuropathic pain. Oral THC (dronabinol) does not seem to be as effective for pain, but it has not been widely studied across various pain conditions. Nabilone may be effective for fibromyalgia-related pain, though it too has not been extensively studied. There is a shortage of well-designed studies evaluating medicinal cannabis for pain. The limitations of these studies include widely varying doses and forms of medicinal cannabis, lack of validated criteria or assessments for certain types of pain (e.g., neuropathic), absence of comparative trials for various formulations and administration routes, selection bias (i.e., some patients may

have had a previous positive response to the medication), difficulty in blinding participants to potentially psychoactive substances, and small study populations.

As healthcare professionals, it is crucial to determine the primary objective of using cannabis before prescribing it, carefully weighing its advantages and disadvantages. A thorough patient assessment regarding cannabis use is essential to decide between prescribing this medication or seeking other alternative methods to manage pain, aiming to provide the best possible care for the patient.

Given the above and the demonstrated results, it is concluded that the use of cannabis and its derivatives has significant potential in treating various types of pain; however, further studies are needed for a better understanding and clarification of the topic. It should always be prescribed with caution, individualized attention, and medical supervision.

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CHAPTER 3

ANATOMY AND TREATMENT OF AORTIC ANEURYSM: A INTEGRATIVE REVIEW

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ABSTRACT: This literature review aims to discuss in detail the anatomy and treatment of aortic aneurysms, emphasizing the most recent advances and ongoing discussions in specialized literature, contributing to a comprehensive understanding of the most effective diagnostic and intervention strategies in the treatment of aneurysms. aortic arteries, through a narrative bibliographic review methodology. Thus, it is observed that atherosclerotic degeneration is the main pathological cause of aortic aneurysm, aggravated by risk factors such as hypertension, smoking, obesity and genetic predisposition, in addition to changes in the arterial wall, intensified by pro-inflammatory cytokines and metalloproteinases, are fundamental in the evolution of the disease, which can vary in symptomatic manifestation depending on the location of the aneurysm, directly influencing the choice of treatment, which ranges from monitoring to surgical interventions such as endovascular repair and open surgery. The study concludes that early detection and a treatment approach adapted to the patient's individual characteristics are crucial to preventing serious complications, pointing to the need for advances in diagnostic and treatment techniques that allow for less invasive and more effective interventions, providing better management of this significant medical condition.

KEYWORDS: Abdominal Aortic Aneurysm, Thoracic Aortic Aneurysm, Thoracoabdominal Aortic Aneurysm, Endovascular Procedures, Post-operative Complications Etiology.

RESUMO: Esta revisão bibliográfica se propõe a discutir de forma detalhada sobre a anatomia e tratamento do aneurisma aórtico, enfatizando os avanços mais recentes e das discussões em curso na literatura especializada, contribuindo para uma compreensão integral das estratégias de diagnóstico e intervenção mais eficazes no tratamento dos aneurismas aórticos, através de uma metodologia de revisão

bibliográfica narrativa. Desse modo, observa-se que a degeneração aterosclerótica é a principal causa patológica do aneurisma aórtico, agravada por fatores de risco como hipertensão, tabagismo, obesidade e predisposição genética, além disso as alterações na parede arterial, intensificadas por citocinas pró-inflamatórias e metaloproteinases, são fundamentais na evolução da doença, que pode variar em manifestação sintomática dependendo da localização do aneurisma, influenciando diretamente na escolha do tratamento, que varia de monitoramento a intervenções cirúrgicas como reparo endovascular e cirurgia aberta. O estudo conclui que a detecção precoce e uma abordagem de tratamento adaptada às características individuais do paciente são cruciais para prevenir complicações sérias, apontando para a necessidade de avanços em técnicas de diagnóstico e tratamento que permitam intervenções menos invasivas e mais eficazes, proporcionando melhor gestão dessa condição médica significativa.

PALAVRAS-CHAVE: Aneurisma da Aorta Abdominal, Aneurisma da Aorta Torácica, Aneurisma da Aorta Toracoabdominal, Procedimentos Endovasculares, Complicações Pós-Operatórias Etiologia.

1. INTRODUCTION

The aneurysm is defined as an abnormal dilation of the affected arterial segment and can manifest in any artery of the body, including those that supply the brain, heart, kidneys, or abdomen. However, it is most commonly found in the aorta, the largest artery in the circulatory system, followed by the iliac and splenic arteries. The etiology of aneurysms is typically multifactorial, involving hereditary, traumatic, infectious, and inflammatory components, but it is estimated that approximately 80% of cases are associated with atherosclerotic degeneration of the arterial wall (Sampson, 2020

Aneurysms can vary significantly in their clinical manifestations, with some being asymptomatic and detected only incidentally, while others are identified through specific screening programs. Notably, aortic aneurysms may occur in both the thoracic and abdominal portions. Treatment for aortic aneurysms includes various surgical and endovascular techniques, though not all cases require immediate intervention, depending on the aneurysm's location, size, and growth rate (Brown, 2022).

This article aims to elucidate, through a literature review, the detailed anatomy of the aorta and the most appropriate therapeutic approaches for treating aneurysms in this vital artery. The study seeks to provide an in-depth understanding for both clinical practice and academic research, highlighting the diagnostic methodologies and treatment options currently available for the effective management of aortic aneurysms.

2. THEORETICAL FRAMEWORK

When reviewing the surgical approaches for the treatment of aortic aneurysm, a critical and organized analysis of the literature highlights the diversity of available techniques and the determining factors in selecting the most appropriate method for each patient. Previous studies, such as those by Sampson (2020) and Netter (2019), provide an essential foundation by emphasizing the main surgical approaches, such as open surgery and endovascular repair, each with its specific advantages and considerations. The selection of the appropriate surgical technique is influenced by a complex interaction of factors, including the location and extent of the aneurysm, the patient's clinical condition, comorbidities, vascular anatomy, and the surgeon's preferences.

The literature also addresses the different levels of complexity and the implications associated with each surgical technique. While open surgery involves an incision in the

abdominal or thoracic wall for direct access to the aneurysm, endovascular repair uses a minimally invasive approach by inserting a stent-graft through catheters to the aneurysm site, reinforcing the weakened aortic wall. The choice between these techniques depends on a careful evaluation of the patient's anatomy, the size and extent of the aneurysm, and the presence of comorbidities that may influence the procedure's outcome.

The risks and complications associated with each surgical approach are fundamental to making an informed decision. Studies such as those by Smith and Johnson (2022) and Brown (2022) highlight specific complications, such as endoleaks and the need for reinterventions in endovascular repair, as well as the increased risk of perioperative complications in open surgery, including longer recovery times and higher perioperative mortality rates. These considerations are crucial in guiding the choice of the most suitable surgical technique for each patient, aiming to optimize clinical outcomes and minimize risks.

Comparatively, recent studies, such as those by Chaikof *et al*. (2018) and Greenhalgh *et al*. (2010), provide important insights into the success rates and complications associated with each surgical technique, enabling a more accurate evaluation of the available therapeutic options. A critical analysis of these data is essential to inform clinical practice and ensure the best possible care for patients with aortic aneurysms. Ultimately, integrating this knowledge into clinical decision-making is essential to provide personalized and high-quality treatment to patients affected by this potentially life-threatening condition.

3. METHODOLOGY

For the development of this study on the anatomy and treatment of aortic aneurysms, a narrative literature review was chosen. This method consists of a critical evaluation and interpretive synthesis of published studies that address the anatomy of the aorta and the surgical and endovascular techniques used in its treatment, as well as the complications associated with these interventions. The objective of this approach is to provide a holistic and in-depth view of current therapeutic practices and their clinical implications for the management of aortic aneurysms.

The methodological support for this review was based on established guidelines for bibliographic research, with particular attention to the works of renowned

methodologists such as Booth, Sutton, and Papaioannou (2016) in their book *Systematic Approaches to a Successful Literature Review*. These authors offer a detailed guide to the essential principles and procedures for conducting effective narrative reviews, ensuring a robust and thorough analysis of the data.

The search for sources was conducted in academically relevant databases, including PubMed, Scopus, and Web of Science, using specific descriptors such as "Abdominal Aortic Aneurysm," "Thoracic Aortic Aneurysm," "Thoracoabdominal Aortic Aneurysm," "Endovascular Procedures," and "Postoperative Complications/etiology." The research period extended from 2004 to 2022.

The selection of articles for this literature review followed clear inclusion criteria, focusing on studies that provide quantitative data on outcomes, complications, recovery times, and other relevant clinical indicators. By applying these rigorous methodological standards, the study aligns with the quality and integrity requirements demanded by academic and practical scrutiny, ensuring a significant contribution to the existing literature and providing a solid foundation for future investigations and clinical practices.

Based on these guidelines, the review sought not only to synthesize existing data but also to contextualize the information within the current landscape of cardiovascular medicine, ensuring the relevance and scientific contribution of the findings to the medical and academic communities. Thus, this review focuses on presenting the latest advances and ongoing discussions in the specialized literature, contributing to a comprehensive understanding of the most effective diagnostic and intervention strategies for the treatment of aortic aneurysms.

4. RESULTS AND DISCUSSIONS

Aortic aneurysms, whether in the thorax or abdomen, are characterized by a pathological dilation that exceeds 50% of the normal vessel diameter due to the weakening of the arterial wall. This condition can be caused by various factors, such as atherosclerosis, which is often considered the primary cause of arterial wall degeneration (Sampson, 2020). In addition to atherosclerosis, factors such as smoking, obesity, genetic predisposition, and trauma also have a significant impact on the development of this pathology.

The aorta is the largest and principal artery of the human circulatory system. It is responsible for transporting oxygenated blood from the heart to the body. This strong

artery originates from the left ventricle of the heart and is anatomically and functionally divided into several parts: the aortic root, aortic arch, thoracic aorta, and abdominal aorta (Netter, 2019).

The aortic root includes the aortic ring, aortic valve, and the sinuses of Valsalva, which are essential for preventing the backflow of diastolic blood into the heart. Following the root, the aortic arch curves dorsally over the heart and is the origin of the major blood vessels that supply the head and upper limbs, including the brachiocephalic artery, left common carotid artery, and left subclavian artery (Netter, 2019).

The thoracic aorta descends posteriorly, crosses the mediastinum, and supplies smaller branches to thoracic structures, such as the intercostal arteries, before passing through the diaphragm. Beyond the diaphragm, the aorta becomes the abdominal aorta, radiating important branches to the abdominal and pelvic organs, including the renal, mesenteric, and iliac arteries, before bifurcating into the common iliac arteries near the level of the fourth lumbar vertebra (Netter, 2019).

The pathogenesis of aortic aneurysms is marked by the complex interaction between biomechanical forces and biological reactions that compromise the structural integrity of the aortic wall. The main layers of the vessel affected are the intima, media, and adventitia, with damage often initiated by hypertension or atherosclerosis. Hypertension exerts chronic stress on the arterial wall, damaging the elastic fibers and collagen in the media layer, which are crucial for the aorta’s resilience against the pulsatile forces of blood pressure (Sampson, 2020).

Atherosclerosis contributes to this pathology through plaque formation, which not only narrows the arterial lumen but also facilitates the infiltration of lipids that promote an inflammatory response. This response is primarily mediated by macrophages and T cells migrating to the aortic intima. Macrophages engulf lipids and transform into foam cells, releasing pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), which recruit more inflammatory cells to the affected area (Brown, 2022).

T cells, particularly the Th17 subpopulation, B cells, and interleukins such as IL-6, play a key role in modulating the inflammatory response involved in aneurysm pathogenesis. Th17 cells exacerbate inflammation by producing IL-17, a cytokine that amplifies inflammation by inducing the release of other pro-inflammatory cytokines (such as IL-6 and TNF-α), chemokines, and prostaglandins by stromal cells and macrophages. Additionally, IL-17 promotes neoangiogenesis and attracts neutrophils, furthering tissue

damage. B cells also participate by producing antibodies that can form immune complexes and deposit in the arterial wall, intensifying the local inflammatory response. Furthermore, IL-6 is notable for its pro-inflammatory action and for inducing the acute phase response, contributing to the degradation of the extracellular matrix (Jones *et al*., 2019).

The degradation of collagen and elastin fibers is critically mediated by matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are activated in the inflammatory environment and stimulated by IL-17. These enzymes break down the structural components of the extracellular matrix, culminating in the pathological dilation of the aorta and eventually the formation of the aneurysm (Smith & Johnson, 2022).

Symptoms of aortic aneurysms vary depending on their location. Thoracic aortic aneurysms may present with cough, chest pain, and respiratory difficulties, while abdominal aortic aneurysms often manifest as a palpable pulsation in the mid and lower abdomen, along with tenderness in this area (Jones *et al*., 2019).

Diagnostic methods for aneurysms include high-precision imaging exams, such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound. CT is particularly valued for its ability to provide detailed images of vascular anatomy, while MRI is useful for not involving ionizing radiation, making it a safer option for patients with contraindications to iodinated contrast (Meyer, 2021).

The risks associated with aortic aneurysms include hypertension, high cholesterol, and demographic factors such as advanced age and male gender, the latter showing a higher prevalence of the condition. For example, abdominal aortic aneurysms occur in 75% to 80% of cases in men (Sampson, 2020). These factors not only increase the risk of developing aneurysms but also heighten the likelihood of aortic rupture, a potentially fatal event due to the resulting internal hemorrhage (Brown, 2022).

Regarding treatment, options vary depending on the severity and location of the aneurysm. Management can range from lifestyle modification and regular monitoring to surgical interventions. There are essentially three main approaches: vigilant observation, particularly for small and stable aneurysms; endovascular repair, which involves placing a stent via catheterization; and open surgical repair, reserved for more severe cases, where a section of the aorta is replaced with a synthetic graft (Smith & Johnson, 2022). These surgical approaches have been developed and refined over the years, each with specific characteristics, as well as clear indications and contraindications, requiring careful evaluation to choose the most appropriate method for each patient.

Open surgery is one of the most traditional techniques, involving an incision in the abdominal or thoracic wall to directly access the aneurysm and replace it with a synthetic graft. This approach is generally reserved for larger aneurysms or those that exhibit rapid growth and is indicated for symptomatic cases or when the patient's anatomy is not conducive to other techniques. However, its use is limited in patients at high surgical risk due to severe comorbidities, given its invasive nature and the higher risk of complications (Greenhalgh *et al*., 2010).

In contrast, Endovascular Aneurysm Repair (EVAR) is a minimally invasive alternative, in which a stent is inserted via catheters to the site of the aneurysm to reinforce the weakened aortic wall. This technique is preferably indicated for fusiform or saccular aneurysms and is particularly advantageous for patients considered high-risk for surgery. However, EVAR may be contraindicated in patients whose aortic anatomy presents short or tortuous necks, making it difficult to achieve proper stent anchoring (Chaikof *et al*., 2018).

Moreover, the hybrid approach combines elements of open surgery and EVAR to treat complex aneurysms that do not fit ideally within a single treatment type. This technique is indicated for cases where neither exclusively endovascular nor surgical approaches are suitable. However, it may not be ideal for patients with extremely complex aortic anatomy (Chaikof *et al*., 2018).

A comparative analysis of statistical data reveals important nuances between these approaches. Studies indicate that open surgery has a higher perioperative mortality rate, ranging from 2% to 5%, compared to EVAR, which has a lower mortality rate of less than 1% (Chaikof *et al*., 2018; Greenhalgh *et al*., 2010). However, EVAR is associated with higher rates of late complications in approximately 20% of patients, such as endoleaks and the need for reinterventions in about 15-20% of patients (Patel *et al*., 2016; Schermerhorn *et al*., 2008).

Studies have also shown that, despite the potential late complications of EVAR, patients undergoing this technique tend to have a faster recovery and better immediate postoperative quality of life compared to open surgery. This is due to the less invasive nature of EVAR and the shorter recovery time (Prinssen *et al*., 2004).

Thus, early identification and appropriate treatment of aortic aneurysms are crucial, as aortic rupture can lead to fatal consequences. Furthermore, it is imperative that individuals at risk undergo periodic examinations and that predisposing conditions, such as hypertension and hyperlipidemia, are effectively managed. The therapeutic

approach should be personalized, considering individual risk factors, the location of the aneurysm, and the patient's overall condition (Wanhainen *et al*., 2019).

5. CONCLUSION

This article conducted a comprehensive review of the anatomy and treatment of aortic aneurysms, highlighting the critical aspects of pathogenesis and the available therapeutic modalities for this significant pathological condition. A detailed understanding of the aorta's structure and the underlying mechanisms in the development of aneurysms is essential for advancing early diagnosis and the most effective treatment of this pathology.

The study's findings indicate that atherosclerosis is the primary cause of arterial wall degeneration, exacerbated by risk factors such as hypertension, smoking, obesity, and genetic predisposition. These conditions contribute to inflammatory and biomechanical changes in the aortic wall, leading to aneurysm formation through the degradation of collagen and elastin fibers and the inflammatory response mediated by T cells, macrophages, and the activation of pro-inflammatory cytokines.

It was also emphasized that thoracic and abdominal aortic aneurysms present different clinical manifestations, reinforcing the need for accurate diagnostic approaches, such as computed tomography and magnetic resonance imaging, for the effective identification of the condition and the aneurysm’s location. Treatment strategies range from non-invasive monitoring to surgical interventions, including endovascular repair and open surgery, depending on the aneurysm’s size, growth rate, location, and the patient’s general condition.

Furthermore, the study highlights the importance of a personalized approach in treating aortic aneurysms, considering the risks and benefits of different surgical techniques. The choice between open surgery and endovascular aneurysm repair (EVAR) must account for the patient’s specific anatomy and aneurysm complexity. While EVAR offers advantages such as lower perioperative mortality and faster recovery, it presents challenges like higher rates of late complications and the need for reinterventions.

In summary, this literature review reiterates the importance of early diagnosis and tailored treatment to significantly improve outcomes in patients with aortic aneurysms. Deepening the understanding of the interaction between modifiable risk factors and the

pathological dynamics of this condition could pave the way for more effective and less invasive therapies in the future, as well as more robust prevention strategies for at-risk populations.

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CHAPTER 4

ANALYSIS OF EFFECTS OF EUGENIA CATHARINENSIS P-CUMARIC ACID IN EMBRYOS OF G. DOMESTICUS TREATED WITH LEAD ACETATE

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ABSTRACT: Heavy metals can damage any biological activity and thus generate distinct cellular responses. Studies have shown that a single exposure to lead during the embryonic period of birds results in significant morphological, physiological and behavioral changes in adult and mainly young individuals. With the action of lead acetate in the development of *Gallus domesticus* embryos, it is possible to analyze possible changes in morphological and biochemical patterns. In order to reduce the toxic actions of heavy metals and consequently the effects they cause on the various organisms studied, we have plants as a natural form of protection. The presence of phenolic compounds, such as p-coumaric acid, of this species seems to be mainly responsible for its protective activity. This project aims to evaluate the effects of *Eugenia catharinensis* p- coumaric acid compound on embryos treated with lead acetate.

KEYWORDS: Lead, P-Coumaric acid, Embryotoxicity, *Gallus domesticus*, Heavy metal.

RESUMO: Os metais pesados podem danificar toda e qualquer atividade biológica e com isso gerar respostas celulares distintas. Estudos têm demonstrado que, uma única exposição ao chumbo durante o período embrionário de aves, resulta em significativas alterações morfológicas, fisiológicas e comportamentais em indivíduos adultos e principalmente jovens. Com a ação do acetato de chumbo durante o desenvolvimento de embriões de *Gallus domesticus*, pode-se analisar possíveis alterações nos padrões morfológico e bioquímico. Para reduzir as ações tóxicas dos metais pesados e

consequentemente os efeitos que estes causam nos diversos organismos estudados, tem-se as plantas como uma forma natural de proteção. A presença de compostos fenólicos, como por exemplo o ácido p-cumárico, desta espécie parece ser o principal responsável pela sua atividade protetora. Desta forma busca-se com este projeto avaliar os efeitos do composto ácido p-cumárico de *Eugenia catharinensis*, sobre embriões tratados com acetato de chumbo.

PALAVRAS-CHAVE: Humbo, Ácido P-cumárico, Embriotoxicidade, *Gallus domesticus,* Metal pesado.

1. INTRODUCTION

Contamination by heavy metals is one of the most severe forms of pollution due to their cumulative toxic effects on the environment and living organisms (Rosa et al., 2003). The main sources of such contamination are urban and industrial waste, which contain toxic compounds. However, lead (Pb) contamination originates from atmospheric emissions, with air serving as the primary medium for the transport and distribution of this metal. Large quantities of lead tend to accumulate near sources such as battery factories (Araújo; Pivetta; Moreira, 1999). Inadequate management of effluents and solid waste from mining and metallurgical industrial activities can cause significant negative impacts on various environmental compartments (biota, air, soil, sediments, surface and groundwater) and human health. Undoubtedly, numerous cases have been reported in Brazil and around the world regarding the damage caused by environmental liabilities generated during or after the closure of industrial activities (Santos, 2017).

Considered a toxic metal for humans and animals, lead has no known physiological function in the body and can cause serious health issues (Uebek, 2017), with carcinogenic, teratogenic, and toxic effects in birds (Narbaitz et al., 1995) and humans (Zarembski et al., 1983; Rothemberg et al., 1999). Contamination occurs through inhalation or ingestion, with the gastrointestinal and respiratory tracts being the primary absorption sites for lead, which, once absorbed, is found in the blood, soft tissues, and mineralized tissues (Uebek, 2017).

According to Lima (2017), lead acetate is considered a multipotent teratogenic agent, capable of causing alterations in embryonic development. Moreover, it interferes with morphogenesis mechanisms, such as developmental delays, alterations in the nervous system pattern, and malformations, which can lead to death.

Teratogenic agents can cause severe congenital anomalies in embryos. These disorders occur during critical periods of development, during the active differentiation of a tissue or organ. Organs have different critical periods during their development, with the brain and skeleton standing out as being more sensitive from the beginning of their formation until birth (Lima, 2017).

Thus, lead is a known neurotoxic agent that can cause severe damage to nervous system tissues, particularly during the development of the central nervous system, leading to neurocognitive and neurophysiological alterations (Alvarenga, 2015). Due to lead's strong interaction with nerve cells, many studies have investigated its toxicity. For

instance, Savolainen and collaborators (1998) observed that lead induces the production of reactive oxygen species (ROS), leading to oxidative stress in nervous system cells. These events seem to be associated with increased neuronal lethality through necrotic and apoptotic mechanisms. Cytotoxicity appears to depend on the administered dose.

During the embryonic stage, the focus of the present study, cell proliferation and differentiation events, as well as the synaptogenesis process, are very intense, so lead intoxication during this period will have severe consequences for the structural and functional patterns of the individuals' bodies (Rivero et al., 2006).

Bird embryos, especially those of chickens, are frequently used as models in experimental embryology. This is due to the ease of handling the eggs, their large size and yolk content, the fact that the embryos develop only in the upper region of the egg, and the relatively short developmental process, which can be observed daily in the laboratory. This allows for the evaluation of the effects of exogenous agents, such as lead acetate, and the changes induced by them during the embryonic period. However, when bioaccumulated, heavy metals interfere with eggshell formation in birds, potentially leading to a reduction in population density, altering community structure, and causing harmful changes in the central nervous system (Silva, 2018). Such deformities were observed in Rivero et al. (2006), where embryos exposed to lead on the seventh day of development and analyzed on the twentieth day exhibited microphthalmia, hydrocephalus, and deformities in the beak, limbs, and trunk, as well as intra- and extra-embryonic hemorrhages and cephalic necrosis.

To reduce the toxic effects of heavy metals and, consequently, the damage they cause to various studied organisms, plants are considered a natural form of protection.

In this regard, several studies have demonstrated the popular use of various species from the Myrtaceae family. For example, *Eugenia uniflora* is used for its anti-rheumatic, anti-diabetic, antipyretic, astringent, analgesic, hypoglycemic, diuretic, and digestive-regulating properties (Serafin, 2006; Saha et al., 2013). Similarly, *Eugenia jambolana*, *Eugenia brasiliensis*, and *Eugenia caryophyllata* exhibit antimicrobial, antiviral, hypoglycemic, antioxidant, anticancer, antinociceptive, and antidepressant activities (Serafin, 2006; Colla et al., 2012; Saha et al., 2013). The presence of phenolic compounds, such as *p-coumaric acid*, in this species seems to be the primary factor responsible for its protective activity (Garmus et al., 2014).

Therefore, it is known that the main cause of neurotoxic damage caused by lead is related to its cytotoxicity. This project aims to evaluate the effects of *p-coumaric acid*, a compound found in *Eugenia catharinensis*, on embryos treated with lead acetate.

2. MATERIALS AND METHODS

2.1 BIOLOGICAL MODEL

For the execution of the project, 60 *Gallus domesticus* embryos were used, originating from the donation of embryonated eggs from Avícola Polastri, Ltda, with sanitary inspection (SERVICE INSTRUCTION No. 014/2007 - CIDASC) for the acquisition of embryos between the 4th and 9th day of incubation or embryonic days (E4 and E9). The sample consisted of homogeneous eggs, beige in color and with an average weight of 65g, which were transported to the Histotechnology Laboratory/DCN/CCEN in appropriate trays made of recyclable paper, featuring individual compartments to prevent egg movement during transport.

2.2 TREATMENTS

The eggs were cleaned with cotton moistened with distilled water and then numbered, weighed, and incubated at a constant temperature of 37.5°C to 38°C. Atmospheric humidity was maintained at 65% through the use of an external water reservoir with automatic replenishment.

The eggs were initially incubated for 2 hours, the time required to restart the development process, as fertilization in *G. domesticus* occurs before egg laying. After this period, embryonic day (E) was adopted as the staging criterion, which establishes that every 24 hours corresponds to 1 day of development (Greener; Kochen, 1983). Embryos at E4 were removed from the incubator and placed in a horizontal position, with the following procedures being performed: (1) a hole was made with a 16-gauge needle in the air chamber area to aspirate the albumen, aiming to detach the inner membrane on the side where the embryo is located; (2) a 1 cm^2 opening was made in the upper part of the egg using fine-point scissors for the administration of the treatment solution, carried out with an ultra-thin 24-gauge hypodermic needle. Both openings were sealed with non-toxic adhesive tape, and the eggs were returned to the incubator for 5 days, with daily

monitoring of temperature and humidity.
The in ovo treatment was performed by opening the lateral wall of the egg, where lead and the plant extract of *p-coumaric acid* from *Eugenia sp.* were administered between the vitelline vessels, directly into the yolk.

At this stage of development, the embryo shows relatively little extraembryonic vascularization, allowing the egg to be opened without compromising development. Once the viability of the embryo was confirmed, the treatment solution was injected into the yolk sac, between the major vitelline vessels (Takamatsu and Fujita, 1987). After treatment, the eggs were returned to the incubator, where they remained until completing 9 days (E9 - 35HH) of incubation. Development was monitored through the opening in the shell, and external characteristics were evaluated according to the description by Hamburger and Hamilton (1951).

A total of 60 embryos were handled, forming 4 experimental groups divided according to the administration and the day they were treated and analyzed (Table 1). The control group received only saline; the group treated only with lead received a pre-established dosage (Schatz, 2003); one group was treated with the plant extract of *p-coumaric acid*, and another group received both *p-coumaric acid* and lead.

Table 1. Four experimental groups according to treatment

Treatment	Treatment Day	Analysis Day	*n sample*
Control Group (0.1ml saline)	E4	E9	15
Lead Group (150µg/ Lead in 0.1ml saline)	E4	E9	15
Plant extract group (1.6µg/g).	E4	E9	15
Lead + Extract Group (150µg/g of Lead in 0.1 ml saline + 1.6µg/g of extract)	E4	E9	15
TOTAL		60	

Source: by the author

Embryos at E9 were removed from the incubator and then placed at a temperature of 4°C for 15 minutes (cryoanesthesia to reduce metabolism, desensitizing the embryo) and decapitated for the use of the brain.
Using a small spoon and surgical scissors, the embryo was separated from the yolk sac and placed in a Petri dish containing saline solution. It was then analyzed under a stereomicroscope (20X) to determine the embryonic development stage according to Hamburger and Hamilton (1951) and to detect visible morphological changes. Afterward, the embryo proceeded to additional morphological and biochemical procedures. The samples were processed for cell viability evaluation using the MTT method and

external morphological analysis, followed by staging and subsequent dissection to expose the brain during the E9 embryonic period.

2.3 EXTERNAL MORPHOLOGICAL ANALYSIS

The external morphology analysis of the embryos was performed using a stereomicroscope (20X) to identify alterations and measure the structures studied in the research. To conduct a more detailed analysis of the embryos' morphological patterns and to determine whether lead and *p-coumaric acid* interfered with the development of embryonic structures, measurements were taken with the aid of a millimeter grid attached to the stereomicroscope.

a. Cephalic height (1): distance measured from the apex (top of the mesencephalon) to the level of the IV pharyngeal arch, passing through the optic vesicle;
b. Anteroposterior cephalic distance (2): measured from the anterior end of the telencephalon to the posterior end of the myelencephalon, passing through the optic vesicle;
c. Cephalic diagonal (3): measured from the anterior end of the telencephalon to the apex (top of the mesencephalon);
d. Anteroposterior distance at the base of the mesencephalon (4): horizontal anteroposterior measurement at the base of the mesencephalon;
e. Diameter of the optic vesicle (5): horizontal measurement at the center of the optic vesicle (Kobus, 2007).

Furthermore, analysis was also carried out of the external structures that underwent alterations, such as upper and lower limbs, jaw and eyes, and ectopia of the heart and digestive tract.

2.4 CELL VIABILITY BY MTT METHOD

Fresh embryos were used for the cell viability assay using the MTT method (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide). The brains were dissected, separating the cerebral hemispheres, which were then weighed and mechanically fragmented. Each sample, with an average weight of 20 mg, was washed with 0.1M PBS (phosphate-buffered saline) (pH 7.6) for 10 minutes, centrifuged at 640 X g for 10 minutes at room temperature. Then, 50 µl of the cell suspension fraction was collected and distributed into 96-well plates (in triplicate), with 150 µl of MTT added at a final concentration of 0.5 mg/ml, and incubated at 37°C for 30 minutes. The formazan crystals were solubilized in 1500 µl of DMSO (dimethyl sulfoxide) and quantified by spectrophotometry at 540 nm. The results were compared with samples of nervous tissue from control embryos, embryos treated with lead, and those treated with both lead and *p-coumaric acid*, with absorbance values analyzed.

2.5 STATISTICS

The data obtained were expressed as mean and standard error for each group and analyzed using the statistical program Statistica® version 6.0 for Windows, to verify the existence of significant differences between the groups, through two-way analysis of variance (Two-Way ANOVA), $p \leq 0.05$, followed by Tukey's post hoc test.

3. RESULTS AND DISCUSSION

3.1 EMBRYO WEIGHT ANALYSIS

The embryonic period is the most susceptible to intoxication by heavy metals such as lead acetate and mercury (Heinz et al., 2006; Scheuhammer, 2007), as these tissues are undergoing significant changes in the intracellular and extracellular environment, with enzymatic machinery and protein components potentially being targets of heavy metal toxicity.

Treatment directly in the yolk sac promotes the slow and gradual absorption of the yolk via blood circulation, thus distributing the substances throughout the embryo's body

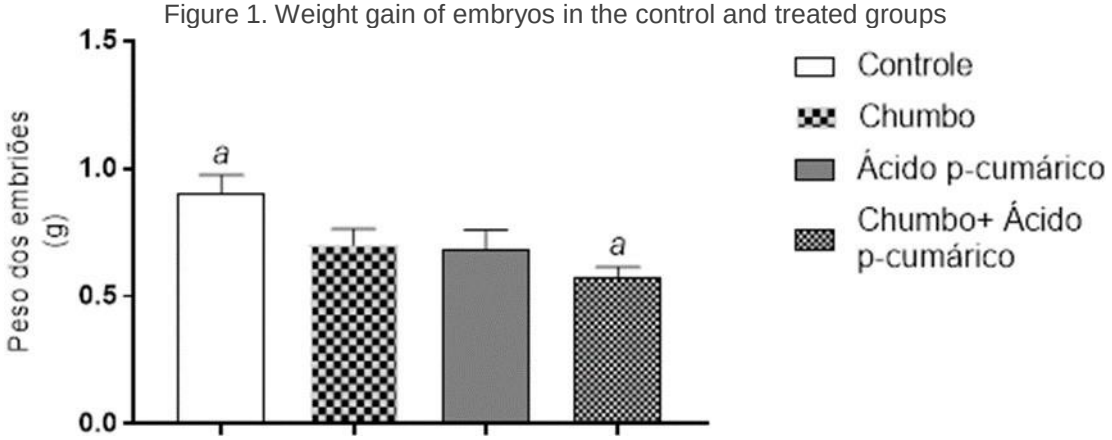
(Cornford; Cornford, 1986; Ek et al., 2012), and it is easily transported by the components of the blood-brain barrier (BBB) (Clarkson, 2006).

The developing CNS seems to be more sensitive to the effects of metals, as its structural organization is immature, such as the BBB, which plays an important role in maintaining CNS homeostasis (Albuquerque, 2016). This, along with the transport mechanisms being more permeable to metals, makes it a site of metal accumulation, and the injuries caused can result in irreversible damage at the cellular, physiological, and cognitive levels in the neonate (Clarkson, 2002; Domowicz et al., 2011). When evaluating the average body weight of the embryos (Figure 1), it was observed that the treated embryos showed lower body weight compared to the control embryos, indicating the deleterious effects of lead acetate and the tested plant fraction on body mass gain, especially when the two substances (*p-coumaric acid* and lead) were analyzed together.

Studies conducted on domestic chicken, duck, and pheasant embryos treated with heavy metal (lead) demonstrated a 15% reduction in body weight (Heinz et al., 2006). This reduction was also observed by Albuquerque (2016), where the total weight of *Gallus domesticus* embryos treated with heavy metal was reduced by 34.32% compared to the control group.

The studies mentioned above demonstrated the impairment of weight gain and, consequently, the growth of the individuals. The affinity for thiol groups and its influence on various bodily systems can affect the body structure and overall metabolism of the individual, thus interfering with body weight gain. The weight loss of animals exposed to environmental toxicity by cadmium, mercury, and lead has been used as a parameter for comparing toxicity and species vulnerability indices induced by heavy metal intoxication, and may be directly related to reduced energy reserves and muscle mass (Correa et al., 2004).

Figure 1. Weight gain of embryos in the control and treated groups



Source: by the author

3.2 ANALYSIS OF EXTERNAL MORPHOLOGICAL ASPECTS OF CONTROL (GC) AND LEAD-TREATED (GT) EMBRYOS

On the third day of development (stage 20 HH), 37 or more pairs of somites are observed along the dorsal region of the body. The head is relatively large compared to the trunk, and the optic vesicle has faint pigmentation. These are the morphological characteristics of the embryo when treated. The hindlimbs are relatively larger than the forelimbs (Hamburger & Hamilton, 1951).

According to Hamburger & Hamilton (1951), between E9 and E10, the distal segments of the wings and legs are proportionally longer. A horizontal groove is clearly visible at the tip of the upper jaw, but the beak is only indicated at the tip of the mandible. The eyelid has a nictitating membrane that covers the anterior scleral papillae and approaches the cornea. The lower eyelid has grown to the level of the cornea, and the circumference of the eyelids is an elongated ellipse with its ventral edge flattened.

Regarding the morphological aspects analyzed in the study, all embryos in the control group exhibited well-developed limbs, as well as the mandible and optic vesicle. Embryos in this group had well-defined upper and lower limbs that were easily identified during observation. The eggs treated with lead exhibited malformations, with variations related to the mandible: two embryos had a present and well-developed mandible, while two others lacked this structure (Figure 2). Both upper and lower limbs were present and well-developed in all embryos of this group. In the group treated only with *p-coumaric acid*, three embryos exhibited absent limbs (Figure 2), and one embryo in this group had limbs with minimal development.

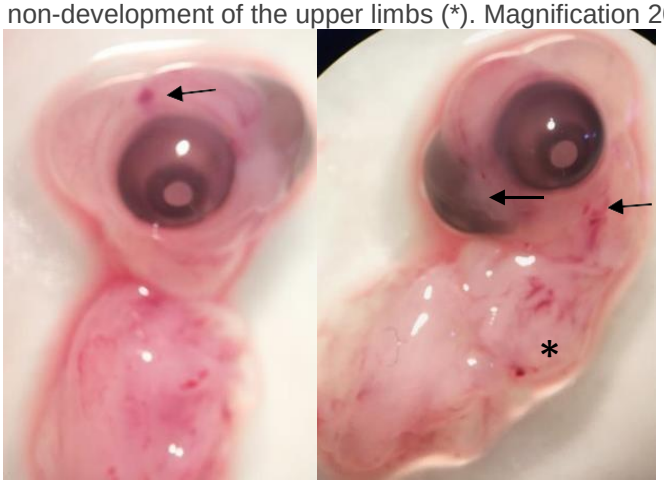
Thus, it is suggested that the treatment day (E4) may be linked to the alterations found in the analyzed embryos. It is expected that the analyzed structures were not yet

fully developed at E4, and as the treatment occurs chronically with the slow and gradual absorption of the tested substances, alterations may become evident at E9 during the removal of the embryos from the egg. The morphological changes most frequently observed were in embryos that received the different treatments (Figure 3).

In this study, embryos subjected to saline (control) showed small hemorrhagic foci but did not exhibit alterations in the characteristic morphology of the species. In embryos treated with lead acetate, significant vascular changes were observed, characterized by blood extravasation within the cerebral vesicles. Narbaitz et al. (1985) administered a single dose of diluted lead nitrate into the air chamber of White Leghorn eggs on the tenth day of incubation. Twenty-four hours after metal administration, small and multiple hemorrhagic foci were observed in most embryos. After forty-eight hours, there was an expansion of the hemorrhagic area in all studied embryos. On the third day after administration, the hemorrhagic area increased, leading to necrosis in the nervous tissue. These results indicate that hemorrhage is the primary injury caused by lead. Morphological alterations such as hydrocephalus, visceral extrusion, and facial malformations were observed in the group treated with lead acetate, compromising the normal development pattern of *Gallus domesticus* and indicating the deleterious action of this metal on the development of the nervous system in this species (Figures 3 and 4).

Furthermore, exposure to heavy metals can, therefore, disrupt the processes of proliferation, differentiation, and cell migration, which are highly regulated during CNS development (Albuquerque, 2016). This fact is reinforced by the number of malformations recorded in our study, indicating that at the dosage used, lead acetate is a multipotent teratogen, interfering with the formation mechanisms of various organ systems.

Figure 2. Malformations observed in the group treated with lead acetate. Hemorrhagic areas (arrows) and non-development of the upper limbs (*). Magnification 20X.



Source: by the author

Figure 3. Images of embryos at E9 and measurements of the brain region of embryos from the control group (a); group treated with lead (b); group treated with p-coumaric acid (c) and with p-coumaric acid and lead. Magnification 20x. Being: 1. Cephalic distance. 2. Cephalic diagonal. 3. AP distance from the base of the mesentery. 4. Height of the mesentery.
5. Diameter of the optic vesicle.

