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CONTENTS

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Missed gall bladder malignancy: A result of ignoring predisposing factors

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Abstract. The underestimation of the prevalence of gallbladder carcinoma, which constitutes a predominant form of malignant neoplasm affecting the biliary tract, poses a significant threat due to its asymptomatic progression. Therefore, this study aimed to analyse the clinical, imaging, and intraoperative outcomes in cases of gallbladder carcinoma. This retrospective investigation was conducted from September 2022 to March 2023 at the Department of General Surgery of FH Medical College. A total of 153 patients deemed suitable for surgery participated in this study and underwent the relevant procedures. Various diagnostic and laboratory tests were administered to the patients, including blood analysis, random blood sugar determination, viral markers, chest X-ray, renal and hepatic functional tests, and comprehensive abdominal ultrasound. Gallbladder specimens were subjected to histopathological examination, and the results were documented and analysed. In histopathological reports, signs of precancerous lesions were noted in 30 out of 153 patients who underwent surgical treatment. The frequency of the disease was higher among women. Among these 30 patients, 22 had ultrasound-diagnosed gallstone disease with acute or chronic cholecystitis, while 8 patients had gallstone disease without gallbladder wall thickening. Additionally, 9 of these patients exhibited focal/irregular/thickening of the wall ≥10 mm. Overall, 16 patients showed elevated liver function, and 4 had an increased glucose level among those with histopathological evidence of precancerous lesions. This study underscores the elusive nature of gallbladder cancer, emphasizing the necessity for a comprehensive assessment, meticulous preoperative evaluation, and a multidisciplinary approach to facilitate early detection and treatment

Keywords: laparoscopic cholecystectomy; gallbladder carcinoma; histopathological examination; computed tomography scan

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Introduction

Gallbladder malignancies, although relatively rare, represent a significant subset of biliary tract cancers, with a global incidence ranging from 0.3% to 1.5% [1]. In India, as reported by V. Jha *et al*. [2], the incidence varies from 0.8% to 1%, with central regions reporting higher rates than the southern part. Gallstones increase the risk of gallbladder cancer (GBC) four to sevenfold, accounting for 70%-80% of cases. GBC and dysplastic tumours may resemble benign illnesses, making diagnosis difficult. 0.2%-3.3% of cases are identified incidentally, either intraoperatively or histopathologically [3, 4]. Carcinoma of the gallbladder (CaGB) accounts for roughly two-thirds of all biliary tract malignancies, making it the most prevalent subtype. Due to its anatomical location and insidious, non-specific symptoms, CaGB is frequently diagnosed at an advanced stage, affording only about 25% of patients the opportunity for surgical intervention. Furthermore, CaGB exhibits a high recurrence rate of approximately 60%-70% post-surgery, resulting in an unsatisfactory prognosis, with a 5-year survival rate reaching from 5% to 15% [5, 6]. The onset of GBC has been associated with a range of genetic and environmental factors, including chronic gallbladder infection, exposure to toxins and heavy metals, as well as dietary elements, all contributing to the development of GBC. CaGB is linked to the female gender and certain geographical areas in developing countries. It is influenced by factors like female hormones, cholesterol metabolism, and Salmonella infections. There are various factors that can contribute to the development of gallstones. These include conditions like porcelain gallbladder and Mirizzi's syndrome, as well as issues like pancreatic bile reflux. Additionally, a family history of gallstones, smoking, chemical exposure, and living in the Gangetic belt can also increase the risk. Elevated levels of secondary bile acids and a diet high in fried foods prepared with recycled oil are also associated with a higher likelihood of developing gallstones [7, 8]. CaGB is challenging to diagnose preoperatively due to vague symptoms and the inaccessibility of the gallbladder for biopsy. It often mimics benign gallbladder diseases and is typically identified late in its progression. Early diagnosis with surgical intervention is not always feasible, as most patients present at an advanced, inoperable stage. Therefore, as J.C. Roa *et al*. [6] emphasize, considering adjuvant therapy is crucial. The prognosis for CaGB patients largely hinges on disease severity and histological subtype. Various tissue diagnostic techniques, such as bile cytology, needle aspiration, and gallbladder biopsy, substantiate clinical and radiological diagnoses [9].

According to U. Dutta *et al.* [8], India carries a significant burden of gallbladder carcinoma, accounting for approximately 10% of the global CaGB cases. Considering potential underdiagnoses in these statistics, it is crucial to ensure that individuals with this condition receive proper treatment for an improved quality of life. Additionally, S. Vuthaluru *et al.* [10] study indicates a projected significant increase in the global prevalence of GBC over the next two decades, marked by regional and demographic variations, further underscoring the importance of addressing this issue for enhanced patient outcomes.

The rationale for conducting this study lies in the critical need to address the challenges associated with missed gallbladder malignancies. GBC is often diagnosed late, resulting in poor prognoses. Therefore, this study sought to investigate clinical, imaging, and intraoperative observations in patients diagnosed with CaGB, to elucidate the factors contributing to missed gallbladder malignancy and underscore the significance of recognizing predisposing factors for early detection and intervention.

Materials and Methods

This retrospective study was conducted within the Department of General Surgery at FH Medical College, spanning from September 2022 to March 2023. Over a period of seven months, a total of 166 patients were admitted for pre-operative assessment and anaesthesia check-up, specifically for cholecystectomy, a surgical procedure to remove the gallbladder. As part of the assessment process, these patients underwent a comprehensive set of medical evaluations including complete blood count (CBC), random blood sugar (RBS) measurement, screening for viral markers, chest X-ray, renal function tests, liver function tests, and ultrasound of the whole abdomen. In cases where there were suspicions of specific gallbladder conditions, magnetic resonance cholangiopancreatography (MRCP) was also conducted. Among the initial group, 153 patients who were deemed fit for surgery due to the presence of large gallstones or polyps underwent the cholecystectomy procedure and were enrolled in the study.

It is noteworthy that individuals with a medical history of conditions such as diabetes, hypertension, immune compromise, or those who expressed unwillingness to participate were excluded from the study. Furthermore, the excised gallbladders of all patients included in the study were subjected to histopathological examination (HPE), allowing for a more comprehensive assessment of the gallbladder conditions, and contributing to the overall findings of the study. For this, the extracted tissue is fixed in a preservation solution like formalin to maintain its structural integrity before embarking on the intricate journey of processing. This involves dehydrating the tissue with alcohol and clearing it using substances like xylene, rendering it receptive to embedding within paraffin wax blocks. These blocks serve as the foundation for microtome sectioning, a delicate process where the tissue is meticulously sliced into exceedingly thin sections. These thin sections are then mounted onto glass slides, a crucial preparatory step preceding the application of specialised staining procedures. Staining the tissue sections with dyes like haematoxylin and eosin facilitates the visualization of cellular structures under the microscope, imparting distinct colours to nuclei, cytoplasm, and various tissue components. The final phase involves microscopic examination by skilled professionals, wherein the stained slides are meticulously scrutinised to identify any aberrations in cellular architecture, indicative of gallbladder carcinoma. The

data were recorded in Microsoft Excel 2019 and presented as mean ± standard deviation for continuous variables and frequency for categorical variables. The authors have collected and preserved written participant consent per international or university standards. The study also adhered to the ethical norms of the Declaration of Helsinki [11].

Results

Of the 153 patients who were operated on, 30 had reports suggestive of pre-malignant lesions in their histopathological reports. Most of the patients were aged >50 years (80.00%), and belonged to the lower middle class (40.00%). Female preponderance was noted among the patients (Table 1).

Table 1. Demographic parameters of enrolled patients identified with CaGB

Demographic parameters		No. of patients [n = 30]	Percentage (%)
Age group	≤ 50 years	6	20.00
	> 50 years	24	80.00
Gender	Male	12	40.00
	Female	18	60.00
Body mass index	< 18.5	6	20.00
	18.5-24.9	2	6.67
	25-29.9	3	10.00
	30-34.9	6	20.00
	35-39.9	8	26.67
	≥ 40	5	16.67
Socio-economic status	Upper class	3	6.67
	Upper middle class	2	3.33
	Lower middle class	12	40.00
	Upper lower class	10	33.33
	Lower class	3	10.00
Duration of symptoms (weeks)	0-10	2	6.67
	11-20	6	20.00
	21-30	7	23.33
	31-40	5	16.67
	> 40	10	33.33

Source: compiled by the authors

Abdominal pain was the predominant complaint, reported by a significant majority of patients, with 26 individuals (86.67%) expressing this symptom. Weight loss was the second most common complaint, though notably less frequent, reported by 8 patients (26.67%). A smaller percentage of patients complained of jaundice (6.67%) and vomiting (6.67%), indicating less frequent but notable clinical presentations. This data underscores the prevalence of abdominal pain as a primary symptom in gallbladder conditions and highlights the need for vigilant assessment and consideration of less common symptoms for early detection and diagnosis (Fig. 1).

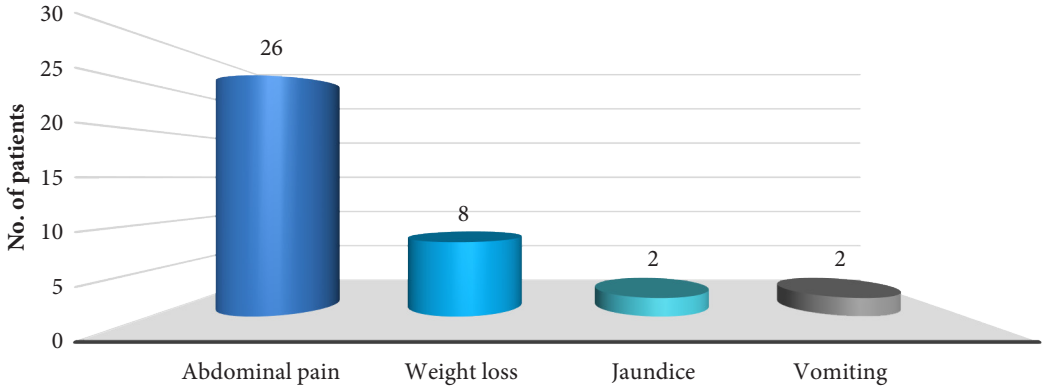

Figure 1. Chief complaints of patients identified with CaGB

Source: compiled by the authors

When examining the duration of symptoms, it was notable that 10 patients had symptoms lasting longer than 40 weeks, while 6 patients reported symptoms lasting between 11 and 20 weeks. After observing weight loss as one of the presenting complaints, it was recorded that most patients (26.67%) had a body mass index (BMI) of 35-39.9 kg/m^2 (Table 1). Data pertaining to the history of smoking reveals that among male patients, 6 individuals (20.00%) reported a history of smoking, while 3 (10.00%) did not have a smoking history. For female patients, 2 individuals (6.67%) indicated a history of smoking, while the majority, 19 patients (63.33%), reported no history of smoking (Fig. 2).

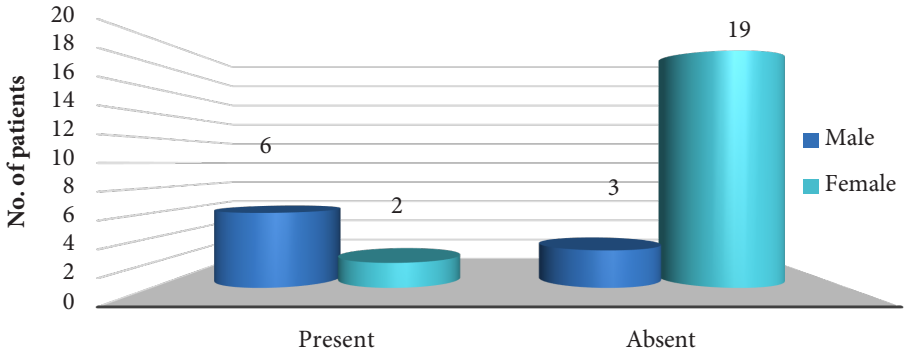

Figure 2. History of smoking in patients identified with CaGB
Source: compiled by the authors

According to the HPE, most of the females had cholelithiasis with intestinal metaplasia (n = 10), while most of the males had cholelithiasis with foci of intestinal metaplasia (n = 6) (Table 2). Another histopathological finding was suggestive of chronic cholecystitis with cholelithiasis, acute on chronic cholecystitis with cholelithiasis and cholelithiasis with xanthochromatous. The preoperative ultrasonography (USG) showed no evidence or suspicion of malignancy, revealing stones (40.00%) in most patients. Of these 30 CaGB patients, 15 patients had USG findings of chronic cholecystitis, whereas the rest of them had polyploid mass (26.67%), difficult cholecystectomy (13.33%) and thickened wall (10.00%) of ≥ 10 mm (Table 2).

Table 2. Findings of patients identified with CaGB

	Findings	No. of patients [n = 30]	Percentage (%)
USG features	Single stone	12	40.00
	Adenomyomatosis	8	26.67
	Wall thickening, stones	4	13.33
	Multiple stones	3	10.00
	Wall thickening, single-stone	3	10.00
HPE	Cholelithiasis with intestinal metaplasia	**Male/female ratio**	**Male/female (%)**
		0/10	0/33.33
	Cholelithiasis with foci of intestinal metaplasia	9/0	30.00/0
	Cholelithiasis with adenomatous hyperplasia	0/3	0/10.00
	Cholelithiasis with foci of adenomatous hyperplasia	6/5	20.00/16.67
Intra-operative finding	Shrunken fibrotic gall bladder with stone (chronic cholecystitis)	15	50.00
	Polyploid mass	8	26.67
	Difficult cholecystectomy	4	13.33
	Thickened wall	3	10.00

Source: compiled by the authors

Among those with premalignant findings in HPE reports, 16 patients with elevated liver function test values and 4 patients with elevated glucose values were observed. HPE of these CaGB cases revealed that most were confined to the gallbladder wall and did not exhibit signs of advanced disease, as the most frequently observed stage was Tis (Carcinoma in situ), with 11 patients (36.67%) falling into this category. T1a was the second most common stage,

accounting for 8 patients (26.67%), followed by T2b with 5 patients (16.67%). T2a included 4 patients (13.33%), and T1b had the smallest representation, comprising 2 patients (6.67%). This data reflects a spectrum of tumour stages, with a substantial number of patients presenting at early Tis and T1a stages, potentially offering better prospects for intervention and management, while others are diagnosed at more advanced T2 stages, posing greater challenges for treatment and prognosis. Understanding this distribution is vital for tailoring treatment strategies based on the specific T-stage of the tumour, as per the American Joint Committee on Cancer (AJCC) 8th classification [12] (Fig. 3).

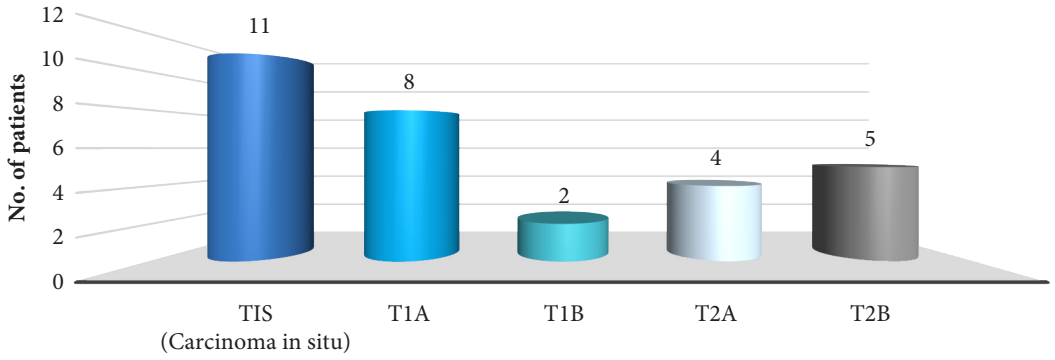

Figure 3. T-Stage of tumour of patients identified with CaGB
Source: compiled by the authors

In this study, the histopathological analysis indicated that all the missed gallbladder malignancies displayed characteristics consistent with adenocarcinoma. Among patients with pre-malignant lesions, predominant symptoms included abdominal pain, emphasizing its importance in gallbladder conditions. Missed malignancies were often confined to early stages (Tis and T1a), suggesting potential for effective intervention, but consistently displayed adenocarcinoma characteristics, highlighting the need for improved detection methods.

The study highlights a notable association between the prolonged duration of symptoms and the advancement of gallbladder malignancies. Patients enduring symptoms for over 40 weeks often presented with more advanced tumour stages. Additionally, the prevalence of specific symptoms, particularly abdominal pain, underscores its pivotal role as a predominant complaint among patients with missed malignancies. This emphasizes the significance of not overlooking common symptoms, as they might indicate underlying pathological conditions. This comprehensive examination and consideration of risk factors within patient assessments align with the broader goal of enhancing early detection strategies. It also emphasizes the imperative need for multidisciplinary collaboration among healthcare professionals to create more comprehensive and effective diagnostic and intervention protocols. Overall, the integration of these insights into clinical practice can substantially impact the timely detection and management of gallbladder conditions, potentially altering patient outcomes positively.

