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POST-THORACOTOMY PAIN SYNDROME – ALGORITHM OF PREVENTION, DIAGNOSIS AND TREATMENT

ABSTRACT

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INTRODUCTION

Although thoracic surgery is a relatively new specialty among surgical disciplines, it has experienced exponential development in the past twenty years, both in terms of radicality and invasiveness. The thoracic surgical procedures practiced today in modern medicine are characterized by increased complexity and radicality while strictly adhering to the principles of minimally invasive approaches. This type of approach has proven its advantages, as patients who have undergone minimally invasive surgical techniques have significantly reduced complication rates, with a minimal duration of pleural drainage, and in some cases, drainage is no longer necessary.

One of the most unpleasant complications experienced by patients is the occurrence of post-thoracotomy pain. Thoracic surgical interventions are known to be among the most painful procedures. The use of minimally invasive techniques and modern analgesic methods have effectively controlled postoperative pain, resulting in a decrease in the average length of hospital stay for patients undergoing thoracic surgery.

A distinct entity is the development of post-thoracotomy pain syndrome, defined as the persistence of pain in the thoracotomy area for more than two months after surgery. Chronic pain that arises in this way can be subjectively experienced differently by each individual patient and can vary in intensity, ranging from a simple sensation of local discomfort to intense and debilitating pain that impairs the daily activities of patients, negatively affecting their quality of life.

The mechanisms underlying the development of this pain syndrome are not fully understood, which is why there is currently no consensus on its diagnosis, evaluation, and management.

This study aims to extensively investigate postoperative thoracic pain, including understanding the mechanisms of post-thoracotomy pain syndrome and its morphological substrate, early identification of preceding signs and symptoms, and the identification of patients at risk of developing this syndrome. The objectives of this study are to develop an algorithm that accurately identifies patients at high risk of developing chronic pain, taking into account the analysis of all conditions that may represent additional risk factors, such as pain threshold sensitivity, the presence or absence of preoperative pain, the type of surgical technique used, the quantity and type of analgesics used both pre- and post-operatively, the duration of thoracic drainage, and so on. Such an algorithm would serve as a valuable tool to assist the surgeon in choosing the optimal surgical approach for the best short, medium, and long-term prognosis for their patients.

This study aims to provide a detailed analysis of the conditions underlying pain, considering all aspects, as well as the means of investigation and modern treatment options by consulting the latest developments in the field found in the specialized literature, and attempting to find new opportunities for selecting the optimal surgical approach.

I believe this study aligns with modern scientific writings because its stated goals align with the global trend in medicine to create increasingly aggressive surgical treatment modalities through minimally invasive approaches that limit the occurrence or reduce the intensity of pain as efficiently as possible.

The reason why a significant percentage of people avoid or indefinitely postpone surgical interventions, sometimes until it is too late, is precisely the fear of the suffering caused by pain. Having less pain means having a happy patient with high morale, good psychosocial and professional reintegration capacity, better compliance with subsequent treatments where applicable, increased trust in physicians, which leads to improved patient follow-up and awareness of the importance of regular medical check-ups. Having less pain overall means a visible improvement, if not in the quality of medical care, at least in the population's perception of the national healthcare system, and it reduces the fear some patients may have about seeking medical attention.

PURPOSE

This study aims to elucidate the conditions underlying the development of chronic pain in patients undergoing thoracic surgeries. Given the complexity of the topic and the subjective nature of pain, we have approached the subject from multiple perspectives:

a. Anatomopathological: by analyzing the histological changes in the intercostal nerves involved in the surgical procedure in patients who developed chronic pain syndromes of unbearable intensity, leading to subsequent surgical intervention for the removal of affected intercostal nerves.

b. Surgical: by analyzing both the surgical approach and the techniques used for thoracic closure.

c. Medical: by analyzing the analgesic therapies used during the initial hospitalization period for thoracic surgery.

The goal of this doctoral study is to establish an efficient algorithm for the prevention, diagnosis, and treatment of chronic pain that occurs following thoracic surgeries.

STUDY PREMISES

In pursuing the objective of this doctoral study, we have started from the following premises:

1. The majority of thoracic surgeries are performed through intercostal space access. As mentioned earlier, the intercostal space is richly innervated, and therefore, the manipulation of surgical instruments during the entire surgical procedure generates pain.
2. It is well-known in thoracic surgery that one of the most frequent intraoperative incidents related to the surgical approach is rib fracture during thoracotomy and placement of the rib spreader. Incidental rib fractures, along with possible malunion, can lead to fibrosis of the intercostal space or bony fusion between adjacent ribs at the thoracotomy site. These fusions can entrap or compress the intercostal nerves, resulting in prolonged pain.
3. In the immediate postoperative period, in most cases, patients have one or two intrapleural drainage tubes placed through separate incisions or through the same incision. These tubes are kept in place for several days until pleural drainage decreases to a minimal level or until complete radiologically evident pulmonary re-expansion is achieved. The drains will compress the intercostal nerve of the space through which they are placed, causing pain.
4. Multiple methods of thoracic closure are described in the literature. Whether using intercostal sutures, intracostal sutures, or other closure techniques, the duration until healing remains a sensitive issue, as thoracotomy itself can potentially generate pain with each respiratory movement.
5. The healing process of the thoracotomy incision can be complicated, leading to varying degrees of inflammatory phenomena that can influence the presence or absence of long-term chest pain.
6. The healing process of the surgical wound can be influenced by the postoperative treatments received by the patient. Oncological patients represent a distinct category because their multidisciplinary and multimodal cancer management often involves various radiation therapy regimens that can lead to malunion, extensive fibrosis of the thoracic wall, pleural thickening that pulls on the surgical incision site, and ultimately, pain.
7. Pain syndromes hinder the recovery of thoracic surgery patients because pain prevents effective coughing, predisposing patients to various respiratory complications, such as respiratory infections, mucus accumulation in the bronchial tree, and secondary pulmonary atelectasis, which can ultimately result in the development or exacerbation of acute respiratory failure.
8. Smokers, particularly those who quit smoking in the postoperative period, are predisposed to developing chronic pain syndromes due to the modifications induced in the tracheobronchial tree. Smoking-induced coughing leads to violent chest muscle contractions and exacerbates pain.
9. Fear of pain can impede the social reintegration of thoracic surgery patients and contribute to their reluctance to continue treatments or undergo additional surgical interventions when necessary.