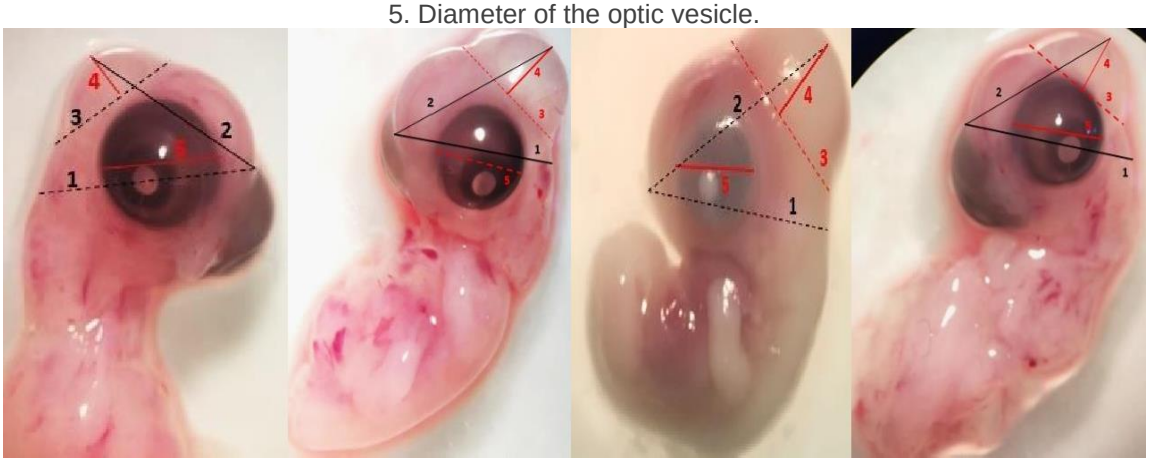


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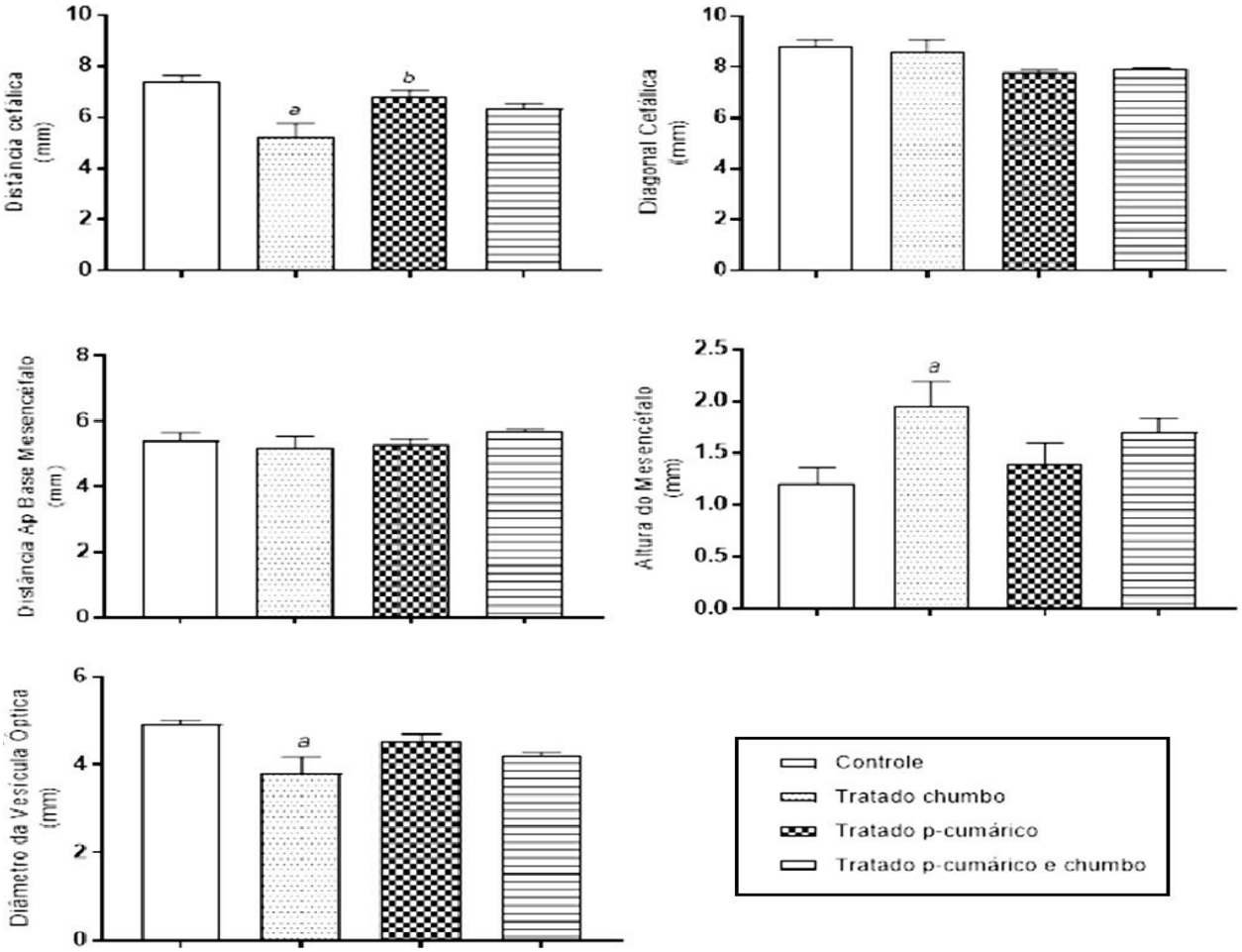
Figure 4. Bar graphs representing mean values (± SEM) of measurements of brain morphological structures



Source: by the author

3.3 CELL VIABILITY ANALYSIS USING THE MTT METHOD

The MTT method is a colorimetric test used to assess cell viability based on mitochondrial dehydrogenase enzyme activity. Mitochondrial dehydrogenases present in viable cells—with active metabolism—cleave and convert the MTT (tetrazolium) reagent into a purple-colored product called formazan, whereas dead cells are unable to perform this conversion (Bochnie, K. A.; Gregório, C. P.; Maciel, R. A. P., 2016).

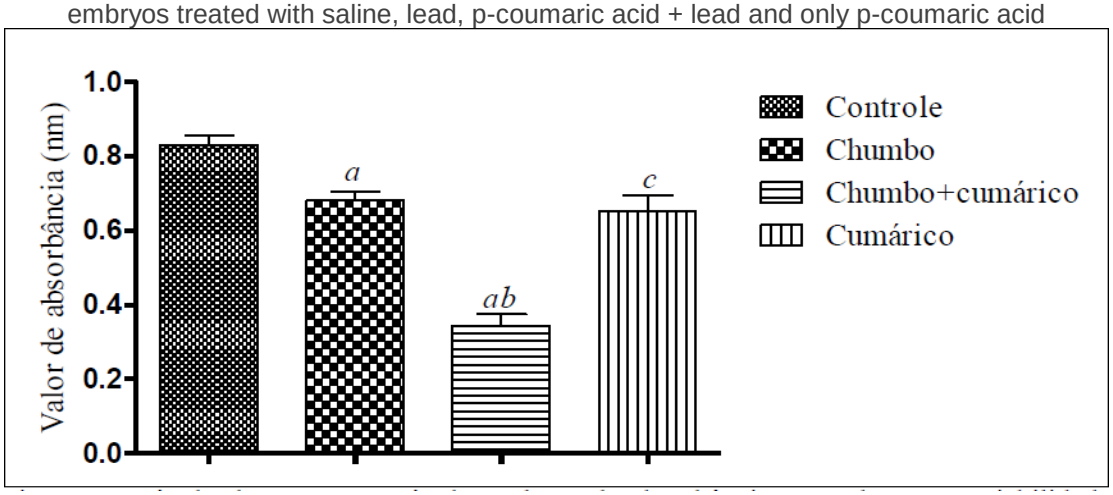
Thus, it is possible to quantify the metabolic activity of the tested cells through absorbance measurements. In this case, the cells from the brain hemispheres of embryos from the four groups were analyzed.

It was observed that lead indeed reduced the cell viability of the brain hemisphere samples from *G. domesticus* embryos, given that it is a toxic substance to the organism. The cellular stress caused by the metal's action on the mitochondrial membrane leads to

its rupture. This means that lead exerts a cytotoxic effect on the embryo's cells and consequently a progressive effect on the tissue, organ, system, and organism as a whole.

Moreover, a significant decrease in cell viability was noted in all other treated groups, indicating that, in addition to lead, *p-coumaric acid* also has a cytotoxic effect ($p \leq 0.05$) on the embryo, and even more so when combined (Figure 5).

Figure 5. MTT method, through absorbance values, to detect cell viability of the cerebral hemispheres of embryos treated with saline, lead, p-coumaric acid + lead and only p-coumaric acid



Source: by the author

4. CONCLUSION

The results presented in this study corroborated with findings on embryonic toxicity due to lead acetate and contributed to the understanding of the embryo's sensitivity to exogenous substances during embryonic development, similarly observed in the group that received *p-coumaric acid*, through external morphological analyses and toxicity testing via the MTT assay.

Thus, the hypotheses proposed in this work are considered partially accepted, as *p-coumaric acid* negatively impacted the embryo's weight gain, in addition to affecting cellular viability and external morphology of the embryos compared to the control group.

Lead acetate is absorbed by the embryo along with the yolk, and the incubation period with lead acetate allowed us to observe that the dose used caused cellular-level alterations, reducing viability and provoking significant external morphological changes. The treatment with *p-coumaric acid* was not able to mitigate the morphological alterations caused by lead, and *p-coumaric acid* proved to be cytotoxic to the embryo, especially when combined with lead.

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CHAPTER 5

CONSTRUCTION OF SCIENTIFIC KNOWLEDGE ABOUT DENGUE (AN ENDEMIC AND NEGLECTED DISEASE) THROUGH PUPPET THEATER IN STATE SCHOOLS IN THE CITY OF MACEIÓ-AL - MEDENSINA PROJECT

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ABSTRACT: Introduction: The use of puppet theater for teaching about endemic dengue allows for a creative approach and the transmission of information in an artistic way with accessible language. Playfulness simplifies learning and content retention, increasing students' interest and interactions. Objectives: To raise awareness among the population about transmissible dengue in the state of Alagoas as well as the importance of control and prevention. Materials and Methods: A puppet theater was performed addressing dengue in Alagoas, accompanied by questionnaires before and after the play to analyze students' knowledge and the impact of the action. Results and Discussions: Two actions were carried out at the Edmilson Pontes State School and Alberto Torres School with sixth and seventh graders respectively. From the data collected from the first action, it was noted that there was an increase in the percentage of correct answers on the questionnaire by the students, demonstrating that knowledge was acquired through the playful activity, despite some students being distracted. In the second action, it was possible to notice that there were more correct answers from the first questionnaire compared to the first school, showing that the students already had some prior knowledge of the disease. Overall, we obtained a satisfactory response regarding the knowledge acquired in both actions after the puppet theater presentation. Conclusion: It is understood that the puppet theater performed achieved the stipulated purpose, as it provided, through the playfulness of puppet theater, an educational environment in which children felt comfortable participating in the project and, above all, sharing the knowledge disseminated.

KEYWORDS: Dengue, Puppet theater, Playful.

RESUMO: O uso do Teatro de fantoche para o ensino sobre a dengue permite uma abordagem criativa e para transmissão de informações de forma artística com linguagem acessível. A ludicidade simplifica a aprendizagem e fixação de conteúdo, aumentando interesse nos alunos e suas interações. Objetivos: Sensibilizar a população sobre a dengue no Estado de Alagoas bem como a importância de seu controle e prevenção. Material e Métodos: Foi realizado um teatro de fantoches abordando a denguecom uso de questionários antes e após a peça, visando analisar o conhecimento dos escolares e o impacto da ação. Resultados e Discussões: Foram realizadas duas ações nas Escolas Estadual Edmilson Pontes e Alberto Torres nos sextos e sétimos anos respectivamente. A partir da coleta de dados da primeira ação, notamos que houve um aumento no percentual de acerto do questionário por parte dos escolares, demonstrando que o conhecimento foi adquirido por meio da atividade lúdica, apesar da dispersão de parte dos estudantes. Na segunda ação, foi possível notar que houve maior número de acertos

desde o primeiro questionário se comparado com a primeira escola, demonstrado que os alunos já possuíam certo conhecimento prévio da doença. Em geral obtivemos uma satisfatória resposta em relação ao conhecimento adquirido nas duas ações após a apresentação do teatro de fantoches. Conclusão: Entende-se que o teatro de fantoches executada alcançou o propósito estipulado, visto que proporcionou, através da ludicidade do teatro de fantoches, um ambiente educativo no qual as crianças se sentiram à vontade para participar do projeto e, sobretudo, compartilhar os conhecimentos difundidos.

PALAVRAS-CHAVE: Dengue, Teatro de fantoche, Lúdico.

1. INTRODUCTION

Endemic diseases are those that exhibit spatial variation in their epidemiological characteristics, meaning a peculiar spatial distribution associated with specific social or environmental processes (Barata, 2000). In this sense, these diseases, predominantly rural, constituted the central concern of Brazilian public health for nearly a century, until various factors, notably urbanization, dismantled the reasons for their existence as a homogeneous body of concern (Silva, 2003). Thus, endemics remain an even greater concern in rural areas, regions marked by low levels of basic sanitation, access to public health, and knowledge about these diseases.

However, the lack of dissemination of information about various topics, including the most prevalent endemic diseases in Alagoas, leads to a process of misinformation within the community (Da Silva, 2021). Many of these diseases are neglected, prevailing in regions with high poverty rates and consequently contributing to the maintenance of the inequality scenario that permeates the country. Examples of these diseases include Dengue, Leishmaniasis, Schistosomiasis, and Malaria (Barreto, 2015; Menezes et al., 2021; Lima, SCG de; Araújo, EC).

The educational process, essential for the entire Brazilian population, presents challenges in disadvantaged communities. Article 205 of the Federal Constitution of 1988 states: "Education, a right of all and a duty of the State and the family, will be promoted and encouraged with the collaboration of society, aiming at the full development of the person, their preparation for the exercise of citizenship, and their qualification for work." In this sense, it is imperative to highlight the importance of education as a means of awareness and change in society, potentially reaching different groups.

Massetto (2003) highlights the teaching process as the main focus of teaching guidelines and learning and offers an in-depth reflection on related issues by questioning which techniques enhance student learning. From this perspective, it falls upon educators to rethink their praxis and reassess their planning, objectives, and methodology to better achieve this goal.

Playful activities can be used to promote learning in school practices, facilitating students' approach to scientific knowledge. In this sense, working with ludicity constitutes an important resource for teachers and students to develop problem-solving skills, enhance concept appropriation, and address the needs of those still in the development process (Dohme, 2001; Campos, 2008).

Puppet theater can and should be used as a new teaching methodology, not only limited to specific teaching but to all curricular content (Dantas et al., 2012). Thus, a playful educational process proves effective in presenting the issues to students, allowing them to develop a better understanding and interest in the topic.

Thus, the research found justification in favoring student learning through puppet theater, promoting cognitive development, supporting students' growth through their own means, and providing conditions for these students to gain knowledge about the transmission, symptoms, and control of diseases that are part of their daily lives.

2. OBJECTIVE

Raise awareness among the population about Dengue (endemic disease) in the State of Alagoas as well as the importance of control and prevention.

3. METHODOLOGY

3.1 TYPE OF STUDY

Cross-sectional observational study

3.2 RESEARCH LOCATION

A cross-sectional observational study was conducted to assess the participants' learning through puppet theater. The research took place at the following schools: Escola Estadual Professor Edmilson de Vasconcelos Pontes, R. Cônego Machado, S/N - Farol, Maceió – AL, and Escola Estadual Alberto Torres, Rua Cônego Costa REGO, SN BEBEDOURO, 57018-095 Maceió - AL. The study was conducted with prior request and consent from the parties involved, ensuring that it was carried out on a mutually agreed-upon date and time.

3.3 SAMPLE

3.3.1 Size and sampling

The sample was obtained through prior contact with the school and conversation about the research. The schools informed us of the number of children who were attending Elementary School 1 and therefore we had the number of 114 children who participated in the research. After reading and signing the Free and Informed Consent Form (FICF), the sampling was obtained by convenience.

3.3.2 Recruitment of participants and acquisition of informed consent

The questionnaires were applied before and after the puppet theater and the TCLE (Free and Informed Consent Form) after a deliberative opinion from the CEP (Research Ethics Committee) to the person responsible for the child so that they were aware of the research and the possibility of withdrawing at any stage and authorizing its realization.

3.3.3 Inclusion criteria

All those whose guardians authorized the TCLE and who were interested in participating in the research and who were studying Elementary School 1, being present on the agreed day of the action, were included.

3.3.4 Exclusion criteria

Children who, for personal reasons or illness, were not present on the day the research took place (the day of the action was previously agreed and announced) did not participate in the research.

3.3.6 Statistical analysis

The data were tabulated in Excel spreadsheets and descriptive statistics were applied. The activities took place in 2023 at public schools, always starting from 1 PM and lasting 4 hours. On both days of the activity, we began by presenting the project and its importance, aiming to foster comprehensive reflections on dengue among the students. The activities included theatrical performances using puppets, supplemented with questionnaires on the topic administered before and after the presentation to assess the students' knowledge before and the impact after the presentation.

In the first session, the theater performance on dengue was presented to two combined 6th-grade classes in an auditorium at Escola Estadual Professor Edmilson de Vasconcelos Pontes. The second session also involved two combined 6th-grade classes at Escola Estadual Alberto Torres. Additionally, the activities covered the definition, identification of signs, symptoms, diagnosis of dengue, and the importance of always consulting a doctor in case of suspected disease.

4. RESULTS AND DISCUSSIONS

The first activity took place on October 30, 2023, from 1:00 PM to 5:00 PM, with 54 6th-grade students from Escola Estadual Professor Edmilson de Vasconcelos Pontes participating (Figure 1). Initially, we set up the puppet house, which had been previously made, reviewed the script, and tested the sound system and microphones. Afterward, with the arrival of the students, we held a preliminary discussion where we presented the project proposal, provided a brief theoretical explanation, and discussed the TALE (Theatrical Activity for Learning and Education) and the questionnaires, which were then filled out. We also explained how the puppet theater performance would be conducted. During these explanations, we noticed some difficulty in keeping the students' attention, requiring interruptions to ask them to pay attention.

Following this, the puppet theater performance began, during which we also observed a lack of focus from the students due to the high level of talking. At the end of the activity, we played a song about dengue (Zum, Zum, Zum by Yasmin Veríssimo) to help reinforce the topic. Finally, we administered the second questionnaire, containing the same questions to assess whether the content had been understood.

Figure 1. First action carried out at the Professor Edmilson de Vasconcelos Pontes State School

Source: survey data

After the first activity, we distributed the questionnaires among the project team members and organized the responses into forms with alternatives, correct answers, errors, and “refused to answer.” Subsequently, we created graphs with these data.

We observed that the first questionnaire had an average of 27 correct answers (50%), and after the puppet theater, the second questionnaire showed an average of 33 correct answers (61%). Questions 3 (26.8%), 4 (9.35%), 6 (9.3%), and 7 (18.5%) had the highest increase in the percentage of correct answers.

From the data collected during the first activity, we noted an increase in the percentage of correct answers on the questionnaire by the students, indicating that knowledge was acquired through the playful activity, despite some students’ distraction.

During the discussion of the questionnaire responses, greater difficulty was noted with questions 1 and 4. For question 1, the number of errors remained consistent with the first questionnaire even after the theater, but for question 4, although the percentage of correct answers increased in the second questionnaire, there were few absolute correct answers.

Therefore, in the second activity of the project, we chose to place greater emphasis on these questions during the presentation.

The second activity took place on November 7, 2023, from 1:00 PM to 5:00 PM, with 60 7th-grade students from Escola Estadual Alberto Torres participating (Figure 2). After setting up the puppet house, reviewing the script, and checking the equipment, a

brief theoretical explanation of the content and explanation of the TALE and questionnaires was provided. In this session, we found the students to be highly engaged and attentive to everything being discussed, making the entire activity easier to manage.

Figure 2. second action carried out at the Alberto Torres State School

Source: Research data

Then, with the start of the puppet theater, we noticed that the students were paying much more attention and were more involved. All this participation on the part of the students culminated in a greater and more satisfactory interaction with them, giving us the certainty that they understood the topic in its entirety and could become multipliers of knowledge. At the end, we played the song about dengue fever to help them remember it.

In the second quiz, we decided to change the dynamics to ensure that they focused as much as possible. We defined a prize (a box of chocolates) and divided them into 6 groups of 10 students, where each one would do their quiz individually and, after that, they would discuss and choose one of the quizzes for us to correct. This change in teaching method proved to be satisfactory and it was clear that it made them pay even more attention to our theatrical presentation.

As we did in the first action, we divided the quizzes among the project members and organized them into forms, generating graphs from these forms.

We observed that in the first questionnaire there was an average of 36.54 correct answers (60.91%) and after the play the second questionnaire presented an average of 42.9 correct answers (71.51%). In the second action, it was possible to notice that there was a greater number of correct answers since the first questionnaire compared to the first school, demonstrating that the students already had some prior knowledge of the

disease. Even so, a greater difficulty was perceived in question number 1 before the explanation, since many were not aware of how to prevent dengue, which after the play there was an increase of 36.5%, totaling 71.7% correct answers. In the analysis of the second questionnaire, a percentage increase in correct answers was also seen in questions number 1 (36.5%), 2 (12.25), 5 (13.5%) and 6 (21.1%), totaling an average increase in correct answers of 6.36 (10.6%). It was noted that it was difficult to get questions 3 and 4 right even after the play, which was below average. In general, we obtained a satisfactory response regarding the knowledge acquired in both actions after the puppet show presentation.

The project also aimed to pursue scientific research, seeking data through questionnaires so that we could have a better-founded work. With this, we submitted the work to the research ethics committee, under approval number CAAE: 71235723.1.0000.0039

The use of the Puppet Theater as a teaching tool provided valuable academic feedback for the medical students. The students not only acquired technical skills in the construction of the material, but also developed pedagogical skills by teaching children about dengue fever, using easy-to-access language. This enriching social experience contributed to the students' significant learning, who had the opportunity to apply their knowledge in an impactful way in the community. In addition to disseminating knowledge, which is a fundamental role in the practice of Medicine, both for patients to have an effective understanding of their health condition and for adherence to guidelines and treatment.

The project aimed to transform people's quality of life, changing the way they think and act through the knowledge acquired through actions, influencing lifestyle and improving health. The initiative's reach was manifested in the dissemination of knowledge about dengue, directly reaching children in schools. The playful approach facilitated the absorption of information, promoting awareness about public health from childhood. However, certain difficulties inherent to the school audience were noticeable, such as: using accessible language; maintaining entertainment so that they pay attention to the dynamics of the puppets and are able to learn, as well as retain the knowledge presented.

5. CONCLUSION

It is understood that the work carried out achieved the proposed objective, as it promoted, through the playfulness of puppet theater, a learning space, in which the children felt comfortable to get involved with the project and, mainly, to share the knowledge disseminated. However, it is understood that there is a need for continuous care and attention with these students, since health education is extremely important in schools.

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CHAPTER 6

ATTENTION DEFICIT HYPERACTIVITY DISORDER IN PATIENTS WITH PHENYLKETONURIA: LITERATURE REVIEW

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ABSTRACT: Characterized by deficiency of the enzyme phenylalanine hydrolixase, phenylketonuria (PKU) presents with an increase serum levels of the aromatic amino acid phenylalanine (Phe) associated with impaired tyrosine formation. Both the accumulation of substrate and the lack of product result in clinical symptoms and signs, mainly related to neuropsychomotor development with global delay, hypotonia, and epileptic seizures when not adequately controlled. Furthermore, there is a high incidence of neurobehavioral disorders in phenylketonurics, mainly related to conditions of dysfunction in the prefrontal cortex, such as attention deficit hyperactivity disorder. In order to better understand these clinical conditions, a bibliographic review of current literature was carried out to evaluate the association between ADHD and phenylketonurics, as well their incidence, understanding their pathophysiological bases, clinical symptoms, treatment and general impacts. An important relationship between

was noted, with an increased prevalence of ADHD in patients with PKU. Dietary control with maintaining serum Phe levels in the therapeutic range was evidenced as fundamental part of better neurocognitive performance as well an important reduction in inattentive and hyperactive symptoms.

KEYWORDS: Phenylketonuria, Inborn error of metabolism, Neurodevelopmental disorders, Attention Deficit Hyperactivity Disorder.

RESUMO: Caracterizada pela deficiência da enzima fenilalanina hidrolixase, a fenilcetonúria (PKU) apresenta-se com elevação sérica do aminoácido aromático fenilalanina (Phe) associado a prejuízo em formação de tirosina. Tanto o acúmulo de substrato quanto a falta do produto resultam em sintomas e sinais clínicos, principalmente relacionados ao desenvolvimento neuropsicomotor com atraso global, hipotonia, crises epilépticas quando não controlada de forma adequada. Além disso, nota-se elevada incidência de distúrbios neurocomportamentais em fenilcetonúricos, principalmente relacionados a condições de disfunção no córtex pré-frontal, como é o caso do transtorno do déficit de atenção e hiperatividade. Com finalidade de entendimento melhor sobre essas condições clínicas, realizado revisão bibliográfica da literatura atual para avaliar a associação entre TDAH e fenilcetonúricos, bem como suas incidências, entendimento de suas bases fisiopatológicas, sintomatológicas clínicas, tratamento e impactos gerais. Notou-se importante relação entre ambas, com aumento da prevalência de TDAH em pacientes com PKU. O controle dietético com manutenção dos níveis séricos de Phe em faixa terapêutica foi evidenciado como parte fundamental para melhores desempenhos neurocognitivos bem como redução importante em sintomas desatentos e hiperativos.

PALAVRAS-CHAVE: Fenilcetonúria, Erro inato do metabolismo, Transtornos neurodesenvolvimento, Transtorno do Déficit de Atenção e Hiperatividade.

1. INTRODUCTION

The accumulation of serum phenylalanine (Phe) due to alterations in its catabolic pathway resulting from genetic mutations related to the enzyme phenylalanine hydroxylase (PAH) is known as phenylketonuria (PKU) (Blau et al., 2010). Considered a rare congenital autosomal recessive metabolic disorder, it presents with variable incidence, with a global average of one in every 10,000 live births (Vockley et al., 2014).

According to PAH enzymatic activity, although there is no consensus in the literature, it can be classified as a total or partial inability to convert Phe into tyrosine (Tyr), presenting with varying serum levels. The accumulation of this substrate is closely linked to impairments in neurological development, particularly related to cognitive function and higher cortical functions (Blau et al., 2009; de Groot et al., 2010).

The spectrum of symptoms is broad, ranging from asymptomatic patients in the first months of life to those with global developmental delay, hypotonia, seizures, irritability, and a characteristic mouse-like urine odor when untreated (Blau et al., 2010).

Diagnosis is most often made through neonatal screening tests for congenital metabolic diseases, using quantitative measurement of Phe (Spronsen et al., 2017). In the presence of hyperphenylalaninemia, the reduction of plasma Phe levels through a low-Phe diet and protein supplementation constitute the pillars of treatment. As a result, the goal is proper neurological development, reducing the likelihood of pathological effects on the central nervous system (Hagedorn et al., 2013).

However, despite regular treatment and adequate control, a large number of patients present with neurodevelopmental disorders. This is related to the reduction in the neurotransmitters dopamine and serotonin, which are closely involved in cognitive dysfunction.

Therefore, the objective of this study was to demonstrate and analyze the relationship between patients with phenylketonuria and neurodevelopmental disorders, particularly attention-deficit/hyperactivity disorder. Given the increased survival of patients with metabolic disorders due to advances in neurogenetics, it is noted that comorbidities associated with these conditions are becoming more prevalent, leading to greater needs for understanding.

2. METHODOLOGY

The methodology used was a narrative literature review, which is characterized by evaluating and synthesizing the most relevant and specific information and updates on the subject in question (Canuto & Oliveira, 2020). Information was gathered through research of relevant articles on the topic in electronic databases: PubMed, SciELO, and Lilacs.

Subject descriptors used as search filters included "phenylketonuria," "phenylalanine," "inborn error of metabolism," "neurodevelopmental disorder," and "attention-deficit/hyperactivity disorder." In addition, the Boolean operator "AND" was used to direct and specify the topic. Inclusion criteria included publications between 1991 and 2024, in any language, that were available in full text. Texts that did not address the topic, were outside the inclusion period, or were duplicated were excluded.

A total of 194 articles were analyzed, with only 40 being selected, as they were relevant publications in journals and pertinent to the topic. An individual analysis was conducted, culminating in the synthesis of the most relevant information.

3. BIBLIOGRAPHICAL REVIEW

Globally, the incidence and prevalence of phenylketonuria vary according to the population analyzed. In the Asian region, for example, Zhan et al. (2009) estimate that in China, about one in every 11,000 people is affected. This number is highly variable when compared to the United States (1:13.5 to 19,000) (National Institutes of Health Consensus Development Panel, 2001), Japan (1:70,000) (Aoki, 2003), Thailand (1:200,000) (Pangkanon et al., 2009), and Latin America (1:12,000 to 52,000) (Borrajo, 2007).

In Brazil, due to the lack of centralized information, it is believed that there are many more cases than current statistics suggest, with an estimate of 1:25,000. Additionally, there is significant variability between states, with higher incidences in states with higher per capita income, corroborating the fact that external factors influence the current numbers. In Sergipe, for example, the incidence is 1:8,690 (Ramalho et al., 2014) and in Rio de Janeiro, 1:25,025 (Botler et al., 2012).

This clinical condition corresponds to the inability or reduced effectiveness in converting the amino acid phenylalanine (Phe) into tyrosine (Tyr) via the enzyme

phenylalanine hydroxylase (PAH). Both the accumulation of Phe and the lack of Tyr are detrimental to the central nervous system. When Phe is in excess, alternative degradation pathways are activated, leading to the production of metabolites such as phenylacetic, phenylacetic, and primarily phenylpyruvic ketone (Flydal & Martinez, 2013).

Currently, when neonatal screening is performed by collecting blood on filter paper, preferably between the third and seventh day of life, phenylalanine levels are quantitatively analyzed (fluorometric analysis or tandem mass spectrometry). When levels exceed 2 mg/dL, confirmation through serum analysis of Phe and Tyr levels is required. In confirmed cases, the latter is usually reduced or normal, with a Phe/Tyr ratio greater than three, while the rest of the serum amino acids are normal (National Institutes of Health Consensus Development Conference Statement, 2001).

It is important to highlight that although this condition is related to a mutation in the phenylalanine hydroxylase (PAH) enzyme, quantitative analysis is not performed because its activity is only expressed in the liver. Furthermore, since PAH is dependent on cofactors, deficiencies in BH4 synthesis (deficiency of guanosine triphosphate cyclohydrolase, 6-pyruvoyl tetrahydrobiopterin synthetase) or BH4 recycling (deficiency of pterin-4α-carbinolamine dehydratase and dihydropteridine reductase) should be ruled out, although they represent a small proportion of identified cases (Santagata et al., 2017).

With the advent of neurogenetics and greater availability of genetic testing, molecular analysis aimed at identifying pathogenic mutations in the PAH gene, which encodes the enzyme involved in the syndrome, has been recommended as part of the diagnostic process and long-term patient monitoring. Although there is no well-established genotype-phenotype correlation, parental counseling, along with a better understanding of the clinical condition, are key elements in the management of any genetically determined chronic condition (Acosta et al., 2001).

The clinical presentation tends to be insidious, with newborns and young infants being asymptomatic. As phenylalanine and its aforementioned metabolites accumulate in the body, they cross the blood-brain barrier and cause irreversible damage to the central nervous system. Initial symptoms include hypotonia and global developmental delay, followed by seizures, irritability, and a characteristic mouse-like odor in the urine (Santos et al., 2006).

When untreated, there is impairment in developmental milestones with progressive global brain dysfunction in all domains. Variable degrees of intellectual

disability and various behavioral disorders (autism spectrum disorder, hyperactivity, attention deficit) are observed, stemming both from the lack of tyrosine (a dopamine and serotonin precursor) and the accumulation of phenylalanine (Vockley et al., 2014).

There is no direct and linear clinical correlation between serum Phe levels and neurological impairment due to individual differences related to blood-brain barrier integrity and metabolic factors (Stevenson & McNaughton, 2013). However, dietary control during the first decade of life has been shown to be an important predictor of outcomes (Waisbren et al., 2007).

Studies have shown that despite regular control of plasma Phe levels, higher cortical functions may still be compromised. Reduced processing speed, lower intelligence quotient, and symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD) are among the subtle clinical manifestations of this spectrum (Stevenson & McNaughton, 2013; Al Hafid & Christodoulou, 2015; Saad et al., 2015).

ADHD, characterized by significant impairments in attention, hyperactivity, and impulsivity, is one of the most prevalent neurodevelopmental disorders in childhood. It has gained prominence due to its impact on social functioning and learning (Chan et al., 2016). Furthermore, approximately one-third of patients continue to exhibit symptoms in adulthood, representing a clear risk factor for psychosocial, physical, and mental health problems, such as anxiety disorders, drug use, and suicide (Barbaresi et al., 2013).

The diagnosis is made through extensive clinical evaluation, with evidence of inattentive, hyperactive, or impulsive behavior causing functional impairment. Studies have shown dysfunction in specific neuronal circuits (dopaminergic, serotonergic, and noradrenergic), which may be associated with comorbid conditions such as autism spectrum disorder, mood disorders, hyperkinetic disorders, among others (Daley et al., 2014).

Few studies have demonstrated an increased prevalence of ADHD in phenylketonuric patients compared to the general population, particularly in relation to poor treatment adherence with elevated serum Phe levels (Saad et al., 2015). The only existing Brazilian study, conducted by Da Silva et al. (2020), involving about 30 patients (both young and adult), showed a 2.5-fold increase in prevalence compared to the general population.

This association is believed to be justified by dysregulation in dopaminergic production, particularly in the mesolimbic, mesocortical, and nigrostriatal pathways, which are related to cognitive processing and attention regulation. Low dopamine levels

in these pathways are found in both ADHD and phenylketonuric patients (Arnsten, 2006; Landvogt et al., 2008; Cleary et al., 2013; Luna et al., 2023; Yu et al., 2023).

There is robust scientific evidence supporting both pharmacological and non-pharmacological treatment for ADHD. Pharmacological treatments include psychostimulant drugs (amphetamines and their derivatives) and other classes considered non-psychostimulants (atomoxetine, guanfacine, and clonidine). Parent training programs, cognitive training, and neurofeedback comprise non-pharmacological treatments (Crescenzo et al., 2017).

Treatment of phenylketonuria involves maintaining serum Phe levels between 2 and 6 mg/dL through dietary restriction of this amino acid, primarily through low-protein foods such as fruits, vegetables, fats, and flours. Additionally, Phe-free formulas supplemented with vitamins and minerals are essential to avoid catabolic states and general protein deficiencies. However, many patients report low adherence to the diet due to the poor palatability of these products (Vockley et al., 2014).

Adherence to treatment should begin as early as possible with the goal of maintaining therapeutic Phe levels within the first few weeks of life. This aims to ensure the formation of neurotransmitters (primarily dopamine and serotonin) and prevent excessive levels that could cause neuronal damage. It is known that delayed treatment can lead to early cognitive decline, with an estimated drop of four IQ points for every four weeks of treatment delay (Spronsen et al., 2017).

4. DISCUSSION

It is observed that the dysfunction of phenylalanine hydroxylase enzymatic activity impairs the formation of precursor amino acids tyrosine and tryptophan, consequently hindering the synthesis of neurotransmitters such as serotonin and dopamine. According to Stevenson & McNaughton (2013), cognitive dysfunction in PKU is directly related to reduced tyrosine levels in the prefrontal cortex.

Reduced serum levels of tyrosine and tryptophan were also found in children with ADHD in a study conducted by Baker et al. (1991), as well as by Posner et al. (2009). Although there is more robust scientific evidence regarding dopaminergic reduction in the prefrontal cortex and striatum in ADHD patients, considering the pathophysiology and higher incidence of this clinical condition in individuals with PKU, it can be inferred that both groups share similar hypodopaminergic and noradrenergic states (Antshel, 2010).

A study conducted by Antshel & Waisbren (2003) empirically evaluated the relationship between ADHD, PKU patients, and children exposed vertically to hyperphenylalaninemia, using a control group for comparison. The study found that the prevalence of ADHD in patients who were vertically exposed to elevated serum phenylalanine levels was eight times higher compared to the control group. Additionally, the prevalence of ADHD in PKU patients was 2.5 times higher.

Moreover, it was noted that inattentive symptoms predominated in PKU patients, while hyperactive/impulsive symptoms were more common in individuals vertically exposed to elevated phenylalanine levels. This led to the conclusion that prolonged prenatal exposure contributes more actively to hyperkinetic symptoms (Antshel & Waisbren, 2003).

Another study exploring the association between PKU and ADHD was conducted by Arnold et al. (2004), using patients with type 1 diabetes as a control group, as both PKU and diabetes are chronic conditions requiring dietary management. The study found a higher prevalence of inattentive symptoms and greater prescription of psychostimulants in the PKU group, with no effect on serum phenylalanine levels, a crucial factor for long-term follow-up in PKU patients.

It is well established that maintaining therapeutic serum phenylalanine levels is associated with better neurodevelopment and improved neurocognitive abilities. Burton et al. (2015) evaluated 38 PKU patients responsive to BH4 (tetrahydrobiopterin synthase), a cofactor involved in phenylalanine hydroxylase activity, using sapropterin (a synthetic copy of BH4). The study demonstrated that after reducing serum Phe levels during treatment, symptoms of inattention were gradually reduced and remained stable over 26 weeks of treatment.

Additionally, another study conducted by Huijbregts et al. (2002) showed that PKU patients with serum phenylalanine levels outside the therapeutic range exhibited slower processing speeds on various tested tasks, reduced capacity to inhibit cognitive interference, less consistent performance, and significant long-term performance decline. These results were compared with controls and patients under adequate control, with no significant differences found between the latter two groups.

Various studies have highlighted strong similarities in the key components of PKU and ADHD, particularly in the dysfunction of prefrontal neuronal circuits associated with behavior inhibition. Due to the high prevalence of this inborn metabolic error and its close relationship with neurocognitive impairment, understanding and recognizing

neurodevelopmental disorders associated with this genetically determined condition are essential to ensuring and promoting a better quality of life for patients and their families.

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CHAPTER 7

UROLIFTR VS HOLEP: POST-SURGICAL SYMPTOM IMPROVEMENT IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT: Justification: Benign prostatic hyperplasia is common in men, especially after the age of 50. The efficacy of prostate enucleation treatments using Holmium Laser (HoLEP) or UroliftR in improving post-treatment symptoms is still uncertain. Objective: To compare the effectiveness of HoLEP and UroliftR surgical procedures in resolving urinary symptoms and patient satisfaction. Methodology: A retrospective study involving 35 patients from a private hospital in Curitiba, treated between August 2021 and March 2023. Analysis and comparison were conducted between groups undergoing HoLEP and UroliftR to evaluate which provided more significant improvement in preoperative urinary symptoms and patient quality of life. Results: The average age of the patients was 67.6 years, with an average prostate volume of 63.9 ml. Both procedures resulted in improvements in postoperative urinary symptom scores (IPSS). There was no significant difference between the procedures in terms of the proportion of patients with urge incontinence or erectile dysfunction. Only 16 patients in the UroliftR group had variables of average and maximum urinary flow collected, showing an improvement in the postoperative obstructive pattern. Conclusion: Both HoLEP and UroliftR improved patients' quality of life, with no significant advantage of one over the other in terms of erectile dysfunction or urge incontinence. Additionally, HoLEP was preferably used in patients with larger prostates.