Moreover, the examination results, notably the ultrasound findings, exhibited certain patterns potentially associated with neglect or oversight of precancerous changes. A substantial portion of patients with missed gallbladder malignancies displayed ultrasound features indicative of chronic cholecystitis or polyploid masses, which might have led to a misinterpretation or underestimation of the severity of the underlying conditions. Furthermore, the history of smoking, although not overwhelmingly prevalent, demonstrated a discernible trend among some patients. This association calls for a more comprehensive consideration of lifestyle factors and their potential impact on the development and progression of gallbladder malignancies.

Discussion

Gallbladder carcinoma typically develops in individuals between their 6th and 7th decades of life and shows a higher incidence among females [2, 12, 13], consistent with the data presented in the current study. The average age of GBC patients in the present study was 61.25 years, whereas M.H. Rather *et al.* [13] reported an average age of 60.07 years in their study. In this study, the prevalence of gall bladder cancer was observed to be 19.6%, which stands in contrast to the lower incidence rates documented in previous investigations, with reported ranges spanning from 0.2% to 3.3% [13-15]. In the current study, a significant proportion of patients diagnosed with CaGB were found to be from the lower middle class (40.00%), followed by the upper lower class (33.33%), the lower class (10.00%), the upper class (6.67%), and the upper middle class (3.3%). These socioeconomic distribution patterns were also noted by M.H. Rather *et al.* [13], who observed a similar trend, with most of their patients originating from lower socioeconomic backgrounds. They further posited that such socioeconomic challenges might lead to delays in accessing cholecystectomy, potentially contributing to the elevated incidence of GBC. In the current study, the majority of

CaGB patients exhibited a BMI falling within the range of 35 to 39.9 kg/m², underscoring a substantial association between a high BMI and CaGB. This association was consistent with the findings of M.H. Rather *et al.* [13], who reported that a significant portion of their patients had BMIs within the 35-39.9 kg/m² range.

Moreover, the current study revealed a substantial history of cigarette smoking, particularly among male patients. In this study, the dominant symptom reported was abdominal pain, accounting for 86.67% of cases, tailed by weight loss, jaundice, and vomiting. The duration of symptoms ranged from a minimum of 0-10 weeks to a maximum of over 40 weeks before undergoing surgical procedures. Similarly, M.H. Rather *et al.* [13] also found that abdominal pain was the predominant symptom, affecting over 90% of their patients. Clinically, patients in study by N. Singh *et al.* [14] commonly presented with right upper quadrant abdominal pain and vomiting, with durations spanning from two to eight months. Pain in the right upper quadrant, loss of appetite, nausea, and vomiting were the most frequently reported symptoms among individuals experiencing these issues, consistent with the present study's findings. Notably, late-stage GBC often exhibits symptoms distinct from typical biliary colic, often including malaise and weight loss [16]. In a different study by V. Jha *et al.* [2], the primary symptom observed in the majority of patients was pain in the right hypochondriac region, experienced by 89% of the study participants. Subsequently, a smaller proportion reported symptoms of nausea and vomiting (6%), while epigastric pain was noted in 3% of cases. In this study, the preoperative USG of patients with CaGB revealed various findings, including the presence of stones in 40.00% of cases, adenomyomatosis in 26.67% of cases, wall thickening combined with stones in 13.33% of cases, multiple stones in 10.00% of cases, and wall thickening alongside a single stone in 10.00% of cases. It's noteworthy that the majority of patients' ultrasonography results indicated the presence of either stones or adenomyomatosis [13]. Among the patients in the study by V. Jha *et al.* [2], chronic calculous cholecystitis was the most frequently observed condition in 3,765 patients (78.43%). Chronic acalculous cholecystitis was reported in 960 patients (20%), while xanthogranulomatous cholecystitis was observed in 40 cases (0.83%). Additionally, 10 cases (0.20%) presented with mucocele, 4 cases (0.08%) exhibited adenomyomatosis, and a singular instance of a cholesterol polyp was identified. Gallstones are significant comorbid risk factors (70-98%) and the incidence of CaGB related to cholelithiasis ranges from 0.3% to 12% [2, 4, 14]. Oestrogen has been implicated as a factor leading to increased cholesterol supersaturation in bile, potentially contributing to the pathogenesis of CaGB associated with gallstones [17]. Gallstones were observed in 74% of all neoplastic cases, consistent with the findings of the studies mentioned above. Remarkably, individuals with symptomatic gallstones are at a heightened risk of developing CaGB compared to those with asymptomatic gallstones, with cholesterol stones emerging as the predominant cause of symptomatic gallstone formations [18].

The current study's intraoperative observations of patients with CaGB revealed diverse findings. Approximately half of the patients presented with a shrunken, fibrotic gallbladder containing stones, while the remaining patients exhibited polypoid masses (26.67%), challenging cholecystectomies (13.33%), and gallbladder walls with a thickness of ≥ 10 mm (10%). Similarly, in the study by N. Singh *et al.* [14], most CaGB cases were characterised by the presence of gallstones and variable wall thickness, as observed both through imaging and gross morphology. Upon gross inspection, 55% of the specimens displayed gallbladder wall thickening in 11 out of 20 cases, while mucosal ulceration was found in two cases (10%). Notably, in 35% of instances, there were no discernible preoperative or macroscopic indications suggestive of malignancy [2]. The majority of CaGB cases in the current study, upon HPE, did not manifest advanced disease characteristics and were primarily confined to the gallbladder wall. In the present study, Tis (Carcinoma in situ) was the most frequently encountered stage, with T1a being the second most common stage. Correspondingly, M.H. Rather *et al.* [13] observed that 5 cases fell within the Tis stage, while 4 cases were categorised as T1a. Similar findings were reported by V.P. Bastiaenen *et al.* [19], B.J.G.A. Corten *et al.* [20]. V. Jha *et al.* [2] identified two cases of CaGB at the pathological tumour 2 (pT2) stage. In the case of Tis and pT1a tumours, simple cholecystectomy is typically sufficient, and the 5-year survival rate is nearly 100%. However, for pT1b tumours, more extensive radical resection is recommended. For pT2 tumours, there is a notable enhancement in the 5-year survival rate, increasing from 20% to 70% when a straightforward cholecystectomy is succeeded by a comprehensive radical cholecystectomy subsequent to the diagnosis of CaGB. Hence, HPE should be performed on all surgically resected gallbladders since it is the sole diagnostic tool capable of accurately detecting CaGB, ultimately enhancing patient survival when compared to CaGB [2]. The present study highlights the complexity of accurately anticipating malignancy in all samples solely relying on imaging or macroscopic features. It emphasizes the importance of evaluating the depth of invasion in CaGB since surgical approaches are contingent upon accurate staging. In the current research, HPE revealed that all cases of gallbladder malignancies exhibited characteristics consistent with adenocarcinoma. These findings align with those from a prior study [10]. Adenocarcinoma of the pancreaticobiliary subtype is the most prevalent subtype observed in histopathological examinations, constituting around 90-95% of all observed gallbladder malignancies. Subsequently, squamous, or adenosquamous carcinomas emerge as the subsequent prevalent subtypes [1, 16, 21]. Most malignant cases in the present study also manifested characteristics consistent with adenocarcinoma, which is consistent with the scientists' findings N. Singh *et al.* [14]. Gallbladder carcinoma primarily affects individuals in their 6th decade of life, with

higher incidence in females. Socioeconomic factors contribute to delayed access to cholecystectomy. Adenocarcinoma is the prevalent subtype, emphasizing the need for accurate staging for optimal treatment.

Conclusions

Ignorance or neglect of certain risk factors can significantly impact the progression from precancerous lesions to malignancy. The study underscores the significance of vigilant assessment, particularly in individuals aged over 50, belonging to the lower middle class, and presenting with abdominal pain, which emerged as a predominant and early symptom in missed gallbladder malignancies. Notably, weight loss, jaundice, and vomiting, though less frequent, were also reported, emphasizing the need for considering diverse clinical presentations for early detection. Histopathological findings revealed premalignant lesions predominantly in females with cholelithiasis and intestinal metaplasia. The prevalence of adenocarcinoma in missed gallbladder malignancies calls for increased awareness and thorough evaluation, with a diverse spectrum of tumour stages observed. The distribution of early and advanced stages highlights the importance of tailored treatment strategies based on the specific T-stage, to improve intervention and management outcomes. Overall, these findings stress the critical importance of comprehensive assessment and timely diagnosis for effective management of gallbladder malignancies. One limitation of this study is its retrospective nature, which relies on historical patient data. This could result in potential data gaps or inconsistencies due to the absence of real-time data collection. Additionally, the study's relatively small sample size of 30 patients may limit the generalizability of the findings to a larger population. Future study on gallbladder malignancies should prioritize prospective studies with a larger, diverse patient cohort for real-time data collection and a longitudinal approach, fostering collaboration among healthcare institutions to improve early diagnosis and intervention strategies.

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Conflict of Interest

All authors declare no conflict of interest.

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Пропущена злоякісна пухлина жовчного міхура: результат ігнорування факторів схильності

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Анотація. Недооціненість поширеності карциноми жовчного міхура, яка є домінуючою формою злоякісного захворювання жовчних шляхів, представляє суттєву загрозу через її безсимптомний прогрес. Таким чином, метою роботи було проаналізувати клінічні, імеджингові та інтраопераційні результати у випадках карциноми жовчного міхура. Це ретроспективне дослідження проводилося з вересня 2022 року по березень 2023 року на кафедрі загальної хірургії Медичного коледжу FH. У ньому взяли участь 153 пацієнти, які були визнані придатними для операції та пройшли процедуру. Пацієнтам були проведені різні діагностичні та лабораторні тести, включаючи аналіз крові, випадкове визначення рівня цукру в крові, вірусні маркери, рентгенографію грудної клітки, функціональні проби нирок та печінки, а також ультразвукове дослідження всієї черевної порожнини. Зразки жовчного міхура були направлені на гістопатологічне дослідження, результати якого були зафіксовані та проаналізовані. У гістопатологічних звітах 30 зі 153 пацієнтів, які отримували хірургічне лікування, відмічено ознаки передракових уражень. Частота захворювання виявилася вищою серед жінок. Серед цих 30 пацієнтів 22 мали діагностовану ультразвуковим дослідженням жовчнокам'яну хворобу з гострим або хронічним холециститом, тоді як 8 пацієнтів мали жовчнокам'яну хворобу без потовщення стінки жовчного міхура. Крім того, 9 з цих пацієнтів мали фокальну/неправильну/товщину стінки ≥10 мм. Загалом у 16 пацієнтів спостерігалася підвищена активність функцій печінки, а у 4 – підвищений рівень глюкози серед тих, у кого в гістопатологічних звітах було виявлено передракові ураження. Це дослідження підкреслює невловимий характер раку жовчного міхура, наголошуючи на необхідності всебічної, ретельної передопераційної оцінки та мультидисциплінарного підходу для забезпечення раннього виявлення та лікування

Ключові слова: лапароскопічна холецистектомія; карцинома жовчного міхура; гістопатологічне дослідження; комп'ютерна томографія

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Tenzel flap for reconstruction of full-thickness inferior ocular defects following basal cell carcinoma resection: Case report

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Abstract. The relevance of this study lies in the development and implementation of an effective method of the Tenzel flap for the reconstruction of full-layer defects of the lower eyelid after resection of basal cell carcinoma. The purpose of this scientific study was to reconstruct the lower eyelid after resection of basal cell carcinoma using the Tenzel flap method and to investigate its effectiveness and results. The main feature of the surgical procedure was the use of a semicircular rotary Tenzel flap to repair moderate eyelid defects. This method involved the formation of a flap that starts from the outer corner of the eye, then moves up and along the temple, without crossing the outer edge of the eyebrow. After that, lateral cantolysis was used. The uniqueness lies in the ability to effectively correct moderate eyelid defects in one step, which simplifies the surgical process and minimises trauma to the patient. A significant condition in this procedure is the preservation of the tarsal plate on both sides of the excision, which allows preserving the structural integrity of the eyelid. Furthermore, this modification involves the use of the chondrocytic part of the nasal septum as a substitute and shows the effectiveness of this approach in the reconstruction of the eyelid after removal of basal cell carcinoma. Thus, the specific feature of the described surgical intervention is its effectiveness for moderate eyelid defects and the possibility of using modified methods of substitutes for complex defects. Given the results of the study, this modified method may become a major step in the treatment of patients with basal cell carcinoma, contributing to satisfactory cosmetic and functional results

Keywords: carcinoma; plastic surgery; non-melanoma malignant tumours of the lower eyelid; microsurgical methods of eyelid reconstruction; surgical methods of treatment

Introduction

The relevance of this study lies in the fact that basal cell carcinoma (BCC) is the most common malignancy of the eyelids, accounting for up to 90% of all malignant tumours [1]. As noted by S. Yinon *et al.* [2], more than 50% of basal cell carcinomas occur in the lower eyelid, 30% in the medial corner of the eye, 15% in the upper eyelid, and 5% in the lateral corner of the eye. The development of basal cell carcinoma is caused by exposure to ultraviolet rays, genetic factors, age, scarring, and chronic skin damage. The studies by K. Taniguchi *et al.* [3], C. Barrancos *et al.* [4] found that sunlight exposure is the main environmental cause of BCC, with the development of the disease being related to the nature of the exposure. The disease has local growth and is characterised by painless spread to the surrounding tissues. Undetected and incurable tumours are doubling in volume every year. The periorbital area is a place where BCC can show aggressive and invasive growth. Given the extensive vascular system, sparse connective tissue and particularly thin skin, basal cell carcinoma can easily penetrate tissues and spread to the surrounding areas, complicating the treatment process. Invasion usually requires orbital exenteration, as noted by N.J. Damico *et al.* [5]. There are several treatment options for basal cell carcinoma. S.K. Zöllner *et al.* [6] point out that the choice of treatment depends

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mainly on the risk of recurrence, which depends on the presence or absence of aggressive clinical and histopathological features. Depending on the size and location of the lower eyelid defect after surgical resection of the BCC and other factors, there are different methods of reconstruction.

Thus, C. Trigaux *et al.* [7] highlight the problem of reconstruction of total defects of the upper eyelid and compare their approach with already known methods. The technique included three clinical cases where it was necessary to remove tumours of the upper eyelid, leading to total defects. A two-stage procedure was used for the reconstruction, including a folding Mustard flap, a rotational flap, and lateral canthoplasty using a periosteal bipedic flap and a Tenzel flap. The results of the study suggest that this approach is an alternative for the reconstruction of total upper eyelid defects. S. Abbasi *et al.* [8] compared the effectiveness of the Tenzel and Cutler-Beard reverse flap in cases of upper eyelid defects. The results showed that the reverse Tenzel flap was superior due to its lack of complications, one-stage surgery, and rapid healing compared to the Cutler-Beard flap, which caused problems with flap entropy and retraction, requiring reoperation and delaying the healing process. A study conducted by J.B. Holds [9] examines the problem of reconstruction of total eyelid defects. The author describes the importance of an expanded arsenal of techniques to achieve the best possible surgical results.

Various methods of reconstruction after resection of basal cell carcinoma of the lower and upper eyelids highlight the need for an individualised approach to achieve the best possible surgical results. Therefore, the purpose of this study was to investigate and implement an effective method of reconstruction for basal cell carcinoma, specifically the Tenzel flap method, to improve the results of treatment and eyelid reconstruction.

Materials and Methods

This study involved a patient aged 80 years who was diagnosed with nodular basal cell carcinoma of the lower eyelid. The study was conducted at the Department of Plastic, Reconstructive and Aesthetic Surgery, L. Pasteur University Hospital and the Faculty of Medicine of Pavol Jozef Šafárik University in Košice during July and September 2022. Before the patient was included in the study, it was found that there was no history of obesity, alcohol consumption, diabetes, Cushing's syndrome, and long-term use of corticosteroids and medicines that affect lipid levels, such as corticosteroids and oestrogens. After explaining the purpose of the study and filling out the consent form, the dermatologist conducted a medical examination, and personal information such as age, gender, location of the lesion and, ultimately, the histopathological type of tumour was recorded in a developed information form. Notably, the patient's preoperative blood test was performed according to the routine surgical treatment of patients in the hospital (5 mL of intravenous blood taken after 8 hours of fasting). The obtained values corresponded to the disease process and did not reveal any parameters that would cause restrictions for the operation, and the data obtained were entered into the information form. After the biopsy, the diagnosis of the biopsy was confirmed by a dermatologist through microscopic analysis of the lesion. Both histological and cytological methods were used. The analysis revealed oval, round, and spindle-shaped cells.

For the reconstruction, authors used the Tenzel methodology, which included the following steps. The Tenzel flap method is one of the techniques for restoring the lower eyelid after removal of a tumour or other surgical procedure. However, for the best defect reconstruction, the Mustard method was also used in this study due to the specific needs of the patient and the characteristics of the defect, which required a more detailed and individualised reconstruction. This technique allows for the reconstruction of defects to be tailored to the patient's individual characteristics and provides greater coverage of the defective area. Surgical intervention was performed under local anaesthesia with propofol sedation, using a 27G-30G needle, and 0.5-1% bupivacaine with epinephrine 1:100,000. The equipment used during the operation is presented in Figure 1 and described below.