OBJECTIVES

The main objectives of this study are:

1. Understanding the cause of chronic pain development in the thoracotomy area by understanding the morphological changes that occur during the healing process of the incision.
2. Histopathological evaluation of the structural changes in the intercostal neural structures in patients with continuous thoracic pain resistant to analgesic treatment, which directly impacts their quality of life.
3. Analyzing the differences in pain perception based on the patients' gender and age.
4. Analyzing the intensity of pain using visual analog scales and its characteristics using the McGill Pain Questionnaire, and correlating the recorded values with the type of incision, number of drainage tubes, duration of pleural drainage, intraoperative incidents during thoracotomy (rib fractures), and type of thoracotomy closure.
5. Analyzing the impact of pre-existing pathology that can cause thoracic pain unrelated to the surgical procedure on the intensity and nature of postoperative pain.
6. Analyzing the techniques of local analgesia in the immediate postoperative period and the impact of using these procedures on chronic pain syndromes.
7. Analyzing the surgical techniques used in patient treatment, identifying technique-related factors that generate pain, and optimizing/modifying them to minimize the detrimental effect on pain perception.
8. Analyzing the stress exerted on patients by pain and evaluating their coping methods with pain.
9. Developing an algorithm to assist thoracic surgeons in selecting optimal surgical procedures to be applied to selected patients in order to prevent postoperative pain, both acute and chronic. If pain does occur, the algorithm aims to minimize its impact on daily activities and quality of life. This goal can be achieved by early recognition of chronic pain symptoms and adjusting the medical and surgical treatment accordingly.

MATERIAL AND METHOD

Considering the topic and objectives of this doctoral thesis, the present study was divided into 3 stages:

- The first stage focused on patients who had previously undergone various thoracic surgical interventions and returned to the clinic with increased intensity of pain at the incision site. This stage aimed to fulfill the first 2 objectives mentioned above and was materialized through a morphological study of microscopic changes occurring in the post-thoracotomy pain syndrome.
- The second stage, more comprehensive, constituted the core of our research, concentrating on all the medical and surgical aspects of the studied syndrome, taking into account all pain-generating elements. In this stage, we implemented a new technique for thoracic closure, which proved to be fully useful and effective in terms of reducing chronic postoperative pain intensity. The results of using this technique were validated through a published article.
- The third stage involved a subset of patients enrolled in the doctoral study who consented to participate in a prospective study where we analyzed the influences of the patients' psychological state on the intensity of postoperative pain by observing the interaction between pain intensity, anxiety, and coping.

For a better understanding of the present doctoral study, we will proceed to present the materials and methods and the results separately for each stage, with discussions and conclusions presented at the end of this thesis.

Stage I - Study of microscopic morphological changes in post-thoracotomy pain syndromes

For the first stage of our study, we selected patients diagnosed with post-thoracotomy pain syndrome who had previously undergone various thoracic surgical interventions at the Thoracic Surgery Clinic of the Emergency Municipal Clinic Hospital in Timisoara over a period of 18 years (2002-2020). A total of 29 patients were included in the study group. All patients underwent preoperative clinical examination. The thoracotomy incision was examined to exclude other causes of pain, and only patients who did not present local signs of infection, tumor recurrence, or other musculo-cutaneous conditions generating pain that could lead to a misdiagnosis of post-thoracotomy pain syndrome were included in the study. As part of the objective examination process, several stimuli were applied to the thoracotomy area, including gentle touch, pressure, and cold and warm stimuli along the posterior, incision, and anterior areas. Each patient was asked to describe the intensity of pain using a visual analog scale and the characteristics of pain using the short-form McGill Pain Questionnaire. All enrolled patients underwent preoperative thoracic CT scans. The number of excised intercostal nerves during the reoperation was noted. Regarding the type of previous incision, we recorded 9 patients who underwent postero-lateral thoracotomy, 19 patients who were operated on through an axillary approach, and one case that underwent video-assisted mini-thoracotomy. The intercostal nerves harvested during surgery were fixed in 4% buffered formaldehyde and sent to the Department of Pathology. The examination slides were prepared using standard techniques, with hematoxylin-eosin (HE) staining used.

Stage II - Study of Acute Pain vs. Chronic Pain in terms of Surgical Technique, Analgesic Medication, and Pathology

The second stage of the doctoral study, which is also the most comprehensive, aims to fulfill the research objectives mentioned above by analyzing chronic and acute pain in terms of surgical technique, analgesic treatment at the time of anesthesia induction, as well as in the immediate and short- and long-term postoperative period. Additionally, this stage of the study takes into consideration the patient's status, such as smoking status, comorbidities, and histopathological diagnosis of the condition for which the surgical intervention was performed.