KEYWORDS: Benign prostatic hyperplasiA, Lower urinary tract symptoms, Prostate, Urinary incontinence, Erectile dysfunction.

RESUMO: Justificativa: A hiperplasia prostática benigna é comum em homens, especialmente após os 50 anos. A eficácia dos tratamentos com enucleação da próstata usando Holmium Laser (HoLEP) ou UroliftR na melhoria dos sintomas pós-tratamento ainda é incerta. Objetivo: Comparar a eficácia dos procedimentos cirúrgicos HoLEP e

UroliftR na resolução dos sintomas urinários e na satisfação do paciente. Metodologia: Estudo retrospectivo com 35 pacientes de um hospital privado em Curitiba, tratados entre agosto de 2021 e março de 2023. Realizada análise e comparação entre grupos submetidos a HoLEP e UroliftR, para avaliar qual proporcionava uma melhoria mais significativa dos sintomas urinários pré-operatórios e na qualidade de vida dos pacientes. Resultados: A média de idade dos pacientes foi de 67,6 anos, com um volume prostático médio de 63,9 ml. Ambos os procedimentos resultaram em melhorias nos escores de sintomas urinários (IPSS) pós-operatórios. Não houve diferença significativa entre os procedimentos em termos de proporção de pacientes com urgeincontinência ou disfunção erétil. Apenas 16 pacientes do grupo UroliftR tiveram as variáveis de fluxo urinário médio e máximo coletadas, mostrando uma melhora no padrão obstrutivo pós-operatório. Conclusão: Tanto o HoLEP quanto o UroliftR melhoraram a qualidade de vida dos pacientes, sem vantagem significativa de um sobre o outro em termos de disfunção erétil ou urgeincontinência. Além disso, o HoLEP foi preferencialmente usado em pacientes com próstatas maiores.

PALAVRAS-CHAVE: Hiperplasia prostática benigna, Sintomas do trato urinário inferior, Próstata, Incontinência urinária, Disfunção erétil.

1. INTRODUCTION

Closely related to aging, benign prostatic hyperplasia (BPH) is the most common benign neoplasm affecting men, directly impacting their quality of life. Approximately 33% of the male population is affected by the condition, with an incidence rate reaching 90% in men over 85 years of age. It is estimated that, globally, 30 million men present some symptom related to this neoplasm [1].

The development of BPH is characterized by the proliferation of stromal and epithelial cells in the transitional zone of the prostate, causing compression and obstruction of urine flow from the bladder, manifesting with lower urinary tract symptoms [2].

The urinary manifestations of BPH are divided into three categories: storage symptoms (pollakiuria, nocturia, urgency, incontinence, and enuresis), voiding symptoms (weak stream, hesitation, straining during urination, and terminal dribbling), and post-voiding symptoms (post-void dribbling and a sensation of incomplete bladder emptying). Men affected by this condition predominantly experience nocturia, weak stream, hesitation, and urge incontinence [3].

For diagnosis, there are tools such as the International Prostate Symptom Score (IPSS), a questionnaire used to assess the severity of urinary symptoms and the patient's quality of life; uroflowmetry, which analyzes the strength and continuity of the urinary stream; and prostate and bladder ultrasound, which evaluates the volume of the prostate, the bladder, and the post-void residual volume [4,5].

Among the numerous treatment proposals, enucleation of the prostate with Holmium Laser (HoLEP) and UroliftR, considered minimally invasive methods, have gained prominence among the most recent techniques. These technical advances in surgical methods enable rapid symptom relief, earlier return to daily activities, and improved post-operative tolerance [5,6].

HoLEP involves the removal of the prostatic adenoma through the emission of high-frequency Holmium laser pulses, capable of cutting and performing hemostasis of prostatic tissue, resulting in the enucleation of the gland. This procedure allows the physician to delineate a plane between the hyperplastic tissue and the prostate capsule, enabling the removal of as much diseased tissue as possible [7]. A significant advantage of HoLEP is the long-lasting relief of pre-existing symptoms, and it can be performed on glands of varying sizes, from small to excessively large volumes. This procedure

improves the quality of life of patients, as evidenced by lower IPSS scores and increased satisfaction rates after the procedure [8,9].

On the other hand, UroliftR is a more recent procedure that relieves urethral obstruction through static implants capable of compressing hyperplastic tissue. In addition to rapid relief of pre-existing symptoms, this surgery presents lower rates of bleeding, incontinence, or changes in erectile function—complications that may occur with HoLEP—since it does not remove or cut male anatomical structures. Its main disadvantages are its high cost and the limitation to smaller prostate volumes [10,11].

1.1 OBJECTIVES

Analyze which procedure—UroliftR or HoLEP—achieved better results in resolving the symptoms of patients with BPH who underwent these procedures at a private hospital in Southern Brazil.

2. THEORETICAL FRAMEWORK

Benign prostatic hyperplasia (BPH) is the most prevalent benign neoplasm in the male population [3]. Autopsy studies have shown the histological presence of BPH in 8%, 50%, and 80% of men in the fourth, sixth, and ninth decades of life, respectively, confirming the increasing incidence of this condition with the aging male population [12]. Gacci et al. (2015), in their meta-analysis, demonstrated that individuals with metabolic syndrome, hypertension, or obesity had larger prostate volumes and an increased risk of developing BPH [13]. Additionally, the genetic factor is also closely linked to the development of this neoplasm [5,14].

The etiology of this condition is influenced by the direct action of dihydrotestosterone (DHT) on prostatic tissue. With advancing age, estrogen levels increase in men’s bodies, sensitizing the prostate gland to DHT. This molecule has a direct effect on prostate cells, causing them to proliferate and leading to an increase in prostate volume [3,5], which can result in urethral compression and obstruction, reducing urine flow and causing the characteristic symptoms of BPH [2].

The main manifestations of the condition are lower urinary tract symptoms (LUTS) [17-19]. These manifestations can be divided into storage symptoms (pollakiuria, nocturia, urgency, incontinence, and enuresis) and voiding symptoms (weak stream,

hesitation, straining during urination, and terminal dribbling) [3]. Irwin et al. (2006), in their population-based study in Canada, Germany, Italy, Sweden, and the United Kingdom, found that the prevalence of storage LUTS was 51.3%, voiding LUTS was 25.7%, and post-voiding symptoms were 16.9% in men [15].

Among the methods to assess the severity of the condition, the need for treatment, response to therapy, and monitoring of BPH, the most prominent are IPSS, uroflowmetry, prostate ultrasound, and bladder ultrasound [3].

The IPSS is a self-administered questionnaire developed by the American Urological Association, considered reliable, valid, and sensitive for assessing patients with BPH, making it an extremely important tool during urological consultations [16]. This score consists of 7 questions regarding the patient's urinary symptoms, which they rate on a scale from 0 to 5, indicating how severe they consider their complaints. Thus, patients whose total score ranges from 0 to 7 are considered to have mild manifestations, 8 to 19 moderate, and 20 to 35 severe [5,16].

The uroflowmetry test is used to assess the speed and pattern of the urinary stream. During the test, the patient urinates into a device that records information about the flow rate and transforms this data into graphs. In men, a maximum urinary flow greater than 15 mL/s is considered normal, while values lower than 10 mL/s suggest an obstruction of the urinary tract [3].

The prostate ultrasound examines the approximate size and weight of the gland, in addition to confirming the presence or absence of a prominent middle lobe. Bladder ultrasound allows for the identification of the bladder’s maximum capacity and whether there is any post-void residual volume in patients with BPH [5].

Treatments are diverse and can be divided into active surveillance (AS), medication, and surgery. Among the available surgical techniques, HoLEP and UroliftR stand out as the most modern options. The development and emergence of different minimally invasive techniques have proven to be highly necessary and effective for patients, showing an improvement in LUTS and a quicker return to daily activities, as well as greater tolerability for men with BPH [5,6].

The HoLEP method uses high-frequency Holmium laser to dissect excess prostatic tissue while simultaneously performing hemostasis, resulting in gland enucleation. To prevent postoperative prostate growth, the physician can separate the adenoma from the prostate capsule during the procedure and remove the hyperplastic tissue, thereby eliminating any remnants that could cause a potential recurrence [5,9].

UroliftR is the most recent technique for BPH treatment. It involves the insertion of permanent trans-prostatic implants that allow the urethra to be unobstructed by the compressed hyperplastic tissue. Its technique does not involve removal, cutting, or enucleation of the prostate. Instead, it creates an open channel to allow better urinary flow [11,17]. The benefit of UroliftR is the rapid relief of LUTS, as it expands the urethral lumen and avoids damage to the dorsal venous complex and neurovascular bundles, significantly reducing the rates of retrograde ejaculation, bleeding, urge incontinence, and erectile dysfunction, symptoms that may occur after HoLEP. It is preferred for smaller prostate sizes [10,18].

Roehrborn et al. (2015) conducted a study in North America and Australia with 206 men, comparing untreated patients with those who underwent UroliftR. The study selected patients with moderate to severe IPSS, a peak flow in uroflowmetry of ≤12 mL/s, and prostate volume between 30 and 80 mL. After 3 years, patients who underwent the surgical procedure showed a 41.1% improvement in IPSS, a 48.8% improvement in quality of life, and a 53.1% improvement in urinary flow. There were no observed events of erectile or ejaculatory dysfunction, and all evaluations of sexual function showed stability or improvement after UroliftR. However, 140 patients required reintervention due to treatment failure within the first 3 years [19].

Considering this overview of recent options for BPH treatment, it has been shown that UroliftR has an advantage over HoLEP by offering better short-term resolution of LUTS and patient experience, with lower rates of adverse effects. However, long-term comparison studies remain scarce, leaving the question of which surgical method provides greater benefits [20].

3. METHODOLOGY

This study is observational, individualized, longitudinal, and prospective, focused on the analysis of indirect documentation through electronic medical records. The sample was intentional and non-probabilistic, consisting of patients who underwent specific surgical procedures at Hospital Nossa Senhora das Graças (HNSG) between August 2021 and March 2023.

Patients who underwent one of the surgical procedures (HoLEP or UroliftR) at HNSG during the mentioned period and were followed up in this specialized service were

selected for the study. Those who were lost to follow-up or underwent the procedure by a physician not part of HNSG's Urology Service were excluded from the research.

The necessary data were accessed through the HNSG electronic medical record system. Patient identities were kept anonymous, with the information recorded in the database in a coded form, with each patient classified by a number. The data were stored in Excel™ spreadsheets on a password-protected drive, accessible only to the researchers. Data collection was conducted only after approval by the Ethics Committee (CAAE: 57634622.5.0000.0020).

The study protocol included data collection on basic sample characteristics such as age and prostate volume, as well as pre- and postoperative information, including the IPSS (International Prostate Symptom Score), mean and maximum urinary flow, presence of urge incontinence, post-void residual volume, and presence of ED. ED was assessed using the International Index of Erectile Function (IIEF), a 15-question survey grouped into five domains: erectile function, orgasm, sexual desire, sexual satisfaction, and overall satisfaction. Each question is rated from 1 to 5, and the sum of the responses generates the final score for each domain. Scores below 26 points or the use of medication for sexual intercourse were criteria for classifying the patient as having ED. Urge incontinence was considered present if patients experienced an uncontrollable and sudden urge to urinate, urinary leakage onto underwear, or the need for diapers/pads.

The collected data were digitized and organized into Excel® spreadsheets for control and identification of missing information. Subsequently, they were analyzed using IBM SPSS Statistics v.29.0 software. Patients were divided into groups according to the surgery performed (HoLEP or UroliftR) and compared regarding the observed outcomes. Quantitative variables were described by mean, standard deviation, minimum, and maximum values, while categorical variables were described by absolute and percentage frequency. The comparison between the groups regarding quantitative variables was performed using the Student’s t-test for independent samples or the non-parametric Mann-Whitney test. For the comparison of categorical variables between the groups, Fisher’s exact test was used. Additionally, pre- and postoperative evaluations within each surgery group were compared using the binomial test to determine the effect of each type of procedure on these variables. The normality of continuous variables was assessed by the Shapiro-Wilk test, and p-values <0.05 were considered indicative of statistical significance.

A total of 35 patients were included in the study, 19 of whom underwent the HoLEP technique and 16 the UroliftR technique. Of the patients who underwent HoLEP, four did not have information on post-void residual volume, so the comparative analysis was performed with data from 15 men. Additionally, patients undergoing HoLEP in this study did not undergo uroflowmetry due to this practice not being customary at the service. The data obtained were essential for the comparative evaluation of surgical outcomes, allowing an in-depth analysis of which technique presents greater benefits in improving symptoms and the quality of life of patients with benign prostatic hyperplasia.

4. RESULTS

4.1 SAMPLE CHARACTERIZATION

The mean age was 67.6 ± 7.4 years. Among the 35 men analyzed, the mean prostate volume, as well as the pre-surgical post-void residual volume, were 63.9ml ± 22.2 and 161.5ml ± 151.7, respectively (Tables 1 and 2). Most patients were classified with an IPSS score of 8 to 19 before the surgeries, indicating a moderate classification, while postoperatively, the majority shifted to a mild classification (Tables 3 and 4).

Table 1. Sample description

Variable	N valid	Results *
Age	35	67,6 ± 7,4; 67 (55 - 84)
Prostate volume	35	63,9 ± 22,2; 60 (30 - 120)
Post-micturition residue	31	161,5 ± 151,7; 140 (5 - 751)

*Category variables are described in frequency (percentage) and quantitative variables in mean ± standard deviation; median (minimum value - maximum value)
Source: The author (2023)

Table 2. Homogeneity of groups regarding age and prostate volume

Variable	Classification	Group		*p**
		HoLEP	Urolift^{R}	
Age (years)	[average ± dp (min-máx)]	69,3 ± 8,1 (57 - 84)	65,5 ± 6 (55 - 77)	*0,130*
Prostate volume	[average ± dp (min-máx)]	73,2 ± 25,2 (40 - 120)	52,8 ± 10,9 (30 - 70)	*0,004*

*Student's t-test for independent samples, p<0.05
Source: The author (2023)

Table 3. GrupoHoLEP

Variable	Classificatio	Assessment	p*

	n	Preoperative (n)	Postoperative (n)	
Post-micturition residue	≤ 50ml	3	15	*<0,001*
	> 50ml	12	0	
IPSS Score	Mild/moderate	18	17	*1*
	Serious	1	2	
Urge urinary incontinence	No	13	17	*0,219*
	Yes	6	2	
Erectile Dysfunction	No	12	11	*1*
	Yes	7	8	

*Binomial test, p<0.05
Source: The author (2023)

Table 4. UroliftR Group

Variable	Classification	Assessment		*p**
		Preoperative (n)	Postoperative (n)	
Post-micturition residue	≤ 50ml	4	16	*<0,001*
	> 50ml	12	0	
IPSS Score	Mild/moderate	12	12	*1*
	Serious	4	4	
Urge urinary incontinence	No	14	15	*1*
	Yes	2	1	
Erectile Dysfunction	No	15	14	*1*
	Yes	1	2	

*Binomial test, p<0.05
Source: The author (2023)

4.2 COMPARISON BETWEEN SURGERIES

When comparing UroliftR with HoLEP, it was observed that the preoperative prostate volume was significantly larger in the enucleation method, with a p-value of 0.004 (Table 2). There was no significant association between IPSS scores before and after surgery (p=0.379), meaning that neither procedure showed an advantage in symptom relief over the other. Furthermore, no greater improvement in rates of urge incontinence or erectile dysfunction was observed with either surgery (Table 5).

Table 5. Comparison of mean and maximum urinary flow before and after performing UroliftR

Variable	Assessment	n	Average	Standard deviation	Median	Minimum	Maximum	Average difference	*p**
Average flow	Preoperative	16	5,46	2,13	6	1,5 ml	9 ml	2,82	*0,002*
	Post-operative	16	8,29	2,33	9	4,1 ml	11 ml		
Maximum	Preoperat	1	13,0	6,71	11,5	4,5 ml	34,5	3,48	*0,0*

flow	ive	6					ml		*41*
	Post-operative	16	16,5	6,00	15	9,5 ml	31 ml		

*Non-parametric Wilcoxon test, p<0.05
Source: The author (2023)

4.3 URGENT INCONTINENCE

Of the 35 patients analyzed, the majority (27) did not have urge incontinence preoperatively (Tables 3 and 4). It was observed that, among the patients who underwent HoLEP, two had unfavorable outcomes (either maintained or developed the symptom), while in the UroliftR group, only one patient did not show a favorable result. Moreover, no significant difference was found in the proportion of patients with urge incontinence between the two time points in either group (Table 5).

4.4 ERECTILE DYSFUNCTION

Of all the patients analyzed during the collection period, 28.6% had erectile dysfunction (ED) postoperatively, representing a 5.7% increase in the number of cases (Tables 3 and 4). Additionally, 17 patients in the HoLEP group and 15 in the UroliftR group had favorable outcomes after the procedure (maintaining previous sexual function or not developing ED), with 2 developing the disorder in the former group and 1 in the latter. Finally, neither method showed an advantage over the other, as there was no significant difference in the proportion of patients with ED between the two time points in either group (Table 5).

4.5 IPSS SCORE

Of the 35 patients analyzed, the majority (30) had a mild or moderate IPSS score before surgery (Tables 3 and 4). When analyzing the improvement in the post-surgical score, a favorable outcome (improvement in urinary symptoms with better IPSS scores than before surgery) was observed in 17 patients who underwent HoLEP and 12 in the UroliftR group. However, neither procedure showed a significant advantage in providing more effective improvement, with a p-value of 0.379 (Table 5).

4.6 UROFLOWMETRY

Of the 35 patients in the study, 16 underwent UroliftR, all of whom had uroflowmetry performed. It was possible to analyze the mean preoperative (5.46 ml ± 2.13) and postoperative (8.29 ml ± 2.33) urinary flow, as well as the maximum preoperative (13 ml ± 6.71) and postoperative (16.5 ml ± 6) flow. When comparing the two time points, a significant increase was demonstrated in both the mean (p=0.002) and maximum (p=0.041) urinary flow after surgery (Table 6).

Table 6. Comparison between patients undergoing HoLEP and UroliftR

Variable	Pre - post	Grupo		*p**
		HoLEP (n)	Urolift^{R} (n)	
IPSS Score	Favorable outcome	17	12	*0,379*
	Unfavorable result	2	4	
Urgent incontinence	Resultado favorável	17	15	*1*
	Unfavorable result	2	1	
Post-micturition residue	Favorable outcome	15	16	*1*
	Unfavorable result	0	0	
Erectile Dysfunction	Favorable outcome	17	15	*1*
	Unfavorable result	2	1	

*Fisher's exact test, p<0.05
Source: The author (2023)

5. DISCUSSIONS

The high incidence of BPH has led to an increase in treatment options for the disease. In the surgical realm, technological advancements have enabled various alternatives for both physicians and patients. Among the most recent operative procedures, UroliftR and HoLEP stand out. In this current scenario, this prospective study aimed to evaluate which of these two surgeries has the better outcome in improving

patients' urinary symptoms. We analyzed and compared preoperative and postoperative data (uroflowmetry, IPSS score, urge incontinence, post-micturition residual, and erectile dysfunction) from a group of patients who underwent UroliftR with another group who underwent HoLEP to observe which procedure achieved more significant improvement in urinary symptoms.

Our sample included 35 men, with 16 undergoing UroliftR and 19 undergoing HoLEP. Patients' ages ranged from 55 to 84 years, a common age range for BPH incidence [12]. Data on metabolic syndrome, hypertension, or obesity, which are risk factors for the disease, were not collected.

Additionally, we were able to collect the prostate volume for all patients in the study. The volume ranged from 30 to 120 ml, with a mean of 63.9 ml ± 22.2. Using the Student's t-test for independent samples, we found that prostates in patients who underwent HoLEP were significantly larger than those in the UroliftR group, as reported in previous studies [21].

We also assessed post-micturition residual urinary volume in the preoperative period. In men without BPH, this value is typically less than 12 ml [22]. In this study, 4 men did not have residual volume information in their records, and thus were excluded from the analysis. Of the 31 patients evaluated, the average residual volume was 161.5 ml ± 151.7, indicating the obstructive pattern of the disease.

Regarding the quantification of urinary symptoms, we used the IPSS score developed by the American Urological Association. This score, based on 7 questions with 5 possible points each, categorizes symptoms as mild (0-7 points), moderate (8-19 points), or severe (20-35 points) [5]. Most patients had moderate symptoms before surgery, with only 5 having severe symptoms. Postoperatively, 82.9% of men scored between 0 and 7 on the IPSS, representing an improvement in pre-existing symptoms. Comparing pre- and postoperative periods between groups, Fisher's exact test showed a p-value of 0.379, indicating that neither method showed an advantage over the other in providing more effective symptom relief.

Urge incontinence, another common symptom in men with BPH [18], was present in more than one-fifth of the patients (22.9%), decreasing by 14.3% postoperatively. However, no significant difference was observed in the reduction of this symptom between the surgical options. Other studies have noted reductions in urge incontinence following these procedures, a benefit that might be more apparent with a larger sample size and longer follow-up [24].

Erectile dysfunction (ED) is a common postoperative symptom associated with prostate procedures. The prostate gland surrounds nerve bundles responsible for erection and urinary continence, which, if damaged, can lead to symptoms affecting erectile and urinary function [25]. Among the collected patients, two developed ED post-surgery, one after UroliftR and one after HoLEP. Despite the lack of significant difference between the two surgical methods, the p-value may have been influenced by the small number of patients in the study.

Urge incontinence is another common symptom in men with BPH and may worsen postoperatively if the nerves responsible for urinary function are damaged during the procedure [17, 25]. In our study, this symptom was present in more than one-fifth of the patients (22.9%), decreasing by 14.3% postoperatively. However, no significant difference was observed in the number of patients with this symptom between the two surgical options. Other studies have noted reductions in urge incontinence following these procedures, which could be identified with a larger patient sample [24].

One common urinary symptom, often assessed during the IPSS, is weak urinary stream, which can be evaluated through uroflowmetry. Obstruction is suspected if the maximum urinary flow is less than 10 ml/s [26]. In our study, only patients who underwent UroliftR had this test performed, as the urology service at the hospital did not require this test for HoLEP patients. Among the 16 patients analyzed, the preoperative maximum flow ranged from 4.5 to 34.5 ml/s, with a mean of 13 ± 6.7, indicating a degree of obstruction. Furthermore, comparing pre- and postoperative periods for UroliftR showed significant improvement in both mean ($p=0.002$) and maximum ($p=0.041$) urinary flow using the non-parametric Wilcoxon test, confirming the benefit of this procedure in improving the complaint of weak urinary stream.

6. CONCLUSION

Thus, the results above demonstrate that both HoLEP and UroliftR are effective in reducing post-micturition residual and improving urinary flow without negatively impacting erectile function or the incidence of urge incontinence. However, it is important to note that the HoLEP group had a significantly larger prostate volume, which may influence the choice of surgical technique. Both procedures have proven to be viable options for the treatment of benign prostatic hyperplasia, with similar benefits across most of the evaluated metrics.

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CHAPTER 8

OVERVIEW OF COLORECTAL CANCER DEATHS IN THE STATE OF PIAUÍ: 2018 TO 2022

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ABSTRACT: Colorectal cancer (CRC) is one of the leading causes of mortality in Brazil, with high incidence in the South and Southeast regions, where access to healthcare services is better. In Piauí, the estimate for 2023 is 360 new cases. The lack of a systematic national screening program results in significant variations in early detection and mortality. This study aims to analyze the profile of CRC deaths in the state of Piauí from 2018 to 2022, identifying regional and temporal patterns. Using data from the Mortality Information System (SIM), the study reveals that the Entre Rios region, including the capital Teresina, accounts for the majority of deaths. It was also observed that mortality is more prevalent among women, individuals with low education levels, and those over 75 years old. The COVID-19 pandemic negatively impacted the pursuit of diagnosis and treatment. The results highlight the urgent need to strengthen CRC prevention and diagnostic strategies, with special attention to the most vulnerable areas and socioeconomic disparities.

KEYWORDS: Colorectal Cancer, Mortality, Piauí.

RESUMO: O Câncer colorretal (CCR) é uma das principais causas de mortalidade no Brasil, com alta incidência nas regiões Sul e Sudeste, onde há melhor acesso a serviços de saúde. No Piauí, a estimativa para 2023 é de 360 novos casos. A falta de um programa nacional sistemático de rastreamento resulta em variações significativas na detecção precoce e mortalidade. Este estudo tem como objetivo analisar o perfil dos óbitos por CCR no estado do Piauí entre 2018 e 2022, identificando padrões regionais e temporais. Utilizando dados do Sistema de Informações de Mortalidade (SIM), o estudo

revela que a região de Entre Rios, incluindo a capital Teresina, concentra a maior parte dos óbitos. Observou-se também que a mortalidade é mais prevalente entre mulheres, pessoas de baixa escolaridade e maiores de 75 anos. A pandemia de COVID- 19 impactou negativamente a busca por diagnóstico e tratamento. Os resultados destacam a necessidade urgente de fortalecer as estratégias de prevenção e diagnóstico do CCR, com atenção especial às áreas mais vulneráveis e às disparidades socioeconômicas.

PALAVRAS-CHAVE: Câncer colorretal, Mortalidade, Piauí.

1. INTRODUCTION

Colorectal cancer (CRC) is the second most frequent neoplasia and one of the leading causes of death in Brazil, with higher incidence in the South and Southeast regions, where there is better access to advanced healthcare services that facilitate early treatment. The high rate of CRC is related to risk factors such as smoking, alcoholism, physical inactivity, and an inadequate diet (Siegel et al., 2023; Toledo et. al., 2023).

In 2020, the Global Cancer Observatory estimated 19.3 million new cancer cases globally, excluding non-melanoma skin cancer. The ten most common cancer types account for more than 60% of new cases, with a notable emphasis on female breast cancer, the most frequent, followed by lung cancer and colorectal cancers, with 1.9 million cases (10.0%). Among men, lung cancer is the most prevalent, followed by prostate and colorectal cancer, while in women, breast cancer is the most common, followed by colorectal and lung cancers. In Brazil, according to data from the INCA, the estimated number of CRC cases for 2023 is 45,630 cases, with 360 cases estimated for Piauí (INCA, 2022).

Prevention involves controlling risk factors, screening with fecal occult blood tests, and colonoscopy for patients with positive results. The recommendation is to begin screening at age 50; however, despite some private initiatives and recommendations from medical societies, Brazil still does not have a national consensus on the implementation of systematic CRC screening programs (Toleto et al., 2023).

In the study by Toledo et al. (2023), CRC screening methods conducted in Brazil were evaluated, demonstrating efficacy with the use of the FIT (Fecal Immunochemical Test) and the modified guaiac method for fecal occult blood testing (a non-invasive method). A variable adherence to screening programs was observed, but the results showed a high detection rate of adenomas and early-stage cancers, which is crucial for reducing CRC mortality. The implementation of these programs is feasible in different contexts, including remote areas, and follows international guidelines for screening and early diagnosis.

CRC mortality varies globally, with increasing rates in developing countries such as Colombia and Costa Rica, while in developed countries like the USA and Canada, these rates have been declining. These differences may be linked to varying lifestyle habits and inequality in access to early diagnosis and treatment. CRC, due to its high morbidity and mortality, has significant social and economic impacts. In the USA, for

example, CRC deaths among individuals aged 50 to 74 resulted in a productivity loss of around USD 2 billion per year, highlighting that many of these deaths are potentially preventable (Muzi, Banegas, and Guimarães, 2023).

Given the relevance and impact of this disease, the objective of this study is to describe the epidemiological profile of CRC deaths in the state of Piauí between 2018 and 2022, identifying regional and temporal variations to support public health strategies.

2. METHODOLOGY

This is a descriptive ecological study with a quantitative approach, focusing on the state of Piauí, whose territorial characteristics, according to data from the Brazilian Institute of Geography and Statistics (IBGE), include an area of 251,755.481 km², a population density of 12.99 inhabitants per km², and a Human Development Index (HDI) of 0.69. The state's health regions include Carnaubais, Chapada das Mangabeiras, Cocais, Entre Rios, Planície Litorânea, Serra da Capivara, Tabuleiros do Alto Parnaíba, Vale do Canindé, Vale do Rio Guaribas, Vale do Sambito, Vale dos Rios Piauí e Itaueiras, and Chapada Vale do Rio Itaim (IBGE, 2024).

An analysis was conducted on data from the period 2018 to 2022, using the Mortality Information System (SIM), accessed through the Department of Informatics of the Brazilian Unified Health System (DATASUS). Additionally, a bibliographic search was carried out using the databases PUBMED (Public/Publisher MEDLINE) and SciELO (Scientific Electronic Library Online).

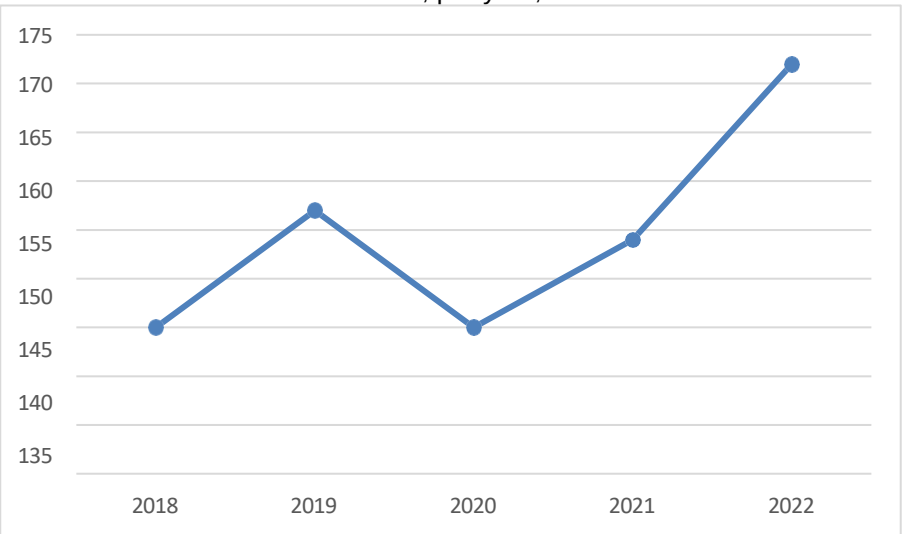
Data collection followed specific inclusion criteria: deaths due to CRC recorded in Piauí between 2018 and 2022, with codes C18, C19, and C20 (according to the 10th revision of the International Classification of Diseases and Related Health Problems – ICD-10), and related sociodemographic information. Exclusion criteria included deaths of individuals not residing in the state of Piauí. The variables analyzed included the year of death, health region of residence, age group, gender, race, and education level. For data organization and analysis, Microsoft Excel® and Microsoft Word® 2013 software were used. The results were presented based on the absolute number of deaths and the corresponding annual percentages. The variables were analyzed through absolute and relative frequencies to identify significant proportions.

As the study is based on public data, it did not require approval from the Research Ethics Committee (CEP) and is in accordance with the current norms established by the National Health Council.

3. RESULTS

During the analyzed period from 2018 to 2022, there were 773 deaths due to CRC. In Graph 1, it is possible to observe the annual variation in the number of deaths, with the highest number in 2022, totaling 172 deaths.

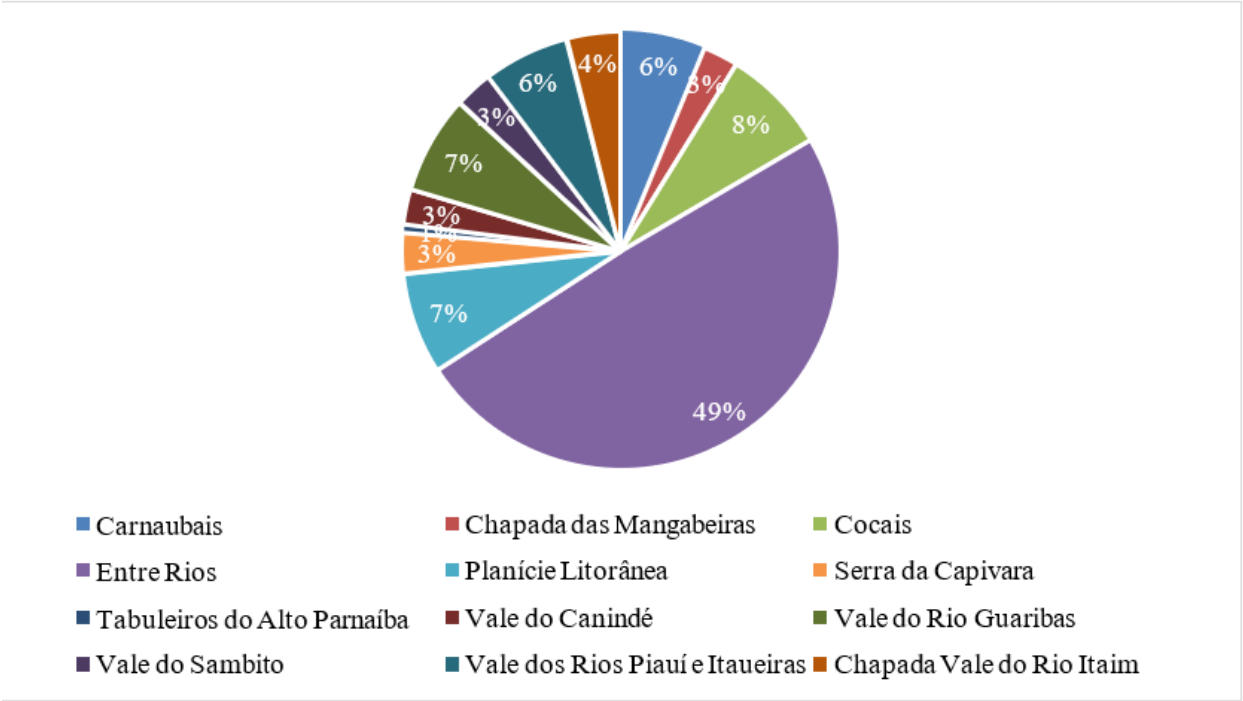
Graph 1. Number of deaths from colorectal cancer, per year, in the state of Piauí between 2018 and 2022



Source: Data extracted from TABNET/DATASUS, 2024

The Entre Rios health region, which includes the state capital, Teresina, accounts for 49% of CRC deaths, holding the majority position in the state of Piauí, as shown in Graph 2.

Graph 2. Distribution of deaths from colorectal cancer, by health region, in the state of Piauí between 2018 and 2022



Source: Data extracted from TABNET/DATASUS, 2024

Regarding gender, the majority of deaths occurred among females, with 399 deaths (51.62%), while 374 deaths (48.38%) were recorded among males, as shown in Table 1. Additionally, the majority of deaths were observed among individuals of mixed race (64.05%), those over 75 years of age (32.71%), and individuals with 1 to 3 years of education (25.22%), although a significant portion had no formal education (21.62%).

Table 1. Distribution of colorectal cancer deaths according to sociodemographic variables in the state of Piauí during the period 2018-2022 (N=773)

Características	N	%
Sexo		
Masculino	374	48,38%
Feminino	399	51,62%
Raça		
Branca	180	23,28%
Preta	50	6,46%
Amarela	6	0,78%
Parda	495	64,05%
Indígena	1	0,13%
Ignorado	41	5,30%
Faixa etária		
5 a 14 anos	1	0,13%
15 a 24 anos	1	0,13%
25 a 34 anos	12	1,55%
35 a 44 anos	39	5,04%
45 a 54 anos	83	10,74%
55 a 64 anos	163	21,10%
65 a 74 anos	221	28,60%
75 anos e mais	253	32,71%
Escolaridade		
Nenhuma	167	21,62%
1 a 3 anos	195	25,22%
4 a 7 anos	92	11,89%
8 a 11 anos	109	14,12%
12 anos e mais	67	8,66%
Ignorado	143	18,49%

Source: Data extracted from TABNET/DATASUS, 2024

4. DISCUSSION

In this study, it was observed that the colorectal cancer (CRC) mortality rate in Piauí showed significant variations over the years. Between 2018 and 2019, there was an increase in deaths, followed by a reduction from 2019 to 2020, and a new rise until 2022. These fluctuations may be closely related to the impact of the COVID-19 pandemic, which led to a decrease in healthcare service utilization and an increase in disease-related complications, directly affecting CRC mortality.

Between 2002 and 2016, a national study identified a rising trend in CRC mortality in Brazil, with a sharper increase in the South and Southeast regions. In the Northeast, the rise in mortality rates was less pronounced compared to other regions. This pattern reflects regional disparities in the disease burden and highlights the urgent need to strengthen prevention and diagnostic strategies (Dominguez and Bierrenbach, 2020).

The influence of human development on cancer transition is evident. In developing countries, an increase in CRC cases is associated with lifestyle changes, while in developed countries, improvements in quality of life have contributed to a reduction in these cases. Simpson's Paradox, which describes how the relationship between variables can be reversed when accounting for strata of a confounding variable, may explain variations in CRC mortality and underscores the importance of health policies addressing socioeconomic and regional inequalities (Muzi, Banegas, and Guimarães, 2023).

In Mato Grosso, Carvalho et al. (2022) identified a rising trend in CRC mortality between 2000 and 2019, attributed to demographic transition and population aging. Similar analyses during the period from 2005 to 2016 showed a correlation between mortality rates and the level of socioeconomic development in the state's mesoregions (Caló et al., 2022).

Between 2015 and 2019, Piauí had a relatively low number of CRC deaths compared to southern states such as Rio Grande do Sul, Paraná, and Santa Catarina, which accounted for the majority of deaths. Analyses showed that CRC mortality is higher among individuals aged 65 or older, with a slight male predominance. In Piauí, despite increasing mortality rates with age, the absolute and age-adjusted rates are significantly lower than in southern states, highlighting a regional discrepancy (Castilho et al., 2023).

In Piauí, the majority of CRC deaths occurred among females (51.62%), with a small difference compared to males (48.38%). The predominant race among deaths was mixed-race (64.05%). Mortality increased with age, especially from the age of 54 onwards, with a notable prevalence among those over 75 years old (32.71%). The Entre Rios health region, which includes the capital Teresina, had the highest death rate (49%). It was also observed that most of the deceased had low educational attainment (1 to 3 years or none).

The findings of Mesquita Neto et al. (2023), evaluated in Piauí from 2016 to 2020, reinforce the observation of a reduction in colorectal cancer (CRC) notifications in Piauí during the pandemic, suggesting a possible increase in underreporting. The study highlighted a break in the growth trends of cases and, when compared to other states, showed a significant mortality rate in the 0 to 19 age group in the state during the analyzed period.

Studies conducted in São Paulo between 2001 and 2017 showed that CRC incidence was higher in areas with high socioeconomic levels, with mortality also being

higher in these areas, ranging from 8.9 to 11.7. In Barretos, the variation was minimal (Ribeiro et al., 2023).