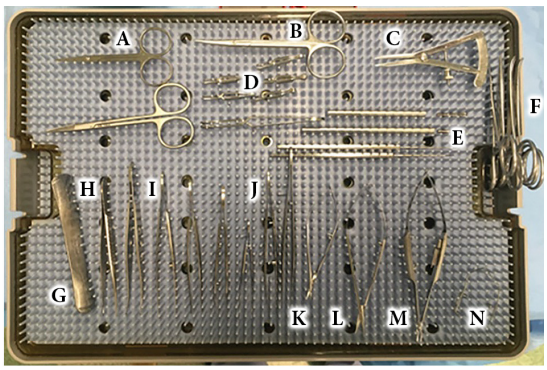

Figure 1. Main devices and equipment used during the operation

Notes: A – iris scissors; B – Stevens scissors; C – surgical callipers; D – bulldog clamps; E – skin retractors; F – arterial forceps; H – tissue forceps; I – small forceps; J – large Adson's forceps; K – Vannas spring scissors; L – Westcott tenotomy scissors; M – needle holder with a lock; N – eyelid mirror

Source: photographed by the authors of this study

First of all, this is a step in which the affected BCC tissue was marked and resected using a standard surgical procedure. Then the upper flap was separated from the upper eyelid for further reconstruction. At the next stage, a small incision was made on the upper eyelid to create a fascia flap, which was then used for reconstruction. The fascia flap created on the upper eyelid was transferred and fixed at the site of the defect. This allowed restoring the eyelid structures. At the end of the procedure, the results were evaluated. This technique required great precision and experience from the surgeon. Subsequently, the upper flap was transplanted to the lower eyelid to close the defect and restore the anatomy. After the surgery, the patient was

under systematic observation and constant monitoring of the postoperative field for a week.

The results of functional recovery and the cosmetic effect of the reconstruction were assessed using standardised scales and clinical indicators. The study was conducted following the ethical standards of the World Medical Association's Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" and the international standard "Good Clinical Practice" – ICH GCP, which define the general principles and requirements for all clinical trials involving human subjects [10, 11]. The patient has given their informed consent to take part in the study and to use this treatment.

Results

The first stage of surgery included marking and resection of the affected basal cell carcinoma tissue according to the standard procedure. This key step was aimed at complete removal of the tumour while minimising damage to the surrounding healthy tissue. In this study, authors chose the method of reconstruction of the lower eyelid after preliminary surgical removal of the tumour, which is presented in Figure 2.

Figure 2. Nodular basal cell carcinoma of the lower eyelid
Source: photographed by the authors of this study

When the defect is moderate within 30-60%, it is possible to use a semicircular Tenzel rotary flap. The incision line of the semicircular Tenzel's musculocutaneous flap started from the outer corner of the eye and led upwards and temporally, without crossing the border of the outer edge of the eyebrow. Figure 3 shows this stage of the operation. Next, the flap was separated for further use in the reconstruction procedure.

The flap was transferred and fixed at the site of the defect, which allowed restoring the anatomical structure of the eyelid. This stage required great precision and experience from the surgeon, as the quality of the reconstruction depended on it. Then lateral cantolysis was performed. After direct suturing of the edges of the defect, the entire flap was mobilised, and a new external angle was formed. This flap was used to close the anterior plate (skin and muscle), but it did not eliminate the defect in the posterior plate. The main condition for this procedure was to preserve the tarsal plate on both sides of the excision.

Figure 3. Condition of tumours after removal with a 5 mm safety line
Source: photographed by the authors of this study

In this study, the patient who took part in the study required a modification of the Tenzel flap method, which is the Mustard technique, where the incision line is extended to the preauricular region. The Mustard method is distinguished by the fact that the incision line is extended to the preauricular region, which gives surgeons more flexibility in the shape and positioning of the flap. Considering the needs of a particular patient and the specifics of the defect, the Mustard method was the best choice to ensure a comprehensive and accurate reconstruction. Its application helped to consider the anatomical features and ensure the best restoration results, which is important for improving the functional and aesthetic aspects of the patient. Figure 4 shows this stage of surgery.

Figure 4. Reconstruction of the Tenzel flap with a tarsal replacement
Source: photographed by the authors of this study

For defects affecting both the anterior and posterior eyelid laminae, the residual tarsal plate does not allow for a straight suture. Therefore, plastic surgery was performed using the Tenzel flap method with the use of pre-plate substitutes (suitable materials can be ear cartilage, chondrosaline part of the nasal septum or nasal mucosa, possibly synthetic substitutes). Figure 5 shows the place where the chondromycotic part of the nasal septum was taken.

Figure 5. Replacing the bridge of the nose – chondromucous part of the nasal septum
Source: photographed by the authors of this study

The use of the chondromycotic part of the nasal septum in surgical interventions was conditioned by several factors. The chondromucosal part of the nasal septum is a biocompatible tissue because it contains chondral components. This can help reduce the risk of rejection and improve the healing process after surgery. The chondromucosal part of the nasal septum has high structural strength and can be used to restore and maintain structures that have lost their integrity due to disease or surgery. The nasal septum is easily accessible for surgery, and its use for chondromucosal tissue harvesting can reduce the need for additional graft sites. Chondromucosal tissue can be well modelled and adapted to the specific needs of reconstruction. This allowed the surgeons to create a precise and individualised shape according to the patient's anatomy. Figure 6 shows the most chondromycotic part of the nasal septum, which was used in this study.

Figure 6. The bridge of the nose is a chondromucous part of the nasal septum
Source: photographed by the authors of this study

Therefore, the use of the chondromucous part of the nasal septum can be the chosen strategy to achieve the best results in reconstructive surgery, providing not only functionality but also aesthetic restoration. Thanks to the Mustard method and lateral cantolysis, it was possible to preserve the tarsal plate on both sides of the excision and ensure effective reconstruction of medium-sized defects in one step. A modified technique was also used, which included the use of pre-orbital substitutes for defects affecting both eyelid plates. This modification of Tenzel's method showed positive results, especially when using the chondrosaline part of the nasal septum as a substitute, which confirmed the effectiveness of these surgical approaches. Figure 7 shows a patient with lower eyelid reconstruction with a Tenzel flap after resection of basal cell carcinoma.

Figure 7. Patient with reconstruction of the lower eyelid with a Tenzel flap after resection of basal cell carcinoma
Source: photographed by the authors of this study

After the procedure, the results were evaluated, paying attention to functional recovery and cosmetic effect. Reproducing the anatomy and ensuring the best appearance were the priority goals. The patient was subjected to systematic observation and constant monitoring for a week after the operation. This included tests that helped determine the patient's health and identify possible reactions to the surgical procedure. Thus, the results of the surgical intervention demonstrate a high level of precision and experience, which contributes to successful reconstruction. Postoperative observation and evaluation confirm the quality of functional and cosmetic recovery, making this method effective in the treatment of basal cell carcinoma.

After reconstruction using the Tenzel flap method in a patient with nodular basal cell carcinoma of the lower eyelid, it is important to note the positive aspects associated with the restoration of functionality and appearance. Visual function was investigated and monitored during the postoperative period. During the recovery, the patient's eye function was observed and evaluated based on close monitoring. The reconstruction helped to restore eyelid mobility, which is a key aspect for comfort and daily activity. When assessing the results of the reconstruction, authors considered not only medical effectiveness, but also the patient's comfort during normal activities and life. The reconstructed area was subjected to scrutiny in terms of cosmetic effect and aesthetic appearance. Efforts were made to bring the reconstructed area as close as possible to its natural appearance, considering cosmetic aspects. In addition, postoperative monitoring was carried out for a week. This period made it possible to consider the dynamics of the patient's condition and conduct the necessary tests to assess their health and identify possible reactions to the surgical procedure.

The reconstruction of the lower eyelid using the Tenzel flap method proved to be successful and effective. Functional aspects were restored, and the appearance is as close to natural as possible. Postoperative monitoring confirmed a stable condition and no negative reactions. Thus, the findings of this study confirm the success and effectiveness of the Tenzel flap method in the reconstruction of the lower eyelid after resection of basal cell carcinoma.

Discussion

Scientific research and reconstruction of the lower eyelid after resection of basal cell carcinoma is an active area in plastic and reconstructive surgery. Many plastic surgeons use the Tenzel technique to reconstruct tissue after tumour removal and other surgical interventions. M.L. Ramsey *et al.* [12] highlighted the importance of choosing the best possible eyelid reconstruction strategy, considering the characteristics of the defect, such as thickness, size, and location. It was found that the ideal method should have several key characteristics, such as maintaining contact without irritation of the bulbar conjunctiva and cornea, comfortable support, versatility for different types of defects, ease of performance, and minimal damage to the donor tissue. Defects of less than 25% of the eyelid area can be closed without complications, while larger defects often require the use of free tissue grafts or flaps. In this study, the Tenzel technique is noted as the best possible choice for restoring anatomy and function after resection of the affected tissue, especially in the case of an elderly patient, and contributes to the expansion of opportunities and the introduction of innovative approaches in medical practice. Analysis of the study conducted by Y. Yan *et al.* [13] focuses on the use of a full-thickness skin graft (FTSG) and local random flaps for the reconstruction of defects in the anterior lid plate. The experiment demonstrates the effectiveness of FTSG for simple defects and the possibility of combining it with vascularised posterior plate replacements for bilamellar defects. Notably, to achieve aesthetic results, it is important to choose donor sites that have a similar colour, thickness, and texture to the periocular area, such as the tissues of the ipsilateral or contralateral eyelid, retroauricular, inner brachial and supraclavicular areas. Complications associated with this technique include hypertrophic scarring, but they can be treated with massage, steroid ointments, and silicone gels. The use of these methods helps to improve the cosmetic result after surgery. In this study, which involved an 80-year-old patient with nodular basal cell carcinoma of the lower eyelid, the Tenzel technique was used to reconstruct the defect. Comparatively, the choice of method is related to the nature of the defect and its histopathological features. An important aspect is the preservation of the aesthetic and functional result, as well as the avoidance of complications, which should be considered when choosing a reconstruction method for basal cell carcinoma of the eyelid.

J. Prohaska *et al.* [14] and O. Ozgur *et al.* [15] discuss various reconstruction methods for correcting upper eyelid and periocular defects. Different types of rotational flaps, including the Mustardé cheek flap and the Tripier orbcularis muscle-dermal flap, can solve the problem of vertical defects of the lower eyelid of various sizes. The advantages and disadvantages of each method were analysed, considering the thickness of the cheek skin, invasiveness of the procedures, risks associated with facial nerve damage, and the specifics of application in concrete clinical scenarios were described. This experiment emphasises the importance and effectiveness of the Tenzel flap method for reconstruction in basal cell carcinoma, specifically, for the correction of lower eyelid defects. The study confirms that the Tenzel method has unique advantages over other reconstruction methods, and its application in medical practice in Slovakia is significant and relevant.

F. Bernardini & B. Skippen [16] and A.M. Hishmi *et al.* [17] found that there are various methods of eyelid reconstruction after removal of basal cell carcinoma, including the use of Tenzel flaps and other modifications. The variability of the methods lies in the size and location of the flaps used, which depends on the location of the defect and contributes to effective reconstruction. Specifically, such methods as the semicircular rotary Tenzel flap used to repair subtotal defects located far from the lateral corner of the eye are described. The reversed Tenzel flap is used to repair the upper eyelid and other defects, but has a limited size, especially in the vertical dimension. The Fricke temporal flap is used to reconstruct large defects of the lower and upper eyelids, as well as lateral defects. However, this procedure can lead to side effects, such as a raised eyebrow and misalignment of the upper eyelid. The use of the Fricke cheek flap instead of the frontal flap allows for more available tissue and avoids raising the eyebrow. Within the framework of the above study, the Tenzel technique was used for reconstruction, including the stages of marking and resection of the affected BCC tissue, as well as the isolation and transplantation of the upper flap to close the defect and restore the anatomy. Compared to previous studies that emphasised different methods of eyelid reconstruction after basal cell carcinoma removal, including the use of Tenzel and other modifications, this study confirmed the effectiveness of the Tenzel method.

K. Yamashita *et al.* [18] and V. Malviya *et al.* [19] analyse various methods of eyelid defects reconstruction, including the use of ear cartilage grafts. Particular attention is paid to high aesthetic effect and reliable support, which is not accompanied by visible atrophy or dissolution of the graft, helping to avoid eyelid retraction and other complications. However, the absence of an inner membrane in such grafts, which is necessary for conjunctival reconstruction, is emphasised, and discomfort from direct contact of the eye with the unprepared surface of the graft is noted. It is highlighted that the preservation of the periosteum or the use of an oral mucosa graft can solve this problem. Posterior plate defects that cover less than 60% of the horizontal length of the eyelashes can be corrected with local tarsoconjunctival flaps, considering the

configuration of the defects. Comparing the results, the present study identifies the Tenzel method as an important approach to reconstruction, specifically in basal cell carcinoma. This method is characterised by a high aesthetic effect and reliable support, avoiding visible atrophy or dissolution of the graft, which helps to avoid eyelid retraction and other complications.

Central defects affecting the lower tarsus and eyelid have different reconstruction options depending on their position. Previously, B. Skippen *et al.* [20] described that these defects can be closed with a flap taken from the tarsoconjunctiva and raised from the residual central upper tarsus. Medial or lateral defects can be effectively repaired using a tarsoconjunctival sliding flap from adjacent eyelid tissue, as described in the studies by P.L. Custer & M. Neimkin [21], J.A. Cha & K.A. Lee [22], and A. Tinklepaugh *et al.* [23]. Defects in the lateral corner of the lower eyelid can be successfully corrected with a Hughes tarsoconjunctival flap, which is transferred from the upper eyelid. Notably, these methods are simple and fully utilise the residual eyelid, but for the stability of the reconstructed eyelid, it is necessary to have an eyelid height of at least 3-4 mm. On the contrary, the Tenzel method requires an additional tarsal substitute due to the absence of this element for the reconstruction of the upper part of the flap. This method is effective and can be used to close medium-sized defects in one step, but complications such as upper eyelid retraction and entropion should be considered. Thus, the choice of eyelid reconstruction method should consider the individual characteristics of each clinical case. The right choice of reconstruction method is an essential aspect of BCC treatment, and lower eyelid reconstruction after tumour removal is important to maintain functionality and achieve the best possible cosmetic results. Additional research and improvements in reconstruction techniques may further improve the treatment of patients with BCC.

Conclusions

This scientific medical study looked at methods of reconstructing lower eyelid defects after surgical removal of a BCC. It was found that the Tenzel flap method is the best approach to the reconstruction of the lower eyelid after resection of basal cell carcinoma and confirmed that predicting the correct reconstruction technique is a key factor in achieving best results and preserving eyelid function. It was shown that creating a suitable reconstruction plan and choosing the best method allows for individualised treatment, providing patients with the best possible outcome that affects both their health and quality of life. The described method of using a semicircular rotary Tenzel flap is a unique and effective approach for the reconstruction of moderate eyelid defects. It simplifies the surgical process and minimises damage to the patient, allowing for effective correction of medium-sized defects in one step. A major prerequisite for reconstruction is the preservation of the tarsal plate on both sides of the excision, which helps to maintain the structural integrity of the eyelid and promotes optimal functional recovery. It was proved that the use of the chondrocytic part of the nasal septum as a substitute and other modifications confirm the effectiveness of this approach in eyelid reconstruction after removal of basal cell carcinoma, specifically for complex defects.

Thus, this study provides practicing surgeons with valuable conclusions and supports the use of the Tenzel flap method as an effective and innovative means of reconstruction after resection of basal cell carcinoma. Studying the effect of the Tenzel flap method on patients and different variations of eyelid defects allows developing treatment approaches optimised for concrete clinical scenarios. A comparison of the effectiveness and advantages of the Tenzel flap method with other already known reconstruction methods may provide additional conclusions about its competitiveness. Further integration of this method can considerably improve patient outcomes and expand the possibilities for reconstruction in basal cell carcinoma, making this study relevant and indicative of the introduction of new, more effective approaches into medical practice in Slovakia.

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Conflict of Interest

The author declares no conflict of interest.