We selected 311 patients who underwent thoracic surgical interventions through thoracotomy incisions, mini-thoracotomy, or video-assisted thoracic surgeries (VATS) admitted to the clinic over a period of 12 months.

The study was interrupted due to the outbreak of the COVID-19 pandemic and was resumed in April 2020 when special protocols and intra-hospital circuits were established, and normal surgical activity was resumed.

Data regarding age, gender, smoking status, associated pathology at admission (only pathological elements that could influence the presence or intensity of chest pain were noted, such as respiratory insufficiency, cardiac insufficiency and its degree, history of myocardial infarction, presence of atrial fibrillation, diabetes mellitus, various neurological disorders, mild psychological or psychosomatic disorders, history of neoplastic diseases, presence or absence of metastases in locations other than the thoracic wall) were collected.

All patients underwent different surgical procedures using the following approaches: axillary/postero-lateral thoracotomy, axillary mini-thoracotomy, or VATS procedures. Three types of thoracic closure techniques were used: peri-costal closure - considered the classic closure technique, extra-costal closure, closure of the chest wall using simple sutures.

Therefore, we chose to divide this cohort into 3 groups as follows:

- The first group underwent parietoraphy using the standard technique with the placement of pericostal sutures.
- The second group underwent an innovative type of thoracic closure technique, discussed and perfected at the Thoracic Surgery Clinic of the Municipal Hospital in Timisoara, called "extra-costal closure."

- The last group had thoracic closure performed using simple sutures of the intercostal space.

Pain was quantified using a pain scale, and the values were recorded on postoperative day 1, 2, 3, 5, and 7, as well as at 6 months after the surgical intervention.

The characteristics of pain were measured using the McGill Pain Questionnaire. Initially, we used the extended form of the questionnaire, but patients complained that it was too difficult to complete. Therefore, in the first few weeks, we abandoned the extended form and used the short form of the questionnaire instead. This questionnaire was applied to evaluate the characteristics of pain at the time of discharge and at 6 months postoperatively when it is assumed that the pain experienced by patients is already part of a chronic pain syndrome.

Stage III - Study of the Influence of the Patient's Psychological Status on Long-Term Pain

In order to have a comprehensive understanding of the impact of post-thoracotomy pain syndrome on patients who have undergone thoracic surgeries, it was necessary to analyze the influence of the patient's psychological status on the perceived intensity of pain.

To achieve this goal, we conducted a study that included 90 patients who volunteered from the larger sample included in Stage II.

To assess the patient's coping style, we used the COPE questionnaire, developed by Carver et al. in 1989, and translated and validated by Crașovan and Sava in 2013.

Four types of coping were analyzed: emotion-focused coping, problem-focused coping, social support coping, and avoidance coping. Each of these styles included three coping mechanisms. The coping style of each patient was considered to be the dominant one among the three (the one with the highest score obtained from the questionnaire).

To assess the patients' anxiety, we used the GAD-7 questionnaire. To assess the patients' pain, we used the McGill Pain Questionnaire and the Visual Analog Scale.

RESULTS

STAGE I

In the studied sample, we had a predominantly female population - 63% female versus 37% male. The average age was 54.78 ± 14.81 years. Patients complained of pain at the thoracotomy site without exception. After completing the McGill Pain Questionnaire, we observed that higher scores were recorded for characteristics such as "throbbing," "sharp," "burning," "aching," "punishing," which are suggestive of describing neuropathic pain. The intensity of pain was significantly higher ($p<0.05$). Regarding the exacerbation of pain upon movement of the ipsilateral upper limb, no significant differences were recorded.

On average, 2.34 ± 1.11 intercostal nerves were removed. We recorded 2 cases in which more than 3 nerves were resected, one case with neurectomy of 4 nerves, and one case in which neurectomy was performed on 5 nerves.

No major postoperative complications were recorded. Two patients developed iatrogenic pneumothorax and required pleural drainage due to accidental opening of the pleural cavity during the operation. The patient from whom 5 nerves were removed developed parietal thoraco-abdominal muscle relaxation in the serratus and external oblique muscles.

In all cases, significantly reduced values of postoperative pain intensity were recorded, with patients reporting that the pain was replaced by a "numbness" that they claimed to be much easier to tolerate, although it could become bothersome on its own.

Regarding the microscopic aspects of the specimens collected during the surgery, histological changes were recorded for all patients.

These changes included:

- Fibrosis;
- Epinerve and perinerve hyalinization; these hyalinization processes were accompanied by intense capillary hyperemia;
- Interstitial edema of varying degrees;
- A degree of myxoid degeneration of the epinerve and perinerve was recorded in 7 cases;
- Moreover, myxoid degeneration was observed in 60% of the examined specimens;
- In all cases, endoneurium, myelin sheath, and axons were visualized with interruptions. The endoneurium was accompanied by the presence of hyperemic capillary vessels;
- Cytoplasmic vacuolization of Schwann cells with total disappearance of axons was also recorded;
- All these histological changes were accompanied by modifications of the tissue surrounding the nerve fibers, characterized by the presence of highly dense and irregular connective tissue.