Overall, CRC mortality in Piauí, between 2000 and 2019, was relatively low compared to other regions of Brazil. While the South presented the highest rates, the North and Northeast, including Piauí, had lower rates. The annual increase of 1.15% in mortality after the age of 45 reflects disparities in access to treatment and diagnosis. In Piauí, socioeconomic factors and limited healthcare infrastructure are significant determinants of mortality rates, similar to the challenges found in other regions with comparable conditions in the provision of medical care and early treatment (Nascimento et al., 2022).

Although this study provides an overview of the profile of CRC deaths in Piauí, it has limitations, such as the reliance on secondary data and the lack of details on individual and contextual factors. Future research should include primary and qualitative data for a deeper understanding of the determinants of mortality. Additionally, investigations into the effectiveness of health policies and longitudinal analyses of interventions could improve prevention and treatment strategies tailored to regional needs.

5. CONCLUSION

In light of the analysis of the epidemiological profile of colorectal cancer (CRC) deaths in Piauí from 2018 to 2022, significant patterns were revealed in the variations of annual and regional CRC mortality rates. It was observed that, although Piauí recorded absolute numbers of CRC deaths lower than those of southern states in Brazil, mortality rates increased with age and were more pronounced among women, mixed-race individuals, and those with low educational attainment. The Entre Rios region, which includes the capital Teresina, showed the highest proportion of deaths. These findings underscore the impact of the COVID-19 pandemic on CRC mortality, with potential interferences in the pursuit of diagnosis and treatment. The discoveries highlight the urgent need to strengthen prevention and diagnostic strategies for CRC, with a special focus on areas with greater socioeconomic and demographic disparities. Furthermore, it is crucial that public health policies are adapted to address regional inequalities and promote more equitable access to healthcare, aiming to reduce CRC mortality rates in the state.

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CHAPTER 9

PROPEDEUTICS AND DIAGNOSIS OF PANCREATIC NEUROENDOCRINE TUMOR

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ABSTRACT: The duodenopancreatectomy (Whipple Surgery) is a complex surgical procedure with a high morbidity rate, primarily indicated for the treatment of pancreatic head cancer. It can also be used for other types of tumors that develop in the same region, such as periampullary tumors (pancreatic adenocarcinoma, duodenal adenocarcinoma, duodenal papilla tumor, distal cholangiocarcinoma), and neuroendocrine tumors. In the 1960s and 1970s, the mortality rate for this surgery was very high, with up to 25% of patients dying due to complications from the procedure. However, with technological advancements and the increased experience of surgical, anesthetic, and intensive care teams, there has been a reduction in complication rates and a significant increase in the safety of the entire surgical technique. This case report discusses the surgical treatment of a 40-year-old male patient at Santa Casa Hospital (VIII Surgical Clinic) in Belo Horizonte, MG, who was diagnosed with a neuroendocrine tumor located in the pancreatic head after surgical resection and histopathological/immunohistochemical analysis of the specimen.

KEYWORDS: Pancreaticoduodenectomy, Neuroendocrine Carcinoma, Pancreatic Neoplasms, Adenocarcinoma, Pancreatitis.

RESUMO: A duodenopancreatectomia (Cirurgia de Whipple) é um procedimento cirúrgico complexo com elevada taxa de morbidade, indicado majoritariamente para o tratamento de câncer da cabeça do pâncreas, podendo também ser utilizado para outros tipos de tumores que se desenvolvem na mesma região, como os tumores periampulares (adenocarcinoma de pâncreas, adenocarcinoma de duodeno, tumor de papila duodenal, colangiocarcinoma distal) e os tumores neuroendócrinos. Nas décadas de 60 e 70 a taxa de mortalidade pela cirurgia era muito alta, até 25% dos pacientes iam a óbito em circunstâncias de complicações do procedimento. Entretanto, atualmente com o avanço tecnológico e da experiência das equipes cirúrgicas, anestésica e da medicina intensiva, observa-se uma redução nas taxas de agravos e um aumento significativo em relação a segurança de toda a técnica cirúrgica em questão. O presente relato de caso aborda o tratamento cirúrgico de uma paciente de 40 anos de idade, sexo masculino, no Hospital Santa Casa (VIII CLÍNICA CIRÚRGICA), em Belo Horizonte, MG, diagnosticado com tumor neuroendocrino localizado na cabeça do pâncreas após ressecção cirúrgica e análise histopatológica/imunohistoquímica da peça.

PALAVRAS-CHAVE: Pancreaticoduodenectomia, Carcinoma Neuroendócrino, Neoplasias Pancreáticas, Adenocarcinoma, Pancreatite.

1. INTRODUCTION

Pancreatic cancer is one of the deadliest neoplasms, ranking seventh in cancer-related deaths. According to data from the National Cancer Institute (INCA) from 2020, this neoplasm accounts for about 2% of all cancer types diagnosed in Brazil. It is more common in individuals over 60 years of age and affects both men and women.

Unfortunately, pancreatic cancer has a high mortality rate due to late diagnosis and the aggressive nature of the disease. Approximately 80% of cases are diagnosed at advanced stages, making treatment difficult and reducing survival chances.

Risk factors for pancreatic cancer include a family history of the disease, smoking, obesity, type 2 diabetes, and exposure to certain chemicals.

The primary therapeutic approach for pancreatic neoplasms consists of the surgical technique known as pancreaticoduodenectomy, commonly referred to as Whipple surgery. This procedure is frequently performed for the resection of tumors located in the head of the pancreas and involves the removal of a portion of the pancreas, the duodenum, the gallbladder, and, in some cases, part of the stomach.

During the procedure, the surgeon makes an incision in the abdominal wall to access the affected area. The goal is to remove the tumor and any compromised surrounding tissue. Depending on the tumor's extent and other factors, the surgeon may also reconstruct the removed structures to allow for the continuity of digestion and bile flow.

It is important to emphasize that the procedure is complex and requires an experienced surgical team. Furthermore, the postoperative period and recovery can be challenging.

2. CASE DESCRIPTION

Patient G.P.D.A, a 40-year-old male, non-insulin-dependent diabetic, former smoker, and former chronic alcohol user, was admitted on April 4, 2023, to Risoleta Neves Hospital with complaints of epigastric pain, loss of appetite, vomiting, fever, hematochezia, and right upper quadrant pain. In this context, an upper gastrointestinal endoscopy, abdominal and pelvic CT scan, colonoscopy, and MRI with MR cholangiography were performed.

The MRI with MR cholangiography revealed the presence of a dilated, tortuous main pancreatic duct with sacculations along its length, without biliary tract involvement.

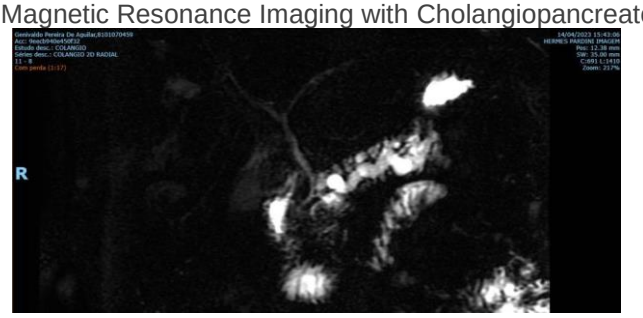
A lesion located in the head/uncinate process of the pancreas measuring 12 mm was observed, which could indicate a primary neoplastic lesion.

On April 20, 2023, the patient was transferred to Santa Casa Hospital in Belo Horizonte, Minas Gerais, for further evaluation. Upon admission, the patient reported that abdominal pain had started more than a year ago; as it was intermittent, he had not sought medical attention, but symptoms had intensified over the past four months. Given the findings, tumor marker tests were ordered, which showed altered results: Carcinoembryonic Antigen (CEA): 126.57 ng/ml and Cancer Antigen 19-9 (CA 19-9): 3172.2 ng/ml.

After a thorough evaluation of the case and discussion with the other surgical members of the 8th Surgical Clinic at Santa Casa Hospital in Belo Horizonte, and in agreement with the patient, a decision was made to proceed with the surgical resection of the nodule located in the head/uncinate process of the pancreas.

Furthermore, MRI findings are shown in Figure 1, as described above.

Figure 1. Magnetic Resonance Imaging with Cholangiopancreatography.



Source: Collection of the VIII Santa Casa Surgical Clinic, 2023

The theoretical framework in a study comprises a critical and organized analysis of the literature relevant to the topic, providing a theoretical contextualization and defining the key concepts. It should comprehensively contain the theories, models and previous research, identifying gaps, contradictions and consensus in the literature that are important for the focus of the work being developed.

2.1 PROCEDURE PERFORMED - DUODENOPANCREATECTOMY

Deciding on cephalic resection, a bilateral subcostal laparotomy was performed, with a greater tendency toward the right side.

Findings: A hardened lesion was observed in the uncinate process of the pancreas.

Stage 1 - Mobilization of the pancreaticoduodenal block was performed with a defined cleavage plane, allowing access to the superior mesenteric vein, which was not invaded, establishing criteria for resectability. Resection of the duodenum and gastric antrum was carried out using a linear cutting stapler. Subsequently, the biliary tract (hepatocolledochus) and other components of the portal triad were sectioned/repaired. Resection of the first jejunal loop and the fourth portion of the duodenum at the level of the Treitz angle was performed; proximal jejunum was sectioned; transposition of the duodenum to the right in the retro-mesentery was done; then, the pancreas was sectioned at the level of the superior mesenteric vein; ligation of the superior, inferior, posterior, and anterior pancreaticoduodenal arteries was performed. The limit of the uncinate process was sectioned, including complete resection, thus removing the entire surgical specimen.

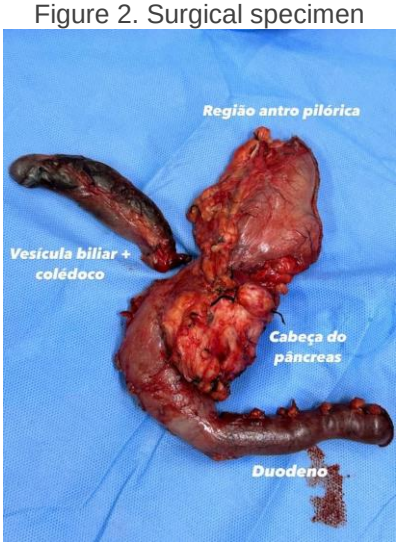
Stage 2 (Reconstruction) - A termino-lateral pancreatojejunostomy was performed using the duct-to-mucosa anastomosis technique; a termino-lateral hepatocolledochus anastomosis was performed in a single plane; and finally, a gastroenterostomy was done with the aid of an 80 mm linear cutting stapler.

Subsequently, drainage of the cavity was performed; a post-anastomotic nasoenteral tube (SNE) was placed under visualization, finishing with the placement of Penrose siliconized sentinel drains near the pancreatic and biliary anastomosis.

Laparorraphy and dressing were performed.

Additionally, an intraoperative image of the resected surgical specimen is shown in Figure 2.

Figure 2. Surgical specimen



Source: Collection of the VIII Santa Casa Surgical Clinic, 2023

2.2 POSTOPERATIVE

The patient was admitted to the Intensive Care Unit (ICU) due to an extended surgical time, the presence of multiple adhesions, and fibrous structures, also presenting with bleeding beyond the usual amount. At the end of the procedure, the patient developed significant blood dyscrasia and was transferred in a hemodynamically unstable condition, undergoing orotracheal intubation under mechanical ventilation (MV).

On the 1st Postoperative Day (POD), the patient was in critical condition, sedated, intubated under MV, and in a trauma response context requiring the use of vasopressors. The patient exhibited rhabdomyolysis, dysglycemia, and hyperkalemia, with no ECG changes and no need for dialysis measures at that time. The surgical wound had minimal sero-hematic secretion, with a Penrose drain in a collection bag showing sero-hematic secretion, predominantly hematological content. Intensive support was maintained, the diet was suspended, and hypokalemic measures were implemented.

On the 3rd POD, the patient remained sedated and intubated on MV in support mode, with a nasoenteral tube (SNE) but no diet. After an attempt to reduce sedation, the patient exhibited periods of agitation, making extubation difficult. The surgical wound was dry and appeared good, with no inflammatory signs, and the drain in the collection bag showed sero-hematic secretion. Amylase levels from the Penrose drain secretion and serum amylase were measured for comparison.

On the 4th POD, the patient demonstrated hemodynamic stability, with sedation reduced, allowing for extubation and the initiation of low-flow enteral feeding. On the 6th POD, the patient was discharged from the ICU and transferred to a surgical ward, where

oral diet was introduced with good tolerance, and the patient had bowel movements and preserved intestinal habits.

The patient progressed without complications, maintaining hemodynamic stability. The surgical wound was dry, with no signs of inflammation, and the Penrose drain showed a small amount of sero-hematic secretion, leading to discharge on the 10th POD.

The patient returned to the outpatient clinic at the Santa Casa de Belo Horizonte Oncology Institute on the 17th POD, presenting in good general condition, without pain complaints, with good tolerance to the oral diet, reporting some episodes of bloating. The surgical wound was dry, with no signs of inflammation, and the Penrose drain showed low output. The Penrose drain was removed without complications. In light of this scenario, the patient remains under follow-up with the surgical clinic and clinical oncology.

3. DISCUSSION

Duodenopancreatectomia is a surgical procedure performed for the resection of tumors located in the head of the pancreas, including neuroendocrine tumors. Unlike adenocarcinoma (originating from ectoderm), neuroendocrine tumors have an embryological origin from the neural crest and develop from neuroendocrine cells found in the endocrine and nervous systems. These cells have the capacity to produce hormones and are responsible for regulating various functions of the organism.

Neuroendocrine tumors can occur in various parts of the body, including the pancreas, lungs, intestines, stomach, and other organs. They can be benign (non-cancerous) or malignant (cancerous). Some neuroendocrine tumors grow slowly, while others may develop more aggressively.

The symptoms and treatment of neuroendocrine tumors can vary depending on the site of development and whether they are benign or malignant. Symptoms may include hormonal changes, abdominal pain, diarrhea, and weight loss, among others.

The diagnosis of neuroendocrine tumors typically involves imaging studies, such as computed tomography and magnetic resonance imaging, as well as the analysis of tissue samples obtained through biopsy. Treatment for this type of tumor may involve surgery, radiotherapy, chemotherapy, targeted therapy, and hormonal therapy, depending on the stage and location of the tumor. The treatment plan is determined by the specialist physician based on the specific characteristics of the tumor and the needs of the patient.

Neuroendocrine tumors of the pancreas can be classified according to various classification systems. A widely used system is the classification of the World Health Organization (WHO), which considers histological characteristics and grade of malignancy.

According to the WHO classification, neuroendocrine tumors of the pancreas are grouped into four main categories:

1. **Well-differentiated neuroendocrine tumors (grades 1 and 2)**: These tumors are generally slow-growing and less aggressive. They are well-differentiated, meaning that the tumor cells resemble normal pancreatic cells. Well-differentiated neuroendocrine tumors are divided into grade 1 (low grade) and grade 2 (intermediate);
2. **High-grade neuroendocrine carcinoma (grade 3)**: Also known as small cell neuroendocrine carcinoma, this type of tumor is more aggressive and has a faster growth rate. The tumor cells are less differentiated and exhibit more aggressive characteristics;
3. **Mixed neuroendocrine tumor**: These tumors have a combination of neuroendocrine and adenocarcinoma characteristics (the most common type of pancreatic cancer). They may have well-differentiated neuroendocrine components and less differentiated adenocarcinoma components;
4. **Neuroendocrine tumors of uncertain origin**: These tumors exhibit neuroendocrine characteristics, but their precise origin cannot be determined.
5. The classification of pancreatic neuroendocrine tumors is important for determining the appropriate treatment, predicting prognosis, and defining the necessary follow-up.

Given the above, the detailed clinical evaluation, along with imaging findings and significantly elevated tumor markers (CA 19-9 / CEA), was decisive for the decision to pursue a surgical approach, representing both a therapeutic and diagnostic conduct for the case in question.

On the other hand, the absence of typical epidemiological characteristics of pancreatic neoplasia, such as advanced age and certain clinical evidence in oncology patients (like significant and unintentional weight loss), combined with the patient's daily alcohol consumption habit, suggested a diagnosis of chronic inflammatory disease (benign). Therefore, the histopathological and immunohistochemical analysis of the surgical specimen was crucial to determining the diagnosis and directing the best therapeutic approach for the case.

In light of the findings from the immunohistochemistry of the surgical specimen, which indicated in the diagnostic report: **"IRREGULAR PROLIFERATION OF NEUROENDOCRINE CELLS INDICATIVE OF GRADE 1 NEUROENDOCRINE TUMOR / NET G1 (WHO)"**, it is concluded that the surgical approach through duodenopancreatectomy was considered an effective procedure, given that it involved a grade 1 neuroendocrine tumor of the pancreas. Thus, there was no need for treatment with adjuvant therapy.

4. CONCLUSION

Although considered a complex procedure, duodenopancreatectomy holds significant relevance in the definitive treatment of certain pancreatic lesions, whether benign or malignant. This report exemplifies a case of a grade 1 neuroendocrine tumor, which is considered less aggressive and has a better prognosis compared to higher-grade neuroendocrine tumors and adenocarcinomas. Therefore, despite the associated risks, the surgical procedure is often curative and offers substantial long-term survival chances.

Thus, when analyzing the clinical outcome of the case, it is important to highlight the significance of outpatient follow-up in the postoperative period to confirm treatment control (tumor markers) and the success of the surgery.

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CHAPTER 10

COMPARISON OF FACTORS ASSOCIATED WITH SPOTTED FEVER IN THE PEDIATRIC AND ADULT POPULATION IN BRAZIL: 2007-2022

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ABSTRACT: Objective: realize a comparative analysis among the clinical and epidemiological characteristics of spotted fever in pediatric and adult populations, associated to the variables used in the study, to understand the differences between age groups. Methods: Epidemiological, observational, cross-sectional study with data from the Notifiable Diseases Information System (SINAN-DATASUS) referring to confirmed cases of spotted fever in Brazil between January 2007 and December 2022, including individuals of all age groups. Results: 2709 spotted fever profiles were analyzed, in both groups, the male sex was the majority, 71.65% in adults and 62.40% in the pediatric group. Fever was the most recurrent symptom, respectively, 91% in adults and 95% in the pediatric population; hospitalization in children occurred more frequently: 72.40%, as compare with adults 58.51%, contact with ticks was similar: 85.96% in adults and 79.10% in pediatrics, adults visited forests more frequently, river or waterfall 80.16% compared to 65.11% pediatric group. Conclusion: Males were more susceptible, with the domestic environment being the place of greatest contagion. Most of the time, children are asymptomatic, while in the adult population the most common symptoms include headache and myalgia. Laboratory diagnosis is often limited, and mortality rates are high.

KEYWORDS: Rocky mountain spotted fever, Tick-Borne diseases signs and Symptoms.

RESUMO: Objetivo: realizar uma análise comparativa entre as características clínicas e epidemiológicas da febre maculosa em populações pediátricas e adultas, relacionando com as variáveis utilizadas no estudo, para entender as diferenças entre as faixas etárias. Métodos: Estudo epidemiológico, observacional, de delineamento transversal com dados do Sistema de Informação de Agravos de Notificação (SINAN-DATASUS) referentes a casos confirmados de febre maculosa no Brasil entre janeiro de 2007 e dezembro de 2022, incluindo indivíduos de todas as faixas etárias. Resultados: Foram analisados 2709 perfis de febre maculosa, em ambos os grupos, o sexo masculino foi o majoritário, 71,65% em adultos e 62,40% no grupo pediátrico. Febre foi o sintoma mais

recorrente, respectivamente, 91% em adultos e 95% na população pediátrica; a hospitalização nas crianças ocorreu com maior frequência: 72,40%, enquanto nos adultos 58,51%, o contato com carrapato foi similar: 85,96 % em adulto e 79,10% no pediátrico, os adultos frequentaram com maior frequência floresta, rio ou cachoeira 80,16 % em comparação 65,11% no grupo pediátrico. Conclusão: O sexo masculino foi mais suscetível, com o ambiente doméstico sendo o local de maior contágio. Na maioria das vezes, crianças são assintomáticas, enquanto na população adulta os sintomas mais comuns incluem dor de cabeça e mialgia. O diagnóstico laboratorial geralmente é limitado, e as taxas de mortalidade são altas.

PALAVRAS-CHAVE: Rickettsiose do grupo da febre maculosa, Doenças transmitidas por carrapatos, Sinais e Sintomas.

1. INTRODUCTION

Spotted Fever is an acute febrile illness caused by *Rickettsia rickettsii*, an obligate intracellular gram-negative bacterium. It is transmitted to humans through bites from infected hematophagous ectoparasites (ticks), occurring primarily in South and North America. According to the latest edition of the Epidemiological Surveillance Guide from the Ministry of Health, any species of tick can serve as a reservoir, particularly those of the *Amblyomma* genus, such as *A. cajennense*, *A. cooperi* (*dubitatum*), and *A. aureolatum* (Brazil, 2022). Equids and rodents, like the capybara (*Hydrochaeris hydrochaeris*), are the most common hosts. Transmission generally occurs when the arthropod remains attached to the host for 4 to 6 hours. Ticks remain infected throughout their lifetime, which typically ranges from 18 to 36 months. The disease is not transmitted from person to person (Ji et al., 2024).

The clinical manifestations of Brazilian spotted fever exhibit a spectrum of severity, which varies mainly depending on the stage of the disease. The clinical presentation is mild and nonspecific in the early days, with rapid progression to severe forms, and death often occurring between the 6th and 7th days of illness (Ji et al., 2024). Clinical characteristics include the sudden onset of headache, chills, and fever lasting approximately two to three weeks, with the appearance of a rash on the extremities and trunk around the 4th day of illness. As a diagnostic criterion, any individual presenting with a suggestive clinical picture, along with a history of tick bites and/or contact with domestic and/or wild animals in areas of potential exposure, should be considered a suspected case (Wyatt et al., 2020).

Laboratory diagnosis is achieved through tests, such as genetic material analysis of the parasite and specific antibodies, as well as other nonspecific and complementary tests. The serological method regarded as the gold standard by the World Health Organization (WHO) for the diagnosis of rickettsioses is the Indirect Immunofluorescence Assay (IFA), based on the detection of IgG and IgM antibodies using species-specific antigen panels (Foccacia et al., 2015).

The only drugs known to be effective for the specific treatment of the infection are Doxycycline and Chloramphenicol. Epidemiological studies comparing these two therapeutic options have demonstrated higher mortality rates in individuals treated with Chloramphenicol, making Doxycycline the first-line antimicrobial. The treatment is administered for a period of 7 days and should be continued for 3 days after the fever subsides (Foccacia et al., 2015).

Despite the decline in confirmed cases of spotted fever since 2005, mortality rates remain around 20 to 30%, due to a lack of awareness of the disease and its symptoms, hindering timely diagnosis and appropriate therapy (Torres-Castor et al., 2022). The epidemiological profile shows a predominance among males, attributed to activities with exposure to the vector, and seasonality in transmission determined by environmental factors, such as periods of lower rainfall between April and October, especially in the southeastern region (Espirito Santo, 2023).

Even with the clear epidemiological significance of spotted fever in Brazil, few studies have focused on analyzing the clinical evolution of diagnosed cases, much less comparing the natural history of the disease in children and adults (Brazil, 2006). Therefore, the present study aimed to identify the clinical-epidemiological characteristics of spotted fever associated with pediatric and adult populations with the same diagnosis, understanding the main clinical features, transmission vectors, and outcomes of the observed groups, as well as their differences.

2. METHODS

An epidemiological, observational, cross-sectional study was conducted using data from the Notifiable Diseases Information System (SINAN-DATASUS) concerning confirmed cases of spotted fever in Brazil between January 2007 and December 2022, including individuals of all age groups. The microdata were extracted directly from the DATASUS server via a script written in the R programming language, available at this link: https://gist.github.com/datahoffmann/0f51ef8965fb0a151d6ff40e2e9820c.

The following variables were included in the study: age, sex, clinical signs and symptoms (fever, headache, abdominal pain, myalgia, nausea, rash, diarrhea, jaundice, conjunctival hyperemia, hepatomegaly, petechiae, hemorrhagic manifestations, lymphadenopathy, seizures, extremity necrosis, prostration, shock/hypotension, stupor/coma, hemorrhagic suffusion, respiratory alterations, oliguria/anuria), reservoirs (tick contact, capybara contact, contact with dogs or cats, contact with cattle, contact with horses, visited forests, rivers, or waterfalls), probable site of infection, clinical and diagnostic data (hospitalization, laboratory diagnosis, IgM serology result, IgM serology titration, IgG serology result, IgG serology titration, isolation result, histopathology result, immunohistochemistry result, diagnostic criteria, case type, disease progression).

For the study's outcome, the variable "age group" was selected, created by categorizing age, with individuals aged 16 years or younger classified as the pediatric group, and those aged 17 years or older as the adult group. Missing data were described in the epidemiological profile table as "not reported."

Pearson's chi-square test was performed to identify associations between explanatory variables and the outcome, considering a significance level of 0.05. The odds ratio (OR), along with its corresponding 95% confidence interval (CI95%), was used as the measure of association.

A logistic regression model was applied to adjust the OR for associated and independent factors.

All analyses were performed using R software, version 4.3.2 (R Core Team, Vienna, Austria).

3. RESULTS

A total of 2,709 cases of spotted fever were reported, with the majority occurring in males. The most common symptoms in the pediatric age group were fever (95.64%), headache (65.31%), myalgia (60.45%), prostration (57.46%), nausea (55.04%), and rash (50.41%). Among adult patients, fever (91.72%) was the most prevalent symptom, followed by headache (78.06%), myalgia (77.24%), prostration (55.35%), and nausea (52.60%) in descending order (Table 1).

Table 1. Epidemiological profile of spotted fever cases according to sex, age and symptoms in Brazil: 2007-2022

Variables	**Adult** N = 2201[1]	**Pediatric** N = 508[1]
Sex		
Female	624 (28,35%)	191 (37,60%)
Male	1577 (71,65%)	317 (62,40%)
Fever		
No	181 (8,28%)	22 (4,36%)
Yes	2006 (91,72%)	483 (95,64%)
Not provided	14	3
Headache		
Absent	472 (21,94%)	170 (34,69%)
Present	1679 (78,06%)	320 (65,31%)
Not provided	50	18
Abdominal pain		
Absent	1290 (60,85%)	251 (51,12%)
Present	830 (39,15%)	240 (48,88%)
Not provided	81	17
Myalgia		
Absent	492 (22,76%)	193 (39,55%)
Present	1670 (77,24%)	295 (60,45%)
Not provided	39	20

Nausea		
Absent	1020 (47,40%)	223 (44,96%)
Present	1132 (52,60%)	273 (55,04%)
Not provided	49	12
Rash		
Absent	1436 (67,58%)	243 (49,59%)
Present	689 (32,42%)	247 (50,41%)
Not provided	76	18
Diarrhea		
Absent	1543 (72,51%)	380 (77,87%)
Present	585 (27,49%)	108 (22,13%)
Not provided	73	20
Jaundice		
Absent	1705 (80,05%)	418 (85,13%)
Present	425 (19,95%)	73 (14,87%)
Not provided	71	17
Conjunctival hyperemia		
Absent	1820 (86,83%)	410 (84,02%)
Present	276 (13,17%)	78 (15,98%)
Not provided	105	20
Hepatomegaly		
Absent	1888 (93,05%)	393 (82,91%)
Present	141 (6,95%)	81 (17,09%)
Not provided	172	34
Petechiae		
Absent	1596 (75,18%)	286 (58,01%)
Present	527 (24,82%)	207 (41,99%)
Not provided	78	15
Hemorrhagic manifestations		
Absent	1823 (85,95%)	384 (78,85%)
Present	298 (14,05%)	103 (21,15%)
Not provided	80	21
Lymphadenopathy		
Absent	1774 (85,99%)	398 (83,09%)
Present	289 (14,01%)	81 (16,91%)
Not provided	138	29
Convulsion		
Absent	1908 (90,17%)	417 (84,93%)
Present	208 (9,83%)	74 (15,07%)
Not provided	85	17
Necrosis of extremities		
Absent	2043 (97,29%)	476 (97,74%)
Present	57 (2,71%)	11 (2,26%)
Not provided	101	21
Prostration		
Absent	955 (44,65%)	211 (42,54%)
Present	1184 (55,35%)	285 (57,46%)
Not provided	62	12
Shock/Hypotension		
Absent	1663 (78,59%)	381 (77,44%)
Present	453 (21,41%)	111 (22,56%)
Not provided	85	16
Stupor/coma		
Absent	1885 (89,93%)	417 (84,58%)
Present	211 (10,07%)	76 (15,42%)
Not provided	105	15
Hemorrhagic suffusion		
Absent	1966 (94,07%)	436 (89,71%)
Present	124 (5,93%)	50 (10,29%)
Not provided	111	22
Respiratory changes		
Absent	1447 (67,87%)	351 (70,62%)

Present	685 (32,13%)	146 (29,38%)
Not provided	69	11
Oliguria/anuria		
Absent	1698 (81,01%)	395 (80,94%)
Present	398 (18,99%)	93 (19,06%)
Not provided	105	20
Age (years)	44,18 (15,34)	7,81 (4,80)

[1]n (%); Média (DP)
Source: Authors

The locations with the highest number of infections were domestic environments, both in adults and the pediatric age group (40.86%; 59.13%), with the majority of cases being of the autochthonous type (73.41%; 75.79%). The most common reservoir hosts were ticks (85.96%; 79.10%) and dogs or cats (46.63%; 52.98%) among those who visited forests, rivers, or waterfalls (80.16%; 65.11%) (Table 2).

Table 2. Epidemiological profile of spotted fever cases according to reservoir and site of infection, in Brazil: 2007-2022

Variables	**Adult** N = 2201[1]	**Pediatric** N = 508[1]
Probable place of infection		
Home	747 (40,86%)	230 (59,13%)
Leisure	563 (30,80%)	119 (30,59%)
Other	118 (6,46%)	31 (7,97%)
Work	400 (21,88%)	9 (2,31%)
Not informed	373	119
Type of case		
Allochthonous	365 (16,59%)	55 (10,83%)
Autochthonous	1615 (73,41%)	385 (75,79%)
Undetermined	220 (10,00%)	68 (13,39%)
Not informed	1	0
Contact with tick		
No	273 (14,04%)	93 (20,90%)
Yes	1671 (85,96%)	352 (79,10%)
Not informed	257	63
Contact with capybara		
No	1493 (79,67%)	377 (87,88%)
Yes	381 (20,33%)	52 (12,12%)
Not informed	327	79
Contact with dog or cat		
No	1013 (53,37%)	205 (47,02%)
Yes	885 (46,63%)	231 (52,98%)
Not informed	303	72
Contact with cattle		
No	1518 (81,05%)	365 (84,69%)
Yes	355 (18,95%)	66 (15,31%)
Not informed	328	77
Contact with horses		
No	1554 (82,97%)	337 (77,65%)
Yes	319 (17,03%)	97 (22,35%)
Not informed	328	74
Frequent forest, rivers or waterfalls		
No	391 (19,84%)	149 (34,89%)
Yes	1580 (80,16%)	278 (65,11%)
Not informed	230	81

Source: Authors

In the majority of adult (58.51%) and pediatric (72.40%) cases, hospitalization occurred, along with laboratory diagnosis (94.93%; 93.22%, respectively). The diagnostic criterion used was primarily laboratory-based (91.72%; 86.73%), and most cases resulted in recovery (Table 3). The results of the serological tests, histopathology, and immunohistochemistry are summarized in Table 3.

Table 3. Epidemiological profile of spotted fever cases according to clinical and diagnostic data, in Brazil: 2007-2022

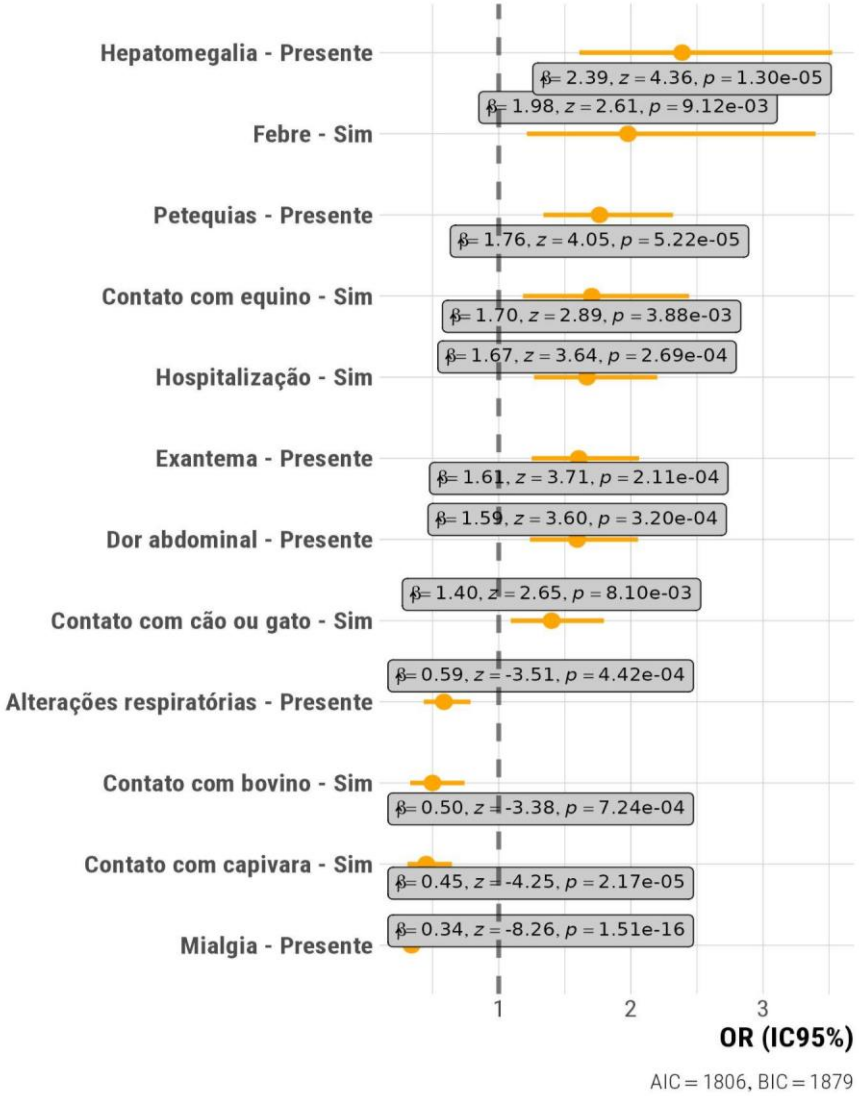
Variables	**Adult** N = 2201[1]	**Pediatric** N = 508[1]
Hospitalization		
No	904 (41,49%)	138 (27,60%)
Yes	1275 (58,51%)	362 (72,40%)
Not provided	22	8
Laboratory diagnosis		
No	85 (5,07%)	24 (6,78%)
Yes	1591 (94,93%)	330 (93,22%)
Not provided	525	154
IgM serology result		
Inconclusive	27 (1,70%)	5 (1,49%)
Not performed	660 (41,67%)	121 (36,01%)
Negative	513 (32,39%)	104 (30,95%)
Positive	384 (24,24%)	106 (31,55%)
Not provided	617	172
IgG serology result		
Inconclusive	19 (1,19%)	6 (1,87%)
Not performed	144 (9,05%)	31 (9,66%)
Negative	858 (53,93%)	184 (57,32%)
Positive	570 (35,83%)	100 (31,15%)
Not provided	610	187
Isolation result		
Detected	219 (15,29%)	55 (18,90%)
Not detected	31 (2,16%)	12 (4,12%)
Not performed	1182 (82,54%)	224 (76,98%)
Not provided	769	217
Histopathology result		
Inconclusive	21 (1,42%)	1 (0,33%)
Not performed	1370 (92,69%)	283 (92,48%)
Negative	16 (1,08%)	2 (0,65%)
Positive	71 (4,80%)	20 (6,54%)
Not provided	723	202
Immunohistochemistry result		
Inconclusive	9 (0,62%)	0 (0,00%)
Not performed	1341 (92,04%)	265 (92,66%)
Negative	13 (0,89%)	0 (0,00%)
Positive	94 (6,45%)	21 (7,34%)
Not provided	744	222
Diagnostic criteria		
Epidemiological	179 (8,28%)	65 (13,27%)
Laboratory	1984 (91,72%)	425 (86,73%)
Not provided	38	18
Evolution		
Cure	1338 (63,84%)	293 (63,28%)
Death	758 (36,16%)	170 (36,72%)
Not provided	105	45

Source: Authors

Analyzing Figure 1, we observe that the pediatric population diagnosed with spotted fever showed a 139% higher likelihood of hepatomegaly, 98% higher likelihood of fever, 76% higher likelihood of petechiae, 61% higher likelihood of rash, and 59% higher likelihood of abdominal pain compared to the adult population. Additionally, contact with horses was 70% more common, hospitalizations were 67% more frequent, and contact with dogs or cats was 40% more prevalent than in adults.

Through the analysis of the clinical profiles, it was found that in the adult control group, myalgia was 66% more frequent than in children. Regarding contact with tick host animals, adults had 55% more frequent contact with capybaras and 50% more frequent contact with cattle, whereas children showed a 70% higher frequency of contact with horses and a 40% higher frequency of contact with dogs or cats compared to the other group. Furthermore, respiratory alterations, such as dyspnea and respiratory failure, were 41% more frequent in the control group.

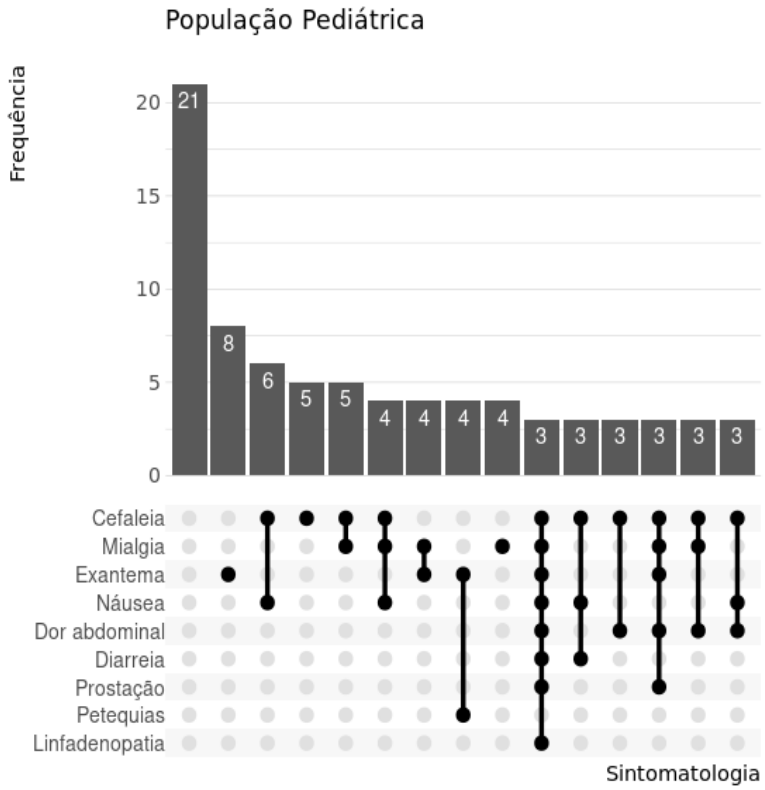
Figure 1. Logistic regression of factors associated with spotted fever among pediatric patients compared with adult patients in Brazil between 2007 and 2022.