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Метод клаптя Тензеля для реконструкції повношарових дефектів нижньої повіки після резекції базальноклітинного раку: клінічний випадок

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Анотація. Актуальність дослідження полягає в розробці та впровадженні ефективного методу клаптя Тензеля для реконструкції повношарових дефектів нижньої повіки після резекції базальноклітинного раку. Метою даної наукової роботи була реконструкція нижньої повіки після резекції базальноклітинної карциноми з використанням методу клаптя Тензеля та дослідження його ефективності й отриманих результатів. У хірургічному втручанні основну особливість становило використання напівкруглого поворотного клаптя Тензеля для відновлення помірних дефектів повіки. Зазначений метод передбачав формування клаптя, який починався від зовнішнього кута ока та направлявся вгору і вздовж скроні, не перетинаючи межі зовнішнього краю брови. Після цього застосовувався латеральний кантоліз. Унікальність полягає в можливості ефективного виправлення помірних дефектів повіки за один етап, що спрощує хірургічний процес та мінімізує травматизацію для пацієнта. Важливою умовою в цій процедурі є збереження тарзальної пластини з обох боків висічення, що дозволяє зберегти структурну цілісність повіки. До того ж, ця модифікація включає використання хондроцитарної частини носової перегородки як замінника і виявляє ефективність цього підходу у відновленні повіки після видалення базальноклітинного раку. Таким чином, особливість описаного хірургічного втручання полягає в його ефективності для помірних дефектів повіки та можливості використання модифікованих методів замінників для складних дефектів. Враховуючи результати дослідження, цей модифікований метод може стати важливим етапом в лікуванні пацієнтів з базальноклітинною карциномою, сприяючи забезпеченню задовільних косметичних та функціональних результатів

Ключові слова: карцинома; пластична хірургія; немеланомні злоякісні пухлини нижньої повіки; мікрохірургічні методи відновлення повік; хірургічні методи лікування

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Effect of combined pharmacotherapy on the quality of life in patients with low back pain

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Abstract. Low back pain is a frequent symptom with which patients turn to doctors of various specialities. This is conditioned by its debilitating course and, not infrequently, to the lack of substantial improvement due to the conducted treatment, resulting in the significant reduction in the quality of life. The purpose of the study was to assess the effect of a medicinal food product and a nonsteroidal anti-inflammatory drug on the quality of life in patients with low back pain. The quality of life was assessed both in the control group (15) and in patients with low back pain (69) at the beginning of the therapy and on day 29, that is, after 28 days of treatment with theramine and tenoxicam and their combination, using the Medical Outcomes Study Short-Form 36 assessment questionnaire. Significant negative changes in indicators of both physical and mental components of health were revealed. It was established that in terms of impact on the quality of life in patients with low back pain, monotherapy with theramine and tenoxicam is inferior to their combined use. The highest physical activity level has been found to follow taking combined medication and the lowest one – after tenoxicam intake, the similar changes having been found with the indicator of physical role functioning. Pain intensity was best affected by combined therapy, the effect of theramin and tenoxicam being similar. It is also shown that theramine prevailed over tenoxicam in terms of its effect on indicators of physical and mental components of health. The results of the research on theramine and its combined use with tenoxicam should be included in the treatment programme for patients with low back pain in order to improve the quality of life

Keywords: vital activity; treatment; theramine; tenoxicam; drug combinations

Introduction

Low back pain (LBP) is among the most common challenges physicians encounter in the clinical practice. According to the expert data, the spread of LBP in industrialised countries has become pandemic [1, 2]. As noted by V.E. Casiano *et al.* [3], LBP is ranking first among all diseases in terms of the years of working life lost, with up to 80% of the global population suffering from it at least once in life. However, pain syndrome is not always eliminated. Diagnosis and management of back pain is a challenging task for both general practitioners and specialists, which is related to the etiological heterogeneity of the disease. It is difficult enough and often problematic to establish etiology, not to mention the fact that treatment is fraught with serious and potentially life-threatening side effects [4]. In order to eliminate the pain syndrome, dexketaprofen and intranasal ketorolac [5], and applications with ketaprofen [6] are used. In patients with exacerbation of dorsalgia, it was established that tenoxicam, in comparison with meloxicam and

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diclofenac sodium, reliably improved the quality of life and indicators of vital activity [7]. According to the recommendations of A. Qaseem *et al.* [8] selective nonsteroidal anti-inflammatory drugs (NSAIDs) should be prescribed for functional improvement in patients with chronic LBP: for reduction or elimination of low back pain, improvement in health-related quality of life, reduction in work disability, return to work, global improvement, number of back pain episodes or time between episodes, patient satisfaction, and adverse effects. Evidence supports that short-term use of NSAIDs has no effect on patients' quality of life. Given the conflicting data on the effectiveness of NSAIDs in patients with urgent pain and the potential risk of side effects (toxicity of the gastrointestinal tract, liver, and cardiovascular system), they are not recommended for the treatment of acute LBP [9]. However, W.E. Shell *et al.* [10] argue that the use of theramine together with ibuprofen has a positive effect on vital activities according to the Roland-Morris scale and the Oswestry disability index. The use of tizanidine and methocarbamol in therapy can reduce the stiffness of the lumbosacral muscles of the back and reduce the intensity of pain syndrome in patients with LBP, especially acute [11, 12]. Quite often, patients with LBP are dissatisfied with treatment, which generally affects the recovery of their work capacity. It accounts for significant economic costs related to health care and disability, and exceeds the costs associated with cardiovascular disease, cancer, and diabetes.

Since young people of working age mostly suffer from this disease, chronic pain is among major medical and socioeconomic problems. It is characterised by debilitating course and, not infrequently, by the lack of substantial improvement due to the conducted treatment, resulting in the significant reduction in the quality of life. Therefore, optimisation of treatment and life quality improvement in patients with LBP of various genesis is a pressing issue that requires comprehensive investigation. The purpose of the study was to assess life quality dynamics of indicators in the patients with low back pain of vertebral genesis under the influence of both separate and combined use of theramine, a therapeutic nutrition, and tenoxicam, a nonsteroidal anti-inflammatory drug.

Materials and Methods

69 patients with LBP of vertebral genesis (39 women and 30 men), as well as 15 healthy individuals (no LBP), were examined and treated in the rehabilitation department for patients with a neurological profile of the Ternopil City Hospital No. 3 in 2018-2022.The criterion for inclusion in the study was the presence of chronic lumboischialgia due to spondyloarthrosis, spondylosis, spinal disc herniation. Patients with tumours, injuries, anomalies of the spine, inflammatory and infectious diseases (of the spine) were not included. In the study, monotherapy with theramine (2 capsules, twice daily, 1 hour before meals) and tenoxicam (20 mg, 1/day) was compared with combined application of theramine (2 capsules, twice daily, 1 hour before meals) + tenoxicam (20 mg, once a day) for 28 days. On the first day, the patients were randomised into three groups: Group 1 (24 patients) received theramine at the specified dose; Group 2 (23 patients) were given tenoxicam at the specified dose; Group 3 (22 patients) took theramine + tenoxicam. Theramine was chosen for the study because it effectively reduces and modifies pain without noticeable side effects, and also stimulates the production of neurotransmitters such as serotonin, γ-aminobutyric acid (GABA), nitric oxide, glutamate, and histamine. The choice of tenoxicam is conditioned by the presence of analgesic, anti-inflammatory, and chondroprotective effects.

The quality of life was assessed both in control group and in LBP patients at the beginning of the therapy and on day 29, that is, after 28 days of treatment, using the SF-36 (Medical Outcomes Study Short-Form 36) [13] assessment questionnaire. It comprises 36 questions, grouped in 8 scales: 1) physical activity; 2) physical role functioning; 3) pain intensity; 4) general state of health; 5) vital activity; 6) social activity; 7) emotional role functioning; 8) mental health.

Maximum value for all scales, with no restrictions and health problems, was equal to 100. The higher the indicator value, the better the score on the scale chosen. 8 scales were grouped into 2 indicators: physical and mental health components. Physical health component included: physical activity; physical role functioning; pain intensity; general health, whereas mental health component included: vital activity; social activity; emotional role functioning; mental health.

Statistical indicators processing was performed on a PC using STATISTICA 10 and MS Excel XP applied software suite by the method of variation statistics. Nonparametric methods (Mann-Whitney U-test for independent samples and Wilcoxon t-test for dependent sampling) were used, difference of indicators being regarded as significant at $p < 0.05$. All procedures performed in studies involving human subjects complied with the ethical standards [14-16]. Written informed consent for the study was obtained from all patients.

Results

Patients with a mean age of (56.2 ± 2.5) years and disease duration of (11.2 ± 2.1) years have been examined. This study has found that low back pain affects the life quality of afflicted patients (Table 1). In particular, they reveal impaired physical activity that restricts ability to do exercises. This is confirmed by 54.6% reduction of this indicator, as compared with controls that is indicative of a certain loss of ability to self-service, to carry loads, to walk, and to climb stairs. Physical role functioning in LBP patients has been found to decline by 44.4% as compared to control group that is indicative of reduced daily activity of the patients owing to their physical condition. This is consistent with pain intensity indicator, which declined significantly in LBP patients in comparison with the control group from (98.67 ± 0.42) to (39.36 ± 1.09) points, ($p < 0.05$), i.e., by 60.1%. In other words, there is an increase of pain syndrome, which restricts patients' activity considerably.

Besides, changes in the life quality have been found to contribute to general state of health. for example, in LBP patients this indicator decreased by 2.68 times ($p < 0.05$), as compared to control.

Table 1. Indicators of life quality in LBP patients who received theramine and tenoxicam (M±m)

	Control n = 15	Before treatment n = 69	Group 1 n = 24	Group 2 n = 23	Group 3 n = 22
Physical activity	91.33 ± 1.15	40.58 ± 0.66*	76.83 ± 2.06^	71.30 ± 0.76^	82.91 ± 1.61^#
Physical role functioning	90.73 ± 0.93	50.15 ± 1.15*	69.25 ± 2.00^	60.87 ± 1.24^	80.04 ± 1.80^#
Pain intensity	98.67 ± 0.42	39.36 ± 1.09*	67.25 ± 1.76^	64.26 ± 1.49^	81.26 ± 1.71^#
General health	95.20 ± 0.93	35.54 ± 1.43*	64.95 ± 2.58^	47.09 ± 1.38^	74.88 ± 1.94^#
Vital activity	96.33 ± 0.74	44.58 ± 1.33*	70.62 ± 2.33^	56.26 ± 1.84^	77.88 ± 2.07^#
Social activity	96.87 ± 0.52	52.42 ± 1.70*	73.76 ± 1.68^	65.35 ± 1.70^	79.21 ± 1.21^#
Emotional role functioning	96.20 ± 0.68	37.73 ± 1.62*	64.83 ± 2.29^	49.09 ± 1.69^	76.00 ± 2.24^#
Mental health	95.60 ± 0.65	41.46 ± 1.35*	70.96 ± 2.25^	54.43 ± 1.53^	78.59 ± 1.56^#

Notes: $p < 0.05$ * – compared with control; # – compared with groups 1 and 2; ^ – compared with pre-treatment period
Source: compiled by the authors

Thus, changes in life quality indicators have been found to affect physical health component (Table 2), the latter being assessed for LBP patients in (41.37 ± 1.07) points, in contrast to the control group (93.98 ± 0.86), that is 56.0% less ($p < 0.05$).

Table 2. Physical and psychological components in LBP patients who received theramine and tenoxicam (M±m)

Life quality components	Control n = 15	Before treatment n = 69	Group 1 n = 24	Group 2 n = 23	Group 3 n = 22
Physical health component	93.98 ± 0.86	41.37 ± 1.07*	69.57 ± 2.10^	60.88 ± 1.22^	79.77 ± 1.76^#
Mental health component	96.25 ± 0.65	44.05 ± 1.50*	70.04 ± 2.14^	56.28 ± 1.69^	77.92 ± 1.77^#

Notes: $p < 0.05$ * – compared with control; # – compared with groups 1 and 2; ^ – compared with pre-treatment period
Source: compiled by the authors

Prior to treatment, LBP patients revealed significant reduction in the indicator of vital activity. Specifically, vital activity level before treatment decreased by 2.16 times ($p < 0.05$), as compared with control, that indicates lost ability to recover energy and vigour, at least to some extent. Along with this, the indicator of social activity also declined by 1.85 times, which is indicative of both physical and emotional deterioration due to social activity and communication.

Before treatment, emotional role functioning in LBP patients was found to reduce significantly, as compared to the control group (37.73 ± 1.62) against (96.20 ± 0.68) points, that is by 60.8%, ($p < 0.05$). This indicates some restriction in doing day-to-day work because of deteriorated emotional state in LBP patients. These changes have been found to adversely affect the mental health state of LBP patients that is confirmed by lower number of points in comparison with the control group (41.46 ± 1.35) against (95.60 ± 0.65), that is by 56.6%, ($p < 0.05$). Clinically, it is manifested in sleep disturbance, worsened mood, and increased anxiety. This, in its turn, affected the indicator of mental health component (Table 2), which decreased by 54.5% ($p < 0.05$), as compared to the controls that is indicative of these patients experiencing depression, anxiety, and mental distress prior to treatment.

Post-treatment life quality evaluation in LBP patients has shown its marked improvement. Specifically, the patients who received theramine, tenoxicam, and combined drug, revealed improved physical activity indicators by 1.89, 1.76, and 2.04 times, respectively. Moreover, combined application of drugs has been found to provide their enhanced efficacy, as indicated by the increase in the physical activity by 7.9% in comparison with theramine application alone, and by 16.3% – with that of tenoxicam ($p < 0.05$). That indicates enhanced physical activity due to health improvement.

Significant increase in the physical activity indicator was found in the LBP patients who had been taking theramine/tenoxicam combination – from (50.15 ± 1.15) to (80.04 ± 1.80) points, i.e. by 59.6% more, whereas the increase for the use of theramine alone was by 38.1% and that for tenoxicam – by 21.4%. Efficacy of the treatment is also confirmed by the improved indicator of pain intensity. It was found to increase reliably in the patients who had been taking theramine and tenoxicam alone and their combination by 1.71, 1.63, and 2.06 times, respectively. As shown in Table 1, combined use was more effective and contributed to the activation of everyday activity (including housework and work outside the home) due to decreased intensity of pain syndrome.

The general state of health has also been found to improve, especially following combined application of theramine and tenoxicam. The improvement was estimated at (74.88 ± 1.94) points against (47.09 ± 1.38) points for the patients who received tenoxicam and (64.95 ± 2.58) for

those who were treated with theramine, that is 59.0 and 15.3% more than their separate use and is promising in view of health improvement. Positive developments in life quality indicators after treatment provided 68.2%, 47.2% i 92.8% ($p < 0.05$) increase in the general indicator of physical health component of the patients who had received theramine, tenoxicam, and their combination, respectively.

In the course of treatment, the indicator of vital activity in LBP patients, who had received tenoxicam, was found to rise by 26.2%; in the patients, who had been given theramine – by 58.4%; in those, who had received tenoxicam/ theramine combination – by 74.7%. This is indicative of recovered vital activity, vigour, and energy. In the post-treatment period, LBP patients reveal enhanced social activity that is confirmed by broadening of social contacts, ability to communicate due to improved physical and emotional status. This primarily refers to the patients who received combined pharmacotherapy, as indicated by 51.1% increase ($p < 0.05$) of the level of social activity. In addition, positive developments were noted on the part of emotional role functioning (ERF). In comparison with pre-treatment period, application of theramine, tenoxicam, and tenoxicam/ theramine combination resulted in 1.72, 1.30, and 2.01-fold increase of ERF indicator, respectively. This is indicative of improved emotional status which contributes to better work performance and daily activity, regarding both amount of work and quality.

Efficacy of mono- and, particularly, combined pharmacotherapy is confirmed by increased indicator of mental health, the latter being by 71.2%, 31.3%, and 89.6% higher in LBP patients who received theramine, tenoxicam, and tenoxicam/ theramine combination, respectively. This, in turn, contributed to the improvement of mood and emotional state, as well as to the reduction of patients' anxiety. The general indicator of mental health component also improved reliably. Specifically, it was 1.28, 1.59, and 1.77 times the value of the patients before treatment after taking tenoxicam, theramine, and theramine/tenoxicam combination, respectively. This results in mood enhancement, increase in positive emotions along with reduced manifestations of depression and anxiety.

Assessment of SF-36 questionnaire research findings in LBP patients revealed significant changes in their life quality, to which points reduced indicators of physical activity, pain intensity, and, somewhat less – of physical role functioning. This leads to significant worsening of their general state of health and eventually to adverse effect on the indicator of physical health component. Along with this, reduced vital and social activity, as well as marked decrease in emotional role functioning and mental health were noted that cause changes in the indicator of mental health component.

Efficacy study of using theramine, tenoxicam, and theramine/tenoxicam combination for the treatment of LBP patients has shown monotherapy to be somewhat inferior to combined therapy in terms of the influence on the life quality. Physical activity level has been found to reach the highest value after taking drug combination, whereas the lowest – after tenoxicam. Similar changes have been found about physical role functioning. Pain intensity indicator was best affected by drug combination, whereas the effect of theramine and tenoxicam was much alike. At the same time, general state of health was revealed to have improved significantly in the patients who received combined treatment, while theramine monotherapy was more effective than that with tenoxicam. Indicators of vital activity and mental health grew the most after combined treatment, theramine being more effective than tenoxicam. As to the influence on the indicators of social activity and emotional role functioning, the best effect was provided by theramine/ tenoxicam combination. In its turn, theramine was superior to tenoxicam, in particular regarding the indicator of emotional role functioning. Treatment with drug combination improved mental health component considerably.