STAGE II

A total of 311 patients were enrolled in this study and divided into 3 groups based on the thoracic closure technique: PC (n=113), EC (n=108), and SC (n=90). Although statistically significant differences were obtained for the entire study population regarding the duration of the surgical procedure and the average number of drainage tubes used, post hoc analysis showed no significant differences between the PC and EC groups. Furthermore, no significant differences were observed in terms of air leakage between these two groups. There were no statistically significant differences between patients in the PC and EC groups in terms of gender distribution, type of surgical intervention, or its duration. Only 2 deaths were recorded in the immediate postoperative period, both in the PC group, unrelated to the type of thoracic closure. No wound infections, wound bleeding, or pulmonary herniation were observed in the entire study population.

There were no significant differences in average VAS scores between PC and EC patients in the first 2 postoperative days (Day 1 - PC: 6.2 ± 1.6 versus EC: 5.4 ± 1.5; Day 2 - PC: 5.9 ± 1.6 versus EC: 4.7 ± 1.7). A significant decrease in pain intensity was observed in the EC group compared to patients in the PC group on Days 5 and 7 ($p<0.001$).

The average value for the pain score at 7 days postoperatively is 2.73 ± 1.99, and the pain score at 6 months postoperatively is 1.68 ± 1.67 for the entire cohort, with a statistically significant value of $p<0.01$.

In the cohort of 311 patients, a pain score higher than 3 on the VAS scale at 6 months was recorded for 96 patients (30.86%). Upon evaluating the differences between the pain scores, between the average pain score at 7 days postoperatively and the average pain score recorded at 6 months, a mean of 4.18 ± 1.62 was observed compared to 3.88 ± 0.9, indicating statistically significant differences between the two values.

The postoperative pain intensity at 6 months was significantly higher in the PC patient group (3.2 ± 1.5) compared to the EC group (1.2 ± 1, $p<0.001$). Patients with consistently increased pain intensity (VAS>7) at the 6-month evaluation were assessed using medical imaging (computed tomography) to identify possible causes of pain. None of the EC group patients had a VAS score > 4 at the 6-month evaluation.

Regarding the nature of pain at discharge and at 6 months postoperatively, after applying the short form of the McGill Pain Questionnaire, statistically significant differences were recorded between the values of the scores at discharge versus 6 months in terms of the characteristics: throbbing ($p=0.003$), sudden ($p=0.028$), cramp-like pain ($p<0.001$), feeling of pressure ($p<0.001$), and splitting ($p=0.036$) in terms of sensory characteristics perceived by patients.

For affective characteristics, statistically significant differences were recorded for the nature of exhausting pain ($p<0.001$), disabling pain ($p=0.019$), and raw or punishing pain ($p<0.001$).

In the studied patient cohort, the smoker/non-smoker ratio was 1.80. No statistically significant differences were recorded regarding the smoker status and the values of pain intensity reported by patients.

Additionally, the associated pathology recorded or diagnosed upon admission did not have a statistically significant influence on the occurrence of chest pain.

No statistically significant results were recorded regarding the histopathological examination obtained following the performed surgical interventions versus acute or chronic post-thoracotomy pain.

STAGE III

In the series of 90 participants included in this study, 40 patients were diagnosed with primary bronchopulmonary neoplasm or had a history of neoplasm (24 vs. 16). 26 patients were diagnosed with benign tumors, while 24 patients had a histopathological result suggestive of inflammatory conditions.

After completing the COPE questionnaire, the results of the analysis led us to divide the patients into 3 categories based on the dominant coping style: problem-focused (n=37), emotion-focused (n=33), and social support-focused (n=37).

The scores recorded regarding coping showed a normal distribution for the entire study group ($p>0.05$) with mean values as follows: problem-focused - 32.40 ± 7.58; emotion-focused - 34.99 ± 5.94; social support-focused - 32.40 ± 6.78.

Considering these 3 types of coping and relating anxiety to them, after analyzing the data obtained from the GAD-7 questionnaire, we found higher levels of anxiety within the social support-focused coping compared to the other 2 coping types ($p=0.028$). Regarding coping style, the social support-focused coping had significantly higher scores than problem-focused coping ($p=0.048$) or emotion-focused coping ($p=0.026$).

Regarding postoperative pain, for the three types of coping, we found that the social support-focused coping style had significantly higher intensity values compared to the other two styles ($p=0.022$). We did not observe statistically significant differences in the perceived pain intensity at one month postoperatively in terms of correlation with anxiety intensity.

DISCUSSION

Postoperative chronic pain remains a significant problem for patients, even in the era of minimally invasive surgery. It affects their quality of life and hinders their ability to carry out daily activities normally. Once present, chronic pain becomes a significant challenge, and its recovery and management are complicated by multiple factors. The presence of comorbidities further limits therapeutic options. Chronic pain should be treated in a multimodal regimen, tailored to the patient and the surgical procedure.

The pathophysiology of post-thoracotomy pain syndrome (PTPS) has not yet been fully elucidated by the scientific community. The mechanisms involved in pain development are highly complex, and the clinical manifestations of PTPS are heterogeneous, making this syndrome difficult to understand and manage. Surgical injury to the intercostal nerve is indicated in the literature as a possible cause of chronic pain, with the occurrence of neuronal degeneration, axonal destruction, as shown in the present study, both intraoperatively and postoperatively, leading to hyperalgesia and allodynia. These neuronal disruptions confer neuropathic characteristics.

The neuropathic nature of pain was also demonstrated in our study during the first stage by identifying the pain characteristics recorded using the McGill Pain Questionnaire.