Source: Authors

Figure 2 shows that among the pediatric population, asymptomatic individuals were the most prevalent, followed in descending order by those presenting only with rash; headache and nausea; only headache; headache and myalgia; headache, myalgia, and nausea; myalgia and rash; rash and petechiae; myalgia; headache, myalgia, rash, nausea, abdominal pain, diarrhea, prostration, and lymphadenopathy; headache, nausea, and diarrhea; headache and abdominal pain; headache, myalgia, rash, abdominal pain, and prostration; headache, myalgia, and abdominal pain; headache, nausea, and abdominal pain.

Figure 2. Combinatorial analysis graph of spotted fever symptoms in the pediatric population in Brazil between 2007 and 2022

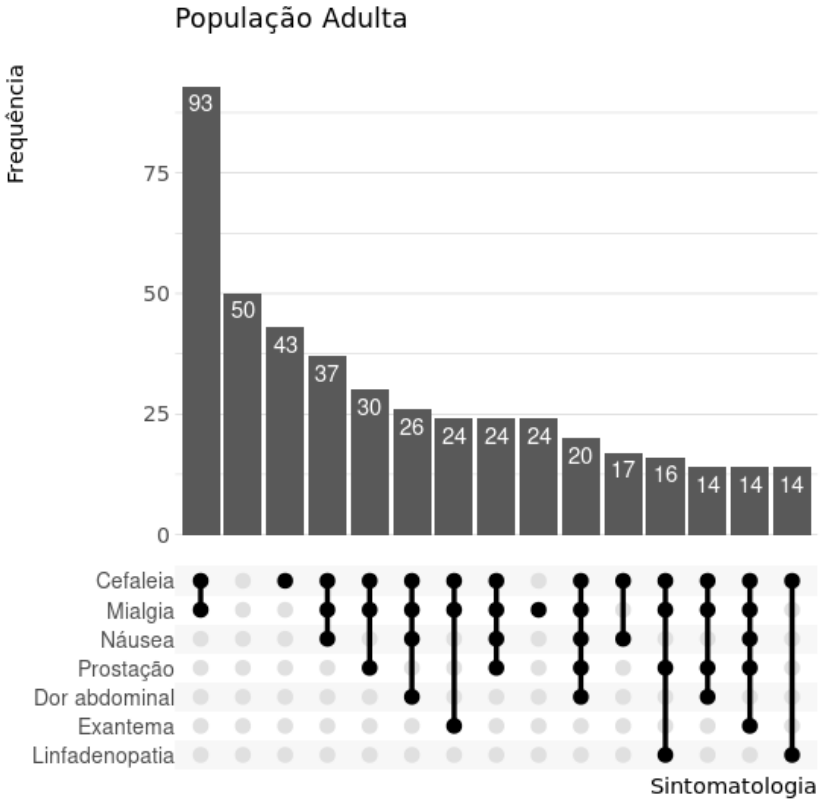


Source: Authors

Analyzing Figure 3, it was observed that in the adult population, individuals with the combination of headache and myalgia were the most prevalent, followed in descending order by asymptomatic individuals; only headache; headache, myalgia, and nausea; headache, myalgia, and prostration; headache, myalgia, and abdominal pain; headache, myalgia, nausea, and prostration; only myalgia; headache, myalgia, nausea,

prostration, and abdominal pain; headache and nausea; headache, myalgia, prostration, and lymphadenopathy; headache, myalgia, prostration, and abdominal pain; headache, myalgia, nausea, prostration, and rash; headache and lymphadenopathy.

Figure 3. Combinatorial analysis graph of spotted fever symptoms in the adult population in Brazil



between 2007 and 2022

Source: Authors

4. DISCUSSÃO

O presente estudo constatou no período analisado que a maioria dos diagnosticados foram pacientes masculinos, em todas as faixas etárias, o que corrobora com aspectos epidemiológicos, clínicos e ambientais publicados de um estudo descritivo realizado na região Sudeste, onde a maioria eram do sexo masculino, que tiveram contato com carrapato, cães, capivaras e equinos no meio urbano, com o critério de confirmação laboratorial. (Rodrigue *et al*., 2023). Os homens realizam atividades ocupacionais em áreas habitadas por capivaras, equinos e bovinos com mais frequência do que as mulheres e, assim, são naturalmente mais expostos à doença, conforme descrito na Lista de Doenças Relacionadas ao Trabalho (LDRT), um instrumento

utilizado para identificar e classificar doenças e danos à saúde ligados direta ou indiretamente ao ambiente de trabalho (Renast Online, 2023).

A análise combinatória mostra que as crianças foram em maioria assintomáticas, e o quadro clínico mais prevalente foi o exantema. Segundo o Guia de Vigilância de 2022, este sinal apesar de ausente em alguns casos, é o mais importante dentre as manifestações clínicas (Brasil, 2022). O terceiro quadro clínico mais comum na população pediátrica foi a associação de cefaléia e náusea, porém não encontramos na literatura dados similares aos nossos.

Foi possível observar maior chance de hepatomegalia nas crianças em relação aos adultos. O aumento anormal do fígado é um achado clínico comum nas crianças, podendo ocorrer por alterações intrínsecas ou sistêmicas (Rocha *et al*., 2009). Além disso, em condições normais, o fígado é proporcionalmente maior e tem tamanho relativo duas vezes maior nas crianças do que adultos.

Os dados aqui descritos também demonstraram que o local mais comum de contágio da doença, tanto em adultos e quanto em crianças, é no meio domiciliar. Contudo, não é possível distinguir os domicílios que ficam em áreas urbanas ou rurais entre os analisados. A exposição de risco referida por pacientes com febre maculosa foi observada que sua maioria teve contato com carrapatos e cães, assim como é descrito pelo Monitoramento da Febre Maculosa publicado pelo Ministério da Saúde (Brasil, 2022).

Nosso estudo também revelou que um quadro clínico com mais de 3 sintomas em associação é incomum na população pediátrica, o que torna o diagnóstico mais suscetível a erros uma vez que pode ser facilmente confundido com outras doenças exantemáticas endêmicas do Brasil, como por exemplo sarampo, dengue, zika, enteroviroses e rubéola, e, consequentemente, retardando o tratamento adequado e provocando complicações graves Álvarez-Hernández *et al*., 2017). Por isso, percebe-se a importância de uma boa investigação clínico-epidemiológica frente a sintomas inespecíficos (Fang *et al*., 2017)

O presente estudo nos mostrou que o principal método diagnóstico é o laboratorial, mesmo com o resultado da sorologia que detecta anticorpo IgG negativa. Este fato pode ocorrer pela dificuldade da coleta do exame, uma vez que são necessárias duas coletas pareadas de soro, uma no início da doença e outra amostra após o 14º dia (Ndip *et al*., 2004). O diagnóstico de febre maculosa pode ser prejudicado quando o paciente faz apenas uma coleta de sangue para a testagem de IgG, em vez de duas coletas pareadas. Isso ocorre porque a febre maculosa é uma infecção

bacteriana que pode levar algum tempo para que o sistema imunológico produza anticorpos IgG em níveis detectáveis. Com apenas uma coleta, pode não haver anticorpos suficientes presentes para serem detectados pelo teste. As coletas pareadas, feitas com algumas semanas de intervalo, permitem que se observe um aumento significativo nos níveis de IgG, o que é mais indicativo de uma resposta imune ativa à infecção. Portanto, a falta de uma segunda coleta pode resultar em um diagnóstico impreciso ou falso negativo para febre maculosa. A importância do teste pareado é ressaltado no estudo realizado na região sudeste onde a sorologia pareada (S1 e S2) ou a Reação de Imunofluorescência Indireta (RIFI) demonstrou sucesso na detecção de reações positivas para infecção recente (IgM) em 49% e 77%, e para infecções tardias (IgG) em 43% e 89% das amostras testadas, respectivamente (Rodrigues *et al*., 2023).

De acordo com o desfecho clínico, foi evidenciado que a maior parte dos adultos evoluiu com necessidade de hospitalização, assim como observado no Monitoramento da febre maculosa publicado pelo Ministério da Saúde no período de 2020 a 2023 (Brasil, 2022). Outro dado demonstrado no estudo foi a prevalência da letalidade em 36% na população geral, semelhante a um estudo transversal com dados do SINAN, no período de 2007 a 2020, e do Boletim Epidemiológico de febre maculosa do Ministério da Saúde publicado em 19 de junho de 2023. Devido a dificuldade em se fazer o diagnóstico precoce, é comum que ocorra evolução rápida, grave e alta letalidade (Faccini-Martínez *et al*., 2018), e, consequentemente, estabelecer a terapia apropriada torna-se um obstáculo. febre maculosa pode evoluir para uma forma grave e necessitar de internação quando não é diagnosticada precocemente e não é tratada adequadamente com antibióticos. A forma grave da doença, conhecida como febre maculosa grave ou febre maculosa complicada, pode levar a complicações graves, como insuficiência renal, insuficiência respiratória, comprometimento do sistema nervoso central e até mesmo à morte (Brasil, 2022).

5 CONCLUSÃO

Este estudo analisou as diferenças clínicas e epidemiológicas entre adultos e crianças com febre maculosa no Brasil. Os resultados indicam que o sexo masculino é mais afetado em ambas as faixas etárias, e o ambiente domiciliar é o principal local de contágio pelo carrapato. Nas crianças, os sintomas são geralmente inespecíficos, como exantema e náusea, enquanto os adultos apresentam sintomas mais característicos, como cefaleia e mialgia. O diagnóstico laboratorial é crucial, mas enfrenta limitações que

podem atrasar o tratamento específico. A taxa de mortalidade é significativa, mas a evolução para a cura é prevalente em ambos os grupos avaliados.

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CHAPTER 11

HEALTH RESEARCH IN SECURITY AGENTS IN THE STATE OF AMAPÁ

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ABSTRACT: Health survey carried out among public security agents in the State of Amapá (Civil Police; Military Police; Military Fire Department; Technical-Scientific Police and Criminal Police) through laboratory tests, sociodemographic characterization, lifestyle and level of stress at work. Its objective was to understand the health profile, sociodemographic characteristics and health background of security professionals in the State of Amapá. As a research method, an observational study design was carried out. The project consists of 3 phases, namely: anthropometric measurements, laboratory tests and application of the health profile questionnaire. The dice was made available for the publication of this article. The entire process was designed to understand the health profile of public security professionals in Amapá and measure vulnerability to stress at work. In the results obtained from the evaluated professionals, it is evident that more than 75% of the participants have an increased Body Mass Index (BMI), more than 97% of the participants consider themselves happy always or most of the time, but 447 employees indicated high levels or very high levels of stress, more than 75% of participants have a perception of having good or excellent health. It is concluded that in the research, in general, the numbers presented in the exams and questionnaires applied

are not alarming, but require a careful and preventive look, prioritizing treatments aimed at improving quality of life, health habits and the environment work of these professionals.

KEYWORDS: Pólice, Occupational health, Health research.

RESUMO: Pesquisa de saúde realizada nos agentes de segurança pública do Estado do Amapá (Polícia Civil; Polícia Militar; Corpo de Bombeiros Militar; Polícia Técnico-Científica e Policiais Penais) através de exames laboratoriais, caracterização sociodemográfica, estilo de vida e nível de estresse no trabalho. Seu objetivo foi conhecer o perfil de saúde, características sociodemográficas e antecedentes de saúde dos profissionais de segurança do Estado do Amapá. Enquanto método de pesquisa realizou-se delineamento de estudo observacional. O projeto é composto por 3 fases, sendo elas: medidas antropométricas, exames laboratoriais e aplicação do questionário de perfil saúde. Os dados foram disponibilizados para a publicação deste artigo. Todo o processo foi elaborado visando conhecer o perfil de saúde dos profissionais de segurança pública do Amapá e a mensuração da vulnerabilidade ao estresse no trabalho. Nos resultados obtidos dos profissionais avaliados, evidencia-se que mais de 75% dos participantes possuem Índice de Massa Corpórea (IMC) aumentado, mais de 97% dos participantes se consideram felizes sempre ou a maior parte do tempo, mas 447 servidores indicaram índices altos ou muito altos de estresse, mais de 75% dos participantes têm uma percepção de ter a saúde boa ou ótima. Conclui-se que na pesquisa, de uma maneira geral, os números apresentados nos exames e nos questionários aplicados não são alarmantes, mas necessitam de um olhar atencioso e preventivo, priorizando tratamentos direcionados à melhoria da qualidade de vida, hábitos de saúde e do ambiente laboral desses profissionais.

PALAVRAS-CHAVE: Policiais, Saúde ocupacional, Pesquisa em saúde.

1. INTRODUCTION

Public security in Brazil is a topic of great importance and relevance within the national context, alongside health and education. The 1988 Federal Constitution, in its Article 5, guarantees the right to security for all citizens. Furthermore, in Article 144, it addresses public security and explicitly defines the agencies responsible for its enforcement, outlining their respective competencies and purposes as follows:

> Art. 144. Public security, a duty of the State, a right and responsibility of all, is exercised to preserve public order and the safety of people and property, through the following bodies:
> I - Federal police;
> II - Federal highway police;
> III - Federal railway police;
> IV - Civil police;
> V - Military police and military fire brigade
> VI - Federal, state and district criminal police. (Brazil, Title 5, Chapter 6, 1988).

Being a public security professional requires numerous technical and behavioral competencies to execute various related tasks with safety, quality, and maximum assertiveness. This requirement is especially emphasized in high-risk activities for professionals, for individuals present at the scene, and for those directly involved and assisted (Brazil, 2012). Another important point to consider is the work in rotating shifts adopted by public security professionals. This type of work brings several negative consequences for the worker, such as sleep disorders, gastrointestinal disturbances, mood disturbances, excessive fatigue, and hypertension, affecting biopsychosocial, familial, and interpersonal aspects. Additionally, it has been identified that workers who operate during the night exhibit a higher prevalence of psychological distress, particularly depression, compared to those who work only during the day (Back, 2021).

Work is the central process that influences the life and death of human beings and, therefore, presents complexity both in terms of well-being and morbidity/mortality (Cavalcante et al., 2008). The work process can transform the relationship among the triad of work, health, and disease, as labor activities can either generate health or lead to illness, accidents, and premature death of the worker (Brazil, 2007).

Due to the nature of their professional activity, police officers are strong candidates for occupational stress, which can lead to the emergence of physical pathologies and dysfunctions such as obesity, heart diseases, gastroduodenal ulcers, cancer, and dermatological disorders, as well as mental disorders like depression, aggression, and

even suicide (Hartley et al., 2012; Lipp; Costa; Nunes, 2017; Bezerra; Minayo; Constantino, 2013).

In Brazil, according to data from the Brazilian Public Security Yearbook (2021), there were more suicides among civil and military police officers than deaths during active police operations in 2018, 2019, and 2020. The pandemic revealed that only COVID-19 surpassed suicide as a cause of death between 2020 and 2021. Public security workers continue to face nearly four times the risk of self-harm compared to non-police Brazilians (Sousa, 2022). Both national and international scientific literature points to a higher risk of stress, psychological distress, and suicide risk among public security professionals, particularly within the police category and also among health professionals (Miranda, 2016; Almeida; Chaves, 2020; Lima; Martins, 2021).

Studies conducted with public security professionals in the United States indicate that these workers are less likely to be disabled or have health issues despite their relatively high injury rates. The study found that police officers and firefighters are less prone to suffer from disability or adverse health conditions such as pain, severe mental illness, or disease compared to other non-public safety occupations (Latourrette; David; Seth, 2008).

Police officers, as individuals, citizens, and workers, have been studied very little from an academic perspective, particularly in the field of occupational health, where there is a lack of knowledge. This work provides an opportunity to delve into the world of Public Security, focusing on the living and health conditions of this category of workers.

The Diagnostic Survey in Public Security aims to gather information regarding the health, security, recognition, and quality of life of Public Security and Social Defense professionals across the country.

In this context, the justification for the present study lies in the scarcity identified in the literature on this topic. In searching for studies addressing this theme, particularly in the field of health among public security professionals, only a few publications were found. Furthermore, the information that stimulated the interest in studying these variables within the context of public security professionals stems mainly from this health professional being part of one of these organizations, the Military Police of Amapá.

2. METHODOLOGY

2.1 DESIGN, LOCATION AND PERIOD OF THE STUDY

Observational studies are those in which there is no intervention by the researcher. The researcher simply observes the patient, the characteristics of the disease or disorder, and its evolution, without interfering or modifying any aspect under observation (Brazil, 2007).

The aim of this work is to conduct an observational study using secondary data collected by the Diagnostic Survey carried out by the Secretary of Security of the State of Amapá from June to August 2022, which has been made available for the purpose of this scientific article (Gama; Siqueira; Silveira, 2023).

Located in the extreme north of Brazil, the State of Amapá covers an area of 142,828 km², with an estimated population of 877,613 inhabitants spread across 16 municipalities. It is the second least populous state in the country, with 74.2% of its population concentrated in just two cities: the capital, Macapá (59.49%), and Santana, which is 16 km from the capital (14.72%). Its demographic density is 4.69 inhabitants per km², and the human development index is 0.708 (Vasconcelos et al., 2020).

In Amapá, there are 7,568 security agents, comprising the Military Police (3,572), Military Fire Brigade (1,274), Civil Police (1,272), Penal Police (922), and Scientific Police (327) in 2022. For the Military Police alone, the forecast was for a staff of 7,000 military personnel.

The population for the survey is a sample of the total number of employees of the Secretary of Public Security of the State of Amapá, which consists of 7,568 professionals (Table 1). The survey was made available in an Excel spreadsheet containing the data from the sample of security agents and was analyzed using R statistical computing software. The population included active public security agents (Military Police, Military Fire Brigade, Civil Police, Penal Police, and Scientific Police) of both sexes.

Table 1. State security institutions of Amapá

Security agencies of the State of Amapá	**Total servers**	**Sampling performed**
MILITARY POLICE	3.532	525
MILITARY FIREMAN	1.274	219
CIVIL POLICE	1.272	174
CRIMINAL POLICE	922	167
SCIENTIFIC POLICE	327	45
SEJUSP	241	53

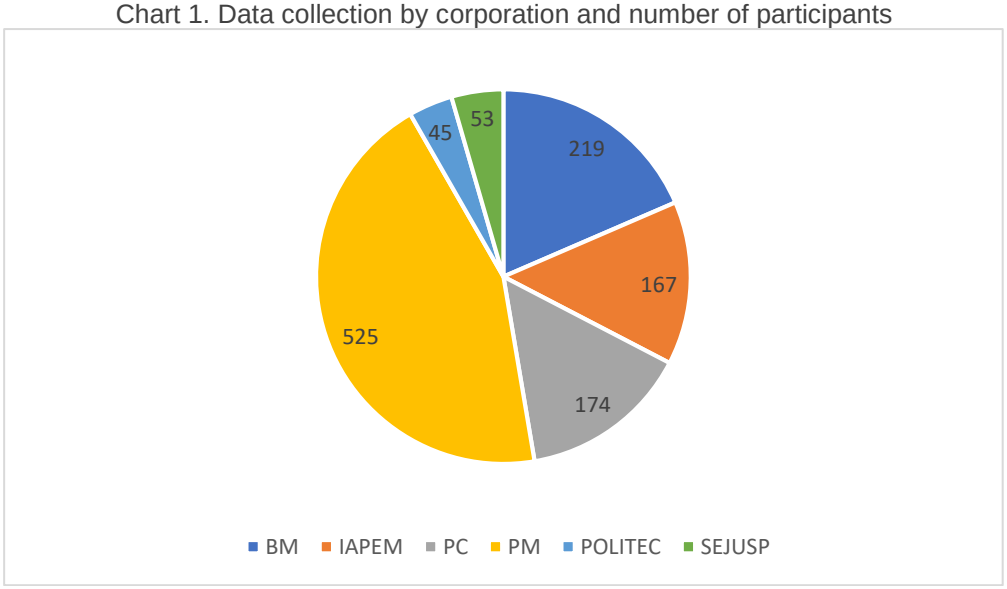
TOTAL	7.568	1183

Source: Own authorship, 2023

2.2 DATA COLLECTION

For participants in the diagnostic research, the first inclusion criterion was being active in the service (not on leave/vacation or not in the process of retirement (Graph 1). Data collection was carried out at the headquarters of the corporations targeted by the research.

Chart 1. Data collection by corporation and number of participants



Source: Own authorship, 2023

3. RESULTS

More than 75% of participants perceive their health as good or excellent, over 60% have visited a doctor for routine check-ups in the past year, and more than 50% underwent preventive examinations within the last year. Nearly 60% have seen a dentist within the last year. Just over 13% of the respondents use controlled medication, with the majority of this group being from the Military Police.

More than 97% of participants report feeling happy most of the time or always. Overall, these individuals claim not to bring work home or do so only occasionally, and they consider their relationships with superiors to be good or excellent. Over 72% of employees own their homes, nearly 80% earn more than four minimum wages, and over 80% hold at least a bachelor's degree. Additionally, 36% express full satisfaction with

their current lives, more than 67% feel they have achieved significant accomplishments, and over 60% believe they have good living conditions.

Regarding lifestyle habits, more than 60% consider their diet to be healthy, although nearly 75% consume sugar daily. Less than 1% of participants smoke, and over 92% either never eat fast food or do so only occasionally. More than 50% do not drink alcohol, and around 80% drink at least five glasses of water per day. However, when asked about their habits, over 75% of participants expressed a desire for support in implementing healthy habits.

More than 35% of participants report experiencing high or very high stress levels, while over 40% rate their stress as moderate. Approximately 15% perceive their stress levels as low, and only 10% state that they do not experience work-related stress (Graph 2).

Among the survey participants, 447 employees indicated high or very high stress levels. The breakdown is as follows: 82 employees from the Fire Brigade (38% of the responding population from this agency); 62 employees from IAPEN (37% of the responding population from this agency); 66 employees from the Civil Police (38% of the responding population from this agency); 208 employees from the Military Police (40% of the responding population from this agency); 13 employees from POLITEC (29% of the responding population from this agency); and 16 employees from SEJUSP (29% of the responding population from this agency).

4. DISCUSSION

Among the assessed professionals, over 75% of participants have an increased Body Mass Index (BMI). Studies indicate a significant percentage of police officers with altered BMI in other states as well (Vasconcelos et al., 2020; Magalhães, 2014).

Based on the information gathered in this study, it can be inferred that there is a notable percentage of police officers with altered BMI, which may increase the risk of cardiovascular problems among these professionals.

To address this issue, it is advisable to initiate a program that promotes physical activity and raises awareness about healthy eating, such as providing nutritional counseling and organizing sports activities.

While less than 35% of employees reported being absent due to work-related pain or accidents, more than 63% experienced pain for over six months. To minimize these two rates, corporate physical rehabilitation is recommended.

5. GENERAL CONSIDERATIONS

Valuing the worker entails ensuring comprehensive conditions for the execution of their functions, thereby promoting their physical and mental health, as well as guaranteeing access to rights. Health attention, both physical and mental, must be accompanied by national guidelines that safeguard rights to occupational health and the valuing of life, including the provision of appropriate personal protective equipment, as stipulated by the Interministerial Ordinance SEDH/MJ No. 02/2010. The capacity of the worker to perform their functions is dynamic, depending on their state of health and overall physical, mental, and social well-being, as defined by the World Health Organization.

Although the numbers presented in the examinations and questionnaires are not alarming, it is essential to adopt a vigilant and preventive approach, prioritizing treatments that enhance the quality of life for workers, in addition to promoting healthy habits and routines. Nearly 80% of the studied population reported experiencing bodily pain either consistently or occasionally during work, indicating the necessity for the implementation of workplace exercise programs, which consist of engaging in low-impact activities and exercises during work hours.

Furthermore, the finding that more than 75% of the evaluated professionals present an elevated Body Mass Index (BMI) suggests an urgent need to initiate programs that encourage physical activity and raise awareness about healthy eating, including nutritional counseling and sports activities, to promote a healthier lifestyle and prevent diseases.

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CHAPTER 12

CASE REPORT: NEUROENDOCRINE TUMOR IN THE TERMINAL ILEUM

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ABSTRACT: The present study is a case report of a well-differentiated low-grade neuroendocrine tumor in the region of the terminal ileum in a female patient in the fourth decade of life, starting symptoms with abdominal pain, subsequently undergoing right colectomy and mesenteric lymphadenectomy. as treatment. The objective is to expose the case of this rare pathology to understand the diagnosis and management carried out and to enable new studies for diagnoses and therapies for similar cases. To this end, a search for scientific works to discuss the reported topic is carried out. Thus, it was observed that there is an increase in new registered cases, which can be justified by the improvement in diagnostic methods.

KEYWORDS: Neuroendocrine tumor, Carcinoid of the terminal ileum, Neuroendocrine neoplasm of the small intestine.

RESUMO: O presente estudo trata-se de um relato de caso de tumor neuroendócrino bem diferenciado de baixo grau na região do íleo terminal em paciente, do sexo feminino na quarta década de vida, iniciando sintomas com dores abdominais, posteriormente submetida a colectomia direita e linfadenectomia mesentérica como tratamento. Objetiva-se expor o caso dessa patologia rara para conhecimento do diagnóstico e conduta realizadas e possibilitar novos estudos para diagnósticos e terapêuticas para casos semelhantes. Para tanto, procede-se à busca de trabalhos científicos para discorrer sobre o tema relatado. Desse modo, observou-se que há um aumento de casos novos registrados, que pode ser justificado pela melhoria dos métodos diagnósticos.

PALAVRAS-CHAVE: Tumor neuroendócrino, Carcinoide de íleo terminal, Neoplasia neuroendócrino de intestino delgado.

1. INTRODUCTION

Neuroendocrine tumors (NETs), also referred to as carcinoids, were first described by the German pathologist Siegfried Oberndorfer in 1907 to characterize ileal tumors with benign behavior. NETs develop from epithelial cells that undergo neuroendocrine differentiation, which are present in various regions of the human body, primarily lining the respiratory and gastrointestinal tracts, allowing for their emergence in any location where these cells are distributed. They account for 0.49% of malignant neoplasms (Viana et al., 2019).

While considered rare, there has been an increase in diagnosed cases over the past few decades, approximately 6% per year, attributed to advancements in imaging diagnostic methods and greater awareness of the pathology (Ahmed, 2020). The incidence of NETs in the United States ranges from 3.65 to 3.89 cases per 100,000 inhabitants (Valadares et al., 2016).

Diagnostic methods, such as neuroendocrine tumor markers, complement imaging techniques. The serum measurement of chromogranin A (CgA) is of significant relevance, along with the 24-hour urinary measurement of 5-hydroxyindoleacetic acid (5-HIAA). Immunohistochemically, NETs are characterized by the presence of ultra-structurally dense central granules and the expression of specific proteins, which may include chromogranin, synaptophysin, specific hormone-producing cells, and neuron-specific enolase (Galetti et al., 2021).

Imaging methods employed for diagnostic purposes include computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). These modalities are indicated for localizing, monitoring, and guiding biopsies for histopathological analysis. Typically, in contrast-enhanced diagnostic methods, NETs manifest as intense uptake during the arterial phase. Higher-resolution techniques such as scintigraphy with 111In-DTPA-octreotide (OctreScan) and positron emission tomography with somatostatin analogs (PET-CT 68Ga) are particularly relevant for identifying patients eligible for somatostatin analog therapy and predicting therapeutic response (Hoff et al., 2015).

Regarding the classification of neuroendocrine tumors, the World Health Organization (WHO) has established a system based on mitotic pattern and Ki-67 expression, categorizing NETs into two groups: well-differentiated and poorly differentiated. Well-differentiated NETs are characterized by uniform nuclei, solid, trabecular patterns, and glandular architecture. This group is further subdivided based

on proliferation rate into low-grade (G1) and intermediate-grade (G2) tumors. The other group consists of poorly differentiated tumors, which exhibit high-grade proliferation (G3) and are potentially aggressive (Belotto et al., 2019).

2. METHODOLOGY

This case report was authorized by the patient, with the necessary informed consent duly signed. A bibliographic survey was conducted online from 2013 to 2024 in the medical literature, utilizing the descriptors "neuroendocrine tumor," "terminal ileum carcinoid," and "neuroendocrine neoplasia of the small intestine." The search included original articles, literature reviews, and other case reports addressing concepts, diagnostic methods, and treatment of neuroendocrine tumors in the terminal ileum region. A total of 36 articles were analyzed, of which nine were utilized in the construction of this case report.

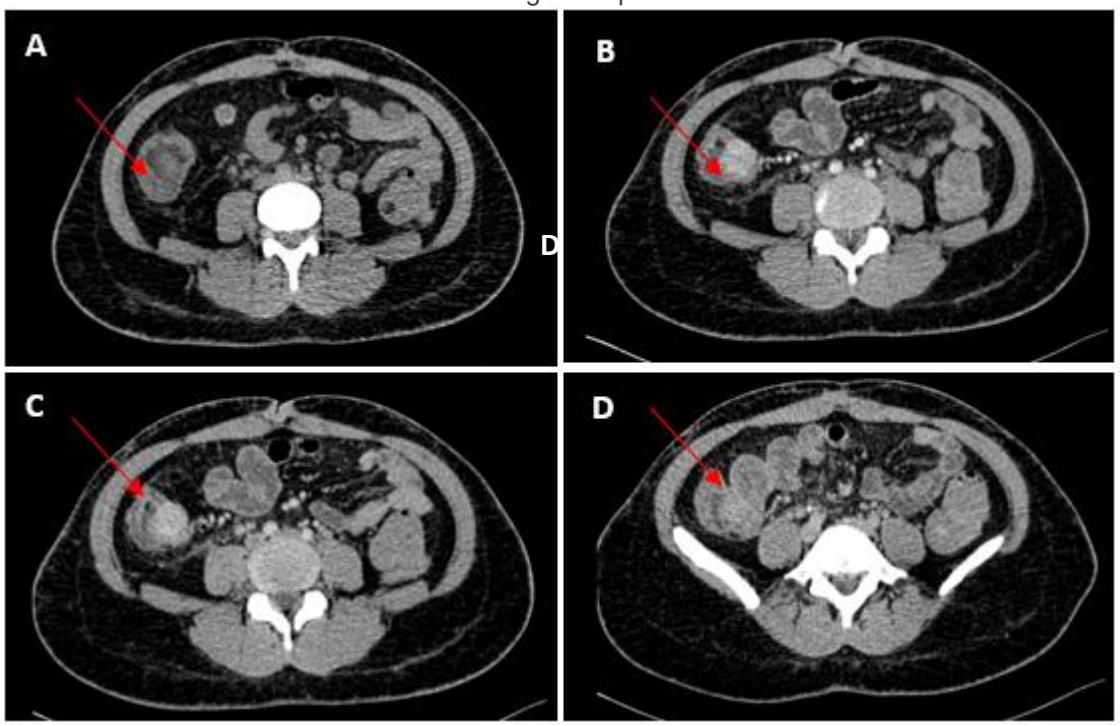
3. CASE PRESENTATION

Patient L.M.M., a 47-year-old female student with a history of hypertension, began experiencing symptoms of diffuse abdominal pain. She was admitted to São Marcos Hospital in Teresina-PI, presenting with severe abdominal pain, nausea, and vomiting associated with food intake. The patient reported constipation over the past few months, necessitating medication assistance for bowel movements, specifically PEG 4000. She denied any drug allergies and was on continuous use of Indapen.

Upon physical examination, the patient appeared to be in good general condition, alert, oriented to time and space, non-jaundiced, afebrile, acyanotic, eupneic, and hemodynamically stable. Bowel sounds were present, and a positive rebound tenderness was noted. The abdomen was soft, with superficial palpation tenderness, no edema, and symmetrical pulsation without signs of deep vein thrombosis.

Initially, complementary examinations were requested, including laboratory tests and imaging studies. A computed tomography (CT) scan of the abdomen with contrast revealed a nodular lesion in the area of the ileocecal valve, exhibiting intense contrast uptake in the arterial phase. In this region, stenosis and signs of sub-occlusion were observed in the distal ileum (Figure 1), along with upstream ectasia. A colonoscopy was also performed, which showed stenosis in the distal ileum and extrinsic bulging at the level of the ileocecal valve.

Figure 1. Abdominal tomography, axial sections demonstrating the lesion in the ileocecal transition (red arrow). A: Nodular lesion in the non-contrast phase. B: Lesion in the arterial phase showing significant enhancement. C: Lesion in the portal phase, which persists with intravenous contrast. D: Late phase showing little uptake



Source: Prepared by the authors themselves

Preoperative examinations, electrocardiogram and preoperative evaluation were performed. Subsequently, partial colectomy surgery without colostomy by videolaparoscopy was indicated.

Figure 2. Surgical specimen of right ileocolectomy with mesenteric lymphadenectomy. Nodule in ileocecal transition (white arrow).

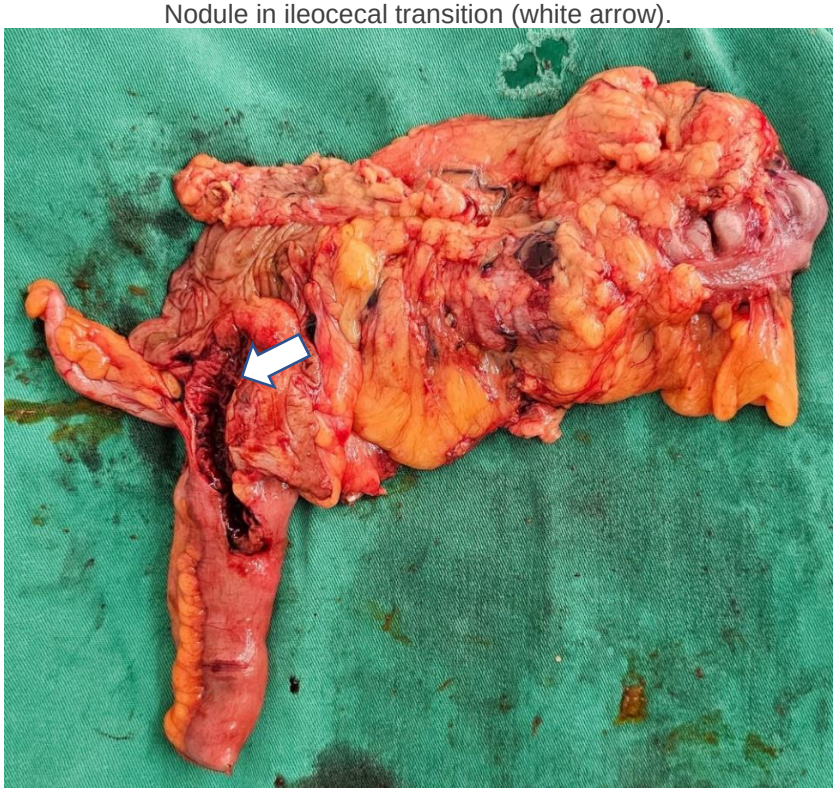


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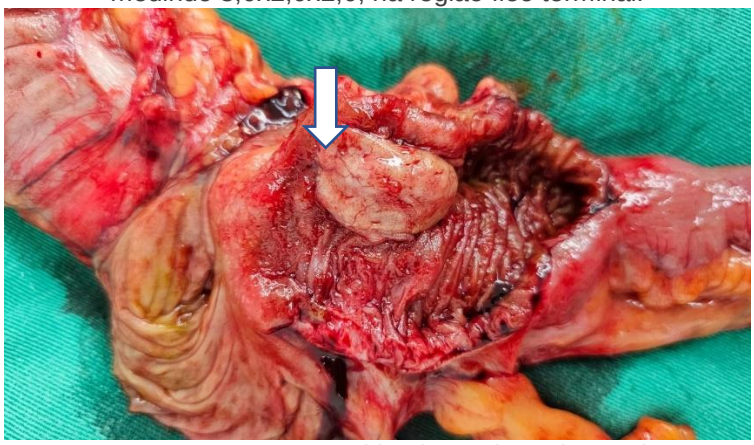
Figura 3. Peça cirúrgica demonstrando tumor neuroendócrino (seta branca) medindo 3,0x2,0x2,0, na região íleo terminal.



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The patient underwent a surgical procedure consisting of right ileocolectomy and mesenteric lymphadenectomy (Figure 2). The extracted biological material was sent for histopathological analysis. Macroscopic examination revealed the presence of a nodular, well-defined, granular, and slightly crusted tumor lesion measuring 3.0 x 2.0 cm in the terminal ileum, affecting the terminal ileum/ileocecal valve (Figure 3). On cross-section, the lesion appeared compact, granular, and yellowish, with a thickness of 2.0 cm, infiltrating macroscopically up to the subserosa. The other regions, including the cecal

appendix, cecum, sigmoid colon, and proximal and distal surgical margins, were free of neoplasia.

Histological diagnosis confirmed the presence of a well-differentiated neuroendocrine tumor (NET) of grade 1. Among the 16 lymph nodes extracted during the mesenteric lymphadenectomy, 2 were found to be compromised. The pathological staging was determined as T3N1M0. The pathologist recommended performing immunohistochemical studies on the material to subclassify the neoplasia.

In the postoperative period, the patient progressed well, without complaints and with normal physiological bowel movements, although she continued to use PEG 4000. Follow-up after the surgery included monitoring by an oncologist, with requested examinations showing no significant alterations related to the procedure performed.

4. RESULTS AND DISCUSSIONS

Approximately 55% of neuroendocrine tumors (NETs) arise in the gastrointestinal tract, with the majority located in the small intestine (Ahmed, 2020), followed by the rectum and stomach. In the ileal region, these neoplasms occur with equal incidence in men and women, primarily affecting patients in their sixth and seventh decades of life, with a frequency ranging from 1 to 2 cases per 100,000 inhabitants. The etiology remains unknown, but a genetic association is suspected (Kamei et al., 2020). The reported case deviates from the literature concerning the patient's age, as she is younger than the most commonly affected demographic.

In terms of dimensions, the reported case aligns with global literature. Most neuroendocrine tumors in the ileal segment exceed 2.0 cm in size and may be either multiple or solitary. These tumors can invade the muscularis propria and metastasize to regional lymph nodes, with hepatic metastases present in 50% of cases depending on tumor size (Ahmed, 2020).

Predominantly, carcinoids are well-differentiated and exhibit an indolent growth pattern. Consequently, patients are initially asymptomatic and may not present significant signs or symptoms, leading to later diagnoses. As a result, patients in more advanced stages will exhibit symptoms such as abdominal pain, nausea, and partial or complete obstruction of the intestinal lumen. This may lead to more frequent metastasis, with the liver being the most commonly affected site (Kamei et al., 2020; Viana et al., 2019). In the current case, preoperative examinations did not reveal any distant metastatic lesions.

For diagnostic purposes, neuroendocrine markers such as serum chromogranin A and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) can aid in the process. The 5-HIAA is an excellent marker for diagnosing cases of carcinoid syndrome, usually in patients with hepatic metastasis. This syndrome is clinically characterized by facial flushing, diarrhea, and, in some cases, wheezing and dermatitis (Waisberg, 2013).