Discussion

LBP is still a pressing issue as it affects most people throughout their lives. Among the drugs that are most often used in the treatment of such pain are NSAIDs. However, their use is limited by side effects, especially from the gastrointestinal tract, which indicates the feasibility of finding new approaches to the treatment of LBP. Anti-inflammatory drugs with precursors that produce NO and help reduce the development of erosions of the gastric mucosa are promising. They are also capable of inhibiting T-cell proliferation and cytokine production. Theramine is known to produce NO similarly to NO-NSAIDs [17]. Theramine, as a source of neurotransmitter precursors, is designed to induce neurotransmitter production of neurotransmitters that modulate nociception and inflammation [18]. The precursors of serotonin, NO, histamine, and GABA are supplied in this dosage form as 5-hydroxytryptophan, arginine, histidine, and glutamine, respectively. Therefore, in the study, teramine with tenoxicam was used in the treatment of BNS with a corresponding assessment of the quality of life of such patients and prevention of the development of side effects from the gastrointestinal tract. The use of theramine and tenoxicam in patients with LBP both in isolation and in combination had a positive effect on the quality of life. However, monotherapy was somewhat inferior to their combined administration, theramine was more effective compared to tenoxicam. These results are consistent with the data of W.E. Shell *et al.* [10], who found that theramine in combination with ibuprofen was superior to their isolated administration in reducing the Roland-Morris Scale and Oswestry Disability Index, and that theramine was more effective than ibuprofen in the effect on chronic pain.

The obtained results to a certain extent coincide with the data of V. Romanenko [11], who established that the combined use of etoricoxib and methocarbamol is effective in acute LBP with pronounced muscle-tonic syndrome. It has also been proven that the combined pharmacotherapy of NSAIDs plus GABA-mimetic antiepileptic drugs

(pregabalin or gabapentin) was more effective than individual NSAIDs in the treatment of nonspecific LBP. This combination pharmacotherapy can be used to simultaneously reduce prostaglandin-mediated pain and neuropathic pain [8]. A. Bhatia *et al.* [19] point to the feasibility of using the tramadol-acetaminophen combination in chronic LBP, since acetaminophen did not affect the quality of life. The authors of this study established that theramine prevailed over tenoxicam in terms of impact on the quality of life of patients with LBP. This is consistent with data from other researchers indicating that NSAIDs had no or little effect based on Roland Morris Disability Questionnaire or Oswestry Disability Index scores [8]. This is explained by the fact that theramine restores and maintains the balance of neurotransmitters in the cells of the nervous system: GABA, nitric oxide, serotonin, acetylcholine, the disturbances of which are associated with pain syndrome and inflammatory conditions. It is known that depletion of neurotransmitters [20-22] and related synapse fatigue can lead to chronic pain states. Depletion of neurotransmitters is caused by an increase in the rate of metabolism of precursors and insufficient intake of precursors from the diet [23]. Theramine solves the problem of such inaccessibility. The results of clinical trials indicate that theramine effectively reduces the severity and modifies pain without noticeable side effects [10]. These results are indirectly confirmed by studies that indicate that duloxetine is an effective drug for reducing the intensity of pain in chronic LBP due to the enhancement of serotonergic and noradrenergic neurotransmission in the central nervous system [24]. The influence of tenoxicam on the quality of life, is related to its analgesic, anti-inflammatory and chondroprotective effect. An important advantage of tenoxicam is its ability to influence not only cyclooxygenase (COX-2), but also matrix prostaglandin (PG) E2 synthetase, which is responsible for the synthesis of the most important mediator of inflammation – PGE2. The effect of tenoxicam on the quality of life that found is consistent with the results of S.B. McMahon *et al.* [25] who found that COX2 NSAIDs are effective in functional improvement. The presence in tenoxicam of the ability to act as an active oxygen acceptor in the area of inflammation and inhibit metalloproteinases (stromelysin and collagenase), which cause the destruction of cartilage [20], affects the quality of life of patients with LBP, since degenerative changes in the spine most often lead to the development of pain syndrome. Evaluating the quality of life of patients with LBP after treatment, it can be stated that the combined use of theramine and tenoxicam is more effective than their isolated use. Moreover, theramine monotherapy turned out to be better compared to tenoxicam.

Conclusions

According to the results of the assessment of the quality of life in patients with pain in the lower part of the back of vertebral origin, significant changes have been established, which is evidenced by a decrease in indicators of both physical and mental components of health. Significant increase in the physical activity indicator was found in the LBP patients who had been taking theramine/tenoxicam combination, i.e., by 59.6% more, whereas the increase for the use of theramine alone was by 38.1% and that for tenoxicam – by 21.4%. Efficacy of the treatment confirmed by the improved indicator of pain intensity which is significantly larger than for those who had been taking theramine and tenoxicam alone and their combination by 1.71, 1.63, and 2.06 times, respectively. The combined use of theramine and tenoxicam has been shown to be more effective than either alone in terms of impact on the quality of life of patients with low back pain, and monotherapy with theramine is superior to tenoxicam. This is confirmed by an increase in indicators of the mental component of health by 1.59, 1.28, and 1.77 times, the physical component – by 68.2%, 47.2% and 92.8%, for those who received theramine, tenoxicam and their combination, respectively.

The assessment of the dynamics of quality of life based on its subjective perception by patients with low back pain of vertebral origin using the SF-36 questionnaire is a sufficiently sensitive criterion for the effectiveness of the used treatment programmes. This indicates the expediency of including in the treatment of patients with low back pain the therapeutic food product theramine and the combination theramine/tenoxicam, which can be used in their clinical practice by doctors of various specialities. In further studies, it is planned to investigate the effectiveness of theramine and its combined use with tenoxicam in patients with osteoarthritis of the hip and knee joints.

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Conflict of Interest

The authors declare no conflict of interest.

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Вплив комбінованої фармакотерапії на якість життя пацієнтів з болем у попереку

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Анотація. Біль у попереку є частим симптомом, з яким пацієнти звертаються до лікарів різних спеціальностей. Це пов'язано з його важким перебігом і, не рідко, з відсутністю істотного поліпшення після проведеного лікування, що призводить до значного зниження якості життя. Метою дослідження було оцінити вплив медикаментозного харчового продукту та нестероїдного протизапального препарату на якість життя у пацієнтів з болями у попереку. Якість життя оцінювалася як у контрольній групі (15 осіб), так і у пацієнтів з болями у попереку (69 осіб) на початку терапії та на 29-й день, тобто після 28 днів лікування тераміном і теноксикамом, а також їх комбінацією, за допомогою анкети Medical Outcomes Study Short-Form 36. Виявлено значущі негативні зміни показників як фізичних, так і психічних компонентів здоров'я. Встановлено, що з точки зору впливу на якість життя пацієнтів із болями у попереку монотерапія тераміном та теноксикамом виявляється гіршою за їх комбіноване використання. Найвищий рівень фізичної активності спостерігається після застосування комбінованого препарату, а найнижчий – після вживання теноксикаму, аналогічні зміни виявлені за показником функціонування за рольовою фізичною активністю. На інтенсивність болю мала найбільший вплив комбінована терапія, ефект тераміну та теноксикаму був подібним. Також показано, що терамін переважав над теноксикамом за впливом на показники фізичної та психічної складових здоров'я. Результати досліджень тераміну та його комбінованого застосування з теноксикамом повинні бути включені в програму лікування пацієнтів з болем у попереку з метою поліпшення якості життя

Ключові слова: життєдіяльність; лікування; терамін; теноксикам; комбінації препаратів

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Influence of cognitive functioning on the effectiveness of treatment of veterans with post-traumatic stress disorder and mild traumatic brain injury

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Abstract. A history of traumatic brain injury in veterans is associated with higher use of mental health services, regardless of psychiatric diagnoses, which makes it important to develop a comprehensive approach to treatment and evaluate its effectiveness. The study aimed to investigate the impact of cognitive functioning among 329 veterans with comorbid post-traumatic stress disorder and mild traumatic brain injury on the effectiveness of combination therapy. The following tests were used to assess cognitive functioning: the Ray-Osterritz test, the Symbolic Communication Test, the Stroop test, and the Verbal Fluency Test. Functioning was assessed using the World Health Organization Questionnaire for the Assessment of Disability. The effectiveness of the combination therapy was also assessed using the Four-Dimensional Symptom Inventory. The influence of cognitive functioning on the effectiveness of 8-week complex therapy for veterans with this comorbidity was confirmed. The results of the Trail Making Test had statistically significant negative correlations with the cognitive sphere scale ($\rho = -0.237$; $p = 0.0117$) and the integral index of the World Health Organization questionnaire for the assessment of disability ($\rho = -0.192$; $p = 0.0424$), as well as positive correlations with the scales of self-care ($\rho = 0.2038$; $p = 0.0311$) and daily activity ($\rho = 0.2048$; $p = 0.0303$). It was found that patients with post-traumatic stress disorder, mild traumatic brain injury and their comorbidity responded differently to therapy, which was determined by the clinical features of their cognitive processes, namely associative performance, control rigidity/flexibility, attention, working memory and executive function. The dynamics of cognitive functioning differed in each group. It was also found that cognitive symptoms were targeted by therapy, as evidenced by their reduction after the intervention. The data obtained will allow for a more efficient and comprehensive organization of specialised psychiatric care for veterans, and cognitive functioning is predictive of the effectiveness and duration of treatment

Keywords: stress-related mental disorder; brain injury; cognitive disorders; executive function; treatment; veterans; comorbidity

Introduction

The comorbidity of post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI) is the most common medical combination among both civilian and military populations and has many common clinical symptoms [1, 2]. Both conditions are characterised by neurocognitive, behavioural, and affective symptoms that are caused by functional impairments in the frontal brain area, including impairments in executive functioning, working memory, planning, multitasking, complex decision-making, judgement, impulsivity, emotional lability, and disinhibition, as well as changes in personality, empathy, and social behaviour [3-5].

L.Z. Kong *et al.* [6], described the pathogenesis of TBI in the military and noted its connection with mechanical impacts resulting from the interaction of an explosive air wave, blunt force trauma and projectile penetration. S.B. Shively *et al.* [7], in their study of the pathophysiology of TBI and its relationship with chronic post-traumatic encephalopathy, showed that direct focal, multifocal

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or diffuse damage to neurons and their processes as well as glia and the vascular network, triggers a dynamic cascade of complex neurochemical and metabolic changes in the cellular and extracellular space of brain tissue, which lead to secondary trauma and represent ischaemic and hypoxic damage, leading to increased intracranial pressure, hydrocephalus, and inflammatory changes [1, 8, 9]. N. Marklund *et al.* [8] indicated that one moderate or severe TBI is associated with at least a twofold increase in the risk of dementia over the course of a lifetime. There is growing evidence of a link between TBI and neurodegeneration due to the accumulation, misfolding and aggregation of many abnormal proteins, including β-amyloid, α-synuclein, tau protein, and tar proteins that bind deoxyribonucleic acid (DNA) [9]. Studies also confirmed a long-term association between TBI and Parkinson's disease, Creutzfeldt-Jakob disease, and amyotrophic lateral sclerosis, and repetitive mild TBI is a risk factor for chronic traumatic encephalopathy (CTE) [10].

Modern neuroimaging studies allowed identifying both nosospecific and general neural substrates common to PTSD and TBI, and thus help to determine the clinical interaction of symptoms, and their diagnostic affiliation and improve the possibility of targeted treatment. While PTSD and TBI demonstrate significant overlap clinically and symptomatically, there is currently no generally accepted way to determine this aetiology beyond clinical judgment. Determination of neurobiological changes in this comorbidity was quite problematic due to its multi-aetiology, time since TBI, and the presence of premorbid TBI and psychiatric conditions [11].

Additional indicators of potential interest for understanding whether neurobiological substrates can correlate with neurocognitive deficits that negatively affect recovery from TBI comorbid with PTSD are genetic indicators that allow assessing markers of vulnerability and resilience, neuroimaging markers, and neuropsychological profile [12]. The literature review revealed a significant correlation between cognitive functioning, including memory, attention, executive functions, and associative performance, in veterans with PTSD and TBI. However, it is important to note that the analysis was not sufficient to fully understand the impact of these features on the effectiveness of 8 weeks of combined therapy. Thus, the study aimed to investigate the impact of cognitive functioning (parameters of memory, attention, executive functions, associative performance) in veterans with PTSD and mTBI on the effectiveness of 8 weeks of combined therapy.

Materials and Methods

During 2018-2020, a study was conducted at the Ternopil Regional Clinical Psychoneurological Hospital of 329 veterans aged 19 to 64 years, who were divided into three groups: patients with PTSD+TBI comorbidity (hereinafter referred to as CTBI) (n=108), patients with PTSD only (n=109), and patients with mild TBI only (hereinafter referred to as mTBI) (n=112). The initial interview included a survey using the Unified Patient Study Card developed by the author, which included a section on General Indicators and Current Life Problems: some socio-demographic indicators (age, gender, family, educational, social and employment status, duration of stay in the combat zone (up to seven days; up to one month; up to three months; up to six months and up to one year). Based on the International Statistical Classification of Diseases and Related Health Problems [13], a modal analysis of the existing problems was conducted, assessing the presence of factors from the following diagnostic categories: Z55, Z56, Z59, Z56, Z60, Z61, Z62, Z63, Z64, Z72, Z73.

The requirements and principles of bioethics were considered in all studies of this research paper, the rules of patient safety were followed, and the rights and canons of human dignity, moral and ethical standards were preserved according to the basic provisions of Good Clinical Practice (GSP) [14]. The Council of Europe Convention on Human Rights and Biomedicine [15], the World Medical Association Declaration of Helsinki on Ethical Principles for Scientific Medical Research Involving Human Subjects [16], and the Code of Ethics for Scientists of Ukraine [17] were also observed.

After providing informed consent to participate in the study, the subjects underwent a course of combined treatment in the form of standard therapy following the Unified Protocols for PTSD and mTBI and additional psychotherapeutic intervention, which consisted of a combination of psychoeducation, motivational interviewing, and Acceptance and Commitment Therapy for PTSD (ACT) (8 psychotherapy sessions 1-2 times a week) and transcranial direct current stimulation (tDCS) (10 sessions daily).

The psychodiagnostic study of cognitive functioning was implemented using Trail Making Test (TMT), in which the TMT-A part included dynamic parameters of attention (the volume and level of its voluntary regulation), and the TMT-B part – executive function; The Ray-Osterrieth Complex Figure Test (ROCFT) to study visual memory and visual-spatial syntheses by copying (ROCFT-1), immediate reproduction (ROCFT-2) and delayed reproduction (ROCFT-3) of a reference figure; The Stroop Color and Word Test (StroopCWIT) – to assess the selectivity of attention, where Stroop-1 is the congruent part of the test, Stroop-2 is the incongruent part of the test, Δ Stroop is the index of rigidity/rigidity of the control; Verbal Fluency Test (VFT) – to assess verbal associative performance (letter part, VFT-1) and lexical system disorders (categorical part, VFT-2).

Functioning was assessed using the World Health Organization (WHO) test for functional evaluation per WHODAS 2.0 scale (World Health Organization Disability Assessment Schedule) [18] in separate domains: CW – cognitive sphere; MW – mobility; SW – self-care; RW –relationships; LW – daily activity; PW – social activity; WHO – total score. The efficacy of the combination therapy was also assessed by the dynamics of clinical symptom severity using the Four-Dimensional Symptom Questionnaire

(4DSQ) with separate scales: DIS – distress; DEP –depression; ANX – anxiety; SOM – somatisation.

The results were analysed using descriptive statistics, Fisher's φ*-angular transformation, Mann-Whitney U-test, Wilcoxon's W-test, Kolmogorov-Smirnov test for two independent samples, and discriminant analysis. The correlation between the WHODAS 2.0 scores and the StroopCWIT, VFT, TMT, and ROCFT scores was determined by calculating Spearman's rank correlation coefficient, as the data did not follow a normal distribution. At the same time, the WHODAS 2.0 results obtained at the initial examination and after therapy were analysed, and the examination using the StroopCWIT, VFT, TMT and ROCFT tests were performed at the initial examination.

Results and Discussion

The influence of cognitive functioning on the effectiveness of 8-week complex therapy for veterans with PTSD and mTBI was conducted separately for each clinical group: PTSD, TBI, and CTBI. In the initial examination of patients with PTSD, statistically significant correlations were found between certain indicators of cognitive functioning and the WHODAS 2.0 questionnaire scales (Table 1), including the mobility scale (MW), self-care scale (SW) and social activity scale (PW). At the same time, the indicators of the incongruent part (Stroop-2) and the flexibility-rigidity coefficient (Δ Stroop) of the Stroop test showed negative correlations only with the indicators of the WHODAS 2.0 mobility scale (ρ≥-0.2; p≤0.0369).