Pain utilizes both nociceptive and neuropathic mechanisms with somatic afferents originating from the intercostal nerves, through the sectioning of the thoracic wall, pleura, lung parenchyma, and hilar structures, as well as visceral afferents through the manipulation of the vagus and phrenic nerves or sectioning of the visceral pleura and pericardium. Nerve impulses are centrally transmitted to the limbic system and somatosensory cortex. Further, the electrical signals lead to hyperexcitability of neurons in the

dorsal horns and onward to higher centers through the activation of NMDA receptors, resulting in central sensitization and chronic pain.

However, the primary event responsible for chronic pain is the injury to the intercostal nerve, as we have shown. This is partially caused by rib fracture during thoracotomy, partially by the choice of incision type (open versus minimally invasive), as well as the length of the incision. An important factor is the use of a rib spreader. Therefore, we recommend protecting the ribs when using a rib spreader by gradually opening it and placing moist compresses between the arms of the spreader that come into contact with the ribs.

Our study identified changes in the neural microstructure in all examined cases, corresponding to Sunderland's grade 2 or 3 classification. Focal edema and dilated capillaries within the nerve, along with fibrosis, were present in all examined specimens, suggesting that nerve fiber changes can have multiple causes, such as nerve adaptation to surgical trauma, wound healing, and the impact it has on the intercostal nerve, as reflected in the imaging findings of patients with chronic pain (narrowing of the intercostal space and presence of synostosis). These findings can provide clues or explain why pain becomes persistent and heterogeneous, changing its characteristics over time.

The morphological changes discovered in this study demonstrate that pain is not solely caused by direct neuronal damage from trauma, but that the wound healing process also plays an important role. Ballooned Schwann cells indicate local edema caused by the post-surgical healing process. However, we believe that more studies analyzing neural changes in thoracic pain syndromes are necessary.

Although we observed mixed-type changes in the study, we cannot attribute these changes solely to surgical trauma, as they may coexist with an ongoing degenerative process. The moment when pain becomes chronic remains a mystery.

Although our study showed that after performing the surgical intervention for chronic pain (intercostal neurectomy), the intensity of pain dramatically decreased, it did not completely disappear in the majority of cases, being replaced by a sensation of numbness that is better tolerated. In our opinion, this sensation still represents a form of post-thoracotomy pain syndrome. Furthermore, due to the arrangement of intercostal nerve fibers, the distal fiber anastomoses with neighboring nerves can lead to partial re-innervation and the recurrence of pain.

The first stage of our doctoral study demonstrated that in all analyzed cases, there are modifications in the structure of the intercostal nerve that are a consequence of the surgical technique. Here, we refer to all the actions performed by the surgeon, from the placement of the scalpel at the skin level to the dissection and sectioning of the parietal structures, the manner in which the intercostal space incision is made, the placement of the rib spreader, the protection of the ribs by using moist compresses placed under the spreader, the careful spreading of the ribs to avoid iatrogenic fractures, the manipulation of the surgical instruments in a way that does not traumatize the thoracic wall, and the optimal choice and impeccable technique in the closure procedures of the thoracic wall.

Our study demonstrates that posterolateral thoracotomy remains the most painful approach in thoracic surgery. This is due, on the one hand, to the length of the incision, with posterolateral thoracotomy ranking high in this parameter. Due to the considerable length of the incision, a significant portion of the underlying structures is invariably sectioned, especially the extrinsic muscles of the chest such as the latissimus dorsi, trapezius, and serratus anterior, and sometimes the paravertebral muscles are also involved. Regarding the intercostal nerve, an extended incision like posterolateral thoracotomy means an extended incision at the level of the intercostal space, exposing the intercostal nerve to surgical trauma throughout the procedure. The posterolateral incision is often extended into the vicinity of the spine, with the sectioning of ligaments at this level to achieve increased laxity of the intercostal space and to avoid rib fracture when applying the rib spreader. The sectioning of the space at this level, especially when electrocautery is used, inevitably leads to neuronal injury. Furthermore, considering that thoracic surgical patients often have advanced age, the goal of avoiding rib fractures becomes unattainable, with a high percentage of patients presenting various degrees of osteoporosis. If rib fracture occurs at the costal angle, the healing process will be flawed, resulting in synostosis over time, which will compress the intercostal

nerve near its origin, with a much larger diameter in this region. These patients will develop chronic pain syndromes of high intensity due, on the one hand, to the ischemia caused by the bony bridges and, on the other hand, due to the edema within the nerve, as demonstrated in the first stage of the present study.

The second type of incision that causes pain after posterolateral thoracotomy is represented by axillary thoracotomy. Usually, this type of incision is performed over a shorter length compared to the posterior incision, thus exposing the intercostal nerve over a smaller surface area. In the execution of this type of incision, fewer muscular structures are involved, mainly affecting the serratus anterior and intercostal muscles. The latissimus dorsi and pectoral muscles are usually not sectioned unless necessary.

The limited dissection at the level of the intercostal space is the explanation for why axillary thoracotomy results in lower pain compared to posterolateral incisions. Our study demonstrates this, but at the same time suggests that axillary thoracotomy still generates chronic pain, predominantly experienced by the patient as a burning sensation, heaviness, and increased sensitivity, indicating a neuropathic-type impairment, similar to the case of the posterolateral incision.