A notable feature of NETs in this region of the small intestine is the desmoplastic reaction leading to mesenteric fibrosis in approximately 50% of cases. This fibrosis may result in mesenteric ischemia in 10% of these patients. A radiological finding of mesenteric fibrosis is the "wheel spoke" pattern, which is associated with a poor prognosis (Ahmed, 2020).

For well-differentiated neuroendocrine neoplasms in the terminal ileum, surgical resection and regional lymphadenectomy are recommended, increasing patient survival by five years. Even in cases with metastasis, surgical intervention is indicated, improving five-year survival rates by 18%.

The surgical procedure is determined based on the tumor's location; if situated in the mid-ileum, segmental resection is preferred. If located in the distal ileum near the ileocecal valve, right hemicolectomy is recommended. Lymphadenectomy is always performed concurrently to prevent symptoms due to compromised blood supply to the intestine, which may result in ischemia (Selberherr, 2017).

Chemotherapy is not indicated for well-differentiated neoplasia, but it is recommended in cases of poorly differentiated NETs. In patients with hepatic metastasis, treatment may be combined with radiotherapy, radiofrequency ablation, transarterial chemoembolization (TACE), transarterial embolization with microparticles, and octreotide (Ahmed, 2020).

5. CONCLUSION

This case report addresses neuroendocrine tumors in the terminal ileum. The association of adequate clinical examination together with appropriate imaging techniques can guide treatments and conduct, thus favoring a good outcome for the patient, giving them a better prognosis, increasing survival.

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CHAPTER 13

CHEST TOMOGRAPHY IN COVID-19 PNEUMONIA: PREVALENCE OF IMAGING FINDINGS AND PREDICTIVE FACTORS OF DEATH

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ABSTRACT: Objective: To evaluate the prevalence of imaging findings on chest CT scans in patients hospitalized for COVID-19 pneumonia and identify changes associated with the fatal stage. Methods: 295 adults hospitalized for COVID-19 were analyzed from March 1 to May 31, 2021. The clinical-demographic characteristics and comorbidities of the participants were evaluated, in addition to images from chest CT scans during hospitalization and compared whether the findings found between the groups of survivors and non-survivors. Results: 371 CT scans were confirmed, 14.8% of which were normal. Lung lesions typical of COVID-19 were also observed, with a predominance of peripheral and bilateral ground-glass opacities, regardless of the outcome. Alveolar consolidations, mixed lesions (alveolar and “ground glass”), thickening of interlobular septa, “mosaic paving” and attraction bronchiectasis were associated with the outcome of death, as well as extensive lesions with a higher percentage of pulmonary involvement, highlighting there is a probability of fatal outcome 7 times greater in the presence of pulmonary involvement greater than 75% ($p<0.01$, PR = 7.53 95% CI 3.22-11.44). Conclusion: Some tomographic changes and the extent of Pulmonary involvement increases the likelihood of progression to a fatal stage during hospitalization due to COVID-19.

KEYWORDS: COVID-19, Tomography, Death.

RESUMO: Objetivo: Avaliar a prevalência dos achados de imagem em tomografias torácicas em pacientes internados por pneumonia por COVID-19 e identificar alterações associadas a desfecho fatal. Métodos: Foram analisados 295 adultos internados por COVID-19 no período de 01 de março a 31 de Maio de 2021. Foram avaliadas as características clínico-demográficas e comorbidades dos participantes, além das imagens das tomografias torácicas durante a internação e comparou-se os achados encontrados entre os grupos de sobreviventes e não sobreviventes. Resultados: Foram analisadas 371 tomografias, sendo 14,8 % normais. As demais apresentaram as lesões pulmonares típicas de COVID-19, com predomínio de opacidades em vidro fosco periféricas e bilaterais, independente do desfecho. Consolidações alveolares, lesões mistas (alveolares e em “vidro fosco”), espessamento de septos interlobulares, “pavimentação em mosaico” e bronquiectasias de tração tiveram associação com desfecho de óbito, assim como lesões extensas e com maior porcentagem de acometimento pulmonar, destacando-se uma probabilidade de desfecho fatal 7 vezes maior na presença de acometimento pulmonar superior a 75% (p<0,01, RP = 7,53 IC95% 3,22-11,44).Conclusão: Algumas alterações tomográficas e a extensão do acometimento pulmonar aumentam a probabilidade de evolução para desfecho fatal durante a internação hospitalar por COVID-19.

PALAVRAS-CHAVE: COVID-19, Tomografia, Óbito.

1. INTRODUCTION

The COVID-19 pandemic represented a challenging moment for humanity and had a dramatic impact on global health and the health systems of countries due to its rapid interpersonal transmission and the potential severity of the disease (Ai T, 2020; Albarello, 2020). However, the variable and unpredictable progression of patients with COVID-19 complicates the establishment of a system to stratify them into different risk groups (Bae, 2021; Bernhein, 2020; Bandhari, 2020). Chest tomography serves as an important tool in this context, encompassing initial diagnosis, evolutionary assessment, and major complications (Bae, 2021; Henkel, 2020; Leonardi, 2020). Furthermore, COVID-19 can lead to persistent symptoms and complications following infection, underscoring the importance of this topic, including its current relevance (Villacis, 2023; Gomes, 2024). National and international studies providing data on the prevalence of key imaging findings and their correlation with clinical signs of worsening and fatality are still scarce, given that this is a recent pathology.

The objective of this study was to evaluate the prevalence of tomographic characteristics of COVID-19 pneumonia, comparing them between survivor and non-survivor patient groups, in order to identify tomographic findings predictive of mortality.

2. MATERIALS AND METHODS

An analytical observational cross-sectional study was conducted, including all patients over 18 years of age, of both sexes, with a confirmed diagnosis of COVID-19 through RT-PCR methods and/or antigen testing via nasal/oropharyngeal swab. These patients were admitted for hospitalization between March 1, 2021, and March 31, 2021, and underwent at least one chest tomography examination.

Information related to the clinical-demographic profile was collected through the following variables: age, sex, comorbidities, symptoms (fever, cough, fatigue, dyspnea, diarrhea, ageusia, and anosmia), and the number of days since the onset of symptoms.

Subsequently, analysis and collection of tomographic data were conducted. The files for each tomographic examination performed during hospitalization were thoroughly reviewed by two radiologists with over 10 years of experience. The terminology from the Fleischner Society glossary was employed for the description and detection of changes (Li K, 2020).

The examinations were performed using a 128-slice computed tomography scanner (Siemens, Germany), with the patient in the supine position during maximum inspiration. The acquired volume covered the lungs from apex to base. Acquisition parameters were set at 120 kV, 100 mAs, pitch 1.5, and collimation of 0.6 mm. All images were reconstructed with a slice thickness of 1.00 mm, 512 x 512. Image review was conducted through analysis in lung and soft tissue windows, in addition to multiplanar reconstructions (MPR) and maximum intensity projection (MIP).

3. RESULTS

A total of 383 patients were admitted with a confirmed diagnosis of COVID-19 between March 1, 2021, and May 31, 2021. Among these, 295 patients (77.0%) underwent at least one computed tomography examination of the chest during hospitalization, thus being included in the study. All evaluated tomographies met the criteria for technical quality, and no exclusions were made.

The age of the patients ranged from 19 to 98 years. The median age found was 55 years in the survivor group and 70 years in the deceased group, representing a significant difference ($p < 0.01$) between the two groups.

As of May 31, 2021, 5.4% (16 patients) had died, while 94.6% (279 patients) survived. There was no significant difference between male and female sexes (51.9% vs. 48.1%; $p = 0.87$).

Of the total patients, 175 (59.3%) had one or more comorbidities, with systemic arterial hypertension (43.7%) and diabetes mellitus (19.7%) being the most prevalent. The comparative analysis of the outcomes showed a significant difference, with a predominance of diabetes mellitus (56.3% vs. 17.6%; RP = 3.1; $p < 0.01$) and cardiovascular disease (31.3% vs. 10.0%; RP = 3.1; $p < 0.01$) among non-survivors. This indicates that the likelihood of an individual with diabetes mellitus or cardiovascular disease progressing to a fatal outcome is three times greater compared to an individual without these comorbidities. Table 1 contains the association between the demographic characteristics and comorbidities of the participants and the outcome.

Table 1. Demographic characteristics and comorbidities of patients hospitalized with COVID-19, according to the outcome at Hospital São Marcos in the period from March 1, 2021 to May 31, 2021. Teresina-PI

	Total (n=295)	**No – survivors (n=16)**	**Survivors (n= 279)**	**Value of *p***	**Prevalence Ratio**
Features					
Sex					
Female	142(48,1%)	8 (50%)	134(48%)	0,87	...
Male	153(51,9%)	8(50%)	5(52%)	..	...
Diabetes	58(19,7%)	9(56,3%)	49(17,6%)	<0,01	3,10
Hypertension	129(43,7%)	8(50%)	121(43,4%)	0,60	...
Cardiovascular Disease	33(11,2%)	5 (31,3%)	28(10%)	<0,01	3,10
Obesity	38(12,9%)	2(12,5%)	36(12,9%)	0,96	...
Lung Disease	11(3,7%)	0(0,0%)	11(3,9%)	0,41	...
Any comorbidity	175 (59,3%)	13(81,3%)	162(58,1%)	0,66	...

Source: own elaboration

3.1 CLINICAL CHARACTERISTICS

The most commonly reported symptoms were dyspnea (56.3%), fever (50.8%), fatigue (47.8%), and cough (47.1%). Dyspnea was more prevalent in the non-survivor group compared to the survivors (15 patients, 93.8% vs. 151 patients, 54.1%, respectively, RP = 1.7, p < 0.01), whereas fatigue predominated in the survivor group in relation to the deceased group (138 patients, 49.5% vs. 3 patients, 18.8%, RP: 0.37).

3.2 TOMOGRAPHIC CHARACTERISTICS

A total of 371 chest CT scans were analyzed, with 14 (3.7%) performed with contrast and 357 (96.2%) without contrast. Of the total CT scans, 350 (94.3%) were conducted on survivors, while the group of patients who died underwent 21 (5.6%) scans. Only 55 (14.8%) of the scans showed no alterations, while 316 (85.2%) exhibited some type of the researched alterations. Among the normal scans, it was found that 33 (60%) occurred in patients with fewer than 7 days of symptoms, encompassing the early and progressive stages of the disease.

The most common tomographic alterations found were ground-glass opacities (83.2%), alveolar opacities (33.3%), and the association of alveolar and ground-glass opacities (32.8%). Some tomographic changes were more prevalent in the group that died, including the presence of alveolar opacities (17 scans, 81.3% vs. 108 scans, 31.7%;

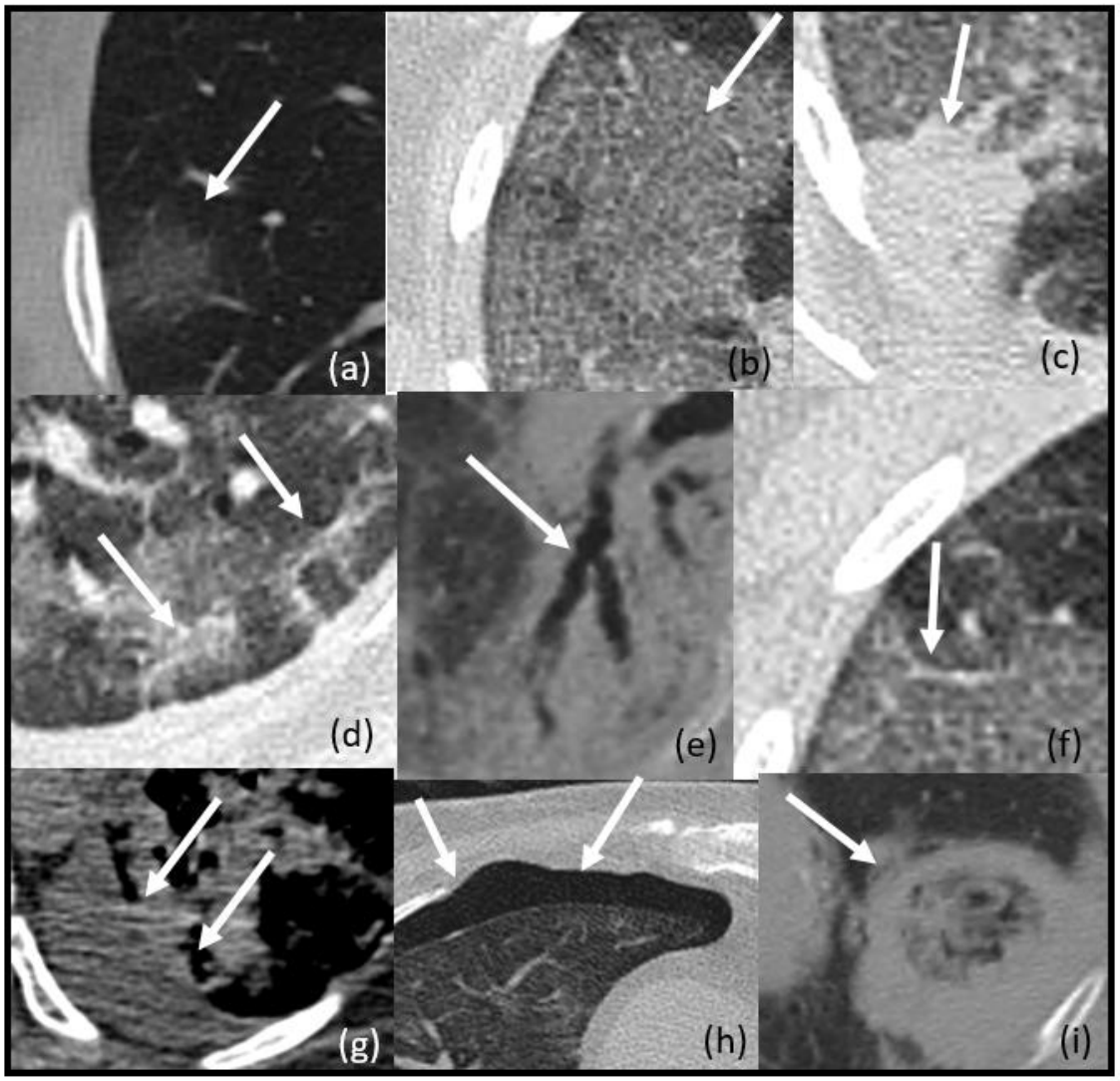
RP = 1.89; 95% CI: 1.28 - 2.80; p <0.01), the association of ground-glass and alveolar opacities (17 scans, 81.3% vs. 105 scans, 30.2%; RP = 1.02; 95% CI: 1.02 - 2.1; p <0.01), interlobular septal thickening (11 scans, 56.3% vs. 63 scans, 19.8%; RP = 2.41; 95% CI: 1.48 – 3.89; p <0.01), mosaic paving (11 scans, 56.3% vs. 63 scans, 18.3%; RP = 2.35; 95% CI: 1.32 – 3.82; p <0.01), traction bronchiectasis (11 scans, 56.3% vs. 66 scans, 19.1%; RP = 2.16; 95% CI: 1.27 - 3.67; p <0.01), and pneumothorax (9 scans, 42.8% vs. 2 scans, 0.05%; RP = 52.8; 95% CI: 11.9 – 233.0; p <0.01), as shown in Table 2 and illustrated in Figure 1.

Table 2. Prevalence of tomographic alterations in patients hospitalized with COVID-19, according to the outcome at Hospital São Marcos in the period from March 1, 2021 to May 31, 2021. Teresina-PI

	Sobreviventes (350)	**Não sobreviventes (21)**	**Total (371)**	**Valor de *p***	**Razão de Prevalência (IC95%)**
Changes found					
Ground-glass opacities	290(82,8%)	19 (93,8%)	309(83,2%)	0,26	-
Alveolar opacities	108(31,7%)	17(81,3%)	125 (33,3%)	<0,01	1,89 (1,28-2,80)
Association of ground-glass and alveolar opacities	105(30,2%)	17(81,3%)	122(32,8%)	<0,01	1,02 (1,02-2,1)
Interlobular septal thickening	66(19,8%)	13(62,5%)	79(21,2%)	<0,01	2,41 (1,48 – 3,89)
Crazy paving	63(18,3%)	11(56,3%)	74 (19,9%)	<0,01	2,35(1,32 – 3,82)
Traction bronchiectasis	66(19,1%)	11(56,3%)	77 (20,7%)	<0,01	2,166 (1,27 – 3,67)
Vascular ectasia	52(15,1%)	0(0,0%)	52(14%)	0,09	-
Inverted halo	2(0,5%)	0(0,0%)	2(0,5%)	0,73	-
Curvilinear lines	87(25,9%)	3(18%)	90(24,2%)	0,52	-
Pneumothorax	2(0,5%)	9(42,8%)	11(2,9%)	<0,01	52,8 (11,9 – 233)
Pleural effusion	10(3,2%)	0(0,0%)	10(2,6%)	0,46	-
Lymph node enlargement	1(0,4%)	0(0,0%)	1 (0,2%)	0,81	-

Source: own elaboration

Figure 1. Tomographic appearance in axial sections and lung window of the lesions (white arrows), which were found in patients hospitalized with COVID-19. a) Ground-glass opacity. b) “Crazy paving”. c) Alveolar consolidation. d) Subpleural curvilinear lines. e) Bronchiectasis. f) Vascular ectasia. g) Pleural effusion. h) Pneumothorax. f) Inverted halo.



Source: authors' personal archive, 2023

The evaluated CT scans were classified based on the visual analysis of lesion distribution into categories: less than 25%, between 25-50%, between 50-75%, and greater than 75%. The scans with a distribution between 25-50% were the most prevalent (30.9%). There was a higher prevalence of scans with greater than 75% distribution in the group of patients who died (11 scans, 52% vs. 21 scans, 6.9%; RP = 7.53; 95% CI: 3.2 - 11.4; p <0.01), as well as a greater prevalence of scans with less lesion extent (less than 25%) in the surviving group (105 scans from survivors, 30.3% vs. 0 scans, 0.0% from the deceased group; p <0.01).

Ground-glass opacities were the most commonly found alterations across all stages. In the initial phase of clinical manifestations (less than 3 days of symptoms), ground-glass opacities were the most prevalent alterations (7.1%). Alveolar opacities

were more frequent between 3-7 days of symptoms (16.6%) and between 8-14 days of symptoms (18.3%), being rarely found with less than 3 days of symptoms (2%). Traction bronchiectasis amidst alveolar opacities, as well as areas of mosaic paving, had low prevalence in the initial phase of less than 3 days (0.0% and 0.6%, respectively), predominating after 4 days of symptoms (12.2% and 8.4%, respectively) and after 7 days (12.8% and 13.2%, respectively). Table 3 demonstrates the association between tomographic findings and the number of days of symptoms of the disease.

Table 3. Association between tomographic changes and stages of days of symptoms of patients hospitalized with COVID-19 at Hospital São Marcos from March 1, 2021 to May 31, 2021. Teresina-PI

	Inicial (<3d)	**Progressivo (4-7d)**	**Pico (8-13d)**	**Tardio (>14d)**	***Valor de p***
Alterações encontradas					
Opacidades em "vidro fosco"	21(7,1%)	121(41%)	123(41%)	44(14,9%)	<0,01
Opacidades Alveolares	6(2,0%)	49(16,6%)	54(18,3%)	27(9,01%)	<0,01
Associação de opacidades em vidro fosco e alveolares	6(2%)	44(14,9%)	54(18,3%)	26(8,8%)	<0,01
Espessamento de septos interlobulares	2(0,6%)	35(11,8%)	45(15,2%)	21(7,1%)	<0,01
Pavimentação em mosaico	2(0,6%)	25(8,4%)	39(13,2%)	19(6,4%)	<0,01
Bronquiectasias	0(0,0%)	36(12,2%)	38(12,8%)	22(7,4%)	<0,01
Ectasia vascuar	2(0,6%)	12(4,0%)	31(10,5%)	12(4,0%)	<0,01
Sinal do halo	0(0,0%)	4(1,%)	0(0,0%)	0(0,0%)	0,51
Linhas curvilíneas	3(1,0%)	40(13,5%)	43(14,5%)	17(5,7%)	0,14
Cavidade	0(0,0%)	0(0,0%)	0(0,0%)	1(0,3%)	0,69
Pneumotórax	0(0,0%)	6(2,0%)	1,0(0,3%)	8(2,7%)	0,01
Derrame pleural	0(0,0%)	2(0,6%)	3(1,0%)	7(2,3%)	0,02
Linfonodomegalias	0(0,0%)	0(0,0%)	1(0,3%)	0(0,0%)	0,69

Source: own elaboration

4. DISCUSSION

Of the total CT scans analyzed, only 14.8% showed normal tomographic findings, which is consistent with literature data, as described by Yang (2020), who reported 11.4% of normal scans in a multicenter study involving 149 hospitalized patients in China. In this analysis, 60% of the normal scans occurred in patients with less than 7 days of symptoms. At this stage (less than 7 days), the symptoms of the disease are due to the

direct action of the virus and the innate immune response, and the tomographic changes are subtle and limited (Lomoro, 2020).

Ground-glass opacities, alveolar consolidations, and the association between alveolar consolidations and ground-glass opacities were the most commonly observed tomographic alterations, aligning with data from the literature (Long, 2020; Magno, 2021). Changes such as pneumothorax, pleural effusion, and lymphadenopathy had low prevalence, as noted in previous studies, and show a weak association with COVID-19 (Parasher, 2021; Vernuccio, 2020).

The presence of alveolar opacities and mixed lesions (association of alveolar opacities and ground-glass opacities), interlobular septal thickening, and mosaic paving were more prevalent in the non-survivor group. Li et al. (2020), in a study that included 128 patients assessing the association between tomographic changes and fatal outcomes, found a predominance of mosaic paving (45.5% vs. 9.5%) and alveolar consolidations (81.8% vs. 42.8%) in the deceased patient group (Zhang, 2020).

Traction bronchiectasis amidst ground-glass opacities was a prevalent finding in our series and predominated in the non-survivor group, as described in global literature (Vernuccio, 2020; Zhang, 2020). A previous study evaluating the correlation between tomographic findings and histopathological results in deceased patients found a significant association of traction bronchiectasis in those with longer durations of symptoms. The mechanism behind this finding remains unclear, but it may be related to a process of bronchopneumonia developed during the consolidative/peak phase of the disease or due to secondary infections, possibly serving as a predictive factor for mortality (Zhang, 2020).

In this study, there was a significant difference between the groups regarding the extent of lesions, with a higher prevalence of extensive lesions (visual analysis greater than 75%) in patients who died, as demonstrated in other studies (Long, 2020; Zhang, 2020). The likelihood of a fatal outcome was 7 times higher in the presence of pulmonary involvement greater than 75% (RP = 7.53; 95% CI: 3.22 - 11.4; p <0.01). This tomographic finding can be considered a predictor of mortality, as generalized involvement of the alveolar space and pulmonary interstitium leads to a reduction in gas exchange surface area, resulting in lower pulse oximetry values and the need for mechanical ventilation, thereby increasing the chances of severe outcomes, including death (Long, 2020).

4.1 LIMITATIONS

This study is a retrospective analysis reliant on information contained in electronic medical records, which may be subject to inconsistent or missing data.

Additionally, late tomographic changes after hospitalization in survivors were not analyzed; thus, future studies examining long-term tomographic sequelae could contribute to a better understanding of the pathophysiology and impacts of COVID-19 pneumonia.

5. CONCLUSION

Characteristics such as advanced age and the presence of comorbidities, including diabetes mellitus and cardiovascular disease, were more prevalent in the group with fatal outcomes. It was possible to identify more prevalent tomographic changes in this same group, such as alveolar consolidations, mixed lesions (alveolar and ground-glass opacities), interlobular septal thickening, "mosaic paving," and traction bronchiectasis, as well as extensive lesions with more than 75% involvement of the parenchyma.

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CHAPTER 14

VITAMIN D: DISABILITY AND SUPPLEMENTATION RELATED TO BARIATRIC SURGERY

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ABSTRACT: The aim of this research is to investigate the literature regarding pre and post-surgical follow-up of patients undergoing bariatric surgery, considering the serum concentrations of vitamin D and its supplementation. To this end, an exploratory study was used, through bibliographic review, seeking information regarding "Vitamin D deficiency x Bariatric Surgery". The results infer the need to control vitamin D levels in the pre- and postoperative period, since the body is unable to absorb normal amounts of nutrients, requiring supplementation. It is concluded that most patients have this vitamin deficiency because they do not expose themselves to the sun or present an inadequate diet. The importance of having a pharmaceutical and multidisciplinary follow-up is emphasized, as there may be associated pathologies that require prescription adjustment to obtain a rational use of drugs and treatments with the lowest possible dosages.

KEYWORDS: Obesity, Vitamin D deficiency, Vitamin replacement.

RESUMO: O objetivo da presente pesquisa é investigar a literatura quanto ao acompanhamento pré e pós- cirúrgico de pacientes submetidos a cirurgia bariátrica, considerando as concentrações séricas de vitamina D e sua suplementação. Para tal, empregou-se um estudo exploratório, por meio de revisão bibliográfica, buscando informações referentes a “Deficiência de Vitamina D x Cirurgias Bariátricas”. Os resultados inferem a necessidade de controle dos níveis de vitamina D no período pré e pós-operatório, visto que o organismo não consegue absorver as quantidades normais de nutrientes, necessitando suplementação. Conclui-se que a maioria dos pacientes

possui essa deficiência vitamínica por não exporem-se ao sol ou apresentarem dieta inadequada. Ressalta-se a importância da presença de um acompanhamento farmacêutico e multidisciplinar, pois podem haver patologias associadas que exijam ajuste de prescrição para obter um uso racional de medicamentos e tratamentos com dosagens menores possíveis.

PALAVRAS-CHAVE: Obesidade, Carência de vitamina D, Reposição vitamínica.

1. INTRODUCTION

Obesity is a chronic disease that has been increasingly prevalent in Brazil and worldwide over the past few decades, affecting the majority of the population over the age of 35. According to the Surveillance of Risk Factors for Non-Communicable Diseases (NCDs) by the Ministry of Health (BRASIL, 2014), 52.2% of Brazilians are overweight, with men comprising the majority (56.5%). However, women exhibit higher obesity rates, reaching 18.2% compared to men at 17.6% (Abeso, 2014).

Fandiño (2004) notes that according to the World Health Organization, the Body Mass Index (BMI) can be classified into levels of obesity. Grade I includes a BMI between 30 and 34.9 kg/m², Grade II between 35 and 39.9 kg/m², and Grade III above 40 kg/m². At this stage, it is crucial to pay attention to the patient's health as it is considered a life risk factor, indicating morbid obesity that may lead to physical complications.

Many individuals with obesity seek treatment through **bariatric surgery**, also known as gastroplasty or stomach reduction surgery, which, as the name implies, involves a surgical alteration of the stomach aimed at reducing the weight of individuals with significantly elevated BMI. According to the Brazilian Society of Bariatric and Metabolic Surgery (2016), Brazil has been performing an increasing number of procedures each year, with 16,000 cases in 2003 and 93,500 surgeries in 2015. Once a patient intends to undergo this procedure, they are required to undergo follow-up examinations, which include laboratory tests and imaging studies, among others.

At this stage, it is common to observe patients presenting with *hypovitaminosis D* prior to surgery, as well as those who will require ongoing monitoring post-bariatric surgery due to the potential for increased deficiency resulting from the surgical process.

In light of the rising rates of obesity in the modern world and the increasing number of bariatric surgeries being performed, it is imperative to conduct a literature review regarding the management of *vitamin D* deficiency, the necessity for its supplementation, and the follow-up of patients undergoing this procedure.

2. LITERATURE REVIEW

Vitamin D, known as calciferol, is a fat-soluble vitamin belonging to the steroid class. It is obtained through the consumption of certain foods and also through the transformation of cholesterol by solar radiation. It plays a significant role in the homeostasis of calcium and phosphorus and is known for its extra-skeletal actions,

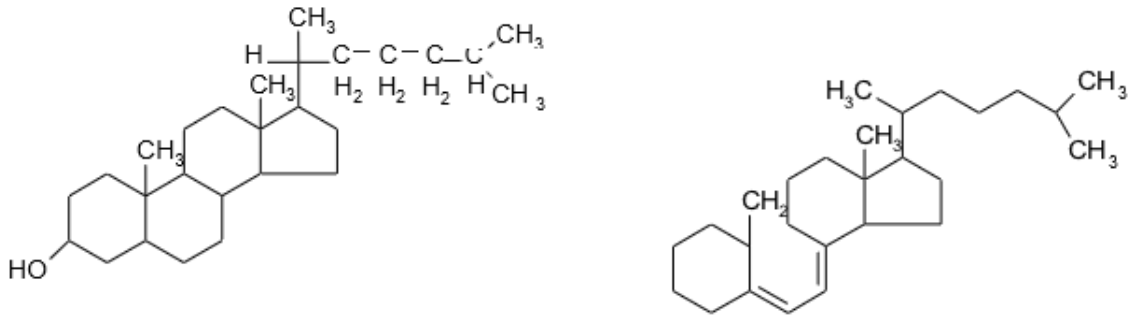
providing protection to cardiac and nervous tissue as well as modulating the signaling of inflammatory recruiters (Bordalo, Mourão, & Bressan, 2011; Smith, 2007, p. 648).

Vitamin D is absorbed from food in the form of *ergocalciferol* or *vitamin D2*. This vitamin undergoes hepatic and renal metabolic pathways, transforming into *1,25-dihydroxycholecalciferol* (1,25-$(OH)_2D_3$). Published studies in the Drug Database of the Brazilian Health Regulatory Agency (ANVISA) authored by Freitas and Melado (2000) state that vitamin D is:

> "[...] the vitamin is derived from the endogenous conversion of cholesterol into *7-dehydrocholesterol* through solar action. *7-dehydrocholesterol* is synthesized by the skin and constitutes the main provitamin found in animal tissues. Exposure of the skin to ultraviolet light converts this provitamin into *cholecalciferol* (or *vitamin D3*), which is then hydrolyzed by the liver to form *25-hydroxyvitamin D* and subsequently by the kidneys to produce *calcitriol* (1,25-$(OH)_2D_3$), the most active form of vitamin D, considered a hormone (Freitas, Melado, 2000, p.1)."

The initial stage in the endogenous synthesis process of vitamin D molecules begins in the deeper layers of the epidermis (the *stratum spinosum* and the basal layer), where the precursor substance, *7-dehydrocholesterol* (7-DHC, Figure 1), is stored and exposed to ultraviolet B radiation (λ = 290-315 nm) (Morris, 1999 apud Castro, 2011, p. 1). This transformation involves the cleavage of the bond between C9-C10, opening the B ring of the molecule. Below in Figure 1 are the molecular structures of the precursor and vitamin D.

Figure 1. Molecular structure of 7-dehydrocholesterol (A) and vitamin D3 (B)



Source: Authors

To produce vitamin D under sun exposure, a UV index greater than 3 is required, with this index in Brazil ranging from 4 to 9 throughout the year. According to specialist Michael Holick, the best time for vitamin D synthesis is from 10 AM to 4 PM, due to the angle of incidence of sunlight. It is advised to remain exposed to the sun for 5 to 20

minutes, three times a week, without the use of sunscreen on the arms, legs, abdomen, or back; however, sunscreen is essential on the face (Holick apud Tôrres, 2013). Although this time frame is optimal for vitamin D synthesis, it is important to exercise caution regarding excessive exposure to prevent skin cancer, as this is when radiation incidence is highest. It is estimated that a light-skinned person exposed to the sun for 20 to 30 minutes on the face and forearms at noon generates the equivalent of 2000 IU of vitamin D (Gupta, 2012 apud Braga, 2014, p. 8).

Vitamin D deficiency in the body is caused by inadequate diet and a lack of UVB absorption by the skin. Vitamin D loss occurs because, after bariatric surgery, the body can no longer absorb the same amount of the vitamin. Nutritional deficiencies result from poor diet, decreased absorption or utilization, increased needs, or increased excretion (Miner, 2007). According to Bordalo, Mourão, and Bressan (2011, p. 1026):

> Patients undergoing bariatric surgery, particularly through the techniques of gastric bypass (Y-derivation) or biliopancreatic diversion/duodenal switch, are at a higher risk of developing nutritional deficiencies. This risk arises mainly from the exclusion of parts of the gastrointestinal tract, which hinders the efficient absorption of nutrients. It is evident that surgical techniques with malabsorptive characteristics have a more significant impact on the absorption of vitamins and minerals and often result in nutritional deficiencies. Therefore, it is essential to provide nutritional clinical follow-up for all patients who undergo bariatric surgery to ensure the maintenance of healthy weight loss.

According to Bittar (2009, p. 34), the deficiency of vitamin D following bariatric surgery can lead to skeletal alterations, calcium deficiency, and vitamin D deficiency, which increase the risk of malignancies (such as colon, breast, and prostate cancer), chronic inflammatory or autoimmune diseases, metabolic alterations, peripheral vascular disease, muscle weakness, and conditions like osteoporosis or osteomalacia. Furthermore, Smith (2007) notes that calcitriol (1,25-(OH)2D3, the active form) is produced only when serum calcium levels are low (stimulated by parathyroid hormone or PTH); conversely, high calcium levels produce 24,25-(OH)2D3 (the inactive form of vitamin D). The primary function of vitamin D is to stimulate calcium absorption by the intestinal mucosa, specifically in the duodenum and jejunum.

Among the clinical tests required in the preoperative assessment, it is common to request the 25-hydroxyvitamin D test, where levels up to 20 ng/mL indicate deficiency, 21-29 ng/mL indicate insufficiency, and 30-100 ng/mL are considered sufficient (Searleman, 2012). In cases where deficiency or insufficiency is detected preoperatively or postoperatively, it is necessary to monitor the levels of vitamin D, calcium, and phosphorus, as well as their supplementation. Supplementation can be achieved through

the intake of foods such as tuna, sardines, salmon, eggs, and mushrooms, or it can be administered orally or via injection.

Thus, this research is justified by the relevance of the topic as a means of informing patients and healthcare professionals who assist obese individuals wishing to undergo bariatric surgery or who have already undergone the procedure, highlighting the importance of monitoring the health of these individuals concerning vitamin D supplementation.

3. METHODOLOGY

The developed study adhered to the methodological principles of an exploratory study through a bibliographic review, aiming to describe and compile information regarding the topic “Vitamin D Deficiency x Bariatric Surgeries” and “its supplementation before and after surgery,” fulfilling the objective of investigating preoperative and postoperative monitoring, methods of supplementation, and pharmaceutical care. To this end, a data survey was conducted for the period from 2010 to 2016 across the databases Scielo, Web of Science, Science Direct, Medline, Medline Pharmacist, American Chemical Society, as well as the websites of ANVISA and the Ministry of Health, in addition to printed literature. The following keywords were utilized in the research: “Vitamin D,” “Vitamin D Dosage,” “Bariatric Surgery,” “Vitamin D Deficit,” and “Obesity.

4. RESULTS AND DISCUSSIONS

In the preoperative phase, a nutritional consultation for the patient is necessary, which includes a detailed dietary history (quantity, quality, taste, appetite, level of satiety, intolerances, food allergies, consumption of alcoholic beverages or drugs, bowel habits, chewing, and food preparation) (Bittar, 2009, p. 34). Laboratory tests such as complete blood count, urea, creatinine, fasting glucose, insulin levels, total protein, albumin, serum iron, ferritin, vitamins B12 and D, folic acid, total cholesterol and fractions, triglycerides, aminotransferases (AST and ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), and total and fractionated bilirubin are also required (Abreu, 2015).

Additionally, a chest X-ray, abdominal ultrasound, cardiological evaluation, digestive endoscopy for Helicobacter pylori, and assessment of respiratory function are recommended, along with consultations from an endocrinologist, psychiatrist and/or psychologist, and physiotherapist. Following this, multidisciplinary meetings are held

prior to the surgery. If the patient presents any pathology, it must be treated before the surgical procedure, which will only be performed under optimal clinical conditions.

Araújo (2013) reports a study involving 123 patients who underwent bariatric surgery, evaluating their levels of vitamin D and parathyroid hormone (PTH) before and one year after the surgery, showing vitamin D deficiency in 86% of the cases before the surgery and in 70% after the surgery.

The therapeutic approach indicated before and after bariatric surgery, according to Ybarra et al. (2005) as cited in Mustafa (2014, pp. 27-28), suggests that patients undergoing obesity surgery face two risks associated with vitamin D deficiency: one related to obesity and the other related to malabsorption caused by the surgery. A prevalence of 81.3% of hypovitaminosis D was found before the surgery and 77.3% afterward (Sáncheszhernández et al., 2005 as cited in Mustafa, 2014, pp. 27-28). The prescription of vitamin D in the preoperative phase is indicated if the level is below 30 ng/mL as detected in the 25-hydroxyvitamin D test, with a recommended dosage of 50,000 IU of oral cholecalciferol per week for six to eight weeks (Flancbaum, 2006 as cited in Bordalo, 2011, p. 118). In the postoperative phase, according to ANVISA (2000), supplementation can be administered orally or intravenously, as outlined in Table 1.

Table 1. Prescription of vitamin D in adults and children. Source: Adapted from ANVISA (2000). Drug Database

PATIENTS	WITHOUT ASSOCIATED PATHOLOGY
Vitamina D – Via Oral	Adults: 400 IU/day in combination with diet and sun exposure Pregnant women: 400 IU/day Infants: predisposed to rickets 30,000 IU/day Premature or infant babies: 400 IU/day
PATIENTS	WITH ASSOCIATED PATHOLOGY
Vitamina D – Via Intravenosa	Hypoparathyroidism: Adults and children over 8 years: start with 50,000 to 200,000 IU/day and maintain at 25,000 to 100,000 IU/day. Children aged 1-8 years: 10,000 to 25,000 IU/day.
	Osteomalacia or rickets: Adults and children over 8 years: 10,000 to 25,000 IU/day. Children 1-8 years: 5,000 to 50,000 IU/day.
	Malabsorption – predisposed to rickets: Adults and children over 8 years: 1,000 to 2,000 IU/day and maintenance of 400 IU/day. Children aged 1-8 years: 10,000 to 25,000 IU/day.
	Hypophosphatemia: Children aged 1-8 years: 25,000 to 100,000 IU/day, associated with high phosphate intake and calcium supplementation.
	Osteoporosis: Adults and children over 8 years of age: 300 IU/day. Elderly: 700 IU/day.
	Hepatobiliary disease (viral hepatitis, fatty liver, cholecystitis, cholelithiasis): Adults and children over 8 years: 10,000 to 40,000 IU/day. Associated with anticonvulsants: 1,000 IU/day.

	Children 1-8 years: 1,000 IU/day.

The literature contains numerous pieces of information regarding vitamin D supplementation; however, most guidelines focus on the dosages presented in Table 1. It is essential to ensure that patients understand the necessity of replenishment and the duration of this supplementation until their levels are stabilized. For patients with associated pathologies, dosages vary according to different societies. The Institute of Medicine recommends 600 IU for individuals aged 51-70 years and 800 IU for patients over 70 years. The American Geriatrics Society recommends 800 IU for all individuals at risk of falls (Lichtenstein et al., 2013), while ANVISA (2000) suggests 300 IU/day for adults and children over 8 years, with a recommended dose of 700 IU/day for the elderly.

Regarding pregnant women, ANVISA establishes a standard of 400 IU/day; however, Pereira and Solé (2015) demonstrated in a randomized study that a supplementation of 4000 IU/day during pregnancy reduces the risk of combined morbidities such as maternal infections, cesarean delivery, and premature birth.