Table 1. Correlations between indicators of cognitive functioning and scales of the WHODAS 2.0 questionnaire at the first examination of PTSD patients

scale		CW	MW	SW	RW	LW	PW	WHO
ROCFT-1	ρ	0.091	0.1453	0.0709	-0.108	0.1336	-0.032	0.1195
	p	0.3469	0.1318	0.4639	0.2642	0.1661	0.745	0.216
ROCFT-2	ρ	0.1724	-0.062	0.0726	-0.086	-0.115	0.0204	-0.011
	p	0.073	0.5233	0.4529	0.3714	0.2337	0.8334	0.9095
ROCFT-3	ρ	-0.072	-0.053	-0.21	0.0034	-0.024	0.0788	-0.019
	p	0.4549	0.5856	0.028	0.9723	0.8011	0.4153	0.8449
TMT-A	ρ	0.044	-0.053	0.2793	-0.024	0.0255	-0.051	0.0594
	p	0.6499	0.5808	0.0033	0.8015	0.7923	0.5983	0.5393
TMT-B	ρ	-0.066	0.2319	-0.222	-0.158	-0.085	0.0157	-0.109
	p	0.495	0.0152	0.0203	0.1012	0.3772	0.8714	0.258
VFT-1	ρ	-0.028	0.1462	0.021	-0.122	0.1076	-0.198	-0.058
	p	0.775	0.1294	0.8285	0.2045	0.2656	0.0385	0.5469
VFT-2	ρ	0.1535	0.0413	-0.101	-0.075	-0.151	0.1552	0.0002
	p	0.111	0.6697	0.2964	0.4389	0.1161	0.1071	0.998
Stroop-1	ρ	-0.087	0.0337	-0.06	0.0096	-0.111	-0.045	-0.118
	p	0.3693	0.728	0.5345	0.9207	0.2499	0.6418	0.2205
Stroop-2	ρ	-0.025	-0.26	-0.044	0.0402	-0.049	-0.045	-0.092
	p	0.7948	0.0064	0.6469	0.6782	0.6108	0.6396	0.341
Δ Stroop	ρ	0.047	-0.2	0.0242	0.0103	0.0603	-0.021	0.0292
	p	0.6278	0.0369	0.8029	0.9153	0.533	0.8262	0.7628

Notes: CW – cognitive domain; MW – mobility; SW – self-care; RW – relationships; LW – daily activities; PW – social activities; WHO – overall score

Source: compiled by the author

The scores of the letter part of the VFT (VFT-1) had subtle but statistically significant negative correlations (ρ=-0.198; p=0.0385) only with the scores of the social activity scale, and the scores of The Ray-Osterrieth Complex Figure Test Delayed Reproduction Scale (ROCFT-3) – only with the scores of the self-care scale (ρ=-0.21; p=0.028). A slightly wider range of correlations was observed in the analysis of the Trail Making Test (TMT): The indicators of its part B had positive correlations with the indicators of the Mobility Scale (MW) of the WHODAS 2.0 at the initial examination of the PTSD group (ρ=0.2319; p=0.0152) and negative correlations with the self-care scale – SW (ρ=-0.222; p=0.0203), while the indicators of part A of the TMT test had, on the contrary, positive correlations with the self-care scale (ρ=0.2793; p=0.0033). Thus, at the time of the initial examination in the PTSD group, more pronounced mobility disorders occurred in those respondents who had greater problems with the use of distributed attention, memory, and executive function, as well as poorer development of sensory and perceptual functions and, conversely, a more pronounced ability to inhibit stronger verbal functions for the sake of colour perception.

The analysis of WHODAS 2.0 data obtained during the re-examination of patients with PTSD indicates a different distribution of correlations (Table 2). The CW scale scores had significant correlations only with the scores of the letter part of the VFT test (ρ=0.1996; p=0.0375), which, in turn, also had negative correlations (ρ=-0.189; p=0.0486) with the LW scale scores of the WHODAS 2.0, and the categorical part of the VFT test with the SW scale scores

(ρ=-0.213; p=0.0263). The Ray-Osterrieth Complex Figure Test only revealed a rather weak negative correlation (ρ=-0.198; p=0.0386) with the RW scale of the WHODAS 2.0 methodology, and part B of the TMT test showed a negative correlation (ρ=-0.245; p=0.0102) with the SW scale. As for the indicators of the StroopCWIT test, the indicators of its congruent part were negatively correlated with the indicators of the RW scale (ρ=-0.227; p=0.0177), and the incongruent part – with the indicators of the SW scale (ρ=-0.241; p=0.0116).

Table 2. Correlations between indicators of cognitive functioning and scales of the WHODAS 2.0 questionnaire at the second examination of PTSD patients

scale		CW	MW	SW	RW	LW	PW	WHO
ROCFT-1	ρ	-0.154	0.1288	0.1642	-0.014	0.0713	0.1441	0.111
	p	0.11	0.1818	0.0881	0.8888	0.4613	0.135	0.2503
ROCFT-2	ρ	-0.021	-0.028	0.0418	-0.198	-0.036	-0.086	-0.144
	p	0.8265	0.7756	0.6659	0.0386	0.7136	0.3717	0.1343
ROCFT-3	ρ	0.0156	-0.048	-0.183	0.0134	0.1137	-0.041	0.0145
	p	0.8718	0.6228	0.0566	0.8899	0.2393	0.6706	0.881
TMT-A	ρ	0.0796	-0.09	0.0619	-0.162	-0.012	-0.096	-0.119
	p	0.4108	0.3521	0.5226	0.0921	0.9008	0.321	0.2176
TMT-B	ρ	-0.089	-0.03	-0.245	0.0267	-0.009	0.0545	-0.045
	p	0.3564	0.7569	0.0102	0.7829	0.9233	0.5732	0.6412
VFT-1	ρ	0.1996	-0.009	-0.155	-0.017	-0.189	-0.058	-0.108
	p	0.0375	0.9277	0.1079	0.8643	0.0486	0.5522	0.2649
VFT-2	ρ	-0.133	0.0894	-0.213	0.0585	0.0528	0.1397	0.0772
	p	0.1677	0.3554	0.0263	0.5454	0.5857	0.1474	0.4247
Stroop-1	ρ	-0.066	0.1618	0.1092	-0.227	0.0869	0.0783	0.0118
	p	0.4935	0.0929	0.2583	0.0177	0.3688	0.4184	0.9031
Stroop-2	ρ	-0.098	0.0276	-0.241	-0.104	0.1613	0.1348	0.0992
	p	0.3104	0.7756	0.0116	0.283	0.0938	0.1621	0.3048
Δ Stroop	ρ	-0.011	-0.068	-0.235	0.0745	0.0298	0.0463	0.0553
	p	0.9095	0.4813	0.0139	0.4411	0.7587	0.6327	0.5679

Notes: CW – cognitive domain; MW – mobility; SW – self-care; RW – relationships; LW – daily activities; PW – social activities; WHO – overall score
Source: compiled by the author

Thus, the peculiarities of the cognitive functioning of patients with PTSD were identified, which in some way prevented the reduction of the symptoms of the underlying disease, namely after completion of treatment, more pronounced disorders in the field of self-care persisted in those patients who, at the time of the start of therapy, had a reduced stock of semantic memory, development of the lexical system and executive functions. However, they demonstrated the ability to distribute attention and working memory more actively. Impairments in the area of relationships persisted to a greater extent in patients who had sufficiently well-developed verbal and language functions, and impairments in daytime activity were lower in those respondents with higher verbal associative performance. On the other hand, patients with PTSD who had more severe impairments in daily activities, self-care, and relationships maintained more severe impairments in the cognitive domain even after therapy. The correlation analysis of the above methods in the TBI group revealed quite different features (Table 3).

Table 3. Correlations between cognitive functioning and WHODAS 2.0 scales in the first examination of patients with TBI

scale		CW	MW	SW	RW	LW	PW	WHO
ROCFT-1	ρ	0.1304	-0.016	0.0514	0.0213	-0.147	0.041	0.0283
	p	0.1706	0.8637	0.5906	0.8238	0.1231	0.6681	0.767
ROCFT-2	ρ	0.0409	0.1052	-0.092	-0.071	-0.07	-0.14	-0.101
	p	0.6685	0.2694	0.3357	0.4551	0.4644	0.1399	0.2917
ROCFT-3	ρ	0.0277	0.0709	-0.036	0.0304	0.0496	-0.004	0.0554
	p	0.7716	0.4573	0.7059	0.7506	0.6034	0.9639	0.5615
TMT-A	ρ	0.0547	-0.201	0.0831	-0.068	0.1333	0.2235	0.0992
	p	0.5667	0.0334	0.3839	0.4789	0.1611	0.0178	0.2982
TMT-B	ρ	0.005	-0.003	-0.021	0.0562	-0.154	0.0203	-0.089
	p	0.9585	0.9728	0.8239	0.5562	0.1045	0.8318	0.3502

Continued Table 3

scale		CW	MW	SW	RW	LW	PW	WHO
VFT-1	ρ	0.1562	0.046	-0.056	-0.197	0.0031	0.0862	0.0597
	p	0.1	0.6298	0.5542	0.0377	0.9738	0.3662	0.5321
VFT-2	ρ	-0.128	0.0187	0.0934	-0.091	0.0804	0.0211	-0.029
	p	0.1802	0.8448	0.3272	0.3416	0.3994	0.8256	0.7624
Stroop-1	ρ	-0.027	0.0534	0.1038	-0.167	0.0476	0.0622	-0.075
	p	0.7803	0.576	0.2761	0.0779	0.6185	0.5147	0.4309
Stroop-2	ρ	0.0377	0.0382	-0.009	0.1008	0.1455	0.0863	0.1264
	p	0.6928	0.6892	0.9233	0.2905	0.126	0.3657	0.1843
Δ Stroop	ρ	0.041	0.0003	-0.103	0.2346	0.069	-0.035	0.1619
	p	0.6677	0.9973	0.2798	0.0128	0.4696	0.7127	0.088

Notes: CW – cognitive domain; MW – mobility; SW – self-care; RW – relationships; LW – daily activities; PW – social activities; WHO – overall score
Source: compiled by the author

There were negative correlations of TMT-A indicators with the MW scale (ρ=-0.201; p=0.0334) and positive correlations with the PW scale (ρ=0.2235; p=0.0178) of the WHODAS 2.0 scale, and the RW scale of this technique had negative correlations with the letter part of the VFT test (ρ=-0.197; p=0.0377) and positive correlations with the StroopCWIT stiffness/flexibility of control (ρ=0.2346; p=0.0128). Thus, among the representatives of the TBI group, at the initial examination, more pronounced impairments in the field of relationships occurred in respondents with low verbal associative performance and a tendency to be released from the influence of the word meaning when it does not correspond to a visual impression, and respondents with insufficient spatial attention and its voluntary regulation had more pronounced impairments in the field of social activity, although they experienced mobility problems to a lesser extent. It is also characteristic that in the TBI group, unlike patients with PTSD, none of the The Ray-Osterrieth Complex Figure Test scores had any statistically significant correlations with the WHODAS 2.0 scores (p≥0.1231).

After the therapy, the clinical picture changed (Table 4). Unlike the first examination, none of the WHODAS 2. 0 tests had statistically significant correlations (p≥0.1461) with the VFT test scores, and the The Ray-Osterrieth Complex Figure Test scores, on the contrary, showed positive correlations: the copying scale (ROCFT-1) – with the RW scale (ρ=0.1863; p=0.0492), and the immediate reproduction scale (ROCFT-1) – with the integral index of the WHODAS 2. 0 (ρ=0.1862; p=0.0493).

Table 4. Correlations between indicators of cognitive functioning and scales of the WHODAS 2.0 questionnaire in the re-examination of patients with TBI

scale		CW	MW	SW	RW	LW	PW	WHO
ROCFT-1	ρ	-0.053	-0.027	-0.12	0.1863	0.0047	-0.094	-0.014
	p	0.5817	0.7791	0.2063	0.0492	0.9609	0.3223	0.8853
ROCFT-2	ρ	0.0688	-0.014	0.1117	0.0761	-0.128	-0.11	0.1862
	p	0.4707	0.8843	0.241	0.4255	0.1776	0.2494	0.0493
ROCFT-3	ρ	-0.027	0.1127	0.0306	0.0113	-0.063	-0.059	0.045
	p	0.7737	0.237	0.7487	0.906	0.5085	0.5383	0.6372
TMT-A	ρ	-0.237	-0.035	-0.093	0.0249	0.0363	0.147	-0.192
	p	0.0117	0.7107	0.3292	0.7942	0.7041	0.122	0.0424
TMT-B	ρ	-0.045	-0.083	0.2038	0.0691	0.2048	0.0742	0.1598
	p	0.6395	0.3839	0.0311	0.4692	0.0303	0.4371	0.0924
VFT-1	ρ	0.0747	0.0288	-0.109	0.1382	0.0746	-0.074	0.0829
	p	0.4339	0.7628	0.252	0.1461	0.4345	0.4357	0.3849
VFT-2	ρ	-0.038	0.0145	-0.118	-0.054	-0.095	-0.136	-0.132
	p	0.6871	0.8794	0.2149	0.5745	0.3208	0.1521	0.1649
Stroop-1	ρ	-0.048	0.1019	-0.051	0.0368	-0.027	-0.002	-0.035
	p	0.6149	0.2852	0.5903	0.7	0.7782	0.9839	0.7116
Stroop-2	ρ	0.0462	-0.197	0.0571	0.0827	0.0637	0.0609	0.0517
	p	0.6284	0.0377	0.5501	0.3859	0.5043	0.5237	0.5879
Δ Stroop	ρ	0.0571	-0.22	0.1014	0.008	0.0864	0.0572	0.0772
	p	0.5499	0.02	0.2875	0.9333	0.3651	0.5491	0.4187

Notes: CW – cognitive domain; MW – mobility; SW – self-care; RW – relationships; LW – daily activities; PW – social activities; WHO – overall score
Source: compiled by the author

The scores of the letter part of the TMT test had statistically significant negative correlations with the CW scale score (ρ=-0.237; p=0.0117) and the WHODAS 2.0 integral score (ρ=-0.192; p=0.0424), as well as positive correlations with the SW (ρ=0.2038; p=0.0311) and LW (ρ=0.2048; p=0.0303) scales. The StroopCWIT scores had statistically significant negative correlations (ρ≥-0.197; p≤0.0377) only with the MW scale of the WHODAS 2.0 methodology, and this applied to both its incongruent part (Stroop-2) and the control stiffness/stiffness index (Δ Stroop).

Thus, the results obtained suggest that after the therapy, patients with a well-developed level of spatial orientation and its regulation experienced a lesser reduction in cognitive impairment and the overall level of disabling effects of TBI, while respondents with a high level of attention span, working memory and executive functions, on the contrary, experienced a more active process of disappearance of impairments in self-care and daily activities. Mobility impairments disappeared more rapidly in patients whose attention was fixed on the meaning of the word at the beginning of therapy, despite the correspondence to the visual impression.

Analysis of the results of calculating Spearman's rank correlation coefficient to identify the relationship between the WHO WHODAS 2.0 Disability Assessment Questionnaire and the StroopCWIT, VFT, TMT, and ROCFT tests in the initial examination of the CTBI group respondents (Table 5), unlike the representatives of the above research groups, did not reveal any statistically significant correlation (ρ≤-0.166; p≥0.0898).

Table 5. Correlation between cognitive functioning indicators and WHODAS 2.0 scales at the first examination of patients in the CTBI group

scale		CW	MW	SW	RW	LW	PW	WHO
ROCFT-1	ρ	-0.02	0.0253	-0.164	0.1229	-0.042	-0.006	0.0049
	p	0.8408	0.7951	0.0898	0.2052	0.6694	0.9482	0.9599
ROCFT-2	ρ	-0.058	0.015	-0.055	-0.108	-0.1	0.1071	-0.089
	p	0.552	0.8777	0.5737	0.2667	0.3024	0.27	0.3609
ROCFT-3	ρ	-0.062	0.0269	0.0869	-0.095	0.1501	-0.017	-0.015
	p	0.5217	0.7826	0.3714	0.3286	0.1211	0.8642	0.8744
TMT-A	ρ	-0.113	-0.074	0.0573	0.0694	0.0099	-0.015	-0.036
	p	0.246	0.4466	0.5555	0.4753	0.9187	0.8752	0.7079
TMT-B	ρ	-0.062	-0.134	-0.036	-0.062	0.0072	-0.108	-0.165
	p	0.5207	0.1666	0.7092	0.5251	0.9409	0.2637	0.0878
VFT-1	ρ	-0.001	-0.196	0.0037	-0.02	-0.044	0.0777	0.0513
	p	0.9894	0.0523	0.9695	0.841	0.6537	0.4244	0.598
VFT-2	ρ	-0.011	-0.146	-0.011	-0.024	0.0451	0.1116	0.0071
	p	0.9069	0.1314	0.9107	0.8037	0.6432	0.2502	0.9418
Stroop-1	ρ	0.122	0.0645	-0.011	-0.024	-0.044	-0.023	0.0353
	p	0.2084	0.5071	0.9104	0.806	0.6489	0.8121	0.7167
Stroop-2	ρ	-0.038	0.0534	0.144	0.0303	-0.166	0.1158	0.0435
	p	0.6951	0.5833	0.1372	0.7558	0.0867	0.2326	0.6549
Δ Stroop	ρ	-0.115	-0.022	0.0745	0.014	-0.085	0.1262	-0.007
	p	0.2339	0.8219	0.4438	0.8855	0.379	0.193	0.9436

Notes: CW – cognitive domain; MW – mobility; SW – self-care; RW – relationships; LW – daily activities; PW – social activities; WHO – overall score
Source: compiled by the author

The calculation of Spearman's rank correlation coefficient of the indicators of these methods and the results of the WHODAS 2.0, which was used to re-examine the respondents after therapy, revealed statistically significant correlations between the CW scale and the delayed reproduction index of the The Ray-Osterrieth Complex Figure Test (ρ=-0.229; p=0.0174) and the ΔStroop scale of the Stroop Color and Word Test and the PW scale (ρ=0.2076; p=0.0311) of the WHODAS 2.0 methodology (Table 6).