Compared to video-assisted mini-thoracotomy, the recorded values for this type of incision are similar, especially in the acute postoperative period, maintaining relatively the same values for both types of incisions. However, as the pain becomes chronic, the neuropathic characteristics of axillary thoracotomy are more prominently represented compared to mini-thoracotomy. This finding also holds true for the affective features of chronic pain, leading to the conclusion that axillary thoracotomy is preferable to posterolateral thoracotomy, only in the hypothesis that the surgical objectives cannot be achieved using mini-thoracotomy.

A plausible explanation for these findings would be the length of the axillary thoracotomy itself. Thus, in the execution of this incision, due to the reduced dissection of the intercostal space, the application of the rib spreader leads to increased pressure on the intercostal nerve and greater tension on the thoracic wall.

In the case of mini-thoracotomy, due to the smaller incision size and the use of video thoracoscopy, which provides better visualization of the working space and magnification, aspects that are lacking in open approaches, the need for increased retraction of the intercostal space is significantly reduced. The surgeon achieves a satisfactory approach with minimal rib spreading. This results in reduced surgical stress on the intercostal nerve.

The scores recorded regarding the neuropathic and affective characteristics of pain are closest to those reported by patients who underwent video-assisted techniques without the use of any rib spreader. Although low postoperative pain is well-documented in the literature, most published studies report low incidence of pain after thoracoscopic procedures. We considered it necessary to pay attention to these techniques in our study and compare the results with other thoracic surgical approaches.

Our analysis confirms the results present in the literature, with patients who underwent these techniques reporting the lowest values of perceived pain intensity, both in terms of acute pain during the perioperative period and pain experienced at 6 months postoperatively. The results obtained from completing the short-form McGill Pain Questionnaire show an overlap of scores reported by patients regarding immediate postoperative pain and long-term pain.

The only exceptions to the perception of pain in the case of thoracoscopy were observed in the sensory characteristics of acute pain: sharp, sudden pain. These differences can be explained by the use of incisions for postoperative drainage. The presence of the drain tube at the incision site always generates pain when the patient moves or coughs. After removing the pleural drain, the pain subsides and has a low tendency to become chronic, with the values recorded at 6 months for these characteristics tending to approach the minimum.

Regarding all other types of pain characteristics, both sensory and affective, the obtained values are superimposable in both the immediate postoperative period and the long term. These values are minimal.

Therefore, the analysis of pain experienced by patients in the short and long term, based on the types of incisions used in surgical interventions, demonstrates a proportional relationship between pain

intensity and pain characteristics on one hand, and the size of the incision on the other hand: the smaller the incision, the lesser the injury to the intercostal nerve, faster healing, and much lower long-term pain.

Another key factor in the presence of postoperative pain is, alongside the type of incision used, the type of thoracic closure technique. In the field of thoracic surgery, few surgeons pay special attention to thoracotomy closure. Thoracic surgical interventions are often labor-intensive due to predominantly neoplastic pathologies and the organs involved, mostly the lungs. Moreover, thoracic surgery involves working through an approach to the major pulmonary vessels that emerge directly from the heart. All these factors contribute to relatively longer surgical durations compared to other surgical specialties. This leads most thoracic surgeons to complete the surgical intervention by applying the easiest, quickest, and most accessible technique of closure, namely pericostal sutures.

The extra-costal parietoraphy technique envisioned and perfected at the Thoracic Surgery Clinic of the Emergency Municipal Clinical Hospital in Timișoara eliminates all the disadvantages described in the aforementioned techniques, being very easy to perform in a very short time, requiring only a few minutes. There is no need for any dissection of the intercostal spaces in its execution, as the sutures are passed from the outside to the inside and back through the body of the intercostal muscles, away from the intercostal nerves. Our technique does not involve any additional costs or equipment, as it exclusively utilizes sutures.

The even placement of these sutures ensures a uniform distribution of pressure on the incised intercostal space and prevents postoperative lung herniation, making it possible to be applied even to longer incisions. The periosteal approximation suture is removed immediately after placing these sutures, resulting in slight relaxation of the incision, favoring the maintenance of low pressure on the nerve.

After applying this specific type of chest closure, no complications related to wound or lung herniation have been recorded throughout the entire study. The only disadvantage of our technique remains the requirement for adequate dissection of the intercostal space at the time of thoracotomy and protecting the incision by applying moist soft material in the event of using a rib spreader, aiming to preserve intercostal muscle mass to ensure the success of the procedure. Any iatrogenic injury to the intercostal musculature may render this type of extra-costal suture application impossible.

This study validates the extra-costal technique as effective in reducing pain intensity at 6 months postoperatively, with an average decrease of 1.8 points compared to the standard periosteal suture. The recorded differences are statistically significant with a p-value < 0.001. Furthermore, in the group of patients who underwent this type of suture (EC), no values of pain intensity on the visual analog scale greater than 4 were recorded at 6 months postoperatively.

The results of the analysis of pain characteristics experienced by patients in the three study groups according to the type of thoracic closure complement the validation of our technique. Regarding the sensory characteristics of the recorded pain, we observe that the group of patients who underwent extra-costal suturing reveals higher values for postoperative acute pain experienced as cramps, sharp pain, or thoracic twinges. These characteristics are specific to acute pain and can be explained by the increased mobility of the intercostal space in the early postoperative days, resulting from the slight relaxation achieved by suppressing the approximating suture of the incised intercostal space.

For chronic pain present at 6 months, the scores recorded through completion of the short-form McGill Pain Questionnaire are similar to those obtained by patients who underwent simple suturing of the intercostal space (small incisions, minimally invasive surgery).