Bordalo (2011, p. 118) states that supplementation after bariatric surgery depends on the type of surgery performed, suggesting that there is no one-size-fits-all dosage for all patients, thus highlighting the need for monitoring through periodic examinations. He further notes that an initial supplementation of 2000 IU/day in the postoperative period should be utilized, considering polytherapy precautions, especially for patients using anticonvulsants, glucocorticoids, heparin, or cholestyramine, who have a higher risk of bone disease. Approximately 50% or more of postoperative patients with vitamin D deficiency supplement with 400-800 IU/day of vitamin D (Coates, 2004; Newbury, 2003; Ybarra, 2005 as cited in Bordalo, 2011). However, Torezan (2013) points out that in cases of severe vitamin D deficiency, replenishment of 50,000 to 100,000 IU/week for 6 to 8 weeks is necessary.

As discussed, individual variations in response to different treatments may exist; thus, reevaluation of plasma values after each cycle is ideal, especially in cases of severe deficiency. After this stabilization period, a maintenance dose should be instituted, varying with the patient's age and conditions. For adults, maintenance doses may range from 400-2,000 IU, depending on dietary intake and sun exposure. For the elderly, a recommendation of 1,000 to 2,000 IU/day or 7,000 to 14,000 IU/week is suggested. Care must be taken with vitamin D replenishment, as excess can be detrimental to health, leading to metaplastic demineralization of soft tissues and vitamin D toxicity. This study illustrates the necessity of pharmaceutical assistance and attention for bariatric patients,

observing synergisms and antagonisms in action between concurrently administered medications, adjusting dosages, forms, or timing of administration in pursuit of rational medication use and comprehensive patient care.

5. CONCLUSION

Obesity has become a global epidemic due to physical and emotional issues, inadequate intake, or increased absorption of vitamin D by adipose tissue, which has significantly raised the number of bariatric procedures performed in recent years. Monitoring serum vitamin D levels pre and post-surgery is crucial for maintaining patient health.

It is recommended that patient care involves the work of multidisciplinary health teams for guidance and replenishment of vitamin D, through the adjustment of an appropriate diet, recommendations for adequate sun exposure, and ongoing vitamin supplementation until stable blood levels are achieved. There is no one-size-fits-all approach for all patients, as each individual has specific metabolic processes and different associated conditions. However, this research leads to the conclusion that there are several commonly employed protocols for pre and post-operative supplementation that align with ANVISA guidelines. The supplementation should be selected by the professionals on the care team and should involve adjustments to dosages and administration according to the patient's needs, while also considering the concomitant use of medications for associated conditions.

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CHAPTER 15

ANATOMIC STUDY OF REDUCTION AND FIXATION WITH TRANSINDESMOIDAL SCREW OF ANKLE FRACTURE-LUXATION

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ABSTRACT: Introduction: It is known that the tibio-fibular syndesmosis is important for ankle joint stability. Its impairment can lead to several complications for the patient, especially when not treated appropriately. Malreduction of the joint and residual instability can drastically affect the postoperative period, leading to bone degeneration and residual pain. Methodology: This is a retrospective study in which data were collected regarding adult patients in the postoperative period of ankle's syndesmotic screw, with a minimum 3 months follow-up. Computed tomography and radiographs were evaluated 6 weeks after surgery, the images were printed, the patient's identification were removed and they were evaluated by 5 specialists in orthopedics and traumatology, not associated to the study. Results and Discussion: Anatomic reduction of the syndemosis is essential to avoid future complications and guarantee the patient's functional recovery. Among the main complications are latent diastasis, instability, more injuries, arthritic changes, chronic pain, osteochondral injuries. Therefore, one must pay attention to the available resources to identify the tibio-fibular injury. It is currently believed that radiography is an inaccurate test for evaluating the distal tibio-fibular syndesmosis, and computed tomography (CT) has proven to be a more sensitive resource to evaluate the integrity of the syndemosis. However, in the present study the proportion between disorders on radiography and tomography were similar. Conclusion: In this study there was no major impact on functionality, daily activities and pain scales, even in those with maleduction of the syndesmosis, several psychosocial or physiological factors may have interfered the study's result. More studies can be developed aiming at long-term follow-up of patients with syndesmosis injury using computed tomographic examination and evaluating post-traumatic and non-traumatic arthrosis in order to improve the treatment and early intervention of these patients.

KEYWORDS: Syndesmosis, Ankle joint, Ankle injuries.

RESUMO: Introdução: Sabe-se como a sindesmose tibiofibular é de extrema importância para estabilidade articular do tornozelo. Seu comprometimento pode acarretar diversas complicações para o paciente, principalmente quando não tratado de forma adequada. A má redução articular e instabilidade residual podem afetar drasticamente o pós-operatório, gerando degeneração óssea local e dor residual. Metodologia: Trata-se de um estudo retrospectivo em que foram coletados dados referentes a pacientes adultos em pós-operatório de osteossíntese de tornozelo com parafuso transsindesmoidal, com seguimento mínimo de 03 meses. Foram avaliadas tomografia computadorizada e radiografias após 6 semanas de cirurgia. Estas imagens foram impressas, foi retirada a identificação dos pacientes e foram avaliadas por 05 avaliadores, não vinculados ao estudo, especialistas em ortopedia e traumatologia. Resultados e Discussão: A redução anatômica da sindemose é essencial para evitar complicações futuras e garantir o retorno funcional do paciente. Entre as principais complicações encontram-se diástase latente, instabilidade, mais lesões, alterações artríticas, dor crônica, lesões osteocondrais. Logo, deve- se ficar atento aos artifícios

disponíveis para identificar a lesão tíbio-fibular. Acredita-se atualmente que a radiografia é um exame impreciso para avaliar a relação tibiofibular distal e, a tomografia computadorizada (TC) demonstrou-se um instrumento mais sensível para avaliar integridade da sindemose. Entretanto em nosso trabalho a proporção entre a visualização de alterações referentes a radiografia e tomografia foram semelhantes. Conclusão: Neste estudo não houve grande impacto na funcionalidade, atividades diárias e escalas de dor, mesmo naqueles com redução não anatômica da sindesmose, diversos fatores psicossociais ou fisiológicos podem ter influenciado neste resultado, mais estudos podem ser desenvolvidos visando o seguimento a longo prazo dos com lesão da sindesmose, utilizando- se do exame tomográfico e avaliando o tempo aproximado para evolução de artrose pós traumática e não traumática afim de melhorar o tratamento e intervenção precoce destes pacientes.

PALAVRAS-CHAVE: Sindesmose, Articulação do tornozelo, Traumatismos do tornozelo.

1. INTRODUCTION

It is known that the tibiofibular syndesmosis is extremely important for the joint stability of the ankle (Pogliacomi, 2021). Its compromise can lead to various complications for the patient, especially when not treated properly (Pogliacomi, 2021; Paiva, Pinto, Magalhães, Lopes, Castilho, Baumfeld, 2018). The incidence of syndesmosis injury varies from 1-18% and can occur in isolation or in relation to ligamentous injuries or fractures (Pogliacomi, 2021; Paiva, Pinto, Magalhães, Lopes, Castilho, Baumfeld, 2018). Ankle fractures are among the most common injuries of the lower limb in adults, and in approximately 10%, injury to the syndesmosis may be associated (Pogliacomi, 2021; Paiva, Pinto, Magalhães, Lopes, Castilho, Baumfeld, 2018). Therefore, the identification of the injury must be performed meticulously to ensure the best prognosis for the patient (Paiva, Pinto, Magalhães, Lopes, Castilho, Baumfeld, 2018).

Diagnosis can be challenging; however, among the existing classifications for ankle fractures, the Danis-Weber classification significantly contributes to evaluating the probable injury of the ligamentous complex, showing an association in more than 40% of type B fractures and in more than 80% of type C fractures (Van Zuuren, Schepers, Beumer, Sierevelt, Van Noort, Bekerom, 2017).

Poor joint reduction and residual instability can drastically affect the postoperative period, leading to local bone degeneration and residual pain (Castilho et al., 2021). With chronic ankle instability being a difficult diagnosis, various radiological examinations contribute to the evaluation of syndesmosis, such as pre- and post-operative X-rays, intraoperative fluoroscopy, postoperative tomography, and even arthroscopic evaluation, with the last two being more specific for assessment (Pogliacomi, 2021; Paiva, Pinto, Magalhães, Lopes, Castilho, Baumfeld, 2018).

The present study aims to evaluate the impact of tibiofibular reduction on functionality in patients after syndesmosis fixation with a transsyndesmotic screw, using two forms utilized in the postoperative period of ankle fractures and functional assessment of lower limb surgeries (Castilho et al., 2021; Metsavaht et al., 2012).

2. METHOD

Study approved by the ethics committee with the identified report number 5.654.731 and CAAE 62873022.9.0000.0081.

The collected data were used solely for analysis, interpretation, and dissemination in health through scientific publications, maintaining the confidentiality of the research participants.

This is a retrospective study in which data were collected from adult patients in the postoperative period of ankle osteosynthesis with a transsyndesmotic screw from December 2021 to December 2022, with a minimum follow-up of three months.

The sample consists of 11 patients, all skeletally mature (closed growth plates) of both sexes, with ankle fracture-dislocation, excluding Maisonneuve injury. All these patients were surgically treated and currently have a minimum follow-up of three months. All patients with postoperative follow-up loss, Maisonneuve injury, or who did not agree to sign a free and informed consent form to participate in the study were excluded.

The study aims to evaluate the impact of syndesmosis reduction and the functional outcome of patients in the postoperative period after three months of rehabilitation, subjected to surgical treatment of ankle fracture-dislocation osteosynthesis and fixation with a transsyndesmotic screw. Complications and failures will also be evaluated.

The open reduction and internal fixation of the fibula fracture were performed using the standard AO technique. The syndesmosis injury was determined by the surgeon's experience, commonly using intraoperative stress testing.

Stress tests with intraoperative radiography assistance were performed after the fibula fracture fixation and before the application of the syndesmotic screw to assess instability, using external rotation and lateral distraction tests. The syndesmosis was reduced under direct visualization of the Mercedez star sign and radiography using a large clamp with the foot in 10 degrees of dorsiflexion. After the fixation of the syndesmotic screw, stress tests were repeated. In the postoperative period, patients used an occlusive dressing and were advised to start early movement with total load restriction. Follow-up appointments were scheduled for 2, 6, 12, and 24 weeks, with partial load allowed from the sixth week. A tomography was performed any time after six weeks of postoperative.

Computed tomography and X-rays were evaluated six weeks after surgery. These images were printed, patient identification was removed, and they were evaluated by five assessors who were not linked to the study, specialists in orthopedics and traumatology with extensive experience in ankle fractures, with an additional evaluator reserved for tie-breaking in categorical response questions.

The researcher selected an axial slice of the ankle 1 cm proximal to the talotibial joint, and X-rays were taken in anteroposterior, true anteroposterior (15 degrees of internal rotation), and lateral views.

In the X-rays, the medial clear space, tibiofibular clear space, and tibiofibular overlap were assessed. In the tomographies, diastasis, anterior translation, posterior translation, rotational deviation, and evaluation of the syndesmosis using the Zwipp method were assessed, which is the angle (degrees) between the tangent to the anterior face of the tibia at its most anterior point and the bisection of the vertical midline (long axis) of the fibula. The angle of the operated side is compared with the contralateral side.

Figure 1. Zwipp Angle Example

Source: Own authorship

Postoperative functional evaluation was performed using two forms. The first is the Olerud-Molander Criteria, a questionnaire validated for the Brazilian version, which assesses postoperative symptoms such as pain, joint stiffness, edema, and the ability to perform daily activities of light to moderate intensity. The second form is the Lower Extremity Functional Scale (LEFS), developed based on the model suggested by the World Health Organization (WHO). It has five numerical possibilities and response categories ranging from 0 to 4 for each of its 20 questions, with a total score ranging from 0 (poor) to 80 (excellent). We also used the Visual Analog Scale (VAS), consisting of a 10 cm line, where 0 represents total absence of pain and 10 represents the maximum pain level the patient can tolerate. We asked the patient about the level of pain experienced in the affected ankle.

The descriptive analysis of the data was performed using the mean and 95% confidence intervals. The means (LEFS, OLERUD MOLANDER, and VAS) were compared using the Student's t-test, and categorical data (failure and complications)

were compared using the Chi-square test. A significance level of 5% (alpha) was considered.

All eligible patients were informed about the nature and purpose of the study through the reading and clarification of the Free and Informed Consent Form (FICF), as well as being made aware of the regulations that will be followed in accordance with Brazilian legislation (466/2012) and the confidentiality of data and participants. Regarding the questionnaires (LEFS, OLERUD MOLANDER, and VAS), the application was conducted using a physical form during outpatient consultation, and all information obtained from these questionnaires will be kept confidential.

3 RESULTS

The sample of the study consisted of 11 patients, with the majority being female. The mean age was 43.1 ± 10.1 years, with the youngest being 33 years old and the oldest 52 years old. We conducted a comparison between the evaluation of radiographic changes and tomographic changes found in the postoperative period of patients with syndesmotic injuries.

There is statistical significance in the distribution of both radiographic (X-ray) and tomographic (CT) alterations, with the highest rate being "Yes," showing 81.8% in X-ray and 90.9% in CT (p-values of 0.003 and <0.001, respectively).

Table 1. Distribution of qualitative factors

		N	%	P-valor
Alteração Rx	Não	2	18,2%	0,003
	Sim	9	81,8%	
Alteração TC	Não	1	9,1%	<0,001
	Sim	10	90,9%	
Sexo	Feminino	6	54,5%	0,670
	Masculino	5	45,5%	

Source: Own authorship

Next, we compared these indices (relative frequencies) of changes between X-ray (RX) and computed tomography (CT), using the same Z test for Two Proportions. We conclude that there is statistical significance in the distribution of both RX changes and CT changes, with the highest rate being "Yes," showing 81.8% in RX and 90.9% in CT (p-values of 0.003 and <0.001, respectively).

Following that, we compared these indices (relative frequencies) of changes between RX and CT, using the same Z test for two proportions.

Table 2. Comparison of the Index of Change between X-ray and CT

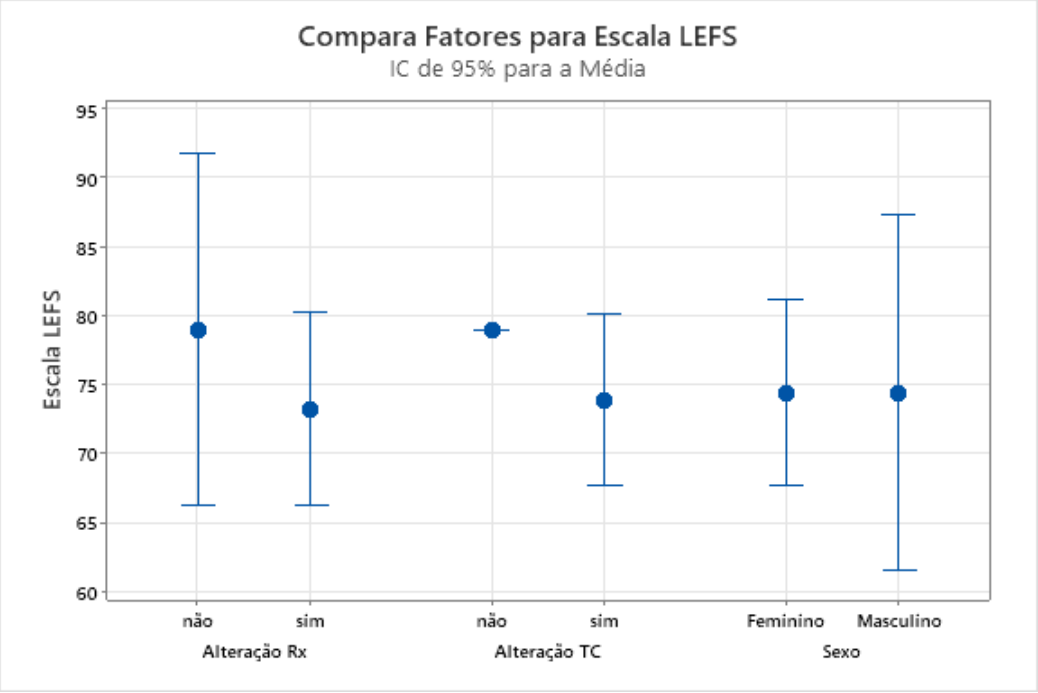
	Alteração RX		Alteração TC		P-valor
	N	%	N	%	
Não	2	18,2%	1	9,1%	0,534
Sim	9	81,8%	10	90,9%	

Source: Own authorship

As seen in Table 2, the alteration index (responding "yes") was 81.8% in X-ray (RX) and 90.9% in computed tomography (CT); however, this difference is not considered significant (p-value = 0.534), highlighting the most frequent alteration as diastasis of the syndesmosis observed in the computed tomography.

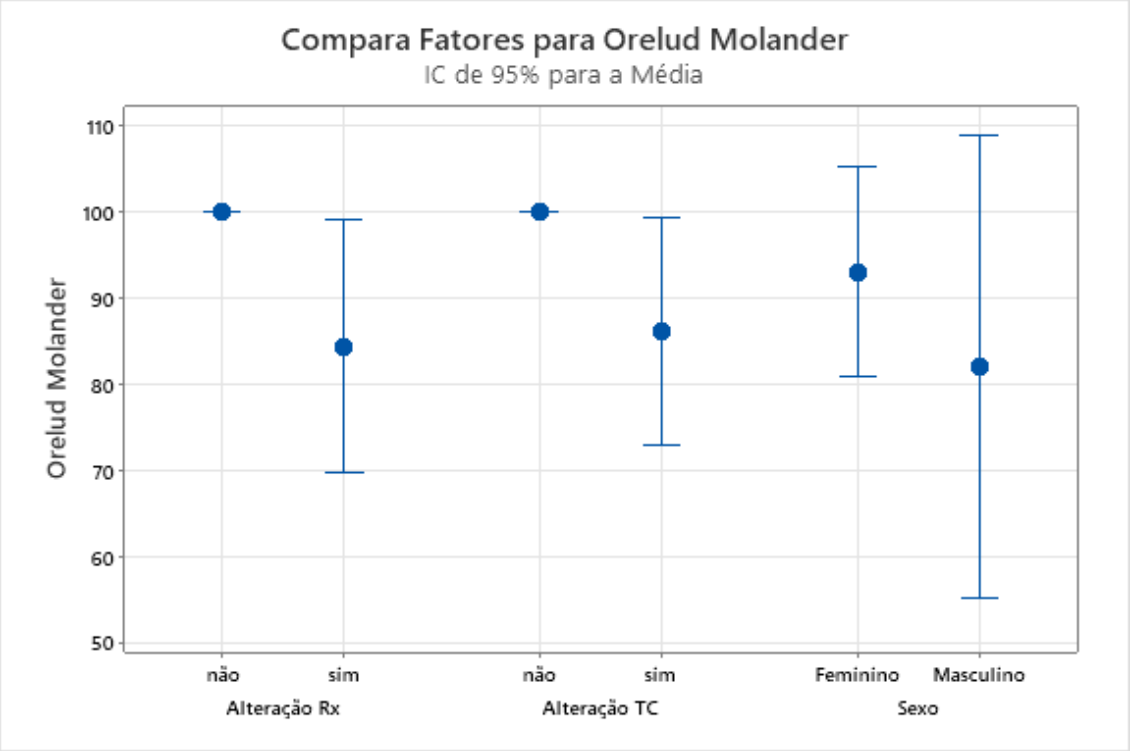
Finally, we compared the qualitative factors of sex, RX alteration, and CT alteration with the quantitative values of: "LEFS Scale," "Olerud Molander," and "EVA," aiming to assess the impact on the daily and functional life of these patients post-surgery, correlating with those who had or did not have alterations in the images.

Graph 1. Comparison of LEFS scale for radiographic changes and sex



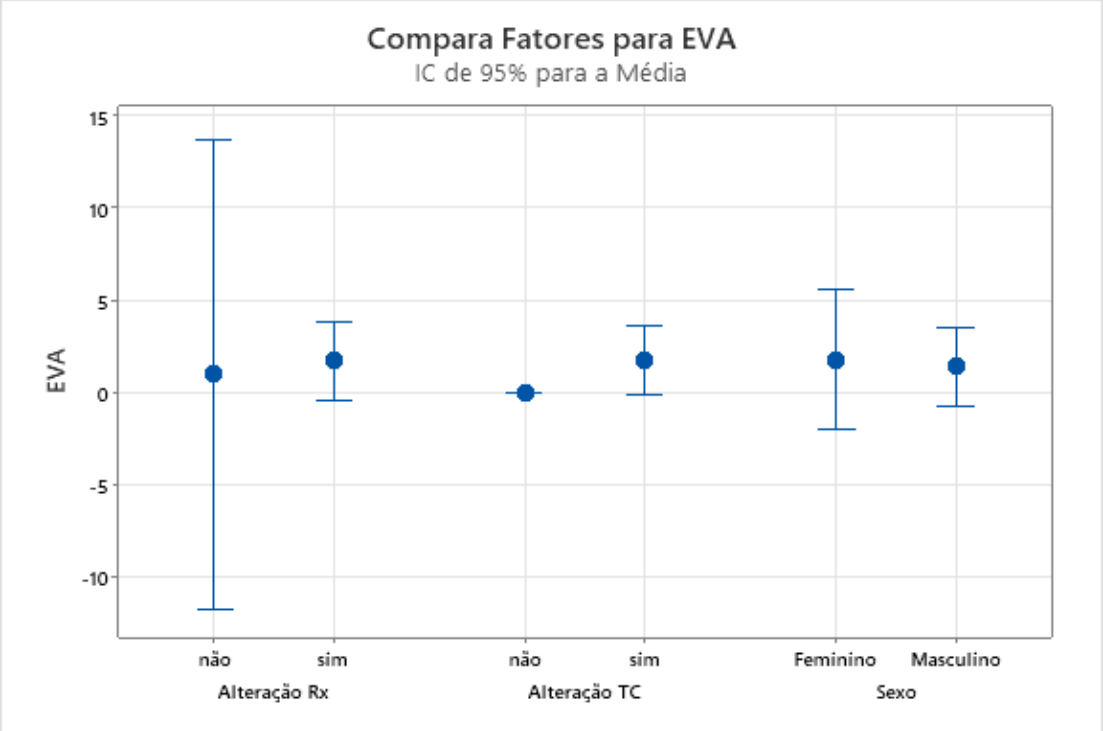
Source: Own authorship

Graph 2. Comparison of Olerud Molander criteria for radiographic changes and sex



Source: Own authorship

Graph 3. Comparison of VAS pain scale for radiographic changes and sex



Source: Own authorship

We concluded in this study that there is no statistical difference in sex, alterations in radiography, or alterations in computed tomography for the scores of the "LEFS Scale," "Olerud Molander," and "EVA."

4. DISCUSSION

The anatomical reduction of the syndesmosis is essential to prevent future complications and ensure the patient's functional return. Among the main complications are latent diastasis, instability, further injuries, arthritic changes, chronic pain, and osteochondral injuries (Rasi, Kazemian, Omidian, Nemati, 2013). Therefore, attention must be paid to the available methods for identifying the tibiofibular injury. It is currently believed that radiography is an imprecise exam for assessing the distal tibiofibular relationship, while computed tomography (CT) has proven to be a more sensitive instrument for evaluating the integrity of the syndesmosis (Ribeiro, Prata, Rizzo, Prado, Campos, 2018). However, in our study, the proportion of observed alterations related to radiography and tomography were similar.

Computed tomography proved useful for identifying up to 3 mm of diastasis and up to 30 degrees of external rotation of the distal fibula. Various methods and criteria have been studied for the tomographic evaluation of the syndesmosis, such as the methods described by Vasarhelyi, Zwipp, and Tang (Knops, Kohn, Hansen, Matityahu, Marmor, 2013). In this work, the Zwipp angle was used, formed by the angle (degrees) between the tangent to the anterior tibial surface at its most anterior point and the bisection of the vertical midline (long axis) of the fibula. The angle on the operated side is compared with the contralateral side. The absolute value of this measurement is normally around 90 degrees (a right angle), from which we subtract 90 degrees from the previous absolute measurement to derive it. This method has shown similar absolute variability among observers (measured in degrees) in other studies, making it a good method for evaluation (Knops, Kohn, Hansen, Matityahu, Marmor, 2013). Another method to enhance examination sensitivity would be the application of a dynamic test in tomography using an adjustable simulated load device; however, it is available in only a few hospitals and its indication is still directed toward subtle evaluations of ankle syndesmosis (Chans-Veres, Vallejo, Galhoum, Tejero, 2023).

In a study involving 1,024 patients with foot and ankle fractures, it was found that 72% of cases represented ankle fractures, and of these, only 1.4% progressed to the late complication of post-traumatic osteoarthritis. This result was not evaluated in correlation with syndesmosis reduction, but all were surgically treated, understanding the severity of the injury (Stéfani, Filho, Lago, 2018). Associated with this, it was noted that the involvement was primarily in the female sex and had an average age of 50.18 years, results similar to those of our study.

In another Australian research, ankle fractures are treated as a public health issue, compromising quality of life and functionality, especially in older patients (Holloway et al., 2014). Among the main concerns are post-traumatic osteoarthritis and chronic instability, with the latter found in 46% associated with syndesmosis injury diagnosed via arthroscopy (Chun et al., 2015). Our work did not cover a sufficient follow-up time for patients to assess late complications. Following the functionality scales, there was no correlation between functionality and pain levels in patients with the anatomical reduction of the syndesmosis evaluated by radiography and tomography; however, it is well described in the literature that ankle joint degeneration may be associated with an imbalance in load distribution, of which the main cause is traumatic (Chun et al., 2015; Vuurberg et al., 2018; Martins, Gomes, 2020).

5 CONCLUSION

Recurrent ankle sprains and ankle fractures with syndesmosis injury are the traumatic events most associated with chronic instability and post-traumatic osteoarthritis. In this study, there was no significant impact on functionality, daily activities, and pain scales, even in those with non-anatomical reduction of the syndesmosis. Various psychosocial or physiological factors may have influenced this result. Further studies could be developed focusing on the long-term follow-up of patients with syndesmosis injury, using tomographic examination and evaluating the approximate time for the progression of post-traumatic and non-traumatic osteoarthritis, in order to improve the treatment and early intervention for these patients.

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CHAPTER 16

RIGHT SUPERNUMERARY RENAL ARTERY

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ABSTRACT: It is known that the knowledge of the anatomical variations of the renal vessels represents an important clinical and surgical application. Objective: To analyze the presence of anatomical variations in the renal irrigation of cadaveric specimens available for anatomical study at the Anatomy Laboratory of the Faculdade de Ciências Médicas de São José dos Campos - Humanitas, as well as classify the variations found. Results: The results showed the presence of an anatomical variation in the pieces studied, in which the existence of two right renal arteries was identified. Conclusions: From the methodology used, it can be concluded that the right supernumerary renal artery found in this study is an anatomical variation because it is not found in most human beings, moreover, it is attributed to this, the classification hilar renal artery, due to the direction of the renal hilum.

KEYWORDS: Anatomy, Variations, Renal artery.

RESUMO: Sabe-se que o conhecimento das variações anatômicas dos vasos renais representa importante aplicação clínica e cirúrgica. Objetivo: Analisar a presença de variações anatômicas na irrigação renal das peças cadavéricas disponíveis para estudo anatômico do Laboratório de Anatomia da Faculdade de Ciências Médicas de São José dos Campos, bem como classificar as variações encontradas. Resultados: Os resultados evidenciaram a presença de uma variação anatômica nas peças estudadas, na qual foi identificada a existência de duas artérias renais direitas. Conclusões: A partir da metodologia empregada, pode-se concluir que a artéria renal supranumerária direita encontrada neste estudo, trata-se de uma variação anatômica pois esta não é encontrada na maioria dos seres humanos, ademais, atribui-se à esta, a classificação de artéria renal hilar, em razão de direcionar-se ao hilo renal.

PALAVRAS-CHAVE: Anatomia, Variações, Artéria renal.

1. INTRODUCTION

In most individuals, each kidney is supplied by a single renal artery that originates from the abdominal aorta artery. Normally, the right renal artery has a downward path to the right kidney, later traversing the inferior vena cava. The left renal artery, on the other hand, has a more horizontal course as it passes posterolaterally to the left renal vein. Knowledge of the anatomical variations of the renal vessels (VAVR) is known to have major clinical implications. In cases of kidney transplantation, careful pre-operative evaluations for renal and ureteral vascular abnormalities are of paramount importance. Harrison et al., 1978, in a study of 166 patients (97 men and 69 women, aged 18 to 54 years), found that the most common VAVR was the presence of multiple renal arteries irrigating the same kidney, followed by prehilar segmental branching. In addition, research conducted by Palmieri et al., 2011, concluded, by means of the study of two hundred renal pedicles in vivo via angiotomography, that there was no difference in laterality (right or left variation) and/or the sex of the patients and that among the VAVR, the renal arteries originated more frequently as prehilar divisions of the main artery and were directed to the renal hilum.

About the percentages found in each type of variation, another study, conducted by Aynur et al., 2005, showed the following results: single hilar artery in 75% of the cases, double hilar artery in 11.1%, artery directed to the lower pole in 10.5% and artery directed to the upper pole in 3.3% of the specimens studied.

It should be noted that the occurrence of multiple renal arteries is more prevalent than that of veins, but the occurrence of anatomical variations in renal veins are also described in the literature, as in the case of the circumaortic left renal vein: "In the first case, the circumaortic renal collar was connected by great anastomosis with the hemiazygos vein and was associated with the presence of the supernumerary left renal artery located below the main left renal artery" (Haladaj, 2019, pg.437 to 443).

In addition, another study, this time conducted by Çınar et. al., 2016, also described no significant difference in VAVR between men and women, in addition to identifying an incidence of accessory renal artery in 24.6% of women and 35.3% of men. Sampaio et al., 1992, described the following nomenclature for possible anatomical variations of the renal arteries: renal artery with early division (this is the branch of the main renal artery prior to the renal hilum region), hilar artery (which enters the kidney following the main renal artery), and polar artery (which may derive from the aorta or common iliac artery, and enters the kidney externally to the renal hilum, directly by the

renal capsule). In addition, these authors used a specific nomenclature for branches coming from the renal artery that penetrate the kidney into the upper pole, external to the hilum, terming them as the extrahilar renal artery.

Studies by Özkan et al., 2006, Holden et al., 2005, and Ugurel et al., 2010, report a higher prevalence of right side accessory renal arteries, and a more recent study by Liang et al., 2020, also describes the occurrence of right VAVR, thus contrasting with studies by Sampaio et al., 19927 and Palmieri et al., 2011, which did not report a large statistical difference between the right and left sides.

There are also reports pointing to differences in the frequency of arterial variations between races: 37% in Africans, 35% in Caucasians and 17% in Indians show changes in renal vascularization.

The reason for large variations in renal arterial vascularization reflects the embryonic origin of these blood vessels. Initially, the primary kidneys, at the onset of fetal development, are located in the pelvis region, ventrally to the sacrum, and as the abdominal and pelvic cavity develops, the kidneys gradually emerge to their retroperitoneal position in the abdomen. During the position variation, the kidneys receive arteries from the vessels closest to them, therefore, throughout this ascent, the kidneys receive new arterial branches, while the more caudal branches undergo involution and disappear. A deficiency in the degeneration of these branches causes the presence of more than one renal artery. In some cases, failure to ascend the kidneys to their final anatomical position causes these arterial branches to persist.

In view of this, the objective of this study is to analyze the presence of anatomical variations in the renal irrigation of the cadaveric parts available for anatomical study at the Laboratory of Anatomy of XXXX, as well as to classify the variations found according to the classification proposed by Sampaio et. al.,1992.

2. CASE DESCRIPTION

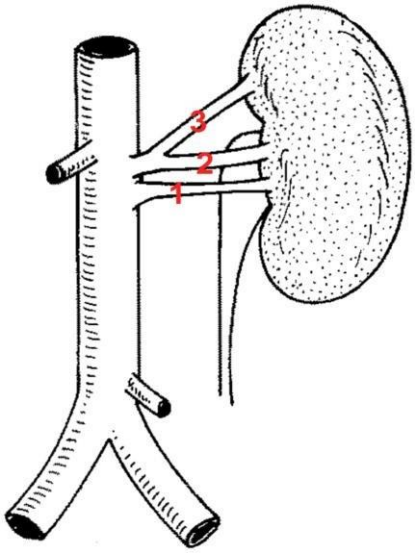
In this study, 6 cadaveric pieces belonging to the Laboratory of Anatomy of XXXX were analyzed. Among the pieces examined, the presence of an anatomical variation in the kidney irrigation of a female corpse was found, black in color and aged 58 years. It had been stored in 10% formaldehyde solution for a period of two (2) years and then in pure glycerin solution (99.5 to 99.7%) of the ULTRA® brand,

year of manufacture 2018, lot ARG.BO180618 with glycerol content resulting from 99,727, during a period of 6 (six) months. During the period of cadaveric dissection, the

left and right kidneys were evidenced, as well as the constituent elements of their hilos, and the abdominal structures anterior to the posterior peritoneum were removed. Both adrenal glands were also sectioned, preserving the abdominal aorta artery, inferior vena cava, and its tributary vessels. It should be noted that during this process pararenal fat, renal fascia and perirenal fat were removed consecutively (with the exception of the posterior face of the left kidney, in which the perirenal fat was kept) from both kidneys, in order to highlight and facilitate visualization of the renal capsules.

Regarding the classification of the anatomical variation found, this study used the nomenclature described by Sampaio et. al., 1992 as a guide. Accordingly, for the renal arteries that penetrate the renal parenchyma from its hilum, the nomenclature of hilar renal artery was used, making a differentiation between the two found by means of the upper and lower position of origin in the abdominal aorta artery. With regard to the terminology used for the branches emitted by each hilar renal artery, the disposition (upper, medial and lower) of each branch was used when entering the renal hilum, for a more precise identification.

Figure 1. Arterial hilar branches

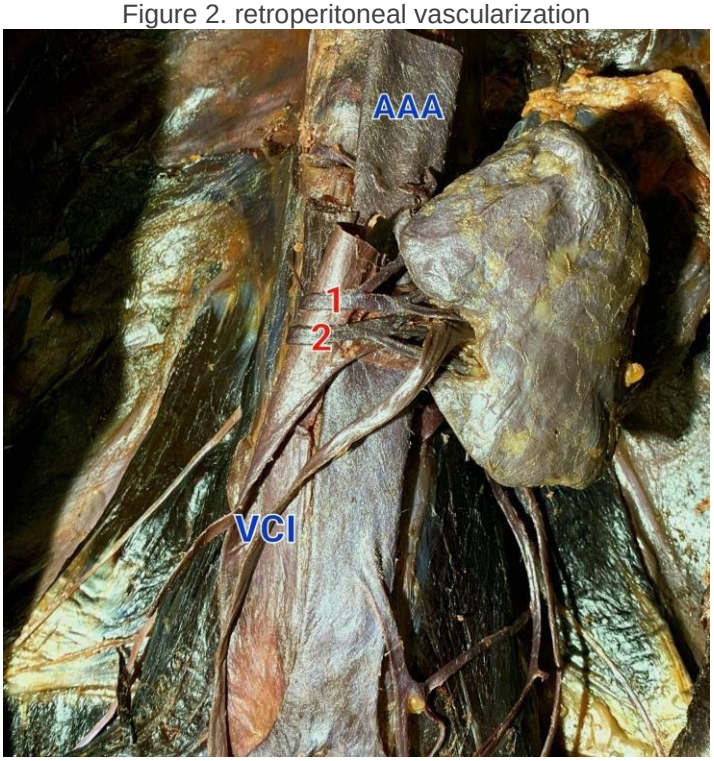


A and B: hilar arteries; C: extra-hilar branch. Source: Modified by Sampaio et al., 19928.

3 DISCUSSION

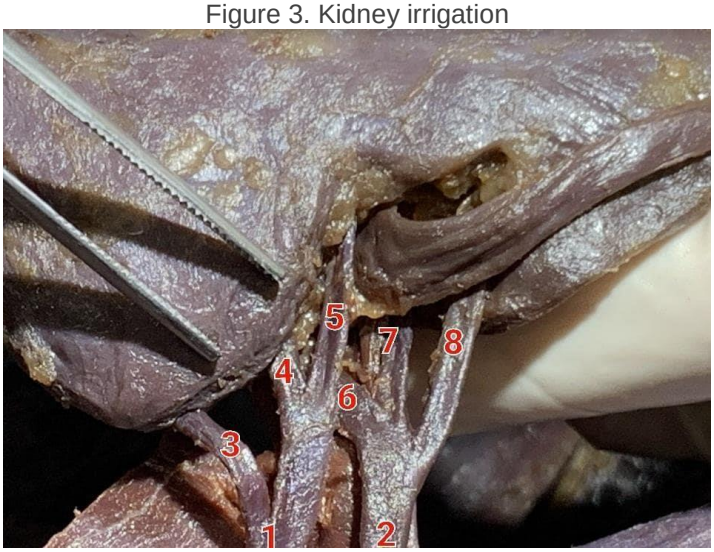
Faced with the anatomical variation found, the existence of two right renal arteries, of regular morphology, both originated in the medial face of the abdominal aorta, one being more superior (artery A) and the other with lower path (artery B), towards the right kidney, with parallel path as shown in Figure 2.

Figure 2. retroperitoneal vascularization



a. right superior hilar renal artery; B. right inferior hilar renal artery; AAA. abdominal aorta artery; VCI-. inferior vena cava.

Figure 3. Kidney irrigation



Source: anatomical laboratory Faculty of Medical Sciences of São José dos Campos

A- right upper hilar renal artery; B- right lower hilar renal artery; C- right upper hilar renal artery; D- right upper hilar renal artery median branch; E- right upper hilar renal artery inferior inferior inferior inferior renal artery inferior branch; F- right lower hilar renal artery superior branch; G- right lower hilar renal artery median branch; H- right lower hilar renal artery inferior renal artery inferior branch.

Source: anatomical laboratory Faculty of Medical Sciences of São José dos Campos

Figure 2 shows the retroperitoneum in the abdominal cavity, with emphasis on the right kidney and its topographical relationship with the abdominal vessels (abdominal aorta and inferior vena cava sectioned, showing the right kidney translocated to the left for better visualization of the hilar renal arteries, both emerging from the abdominal aorta artery and following in parallel course towards the right kidney).

Figure 3 shows the right kidney with two right renal arteries entering the renal hilum in a parallel path, with artery A being the renal artery with superior disposition to the inferior renal artery, identified in the image as artery B.

According to the classification of Sampaio, et al., 1992, the upper right renal artery and lower right renal artery are classified as hilar arteries, since these are directed to the renal hilum.

It should be noted that both hilar arteries mentioned above emit three hilar branches, one lower, one median and one upper each, identified by the letters C to H in Figure 3.

It should be noted that the superior branch (artery C) emitted by the superior hilar artery (artery A), according to the nomenclature adopted in this study, can be classified as an extra hilar superior polar artery branch, since it is a branch coming from a hilar renal artery that enters the kidney through the upper pole.

In agreement with the studies presented by Özkan et al., 2006, Holden et al., 2005, and Ugurel et al., 2010, the variation in renal irrigation found in the present study was identified on the right side.