Table 6. Correlation between cognitive functioning indicators and WHODAS 2.0 scales in the repeated examination of patients with PTSD+TBI

scale		CW	MW	SW	RW	LW	PW	WHO
ROCFT-1	ρ	0.0081	-0.083	-0.178	0.0145	-0.001	0.0192	0.0158
	p	0.9339	0.391	0.0648	0.8816	0.9902	0.8433	0.8713
ROCFT-2	ρ	-0.083	-0.177	0.1239	0.0909	-5E-04	0.0445	0.0183
	p	0.3903	0.0662	0.2015	0.3496	0.9961	0.6471	0.8512

Continued Table 6

scale		CW	MW	SW	RW	LW	PW	WHO
ROCFT-3	ρ	-0.229	0.007	0.0503	0.0842	-0.015	-0.116	-0.158
	p	0.0174	0.9427	0.605	0.3861	0.8755	0.2332	0.1019
TMT-A	ρ	0.0663	-0.046	-0.061	0.0802	0.0886	0.076	0.165
	p	0.4952	0.6393	0.5329	0.4091	0.362	0.4346	0.0879
TMT-B	ρ	0.0157	0.0747	-0.031	-0.12	0.0488	0.0049	0.0093
	p	0.8715	0.4422	0.7498	0.2143	0.6159	0.9601	0.9238
VFT-1	ρ	-0.042	0.1233	0.0728	0.1301	0.0542	0.1227	0.1659
	p	0.6635	0.2038	0.4542	0.1795	0.5775	0.2059	0.0862
VFT-2	ρ	-0.017	-0.043	-0.126	0.1324	0.0127	-0.019	0.0203
	p	0.8629	0.6577	0.1956	0.1721	0.8963	0.8449	0.8346
Stroop-1	ρ	0.0398	-0.07	0.0326	0.0497	0.0876	-0.031	0.0438
	p	0.6829	0.4721	0.7376	0.6097	0.3674	0.7528	0.6524
Stroop-2	ρ	-0.027	0.0329	0.0276	-0.078	0.0065	0.1718	0.0762
	p	0.7815	0.7357	0.7766	0.4235	0.9465	0.0755	0.4329
Δ Stroop	ρ	-0.056	0.0636	-0.02	-0.093	-0.031	0.2076	0.0726
	p	0.5681	0.5134	0.8355	0.3408	0.7478	0.0311	0.4555

Notes: CW – cognitive domain; MW – mobility; SW – self-care; RW – relationships; LW – daily activities; PW – social activities; WHO – overall score
Source: compiled by the author

Thus, while there were no correlations between the indicators of these methods during the initial examination of the CTBI group, there were no correlations between the indicators of these methods. After the therapeutic intervention, the reduction of cognitive impairment was more pronounced in patients who, before treatment, showed less ability to perceive the holistic structure and features of the drawing copying strategy, and impairment in the field of social activity was more effectively levelled in those who, at the beginning of therapy, had a good ability to inhibit the more naturally strong verbal functions in favour of colour perception.

Spearman's rank correlation coefficient was also calculated for the StroopCWIT, VFT, TMT, and ROCFT, which were used in the initial examination and the 4DSQ test, which was used in the initial and repeated examination (Table 7-9).

Table 7. The relationship between cognitive functioning and the 4DSQ test in the PTSD group at baseline and after therapy

Examination		First					After therapy				
scale		DIS	DEP	ANX	SOM	4DSQ	DIS	DEP	ANX	SOM	4DSQ
ROC-1	ρ	-0.024	0.0419	0.0602	0.0529	0.0577	-0.005	0.0215	0.0249	0.0839	0.0205
	p	0.8025	0.6655	0.5339	0.5849	0.5511	0.9553	0.8247	0.7968	0.3857	0.8322
ROC-2	ρ	-0.008	0.0905	-0.056	0.0113	-0.003	0.0055	-0.101	-0.119	-0.06	-0.096
	p	0.9341	0.3493	0.5636	0.9073	0.9739	0.9547	0.2946	0.2159	0.5376	0.3217
ROC-3	ρ	0.092	-0.123	-0.034	0.0688	0.018	-0.197	-0.046	0.1083	-0.111	-0.095
	p	0.3414	0.2027	0.7288	0.4769	0.8526	0.0401	0.6363	0.2621	0.2488	0.3283
TMT-A	ρ	0.0019	0.0542	-0.005	-0.138	-0.028	0.19	0.1756	0.0505	-0.012	0.1797
	p	0.9847	0.5757	0.9588	0.1513	0.7752	0.0478	0.0678	0.6023	0.8975	0.0616
TMT-B	ρ	-0.134	0.0536	-0.039	0.0005	-0.11	0.0586	-0.013	-0.027	-0.043	0.043
	p	0.1653	0.5802	0.6878	0.9962	0.253	0.5452	0.8963	0.7795	0.66	0.657
VFT-1	ρ	0.0768	-0.163	-0.162	-0.19	-0.124	-0.01	0.0973	-0.01	0.1954	0.0549
	p	0.4272	0.0907	0.0926	0.0477	0.1993	0.9204	0.3142	0.9168	0.0417	0.5711
VFT-2	ρ	0.1538	-0.018	0.0046	0.026	0.1503	0.0234	0.0256	-0.045	0.021	0.0353
	p	0.1102	0.856	0.9621	0.7886	0.1189	0.8092	0.7913	0.643	0.8281	0.7156
Stroop-1	ρ	-0.018	0.0771	-0.036	-0.099	-0.04	0.0159	-0.12	0.073	0.0032	0.0047
	p	0.8565	0.4254	0.7102	0.304	0.6805	0.8693	0.2129	0.4506	0.9736	0.9617
Stroop-2	ρ	-0.037	0.0141	-0.128	0.0782	-0.01	-0.07	0.0177	-0.166	-0.03	-0.138
	p	0.7012	0.8845	0.1859	0.4191	0.9192	0.4681	0.8551	0.0854	0.756	0.1529
Δ Stroop	ρ	-0.018	-0.047	-0.063	0.1159	0.012	-0.081	0.0876	-0.18	-0.003	-0.114
	p	0.8551	0.624	0.5141	0.23	0.9015	0.4042	0.3648	0.0604	0.9746	0.2362

Notes: DIS – distress; DEP – depression; ANX – anxiety; SOM – somatisation; 4DSQ – Four-Dimensional Symptom Questionnairee
Source: compiled by the authors

For the PTSD group (Table 7), during the initial examination, statistically significant correlations were found only between the SOM scale of the 4DSQ and the letter part of the VFT test (ρ=-0.19; p=0.0477). After the therapy, the DIS scale of the 4DSQ had statistically significant correlations with the delayed recall scale of The Ray-Osterrieth Complex Figure Test (ρ=-0.197; p=0.0401) and positive correlations with the indicators of part A of the TMT (ρ=0.19; p=0.0478). In addition, the SOM scale had a significant correlation with the categorical part of the VFT test (ρ=0.1954; p=0.0417). Thus, before the therapy, it was found that greater severity of somatoform disorders occurred in patients with low verbal associative productivity, but after the therapy, the situation changed polarly – it was patients with high verbal associative productivity who showed a greater tendency to somatize psychological conflict by developing somatoform disorders. After the therapy, the symptoms of distress were most effectively reduced in those patients who had well-developed dynamic parameters of attention, the level of voluntary regulation, and visual-motor coordination at the time of treatment.

In representatives of the TBI group (Table 8), at the initial examination, statistically significant negative correlations were observed between the integral somatisation index of the 4DSQ test and the index of the categorical part of the VFT technique (ρ=-0.189; p=0.0465), as well as between the ANX scale and the immediate reproduction scale of the The Ray-Osterrieth Complex Figure Test (ρ=-0.186; p=0.0494). After the therapy, significant correlations were observed only between the scores of the The Ray-Osterrieth Complex Figure Test and the 4DSQ, with the delayed reproduction scale having negative correlations (ρ≥-0.188; p≤0.0468) with the DEP scale and the 4DSQ integral score, and positive correlations between the immediate reproduction scale and the DIS scale of the 4DSQ (ρ=0.2018; p=0.0329).

Table 8. The relationship between cognitive functioning and the 4DSQ test in the TBI group at baseline and after therapy

Examination		First					After therapy				
scale		DIS	DEP	ANX	SOM	4DSQ	DIS	DEP	ANX	SOM	4DSQ
ROC-1	ρ	-0.069	0.1529	-0.186	-0.011	-0.118	-0.069	-0.068	0.0589	-4E-04	-0.025
	p	0.47	0.1076	0.0494	0.9104	0.2135	0.4722	0.4781	0.5372	0.9964	0.793
ROC-2	ρ	0.0413	-0.072	0.1044	-0.018	0.0332	0.2018	-0.033	-0.014	0.1274	0.1553
	p	0.6657	0.4484	0.2734	0.8476	0.728	0.0329	0.7331	0.8842	0.1808	0.102
ROC-3	ρ	-0.048	0.0219	-0.119	-0.031	-0.168	-0.176	-0.188	-0.053	-0.153	-0.286
	p	0.614	0.8186	0.2112	0.7435	0.076	0.0629	0.0468	0.5778	0.1083	0.0022
TMT-A	ρ	-0.008	-0.114	-0.095	-0.039	-0.168	-0.015	-0.006	0.1231	-0.102	0.0553
	p	0.9301	0.2327	0.3216	0.6849	0.0766	0.8723	0.9528	0.1961	0.285	0.5626
TMT-B	ρ	0.074	0.1359	-0.047	-0.02	0.0912	0.0071	0.1428	-0.025	0.1133	0.1085
	p	0.4381	0.1532	0.624	0.8375	0.3387	0.941	0.1332	0.7917	0.2343	0.255
VFT-1	ρ	0.0635	-0.065	-0.079	0.0079	0.0215	-0.04	-0.046	-0.032	-0.052	-0.05
	p	0.5062	0.4931	0.4099	0.9343	0.8218	0.6786	0.6306	0.7351	0.5831	0.6021
VFT-2	ρ	-0.108	-0.024	-0.15	-0.083	-0.189	0.0664	-0.061	-0.062	-0.065	0.01
	p	0.2563	0.8003	0.1144	0.3846	0.0465	0.4864	0.5232	0.5133	0.494	0.9165
Stroop-1	ρ	-0.141	-0.028	0.0299	0.1047	-0.065	0.0956	-0.052	-0.176	0.0001	-0.03
	p	0.1368	0.7702	0.7546	0.2721	0.4945	0.3158	0.5832	0.0628	0.9988	0.7539
Stroop-2	ρ	-0.175	0.0338	0.0455	0.0483	-0.086	-0.066	-0.137	-0.074	5E-05	-0.07
	p	0.0645	0.7237	0.6338	0.6132	0.3677	0.4903	0.1489	0.437	0.9995	0.4624
Δ Stroop	ρ	0.0297	0.0361	0.0487	-0.071	0.0357	-0.135	-0.042	0.12	0.0137	-0.022
	p	0.7557	0.7057	0.6104	0.4573	0.7089	0.1545	0.6606	0.2074	0.886	0.8201

Notes: DIS – distress; DEP – depression; ANX – anxiety; SOM – somatisation; 4DSQ – Four-Dimensional Symptom Questionnaire

Source: compiled by the authors

Thus, at the time of the initial examination, patients with TBI had a more pronounced somatisation of psychological conflict, the less developed their executive function and the smaller their semantic memory. At the same time, after the therapy, these features were levelled out, although a greater degree of somatisation remained in patients with an insufficient ability to perceive the integral structure and features of the visual-manual coping strategy. As opposed to the research groups described above, at the time of the initial survey of the respondents of the CTBI group (Table 9), no correlations were found between the indicators of the techniques under consideration, except for the relationship between the letter part of the VFT test and the ANX scale of the 4DSQ (ρ=0.2295; p=0.0169).

Table 9. The relationship between cognitive functioning and the 4DSQ test in the CTBI group at baseline and after therapy

Examination		First					After therapy				
scale		DIS	DEP	ANX	SOM	4DSQ	DIS	DEP	ANX	SOM	4DSQ
ROC-1	ρ	0.0336	-0.159	0.0867	-0.138	0.036	0.1911	-0.014	0.1807	0.069	0.2481
	p	0.7298	0.0996	0.3721	0.1546	0.7117	0.0575	0.8823	0.0612	0.476	0.0096
ROC-2	ρ	0.1214	-0.01	-0.157	0.027	0.0006	0.0735	-0.089	-0.111	-0.188	-0.064
	p	0.2108	0.9179	0.1046	0.7815	0.9949	0.45	0.3597	0.2548	0.051	0.5101
ROC-3	ρ	0.0822	-0.118	-0.099	-0.024	-0.084	-0.136	-0.11	-0.092	0.123	-0.108
	p	0.3975	0.2236	0.3071	0.805	0.3848	0.1594	0.2556	0.3439	0.206	0.2676
TMT-A	ρ	-0.087	-0.118	0.1197	0.0603	-0.015	-0.042	0.1159	1E-05	0.052	-0.009
	p	0.3679	0.2258	0.2172	0.5351	0.8738	0.6653	0.2324	0.9999	0.594	0.9276
TMT-B	ρ	-0.036	-0.026	0.099	-0.174	-0.015	0.0134	0.0342	-0.048	-0.004	-0.013
	p	0.7105	0.7925	0.3082	0.0719	0.8764	0.8907	0.7256	0.6234	0.964	0.8942
VFT-1	ρ	0.049	-0.109	0.2295	-0.033	0.1465	-0.014	-0.2	-0.126	-0.079	-0.154
	p	0.6148	0.2626	0.0169	0.7319	0.1304	0.8886	0.0379	0.1945	0.414	0.1118
VFT-2	ρ	0.0853	-0.153	0.1719	-0.047	0.1374	-0.14	-0.076	0.0021	0.005	-0.094
	p	0.3799	0.1129	0.0753	0.6273	0.1561	0.148	0.4339	0.9825	0.958	0.3353
Stroop-1	ρ	-0.125	-0.007	0.0024	0.0215	-0.107	0.006	0.0532	0.0238	0.241	0.0735
	p	0.1985	0.9452	0.9802	0.8253	0.2717	0.9511	0.5843	0.8067	0.012	0.4497
Stroop-2	ρ	-0.036	0.0728	0.1452	-0.117	0.0828	-0.096	0.0924	-0.092	-0.063	-0.099
	p	0.7134	0.4541	0.1338	0.2289	0.3944	0.3229	0.3417	0.3448	0.52	0.3091
Δ Stroop	ρ	0.0646	0.0843	0.1431	-0.143	0.1584	-0.027	0.0083	-0.102	-0.194	-0.098
	p	0.5068	0.3857	0.1395	0.1411	0.1015	0.7842	0.9323	0.2952	0.044	0.3146

Notes: DIS – distress; DEP – depression; ANX – anxiety; SOM – somatisation; 4DSQ – Four-Dimensional Symptom Questionnaire

Source: compiled by the authors

When analysing the results of the repeated examination using the 4DSQ test, positive correlations were found between the SOM scale scores and the congruent part, as well as the Stroop stiffness-rigidity test ($\rho \geq -0.194$; $p \leq 0.044$); between the DEP scale and the letter part of the VFT test ($\rho = -0.2$; $p = 0.0379$), as well as positive correlations between the 4DSQ integral index and the ROCFT copying scale ($\rho = 0.2481$; $p = 0.0096$). Thus, in the initial study, somatisation of anxiety symptoms occurred to a greater extent in respondents with low verbal associative performance, which cannot be controversial. After the therapy, patients with CTBI whose associative productivity was, on the contrary, well-developed, more easily got rid of somatized depressive symptoms, and patients who focused mainly on the effects of the word meaning when it did not correspond to a visual impression had better results in getting rid of somatoform disorders.