The classic parietoraphy technique (pericostal sutures) resulted in significantly higher pain scores at 6 months compared to the technique developed in our clinic for all sensory types of pain.

The most interesting results related to the types of thoracic closure were obtained for affective characteristics, specific to chronic neuropathic pain. The highest pain scores were observed in the group of patients who underwent classic pericostal closure, while the extra-costal sutures yielded scores comparable to those obtained in the group of patients who underwent simple suturing and minimally invasive surgeries.

Patients included in the simple suture group (SC) had lower pain scores because the incisions were significantly smaller (maximum length of 3 cm) and rib spreaders were not used. For these patients, the incisions served as the site for pleural drainage, thus avoiding compression on other intercostal nerves. However, pain at 6 months was still present, albeit of lower intensity.

Therefore, the overlap of values recorded using the extra-costal suture with those obtained through minimally invasive techniques demonstrates the validity of our procedure, which, unlike simple suturing, is applicable even for much larger incisions than those used in minimally invasive surgery. It has been successfully used for larger thoracotomies, such as axillary thoracotomy.

The third phase of our doctoral study provides insight into how patients perceive pain at a psychological level. Any patient undergoing surgery, especially for a serious medical condition, will experience high levels of stress. Preoperative stress is a common interdisciplinary issue and can have a potential negative impact on the patient's postoperative recovery by worsening pre-existing comorbidities. Therefore, identifying and addressing preoperative stress are essential for ensuring high-quality medical care.

Patients facing a diagnosis suspected of intrathoracic malignancy may experience psychological disorders, most commonly anxiety or depression. These disorders are pathological emotional defense responses of the body. If these psychological manifestations are ignored, they can have negative repercussions on patients, reducing their quality of life and even limiting their chances of survival due to immune system suppression. They can also impact the patients' families and other members of society.

In the postoperative period, stress can worsen pain and cognitive function, while anxiety and depression can compromise the postoperative prognosis. Increased anxiety leads to hyperexcitability of the sympathetic nervous system, resulting in higher requirements for analgesic and anesthetic medications and increased hospitalization costs. Stress generates anxiety, which further exacerbates the perception of pain, leading to a continuous cycle of increased stress. This can ultimately lead to complications and prolonged recovery.

The aim of the third stage of our study was to evaluate the impact of postoperative pain on patients' psychological well-being and to determine if there is any connection between patients' coping mechanisms in stressful situations, such as those imposed by the possibility of surgery, and the influence these mechanisms can have on pain.

Our findings suggest that coping styles for stress, anxiety, and pain have an influence on the variability of postoperative pain, highlighting the need for psychological assessment of patients preoperatively to identify those with high anxiety scores and those who employ coping strategies focused on social support. This group of patients is predisposed to increased postoperative pain, as demonstrated by our study.

Therefore, psychological interventions, especially for patients with anxiety symptoms, can have a beneficial impact on postoperative pain. While our doctoral study primarily focuses on the surgical aspects of postoperative pain and less on the psychological component, this branch deserves further exploration in future studies.

Lastly, in order to prevent, diagnose, and manage postoperative chronic pain following thoracic surgeries, the surgical team must pay maximum attention to all aspects related to the surgical procedure.
A candidate for thoracic surgeries should be carefully selected, and the surgical indication should be clearly established by the thoracic surgeon, taking into account several factors:

- The surgical pathology for which the patient consults the surgeon.
- The patient's associated pathologies (respiratory, cardiovascular, neurological, psychological, or psychiatric disorders).
- The patient's surgical history, especially concerning previous thoracic surgeries.
- The patient's thoracic anatomy (chest constitution, shape, congenital parietal pathologies, etc.).
- The presence or absence of chest pain at the time of examination.
- The findings of preoperative imaging tests (X-ray, CT scan, MRI) that identify the location, shape, size, and neighboring relationships of the intrathoracic lesions revealed by these tests.

- The presence of sequelae from other pleuropulmonary pathologies on the imaging examinations.

The surgical strategy adopted by the thoracic surgeon depends on all these factors mentioned above. The choice of thoracic incision type directly depends on the size, shape, and location of the excised lesion, as well as the type of associated lesions. Therefore, large lesions or patients with significant residual lesions identified by imaging investigations favor the use of large incisions, such as posterolateral thoracotomies, while small lesions can benefit from minimally invasive surgical approaches, which are less painful.

At the start of the surgical intervention, the thoracic surgeon must not overlook any surgical step. They must pay particular attention to the surgical technique from the moment of incision, dissection of the subcutaneous tissue, division of the muscle planes, and incision of the intercostal space to preserve as much as possible of the anatomical structures involved in the incision. The thoracic surgeon should choose to operate through the smallest possible incision that allows the surgical objectives to be achieved.

Less surgical trauma at the tissue level results in better postoperative healing, with limited inflammatory and scar formation processes, and consequently less tissue injury that generates postoperative pain.

Protecting the ribs by applying wet compresses to the arms of the rib spreader and gradually spreading the ribs, combined with appropriate muscle relaxant medication administered by the anesthesia team, significantly reduces the risk of iatrogenic rib fractures, which can be a source of pain, especially in elderly patients who may have osteoporosis.

The choice of thoracic closure technique should consider all the anatomical peculiarities of the patient, the size of the incision, and the undesired intraoperative events.