It is worth mentioning that anatomical variations in abdominal vessels are not restricted to renal vasculature only, cases that mention variations in other abdominal vessels such as variations in the portal vein and celiac trunk are described in the literature.17,18

Regarding the prevalence of anatomical variation found in the present case, two right hilar arteries with an upper polar extra-hilar arterial branch were found in only 3.4% (9/266) of the kidneys analyzed in the study published by Sampaio et al., 1992. At the same time, when the presence of the extra-hilar upper polar branch was described, the presence of two hilar arteries, found in this study, is presented in the literature as the most prevalent variation.

4 CONCLUSION

According to the objective based on the presentation and analysis of the presence of variations of the right renal artery and its respective segmental arteries and on the anatomic description and classification of such variations, it can be concluded that the right supernumerary renal artery found in this study, is an anatomical variation because it is not found in most humans, besides, it is attributed to this, the hilar renal artery classification, because it is directed to the renal hilum.

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CHAPTER 17

CONTAMINATION BY CHAGAS DISEASE IN BLOOD DONORS: SCIENTIFIC BASIS FOR HEALTH CARE

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ABSTRACT: Chagas disease is an infectious disease, which after the contamination of the human organism by Trypanosoma cruzi can be transmitted, especially, via oral, transplacental, organ transplantation, intravenous drug use, and blood transfusion. In this group, the blood donors stand out, who, based on the actions of prevention in health aimed at controlling the propagation of the disease, pass through a qualified screening so that transmission does not occur in the person who is going to receive the donation. In this context, this study seeks to analyze the scientific productions referring to the evidence on Chagas Disease Infection in blood donors. It is an integrative literature review, descriptive, exploratory and qualitative. The search for the articles was carried out in the databases: Latin American and Caribbean Literature in Health Sciences (LILACS), Medical Literature Analysis and Retrievel System Online (MEDLINE), and in the virtual libraries Google Academic and Scientific Electronic Library Online (SciELO). The criteria for inclusion of the research were: complete articles, free of charge, published between 2013 and 2023, bringing together 10 articles on the theme. Descriptive statistics and two tables were used for the best assessment. During the analysis, the articles of the years 2014 and 2021 were prevalent, and, it was noticed that in all regions of Brazil that were studied, the male sex was predominant. The studies show that even in the face of preventive health actions, several factors are responsible for the persistence of the risk of transfusion transmission of Chagas Disease. It is also concluded, by means of the analyzes, that in Brazil, haemovigilance, the set of primordial actions that result in the prevention and promotion of people who are going to donate and receive blood byproducts, has consolidated itself as a fundamental strategy in the monitoring and control of the disease.

KEYWORDS: Chagas Disease, Blood donation, Comprehensive review.

RESUMO: A Doença de Chagas é uma patologia infecciosa, que após a contaminação do organismo humano pelo Trypanosoma cruzi, pode ser retransmitida, especialmente, via transmissão oral, transplacentária, por transplante de órgãos, uso

de drogas intravenosas e transfusão sanguínea. Nesse grupo, destacam-se os doadores de sangue, que baseado nas ações de prevenção em saúde voltadas ao controle da propagação da doença, passam por uma triagem qualificada para que não ocorra a transmissão naquele que irá receber a doação. Nesse contexto, este estudo busca analisar as produções científicas referentes às evidências sobre a Infecção por Doença de Chagas em doadores de sangue. Trata-se de uma revisão integrativa da literatura, descritiva, exploratória e qualitativa. A busca pelos artigos foi realizada nas bases de dados: Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Medical Literature Analysis and Retrievel System Online (MEDLINE), e nas bibliotecas virtuais Google acadêmico e Scientific Electronic Library Online (SciELO). Os critérios de inclusão da pesquisa foram: artigos completos, gratuitos, publicados entre 2013 e 2023, reunindo 10 artigos sobre o tema. Utilizou-se a estatística descritiva e exposição em dois quadros para a melhor apreciação. Durante a análise, os artigos dos anos de 2014 e 2021 foram prevalentes, e, percebeu-se que em todas as regiões do Brasil que foram estudadas, o sexo masculino foi predominante. Os estudos evidenciam, que mesmo diante de ações de saúde preventivas, vários são os fatores que propiciam a persistência do risco de transmissão transfusional da Doença de Chagas. Conclui-se ainda, por meio das análises, que no Brasil, a hemovigilância, o conjunto de ações primordiais que resultam na prevenção e na promoção de pessoas que irão doar e receber hemoderivados, consolidou-se como uma estratégia fundamental no monitoramento e no controle da doença.

PALAVRAS-CHAVE: Anatomia, Variações, Artéria renal.

1. INTRODUCTION

Chagas Disease (CD) is a zoonosis caused by the monoflagellate protozoan *Trypanosoma cruzi*. The parasite has a complex biological cycle, classified as heteroxenous, and undergoes different evolutionary forms inside its vertebrate hosts (humans, coatis, opossums, armadillos, bats, pacas, porcupines, monkeys, dogs, cats, among others), as well as in insect vectors: *Triatoma infestans, Triatoma sordida, Triatoma rubrovaria, Triatoma pseudomaculata, Triatoma brasiliensis, Panstrongylus lutzi, Panstrongylus megistus,* among others. Throughout the Southern Cone (Argentina, Bolivia, Brazil, Chile, Paraguay, and Uruguay), *Triatoma infestans* was the main agent responsible for Chagas endemicity (Menezes et al., 2019).

Vector-borne transmission of CD is considered the most epidemiologically significant route, accounting for 80% of the disease cases. However, recent studies show that in Brazil and several other Latin American countries, the occurrence of Chagas infection transmission in urban areas through blood transfusions has significantly contributed to the increase in disease cases (Araújo, 2022).

The first record of transfusional transmission of CD was confirmed in Brazil in 1952 by Pedreira de Freitas in São Paulo, who reported two cases of patients infected by this route. Since then, various studies have been conducted to monitor and promote actions to prevent this form of transmission in both rural and urban populations (Moraes-Souza et al., 2006).

It is estimated that 60% of contaminated individuals reside in urban spaces and large cities, with 50% of these cases identified in the chronic phase, constituting a group of potential blood donors, thus increasing the risk of transfusional CD (Costa et al., 2013).

The rural-to-urban migration process over the last few decades, driven by the industrialization of Brazil, led to the urbanization of “Chagas patients.” This phenomenon was responsible for the high prevalence of Chagas-positive donors in the country’s blood banks (Moraes-Souza et al., 2006).

In the 1970s, blood donations were concentrated in major urban centers, and the technological infrastructure for blood collection was rudimentary. At that time, donors were remunerated, and in large numbers, there was no control over the

transfused blood. In 1976, the Ministry of Health established the need to implement public blood centers based on voluntary donations (Costa et al., 2013). However, it was only during the VIII National Health Conference in 1986 that the issue of Chagas disease transmission via blood transfusion was addressed.

In 1988, the new Brazilian Constitution expanded chemical vector control to approximately 2,450 municipalities. Moreover, it banned paid blood donors, regulated blood therapy practices, created a national blood and blood derivatives system, and instituted mandatory serological screening of donation candidates. These measures significantly contributed to the reduction in disease prevalence among blood donors (Costa et al., 2013).

In addition to blood transfusion transmission, other forms of transmission between humans and animals deserve mention, including infected feces, oral transmission, transplacental transmission, organ transplantation, intravenous drug use, and workplace accidents involving contaminated objects. Despite this extensive list, blood transfusion remains the second most common transmission route of this disease, necessitating serological screening capable of detecting the presence of the parasite. Thus, investigating the main scientific evidence on CD among blood donors is epidemiologically important to understand this population's profile, screening procedures, and possibly the most effective care strategies.

Based on these premises, this study aims to analyze the scientific literature regarding evidence on Chagas infection in blood donors.

2. METHOD

This is an integrative literature review, descriptive, exploratory, and qualitative in nature. As such, the search for articles was conducted in the following databases: Latin American and Caribbean Literature in Health Sciences (LILACS), Medical Literature Analysis and Retrieval System Online (MEDLINE), and the virtual libraries Google Scholar and Scientific Electronic Library Online (SciELO).

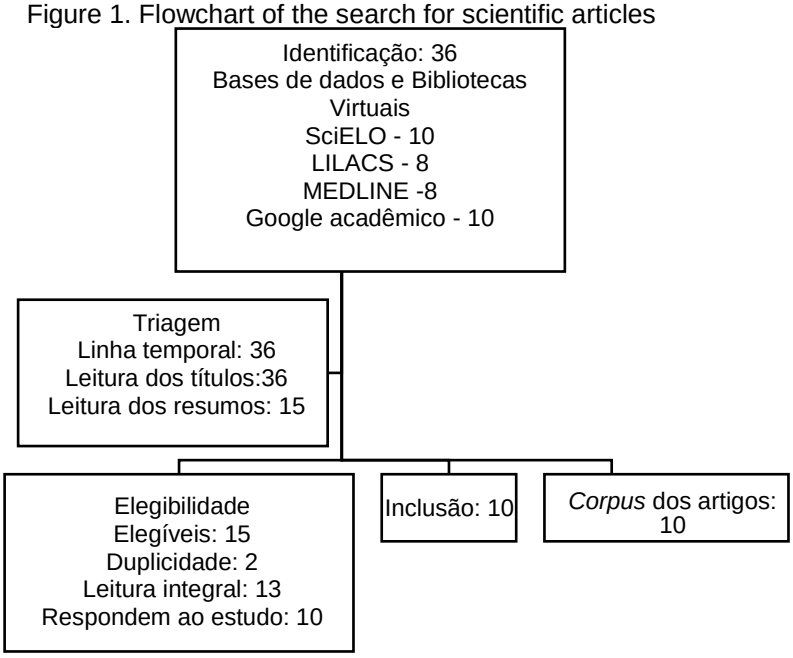
The inclusion criteria for the research were: full-text, free articles published between 2013 and 2023, in Portuguese, English, and Spanish, that answered the research objective and its research question. The following were excluded:

dissertations, theses, and papers published in conference proceedings. The research descriptors defined were: Chagas Disease; Evidence-based clinical practice; Blood donation; Care; Health, following the Health Sciences Descriptors (DeCS), combined with the Boolean operator “AND.” Data collection took place in June 2023.

In the first stage of the search, following the inclusion criteria, the descriptors were defined, as previously mentioned. Then, the databases/libraries to be used were established, as previously defined. Next, the Boolean operators were chosen, with “AND” being the selected option. The search was conducted according to the outlined inclusion criteria. Initially, the temporal filter (2013–2023) was applied, followed by the language filter, and then titles were reviewed. Subsequently, the abstracts of the articles selected based on title analysis were read, and only those meeting the inclusion criteria had their abstracts further analyzed. After that, the remaining articles were read in full. During the final reading, the articles were cataloged to extract variables in an organized manner. At this point, the body of the research was formed with the articles that were fully read and confirmed according to the inclusion criteria.

The publications were organized in a single table using Microsoft Word, where the information characterizing the materials found was displayed: authors, titles, objectives, journal/databases/virtual libraries of publications, and the method used. A second table was prepared, listing the year of publication and the most relevant aspects of the theme highlighted in each publication. Descriptive statistical analysis was chosen to provide an overview of the topic in an organizational and inductive manner. The following flowchart presents the number of articles at each stage for better visualization:

Figure 1. Flowchart of the search for scientific articles



Source: Research data (2023)

3. RESULTS AND DISCUSSION

It is understood that integrative literature review studies introduce the reader to an update of ideas and opinions on a given topic, in addition to gathering recent information described through characteristics that address the knowledge surrounding it, thereby promoting an improvement in clinical practice on the subject the study was developed. Therefore, exploring the results in an integrative review is pertinent, as it allows for the expansion of knowledge and the systematization of scientific findings (Mendes, Silveira, Galvão, 2008). The results were organized based on the following data: authors, title, objective, journal, method used, and the most relevant aspects of the theme.

Table 1. Presentation and characteristics of the scientific articles found, 2023

Authors	Title	Purpose	Periodic	Method
PEDROSA *et al.*	Estudo retrospectivo de sororreatividade para *Trypanosoma Cruzi* em doadores de sangue da região Noroeste do Rio Grande do Sul, Brasil.	Investigate the results of the serological screening for CD of donors from the Blood Bank of the municipality of Santiago, Rio Grande do Sul, in the period from June 2001 to May 2011.	Journal of Tropical Pathology	Quantitative study using HEMOVIDA system using descriptive statistics and documentary data.
TELES *et al.*	Prevalência de infecção pelo *T. cruzi* em doadores de sangue.	To know the prevalence of *Trypanosoma* cruzi among the candidates for blood donation, in a blood center in a region of northeastern Brazil.	Hematol Transfus Cell Ther	The data was obtained by the computerized system of the Hemocenter in the period from January to December in the year 2019.
COSTA *et al.*	Inaptidão de candidatos à doação de sangue relacionada à soropositividade para a infecção chagásica nas diferentes regiões do Brasil	To analyze the prevalence of incompetence in candidates for blood donation with positive serology for CD by regions of Brazil between the years 2000 to 2013.	Electronic Magazine of the Faculty of Ceres	Quantitative and comparative study, with use of descriptive method.
SILVA *et al.*	Soroprevalência da DC em candidatos a doadores de sangue no Instituto de Hematologia e Hemoterapia do Amapá (HEMOAP)	To analyze the seroprevalence of CD in potential blood donors at the Amapá Hematology and Hemotherapy Institute (HEMOAP), in the period from January 2015 to September 2018.	C Biological Agrarian and Health Trials and Science	Retrospective, quanti-qualitative research in which the donor records in the HEMOAP system reagents to CD were analyzed.
COSTA *et al.*	Prevalência da infecção pelo *T. cruzi* em doadores de sangue	Estimate the prevalence of T. cruzi in blood donors from the state of Ceará.	Brazilian Archives of Cardiology	Descriptive retrospective study carried out in the period 2010 to 2015, from data recorded in the computerized system of the Center for Hematology and Hemotherapy of

				Ceará (HEMOCE).
COGO *et al.*	Perfil epidemiológico de doadores de sangue soropositivos para DC na região sul	To know the epidemiological profile of HIV positive donors for CD.	Revista Saúde.	Quantitative study, in which a serological screening of 25,207 donations was carried out in the period from January 2004 to December 2007 in the Hemotherapy Service (SHT) of the University Hospital of Santa Maria (HUSM).
NOGUEIRA *et al.*	DC: prevalência de anticorpos anti-*Trypanosoma cruzi* em doadores de sangue do hemocentro regional de Catalão, Goiás.	He analyzed the seroprevalence of CD at the Regional Haemocenter of Catalão.	Ciências Biológicas do Sudeste Goiano.	The research method was guided by data collection carried out at the Regional Hemocenter of Catalão, Goiás, through the donor database in the period from January 1 to December 31, 2010.
TEIXEIRA; OLIVEIRA.	Perfil de pacientes portadores de DC em Rio Branco, Acre, Brasil.	To evaluate the profile of patients with CD followed up in the Specialized Care Service (SAE) of the Hospital das Clínicas of Rio Branco, Acre, from 2004 to 2011.	Revista da Sociedade Brasileira de Clínica Médica	Records of patients with CD were evaluated in the SAE, in the period from 2004 to 2011, regarding the age group, gender, presence of comorbidities and the municipality of provenance.
TELES *et al.*	Prevalência da DC no hemocentro coordenador de Sergipe.	Analyze the epidemiological profile of HIV-positive candidates for CD.	*Brazilian Journal of Health Review*	Retrospective analysis of 77,791 individuals who were candidates for blood donation who were treated by Hemosis, in the period from 2015 to 2017.
PEREIRA *et al.*	Perfil clínico e epidemiológico da DC aguda no estado de Minas Gerais.	Know the clinical and epidemiological aspects of acute CD in the state of Minas Gerais.	Health Care Magazine	This is a descriptive, documentary study, with a quantitative approach, which

				had as its scenario the state of Minas Gerais.

Source: Research data (2023)

Continuously, Table 2 presents the main evidence found in the scientific productions analyzed in this research. It is of great importance to examine the year of publication and the evidence identified, as this allows for the mapping of when the publication was produced, bringing the most recent ones into consideration for the construction of new integrative reviews. By supporting the table below, it is understood that research seeking evidence is closely linked to improving decision-making in healthcare, which in this case refers to Chagas disease and all the context surrounding it and the blood donor (Faria; Oliveira-Lima; Almeida Filho, 2021).

Table 2. Relevant aspects and evidence on the topic in the scientific articles found, 2023

Authors	**Publication Year**	**Scientific evidence**
PEDROSA *et al.*	2016	Even though there are serologic tests and clinical screening, CD may go unnoticed. The study noted that no symptoms can be neglected, and the patient needs to be evaluated in a biopsychosocial way.
TELES *et al.*	2021	Knowing the donor profile is essential for the prevention of CD, as well as a good clinical and serological screening.
COSTA *et al.*	2015	The Southeast Region was the one that presented the majority of prevalences in relation to the DC. Transfusion evaluation is necessary to ensure patient safety in blood transfusion.
SILVA *et al.*	2021	The epidemiological profile of the greatest quantity was the male sex, in Amapá. Haemovigilance is the main health care strategy in preventing CD.
COSTA *et al.*	2020	In Ceará, there is a need for new tests with greater accuracy about CD, with more security and care for the families.
COGO *et al.*	2014	Predominance of males with diagnosis of CD. It points out more than 60% of positive cases in the screening for blood donation, being important the greater monitoring of cases and prevention strategies.
NOGUEIRA *et al.*	2014	Screening is indispensable in all cases for DC investigation. The seroprevalence of CD among blood donors of the Hemocenter was evidenced, exposing the need for control actions for the infection.
TEIXEIRA; OLIVEIRA.	2016	Male ancestry regarding infection, with patients over the age of 40. In Acre, there is a certain predominance of CD along with other chronic diseases, showing the vulnerability of the population.
TELES *et al.*	2021	Predominance of the male sex, above 25 years of age, with the highest index in the interior of the state of Sergipe. Need for greater recognition of symptoms to minimize disease infections.
PEREIRA *et al.*	2017	It is important to know the CD, prevalence and clinical manifestations to expand the

		scenario of implementation of actions and care.

Fonte: Dados da pesquisa (2023)

During the analysis, articles from the years 2014 and 2021 were prevalent, and, it was noticed that in all regions of Brazil that were studied, the male sex was predominant. The studies show that even in the face of preventive health actions, several factors are responsible for the persistence of the risk of transfusion of CD. The main factors involve: failures in clinical and serological screening, the prevalence of the disease in the region, the form and amount of transfused infected blood product, the immune situation of the recipient, the low level of serology coverage for T. cruzi in the hemotherapy services and the degree of sensitivity of the tests for serological diagnosis used in the possible donors (Menezes et al., 2019; Pedrosa et al., 2016).

The selected studies show that the prevalence of reagent serology for CD in the screening of blood donors, in the period of the 10 years analyzed, was 1%. In the literature, the studies produced over a decade ago, few analyzed the prevalence of this disease, using as a unit of analysis the donor, and not the donations. This framework limits and makes it difficult to carry out comparative analyzes. E, Sobreira et al. described that 1.9% among donors of the Iguatu hemocenter (Ceará) in 1996-1997, and Soussumi, 2.5% among first-time donors in Ribeirão Preto (São Paulo), between 1996-2001 (Santana, et al., 2018; Teles et al., 2021; Costa et al., 2015).

Other studies refer to the prevalence of the disease among donations, varying in Brazil between 0.1 and 0.3%, according to the most recent studies. The report of Brazilian hemotherapy production, with data from 2013, indicates 0.34% of reagent donations to CD in the screening among donors, with the highest percentages (0.5%) in the Northeast and Southeast. It should be pointed out that the comparison of the different prevalences between the regions and services should take into account, besides the real magnitude of the infection in the corresponding geographical region, the sample size, the serological techniques used and the methodology employed in the study (Santana et al., 2018; Silva et al., 2021; Costa et al., 2020; Cogo et al., 2014).

Regarding the characteristics of the donors, when comparing the finding of higher prevalence among males, a variation was observed in the literature, depending on the area and year of the study. As for the higher prevalence of individuals with a date of birth before 1960, similar to the one identified in other studies, it may be related

to the actions of vector control, more intense from the 1980s onwards. Unfortunately, the second highest prevalence was identified among individuals with a birth date after 1991, requiring research to understand what is occurring (Brito et al., 2022; Nogueira et al., 2014).

The higher prevalence between reagent serology and low schooling was also identified in other studies, as well as among those who reside in municipalities with lower urbanization rate, although the differences were not statistically significant, in relation to the urbanization rate (Brito et al., 2022; Teixeira; Oliveira, 2016).

In previous studies, the highest frequency of confirmed cases among first-time donors was also observed, although the highest prevalence found was among return donors, and this difference was not statistically significant. Unlike the higher prevalence presented here, higher percentages of positive in birth strata between 1981 and 1990 are noted, and among individuals with schooling in the full middle category, demanding caution in the interpretation of results (Brito et al., 2022; Teles et al., 2021).

Pereira et al. (2017), among 216 municipalities evaluated, there were HIV-positive people for DC in 131 (60.6%) of them. A distribution of the frequency of municipalities by very similar prevalence ranges is observed between the two studies (Santana, et al., 2018). Prevalence among donors is expected to be always lower in relation to the population in general, since these are individuals previously screened clinically and a large part of them already screened serologically as well, in the case of returning donors. Therefore, the finding of prevalence suggests an increase in the number of cases in the last few years. It is important to emphasize, however, that these results refer to reagent serology in the screening of donors, carried out with Elisa methodology, which may not have its result reproduced by another methodology, may not be, in some cases, Chagas infection (Santana, et al., 2018; Pereira et al., 2017).

4. FINAL CONSIDERATIONS

The study concluded that the need for screening and serologic testing beyond the procedure to investigate the donor as a whole is of paramount importance. However, it is necessary to know the epidemiological profile of each region, so that health prevention strategies can be developed.

Thus, it is understood that the existing serologic tests are pertinent to the use in the screening of blood donation, but, a general assessment of the donor, his life context, the apparent symptoms and the history of other diseases is necessary. In response to the problematic questions of this study, the main evidence on the theme is around understanding and analyzing the donor profile, i.e., it is important for health care and for the prevention of diseases in a transfusion process.

In this context, what is currently being held on the theme is that there is a need for a wider and biopsychosocial screening of the patient who is going to donate blood. It is known that the male sex is predominant, it is ideal to encourage men to care for their health and to seek to follow up their clinical situation, so that when donating blood, it does not compromise those who will receive the donation. These actions are part of a set of strategies needed to verify the epidemiology, care and the pipelines that surround CD.

Further research on the topic, especially direct in the field, is recommended to point out new results and evidence on the subject. CD is a transmissible disease, and in this study, because the male sex is predominant in the occurrence in this condition, it is pointed to the need for special attention in the serological screening for this group of individuals. In addition, epidemiologically, each region of Brazil has social and economic differences, in which it can be concluded that the study of the epidemiological profile of each state, based on epidemiological surveillance actions, becomes indispensable to identify CD and prevent contamination.

To carry out analyzes retrospectively is of paramount importance in the control of the spread of Chagas infection, and it is also necessary, in addition to researches investigating this theme, the constant improvement of DC surveillance actions, above all, hemovigilance, which is currently one of the main preventive strategies of monitoring, guided by a set of actions that result in the prevention and promotion of people who will donate and receive blood byproducts.

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CHAPTER 18

STINGRAY INJURIES IN BRAZIL: A BRIEF SYSTEMATIC REVIEW

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ABSTRACT: Injuries caused by freshwater stingrays are frequent in the Paraná, Paraguay, Araguaia, Tocantins rivers, and their tributaries in Brazil. These injuries initially result in acute pain, which can progress to life-threatening conditions in the absence of appropriate therapeutic interventions. The aim of this review was to identify the main aspects of freshwater stingray injuries in Brazil, with special emphasis on stingray biology, clinical management of morbid events, and available therapeutic strategies. The review was conducted using PubMed, LILACS, and SciELO databases with a defined search strategy. Initially, 393 articles were identified from the search phrase. After applying inclusion and exclusion criteria, 10 articles were selected for the study according to the PRISMA protocol. The results indicate that understanding the characteristics of freshwater stingray injuries is crucial for accurate diagnosis and implementation of effective treatments. Such injuries can lead to severe complications,

including potential mortality risks. This study underscores the urgent need for further research in this scientific field to improve clinical management and therapeutic strategies for these challenging conditions.

KEYWORDS: Brazil, Poisonous animals, epidemiology, stingrays.

RESUMO: As lesões provocadas por arraias de água doce são frequentes nos rios paraná, paraguai, araguaia, tocantins e seus afluentes no brasil. Essas lesões inicialmente resultam em dor aguda, podendo evoluir para condições letais na ausência de intervenções terapêuticas adequadas. O objetivo desta revisão foi identificar os principais aspectos das lesões por arraias de água doce no brasil, com especial ênfase na biologia das arraias, na gestão clínica dos eventos mórbidos e nas estratégias terapêuticas disponíveis. A revisão foi realizada nas bases de dados pubmed, lilacs e scielo com uma estratégia de busca definida. Foram inicialmente identificados 393 artigos a partir da frase de pesquisa. Após a aplicação de critérios de inclusão e exclusão, 10 artigos foram selecionados para o estudo, de acordo com o protocolo prisma. Os resultados indicam que compreender as características das lesões provocadas por arraias de água doce é crucial para o diagnóstico preciso e para a implementação de tratamentos eficazes. Tais lesões podem desencadear complicações graves, incluindo riscos potenciais de mortalidade. Este estudo sublinha a necessidade premente de novas investigações neste campo científico para melhorar a gestão clínica e terapêutica dessas condições desafiadoras.

PALAVRAS-CHAVE: Brasil, Animais peçonhentos, Epidemiologia, Arraias.

1. INTRODUCTION

Injuries in humans caused by marine or freshwater fish are referred to as ictism. These injuries can be classified as sarcotoxic, which refers to the ingestion of toxins present in the animals' tissues, and acanthotoxic, which occurs due to stings or bites from fish such as stingrays, for example (FUNASA, 2001).

Injuries occur when the victim invades the animals' habitat or during handling. Stingrays possess sharp, serrated stingers, covered by a tegument sheath under which venom glands are found, located on the dorsal, pectoral fins, or tail (FUNASA, 2001). Acanthotoxic injuries are mainly caused by marine stingrays (*Dasyatis guttatus, D. americana, Gymnura micrura*, etc.), and freshwater stingrays (*Potamotrygon hystrix, P. motoro*) (FUNASA, 2001).

Freshwater stingrays in Brazil belong to the *Potamotrygonidae* family and are adapted to live and reproduce exclusively in freshwater. These animals are predominant in South America, and in Brazil, they are found in the Amazon, Tocantins-Araguaia, Paraná, and Parnaíba river basins (Garrone Neto, Domingos; Haddad Júnior, Vidal, 2010).

In cases of injuries caused by stingrays, the primary symptom reported is intense localized pain, associated with erythema and edema. In some cases, the condition may progress more severely, leading to cutaneous necrosis of varying severity and systemic effects such as fever, tachycardia, cold sweating, nausea, vomiting, and agitation.

Secondary bacterial infection may also occur, requiring treatment with antibiotics. The lack of knowledge on the subject and the absence of a clinical protocol may lead to inadequate treatment, aggravating the patient's condition (Garrone Neto, Domingos; Haddad Júnior, Vidal, 2010).

Given the need for a clinical protocol to address stingray injuries, the objective of this article is to review the available treatment data used in patient care and to demonstrate the impacts of stingray-caused injuries (Garrone Neto, Domingos; Haddad Júnior, Vidal, 2010).

2. METHODS

The search for articles was conducted in the following electronic databases: U.S. National Library of Medicine (PubMed – https://pubmed.ncbi.nlm.nih.gov/), Latin American and Caribbean Health Sciences Literature (LILACS – https://lilacs.bvsalud.org/), and Scientific Electronic Library Online (SciELO – https://www.scielo.br/). Initially, the research focused on finding original articles, without date restrictions, that addressed the following topics: (I) Freshwater stingray injuries and (II) Management of freshwater stingray injuries. The search terms were selected according to the Health Sciences Descriptors (*DeCS/MeSH* – https://decs.bvsalud.org/) from the Virtual Health Library, using the boolean operator "AND": "Brazil", "Stingrays", "Epidemiology", "Poisonous Animals" (Table 1).

Table 1. Search strategy used in the literature review and the results found in the databases.

Search strategy	LILACS	PubMed	SciELO
"*Brazil*" AND "*Stingrays*"	22	77	5
"Brazil" AND " Poisonous Animals"	0	20	16
"Poisonous Animals" AND "Stingrays"	7	1	2
"Epidemiology" AND "Stingrays"	5	25	1
"Epidemiology" AND "Poisonous Animals"	166	32	14
TOTAL	200	155	38

Source: prepared by the authors

The inclusion of studies was based on the following criteria: (a) original articles, (b) information on the diagnosis of freshwater stingray injuries in Brazil, and (c) information on the therapeutic management of injuries caused by freshwater stingrays present in the country. Accordingly, all manuscripts that could be classified under at least one of the following items were excluded: (i) articles focused on animals other than freshwater stingrays, (iii) texts addressing marine stingray injuries, and (iv) manuscripts that did not describe the diagnosis and/or therapeutic management of freshwater stingray injuries.

Articles published up until January 31, 2022, were analyzed, and no restrictions were imposed regarding language, location, or type of study. Following the analysis, 10 articles were selected, which were supplemented by other texts, such as book chapters and official documents from national and international institutions, to compose the present review. The information was organized into the following topics:

(1) Clinical Findings, (2) Therapeutic Approach, and (3) Prevention, using the articles selected in Table 2 for results and discussion.

Table 2: List of articles selected for the study

Work and Reference	Research Method	Problems addressed	Study category
Garrone Neto el al (2010) Arraias em rios da região Sudeste do Brasil: locais de ocorrência e impactos sobre a população.	Interviews with riverside residents and health professionals to gather information on the occurrence of stingrays and accidents associated with these animals.	Describe the colonization process of the Upper Paraná Basin, Southeast Brazil, by stingrays, demonstrating its current situation and probable trend.	Case report
Rensch GP, Elston DM. (2019) Aquatic antagonists: stingray injury update	Review of injuries caused by stingrays.	Need for prevention strategies and use of leg protectors to reduce stingray injuries.	Literature Review
COSTA, J. A. et al (2021) Acidentes causados pela arraia fluvial Potamotrygon motoro em comunidades lacustres em Território do bioma Oriental da Amazônia.	Semi-structured questionnaires with the participation of artisanal fishermen.	The article discusses injuries caused by freshwater stingrays that are common among fishermen.	Cross-sectional descriptive analysis.
SANTOS, Juliane Monteiro dos. (2020) Estudo da interação organismo-ambiente-sociedade: uma perspectiva ecológica sobre as arraias de água doce (família Potamotrygonidae).	Describe the aspects of the distribution, biology and physiology of potamotrigonids of the upper and middle Tocantins River from the point of view of organism-environment interaction.	Organism-environment interaction.	Qualitative study.
PIMENTA, R. S. et al. (2017) An efficient protocol for avoid sequelae over stingray sting injury.	Mechanism of venom, clinical picture, injury and treatment.	Injuries caused by stingrays and implemented therapies.	Technical Note
Afonso, P. M. A. et al. (2017) Injuries caused by freshwater stingrays in the Tapajós River Basin: a clinical and sociodemographic study.	A convenience sample of 300 local adults was used to obtain data through questionnaire/interview.	Identify sociodemographic, clinical and therapeutic aspects related to stingray injuries	Cross-sectional descriptive analysis

Almeida. J. G. S. et al.(2018) Delayed healthcare and secondary infections following freshwater stingray injuries: risk factors for a poorly understood health issue in the Amazon.	cross-sectional study used surveillance data from 2007 to 2014 to identify factors associated with secondary infections from stingray injuries.	to describe the lesion profile of freshwater stingrays in the State of Amazonas, Brazilian Amazon, and to identify the associated risk factors for secondary infections.	Cross-sectional descriptive analysis
HOLANDA, Marlon Negreiros de et al. (2019) Acidente e lesão vascular com arraia no Alto Juruá, Acre, Brasil: um relato de caso.	Describe an accident and vascular injury with venomous animals of the stingray type at the top of Juruá, Acre, Brazil.	Vascular injury caused by stingray.	Case report.
Oliveira ,Adriano Teixeira de Oliveira de et al. (2020) Conhecimento tradicional de pescadores de arraias de água doce da região Amazônica.	Analysis of the socioeconomic profile and traditional knowledge about freshwater stingrays in reports from fishermen in the municipality of Barcelos, Amazonas	Injuries caused by stingrays and the therapy used in the municipality of Barcelos, Amazonas.	Transversal
Lameiras,Juliana. (2013) Arraias de Água Doce. (Chondrichthyes Potamotrygonidae):Biologia, Veneno e Acidentes.	Review of publications on the biology, venom and accidents related to freshwater stingrays.	Assess injuries caused by stingrays and appropriate treatment.	Literature review.

Research deadline: 01/31/2022.
Source: prepared by the authors.

3. RESULTS AND DISCUSSION

3.1 CLINICAL FINDINGS

The frequency and severity of injuries caused by *Potamotrygon motoro* in two municipalities in the Eastern Amazon biome revealed that the primary symptom associated with the injury was pain, along with edema, which was present in all cases (Rensch GP, Elston DM, 2019). Regarding pain intensity, it was reported as unbearable in 70% of cases, bearable in 17.5%, and mild in 12.5%. Additionally, ulcers were observed in 52.5% of the victims, and necrosis occurred in 70% of the reported cases (Rensch GP, Elston DM, 2019). The researchers also noted that most victims

did not seek hospital care, instead using unconventional treatments such as smoke from burnt burlap sacks, potato starch, stingray fat, saliva, and even human feces applied to the wound. This underscores the urgent need for intervention and the development of a clinical protocol to address the medical needs of this population (Rensch GP, Elston DM, 2019).
Bacterial infection is one of the main causes of complications in stingray injuries. Various bacterial species inhabit stingray mucus, human skin, and the aquatic environment and can be introduced at the time of the puncture. Common causes of soft tissue infections include *Staphylococcus* and *Streptococcus* species, as well as *Aeromonas* and *Mycobacterium* species, which have been reported to exhibit antibiotic resistance. However, it is crucial to emphasize the importance of addressing vaccination with the patient, as there are reports of severe tetanus cases following stingray injuries (Rensch GP, Elston DM, 2019).

3.2 THERAPEUTIC APPROACH

Freshwater stingray stings represent a significant concern in regions where these animals are common, such as rivers and their tributaries in South America. These incidents are known to cause intense pain, localized inflammation, and, in severe cases, can result in serious complications if not properly treated (Costa, J. A. DA; Martins, A. P. B.; Feitosa, L. M. et al, 2021).

Initial treatment for a freshwater stingray sting typically involves the immediate immersion of the affected area in hot water, around 45°C, for approximately 60 minutes. This procedure aims to denature the venom's toxins, reducing pain and limiting the extent of envenomation (Costa, J. A. DA; Martins, A. P. B.; Feitosa, L. M. et al, 2021). Additionally, it is essential to thoroughly disinfect the wound to remove any fragments of the stinger and reduce the risk of secondary infections (Costa, J. A. DA; Martins, A. P. B.; Feitosa, L. M. et al, 2021).

Early administration of analgesics and anti-inflammatory drugs is crucial for controlling the pain and swelling associated with the sting. Broad-spectrum antibiotics are often prescribed to prevent secondary bacterial infections, especially in cases

where the sting penetrates deeply into the skin or involves areas at high risk of contamination (Costa, J. A. DA; Martins, A. P. B.; Feitosa, L. M. et al, 2021).

Recent studies (Costa, J. A. DA; Martins, A. P. B.; Feitosa, L. M. et al, 2021) highlight the importance of prolonged antibiotic therapy, lasting up to 21 days, combined with continuous wound hygiene care to prevent severe complications and promote complete healing. Adequate antibiotic therapy not only controls potential infections but also significantly improves functional and aesthetic outcomes post-injury. Future research should focus on the development of more targeted therapies, such as the use of specific antidotes for freshwater stingray injuries, which can effectively neutralize the venom's toxins. Furthermore, investigating new analgesic and anti-inflammatory agents with fewer side effects could further improve the clinical management of these cases. It is important to emphasize that clinical protocols should be developed by researchers in the field, based on patient care, and this article only discusses observed/researched facts.

3.3 PREVENTION

It is crucial that tourists and swimmers in areas inhabited by stingrays are properly informed about preventive measures to avoid injuries. When entering rivers known to be stingray habitats, it is recommended to use a wooden stick to push the stingrays away before stepping into the area, thus reducing the risk of accidental stings. Additionally, the use of polarized sunglasses can help to spot stingrays in shallow waters, increasing situational awareness and preventing unexpected encounters (Costa, J. A. da; Martins, A. P. B.; Feitosa, L. M. et al., 2021).

For fishermen and riverside populations who frequently come into contact with stingrays during their activities, investing in protective gear for the lower limbs is essential. This equipment minimizes the risk of direct contact with the fish, thereby reducing the chances of being stung. Specific gloves are also recommended when handling fish by hand, providing an extra layer of protection against stingray injuries (Almeida, J. G. S. et al., 2018; Holanda, M.N de et al., 2019; Oliveira, A.T.O de et al., 2020).

The implementation of these preventive measures not only protects individuals from painful and potentially dangerous stings but also contributes to maintaining health and safety in aquatic environments where stingrays are present. Public awareness and continuous education on these practices are essential to ensure safe and sustainable aquatic spaces for all users, promoting harmonious coexistence between humans and aquatic fauna (Costa, J. A. da; Martins, A. P. B.; Feitosa, L. M. et al., 2021).

By adopting simple and effective preventive measures—such as the use of wooden sticks, polarized sunglasses, protective gear, and specific gloves— the risk of stingray injuries can be significantly reduced. These actions not only help prevent potentially serious injuries but also enhance awareness and safety in aquatic environments, benefiting both local residents and visitors (Silva, P.M., 2019; Lameiras, J., 2013).

4 FINAL CONSIDERATIONS

Injuries caused by stingrays represent a serious risk, particularly for populations such as fishermen, swimmers, and riverside communities in both marine and freshwater environments. These injuries often result in intense localized pain, skin necrosis, and, in severe cases, complications that can lead to death. The management of these complications is further complicated by secondary infections and the retention of stinger fragments in the wound—issues that remain understudied due to underreporting in remote areas where these accidents occur.

Current treatment for stingray injuries primarily involves symptomatic measures, such as the use of hot water to control pain. Effective preventive measures are virtually nonexistent, underscoring the urgent need for the development and implementation of more robust prevention strategies. The lack of specialized technical knowledge for the appropriate treatment of these injuries can result in additional complications and worsening of the clinical condition, highlighting the importance of continuous training and education for healthcare professionals working in areas prone to such incidents. It is important to note that, unlike many other venomous animals such as snakes, scorpions, and spiders, stingrays primarily use their stingers for self-defense rather than for prey capture. This behavior reinforces the need for greater understanding of

the ecology and behavior of these animals to better inform preventive measures and risk management strategies. Additional research in this field is imperative to fill knowledge gaps and develop more effective approaches for preventing and treating stingray injuries.

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