To reduce postoperative pain, the extra-costal closure of the thorax is preferable, as we have shown, if possible. In case this technique is not feasible, other types of closure described in the specialized literature, different from pericostal closure, can be chosen if the surgeon believes that it will bring significant benefits regarding postoperative pain.

If pericostal closure is chosen, we recommend placing multiple sutures to distribute the pressure on the intercostal nerve as evenly as possible. These sutures should not be tightly approximated, as this would lead to overlapping ribs and significant compression of the intercostal nerves.

The anesthesiologist plays an important role in reducing postoperative pain. They should administer appropriate analgesic medication according to the magnitude and duration of the surgical intervention, starting from the moment the patient wakes up, to ensure their comfort during transportation to the ward or intensive care unit.

Efficient management of acute postoperative pain will encourage the patient to mobilize early, cough effectively, and have unrestricted movement of the chest. Early mobilization and effective coughing lead to uniform lung expansion postoperatively, and normal respiratory excursions contribute to wound healing without sequelae of the thoracic incision. This reduces the long-term risk of chronic postoperative pain by decreasing local inflammation and its negative effects on the intercostal nerves, as demonstrated in our morphological study.

After discharge, patients should be encouraged to mobilize, take short walks, and avoid strenuous physical exertion, sudden movements of the chest, or lifting weights with the operated arm.

We also encourage patients to seek respiratory rehabilitation and respiratory physiotherapy services to ensure appropriate postoperative healing, which reduces the risk of chronic pain. A valuable tool for evaluating short-, medium-, and long-term postoperative pain would be the use of a journal in which the patient records the progression of painful symptoms, analgesic treatments used, and physical activity performed on each day. This journal could serve as a valuable starting point for further detailed study of post-thoracotomy pain syndrome.

Depending on the pathology for which the patient underwent the initial surgical intervention, additional treatments such as oncological therapies may be necessary. These treatments can negatively influence the development of chronic pain. Chemotherapy, for example, may have side effects that cause immune deficits, affecting the healing process. Locoregional radiotherapy, on the other hand, can lead to

trophic or fibrotic changes in the parietal thoracic nerve structures intersected by the radiation beams during treatment and may worsen chest pain.

In conclusion, we can affirm that thoracic pain has been and will remain a challenging entity to treat, considering all the aspects in which it manifests.

CONCLUSIONS

1. Thoracic surgical interventions are among the leading causes of chronic postoperative pain. This continues to be a real problem for thoracic surgical patients and a challenge for both the thoracic surgeon and the anesthesia team.
2. Chest pain is still poorly understood by the medical scientific community.
3. Pain is a subjective and highly polymorphic symptom, experienced differently by each individual patient. Therefore, the management of post-thoracotomy pain should be multimodal and performed by an interdisciplinary team.
4. Patients diagnosed with post-thoracotomy pain syndrome exhibit complex changes in neural structures within the operated region.
5. In most cases, these neural injuries are irreversible and are the cause of persistent pain.
6. Neural injuries are attributed to both surgical trauma and the wound healing process.
7. Surgical trauma is the main cause of chronic pain. Therefore, the thoracic surgeon must pay special attention to all stages of a surgical intervention.
8. The intensity of chronic postoperative pain is directly proportional to the length of the incision. The larger the incision, the more intense the pain.
9. Posterolateral thoracotomy has the highest incidence of chronic post-thoracotomy pain and should be reserved only for cases that cannot be resolved through other surgical approaches.
10. Axillary thoracotomy is a highly feasible alternative to posterolateral thoracotomy, and its use is encouraged because it is less painful.
11. This doctoral study once again demonstrates the advantages, in terms of pain, offered by minimally invasive surgery. The development of thoracoscopy in the last decade has seen exponential progress, making a wide range of surgical interventions using this approach possible. For this reason, all thoracic surgeons must familiarize themselves with and apply minimally invasive techniques.
12. Methods of chest closure are extremely important in terms of the long-term painful prognosis of patients undergoing thoracic surgery.
13. Pericostal suturing is a closure method that causes long-term chest pain due to the pressure it exerts on the intercostal nerve associated with the incision.
14. In many cases, pericostal suturing is associated with malunion of the thoracic wall, resulting in compressive costal synostosis on the intercostal nerve. Therefore, the thoracic surgeon must pay special attention when tying the sutures to maintain minimal intercostal space and avoid this pain-generating complication.
15. The original procedure developed and perfected in the Clinic of Thoracic Surgery at the Municipal Emergency Clinical Hospital in Timișoara has evident advantages in terms of chronic postoperative pain compared to classical parietoraphy techniques. It is cost-effective, easy to perform, devoid of complications, and can be successfully used even for long incisions.
16. To prevent chronic pain, the thoracic surgeon must establish clear indications regarding surgical techniques for chest wall incision and closure. The indication must be personalized, taking into account the patient's pathology, medical history, comorbidities, and, last but not least, the anatomical peculiarities encountered in each case.

17. The algorithm for prevention, diagnosis, and treatment of post-thoracotomy pain syndrome can serve as a useful guide in choosing surgical approaches, chest closure techniques, analgesic treatment, and complementary methods for pain management for all thoracic surgeons.
18. Further studies on larger patient series are necessary for a better understanding of chronic postoperative thoracic pain and to provide better statistical significance.
19. The psychological and psycho-affective component influences the intensity of pain experienced by thoracic surgical patients. Understanding how pain affects the psyche of thoracic surgical patients, as well as how patients cope with this extremely unpleasant complication, can provide valuable insights to optimize treatment strategies.