Thus, this study determined that in different clinical groups, different cognitive characteristics influenced the effectiveness of treatment. PTSD patients had a range of characteristics (high verbal associative performance, developed dynamic parameters of attention, sufficient level of voluntary regulation, and visual-motor coordination). On the contrary, other features of cognitive functioning in patients with PTSD (reduced semantic memory, reduced development of the lexical system and executive functions) in some way impeded recovery during therapy. In patients with TBI, the effective reduction of impairments in self-care, mobility, and daytime activity was influenced by a high level of attention span, working memory, and executive functions, and a higher level of control flexibility. In patients with comorbid PTSD/TBI, individuals with high control flexibility and high associative performance demonstrated a rapid reduction in cognitive impairment during therapy and somatized depressive symptoms.

Existing studies examined various aspects of the psychiatric consequences of TBI in patients with PTSD and their impact on recovery during treatment, but there is no data from Ukrainian scientists whose area of interest is cognitive features in the comorbidity of PTSD and TBI. M.L. Timmer *et al.* [5], investigating the range of long-term behavioural disorders and care provided after traumatic brain injury, indicated that only half of patients resumed work regardless of the severity of the injury, which indicates that the presence, but not the severity of long-term behavioural disorders prevents return to work, which emphasises the importance of early detection and appropriate treatment of behavioural disorders in patients with TBI. This study provided a detailed analysis of the cognitive features that facilitate rehabilitation therapeutic interventions in veterans with comorbidity of TBI and PTSD.

S.M. Lippa *et al.* [4], studying PTSD symptoms associated with cognitive function after TBI, found that the

potential impact of PTSD symptoms on cognitive function should be taken into account in military personnel and veterans with a history of mild/medium TBI. In addition, the authors indicated that the severity of PTSD symptoms should be taken into account to assess cognitive dysfunction in comorbidity with PTSD. The study results were consistent with the results obtained in this paper regarding the impact of the severity of clinical symptoms of PTSD on cognitive dysfunction, but additionally, the impact of TBI symptoms on cognitive functioning and treatment effectiveness was analysed.

A.R. Mayer *et al.* [19], J.B. Patel *et al.* [20] and M.B. Stein *et al.* [21] demonstrated neuroimaging indicators of the combined effect of TBI and PTSD on the white matter of the brain in the form of a larger number of spatially heterogeneous areas of abnormally low fractional anisotropy, or "potholes", which was found in veterans with a history of mild TBI and was not associated with age, time after injury, PTSD, mood disorders or alcohol use with harmful effects [20-22]. However, A.R. Mayer *et al.* [19] described only cases of psychiatric illness that occurred after traumatic brain injury, without considering the different time points of occurrence of these conditions. A.I. Esagoff *et al.* [22] did not conduct a targeted neuropsychological study of cognitive functioning and its impact on the effectiveness of treatment, unlike the present study. N.L. de Souza *et al.* [23] described the neuroimaging and neuropsychological profile only in active military personnel, unlike the present study, which examined veterans and demobilised military personnel.

The results of neuroimaging studies demonstrated that in relatively young veterans with mild TBI, the finding of Deep white matter hyperintensities (DWMH) has a different and negative impact on memory performance than the impact of PTSD symptoms [24-26]. The present study did not use neuroimaging data due to the heterogeneity of the technical features of diagnostic devices and the unstructured nature of general imaging descriptions.

D.L.G. Van Praag *et al.* [27] studied the impact of neurocognitive functioning on the course of PTSD and found that strong sustained attention was associated with improved symptoms of post-traumatic stress disorder, leading to the conclusion that assessing cognitive abilities can help identify individuals at risk of developing (persistent) PTSD after TBI and provide opportunities to inform treatment strategies. However, the present study did not assess the prognostic value of the treatment effectiveness, which was conducted by the authors of this study. Consequently, concurrent PTSD and mTBI should be considered as a risk factor for poor neuropsychological outcome, which requires early and comprehensive intervention.

Conclusions

The study results confirmed the impact of cognitive functioning on the effectiveness of complex therapy for veterans with PTSD and mTBI. The developed dynamic parameters of attention in the PTSD group, a sufficient level of voluntary regulation and visual-motor coordination in individuals with PTSD at the time of treatment, provided effective suppression of symptoms of distress after therapy. On the contrary, the peculiarities of cognitive functioning of patients with PTSD, which in some way hindered, first, the restoration of self-care, were reduced semantic memory, development of the lexical system and executive functions. In addition, well-developed verbal and language functions were associated with less effective reduction of disorders in the field of relationships.

A high attention span, working memory and executive functions in the TBI group predicted the effectiveness of the process of recovery of self-care and daily activities. A higher level of control flexibility in people with TBI was associated with effective mobility recovery. Developed executive function and a smaller semantic memory reserve led to a more pronounced somatisation of symptoms at the beginning of the study, which was effectively levelled after the therapy, although a greater degree of somatisation remained in patients with the insufficient ability to perceive the holistic structure and features of the visual-manual copying strategy.

Reduction of cognitive impairment in the CTBI group was more pronounced in patients who demonstrated impaired perception of the integral structure in copying a picture before treatment, and impairment in social activity was more effectively levelled in individuals with high control flexibility. In addition, individuals with low verbal associative performance at baseline had the highest somatisation of anxiety symptoms. High associative productivity provided for an effective reduction, firstly, of somatized depressive symptoms, and high control flexibility led to better results in getting rid of somatoform disorders.

A detailed study and analysis of cognitive indicators is promising for clinical practice, as it is necessary to determine the scope of medical and psychotherapeutic interventions for comorbidity of PTSD and TBI and to predict the effectiveness of therapy. Further research should consider the development of an individual approach to the treatment of patients with PTSD and coexisting mild TBI, tailored to their cognitive status.

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Conflict of Interest

There are no potential sources of conflict of interest that affect the author's objectivity.

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Вплив когнітивного функціонування на ефективність лікування ветеранів з посттравматичним стресовим розладом та легкою черепно-мозковою травмою

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Анотація. Анамнез щодо травматичного ушкодження мозку у ветеранів пов'язаний з більшим використанням послуг охорони психічного здоров'я, незалежно від виставлених психіатричних діагнозів, що робить актуальним розробку комплексного підходу до лікування та оцінки його ефективності. Метою роботи було дослідити вплив особливостей когнітивного функціонування серед 329 ветеранів з коморбідними посттравматичним стресовим розладом та легкою черепно-мозковою травмою на ефективність комбінованої терапії. Для дослідження когнітивного функціонування проводились: тест Рея-Остерріца, тест зв'язку символів, тест Струпа, тест вербальної швидкості. Оцінка функціонування проводилась за опитувальником Всесвітньої організації охорони здоров'я для оцінки інвалідизації. Ефективність комбінованої терапії також оцінювалась за Чотиривимірним опитувальником симптомів. Підтверджено вплив когнітивного функціонування на ефективність 8-тижневої комплексної терапії ветеранів з вказаною коморбідністю. Показники тесту зв'язку символів мали статистично значущі негативні кореляційні зв'язки з показником шкали когнітивної сфери ($\rho = -0{,}237$; $p = 0{,}0117$) та інтегральним показником опитувальника Всесвітньої організації охорони здоров'я для оцінки інвалідизації ($\rho = -0{,}192$; $p = 0{,}0424$), а також позитивні кореляційні зв'язки з шкалами самообслуговування ($\rho = 0{,}2038$; $p = 0{,}0311$) та денної активності ($\rho = 0{,}2048$; $p = 0{,}0303$). Виявлено, що пацієнти з посттравматичним стресовим розладом, легкою черепно-мозковою травмою та їх коморбідністю по-різному реагували на проведення терапії, що визначалось клінічними особливостями їх когнітивних процесів, а саме асоціативної продуктивності, ригідності/гнучкості контролю, уваги, робочої пам'яті та виконавчої функції. Динаміка когнітивного функціонування відрізнялась у кожній групі. Також встановлено, що когнітивні симптоми ставали мішенями терапії, про що свідчила їх редукція після проведеного втручання. Отримані дані дозволять більш ефективно та комплексно організовувати надання спеціалізованої психіатричної допомоги ветеранам, а когнітивне функціонування має прогностичне значення щодо ефективності та тривалості лікування

Ключові слова: психічний розлад, пов'язаний зі стресом; травма мозку; когнітивні розлади; виконавчі функції; лікування; ветерани; коморбідність

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An observational study on spectrum of complications in gallstone disease in Western Maharashtra

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Abstract. Gallbladder calculus prevalence exhibits significant regional disparities, affecting public health. This study aimed to assess the incidence of complications in diagnosed cases of gallbladder stones using a prospective observational approach. Methods encompassed comprehensive history-taking, clinical examinations, imaging, and biochemical markers' analysis. In this study encompassing 238 cases of symptomatic gallstones, a comprehensive analysis revealed that 31.9% of patients presented with complications. Among these, choledocholithiasis emerged as the most prevalent complication, affecting 13.45% of the cases. Acute cholecystitis and gallstone pancreatitis were also significant complications, occurring in 10.9% and 6.7% of the cases, respectively. Noteworthy is the consistent alignment between clinical diagnoses and imaging findings, highlighting the accuracy and reliability of the diagnostic process. Turning to the exploration of management modalities, the data showcased laparoscopic cholecystectomy as the predominant surgical intervention. Both early and delayed laparoscopic cholecystectomies were frequently performed, reflecting the versatility of this approach in addressing symptomatic gallstone cases. However, it is essential to note that an overall 6% conversion rate from laparoscopic to open cholecystectomy was observed, underscoring the importance of adaptability in surgical strategies. These findings not only contribute to a deeper understanding of the prevalence and complications associated with symptomatic gallstones but also emphasise the significance of accurate diagnostic measures and the need for surgical flexibility in managing these cases.

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The results presented in this study offer valuable insights that can inform clinical decision-making and enhance the overall management of patients presenting with symptomatic gallstones

Keywords: laparoscopic cholecystectomy; choledocholithiasis; gallbladder calculus; open cholecystectomy; acute cholecystitis

Introduction

Gallstone disease poses a significant global public health challenge, demanding an in-depth understanding of its complications for optimizing patient care. Recent global research has contributed valuable insights into various facets of gallstone disease complications; however, there remains a gap in localised investigations, particularly within the unique demographic of Western Maharashtra. S. Mukai *et al.* [1] extensively explored urgent interventions, focusing on the timely management of complications. Their work sheds light on the critical decision-making processes in emergency scenarios, emphasizing the need for prompt medical attention. However, their study primarily delves into the acute aspects, leaving room for further investigation into the broader spectrum of complications that may unfold over time. M. Di Martino *et al.* [2] investigated the optimal timing of cholecystectomy in gallstone disease cases. Their findings underscore the importance of strategic planning for surgical interventions, particularly in preventing recurrent complications. While their research contributes significantly to the understanding of cholecystectomy timing, there is still a need to explore the diverse complications that may necessitate different intervention timelines. M. Zhu *et al.* [3] delved into causal associations in gallstone disease, examining the factors that contribute to the development of complications. Their work highlights the multifaceted nature of the disease, linking various risk factors to specific complications. However, a comprehensive understanding of the entire spectrum of complications within a specific population, such as Western Maharashtra, is yet to be explored. P.S. Kumar & S. Harikrishnan [4] explored unusual complications of gallstone disease, providing insights into less common manifestations. Their work broadens the scope of understanding beyond typical complications, offering crucial information for clinicians. However, their focus on unusual complications necessitates further investigation into the more prevalent complications within the Western Maharashtra demographic. N.Y. Cho *et al.* [5] contributed to the understanding of gallstone disease complications, emphasizing the significance of tailored approaches to patient care. Their research underscores the need for personalised strategies based on patient demographics and characteristics. Nevertheless, their study primarily focuses on general considerations, warranting a specialised investigation into the unique complications prevalent in Western Maharashtra. M. Lodha *et al.* [6] provided insights into specific complications in gallstone disease, contributing to the overall knowledge base. Their work offers valuable perspectives on the complexities of managing particular complications.

However, a comprehensive analysis encompassing the entire spectrum of complications specific to Western Maharashtra is yet to be undertaken. This study aimed to comprehensively analyse the spectrum of complications associated with gallstone disease in the unique demographic of Western Maharashtra through a single-centre approach.

Materials and Methods

In this prospective observational study, conducted at a tertiary care centre in Western Maharashtra, a total of 238 patients with symptomatic gallstone disease and its complications, admitted to the hospital between January 2021 and January 2023, were included, excluding those with asymptomatic gallstone disease and primary choledocholithiasis. On admission, detailed history and clinical examination findings were recorded. In history, pain in the abdomen, dyspepsia, vomiting, fever, abdominal distension, and features of jaundice were recorded. In clinical examination, presence of right upper quadrant (RUQ) tenderness, Murphy's sign, rebound tenderness/guarding, palpable liver/gall bladder and ascites were documented.

Upon admission, all patients underwent biochemical evaluation, including serum bilirubin, liver enzymes (including Serum Aspartate Transaminase, Alanine Transaminase, Serum Alkaline Phosphatase, and Gamma Glutamyl Transferase), and pancreatic enzyme assay. These investigations were conducted using an automatic biochemistry analyser employing spectrophotometric techniques. Normal laboratory values were as follows: Alanine Transaminase: 4 to 36 IU/L, Aspartate Transaminase: 5 to 30 IU/L, Alkaline Phosphatase: 30 to 120 IU/L, Gamma-Glutamyl Transferase: 6 to 50 IU/L, Bilirubin: 2 to 17 μmol/L, Direct Bilirubin: 0 to 6 μmol/L, Pancreatic amylase up to 85 IU/L and Pancreatic lipase up to 160 IU/L were considered normal.

All patients underwent an ultrasound (USG) abdomen in the radiology department and findings were recorded. Evaluation with advanced imaging techniques, including contrast-enhanced computed tomography (CECT) abdomen (if indicated), magnetic resonance cholangiopancreatography (MRCP) (if indicated), and endoscopic retrograde cholangiopancreatography (ERCP) (if indicated) were also performed.

The diagnosis of complications was established through a combination of clinical findings, imaging results, and biochemical markers. The study specifically addressed complications related to the location of the stone, encompassing gall bladder complications such as acute cholecystitis, Mirizzi Syndrome, mucocele, abscess-empyema, and gallbladder perforation; common bile duct complications including choledocholithiasis, obstructive jaundice, gallstone pancreatitis, and cholangitis; and intestinal complications, specifically gallstone ileus.

Logistic regression was employed to identify factors associated with specific complications, providing a quantitative assessment of the impact of variables while considering potential confounding factors. The coordination between diagnostic methods embraced a multidisciplinary framework, fostering close collaboration among clinicians, radiologists, and gastroenterologists. Through regular meetings and discussions, each specialist contributed their unique insights, facilitating a holistic interpretation of findings. The study protocol adheres to national ethical guidelines for biomedical and health research involving human participants according to the Declaration of Helsinki [7], as well as the Guidelines for Good Clinical Practice. Prior to participation, informed consent was obtained from all individuals involved. Approval for the study was obtained from the Institution Ethics Committee, ensuring compliance with ethical standards throughout the research process.

Results

Varied patterns across patient groups. The study population encompassed a diverse range of age groups, providing a comprehensive perspective on the prevalence of gallstone disease across various life stages (Table 1).

Table 1. Frequency table for age distribution

Age Group	Frequency	Percent
<= 20	4	1.7
21-30	45	18.9
31-40	55	23.1
41-50	56	23.5
51-60	38	16.0
61-70	30	12.6
71+	10	4.2
Total	238	100.0

Source: compiled by authors

The majority of participants fell within the middle-aged brackets, with notable representation from individuals aged 31 to 60. Specifically, individuals in the age group of 41 to 50 constituted the largest proportion, comprising 23.5% of the total cases. Moreover, participants aged 21 to 40 collectively accounted for approximately 43% of the study cohort, emphasizing the significance of gallstone disease within the adult population. Notably, the study included a considerable number of participants aged 60 and above, with individuals in the age group of 61 to 70 representing 12.6% of the total cases. This broad age distribution ensures a holistic understanding of the implications and variations in gallstone disease prevalence across different generational segments.

Varied presentations in patients with gallstone disease. The study meticulously documented the symptomatic manifestations among participants diagnosed with gallstone disease (Table 2).

Table 2. Presenting symptoms and its frequency

Symptoms (N=238)	Pain abd.	Dyspepsia	Vomiting	Fever	Abd. distension	Yellowing of eyes	High colour urine	Clay coloured stools	Pruritis
Frequency	208	67	123	35	1	14	15	10	3
Percentage	87.4	28.2	51.7	14.7	0.4	5.9	6.3	4.2	1.3

Source: compiled by authors

The predominant symptom reported was pain in the abdomen, with a staggering 87.4% of individuals experiencing this discomfort. Dyspepsia, characterised by indigestion or discomfort after eating, was noted in 28.2% of cases, highlighting its significant prevalence. Vomiting, a common symptom associated with gallstone-related complications, was reported by 51.7% of participants. Fever, a potential indicator of an inflammatory response, was observed in 14.7% of cases. Interestingly, abdominal distension, indicative of bloating, was relatively rare, reported by only 0.4% of individuals. Yellowing of the eyes was observed in 5.9% of cases, while high colouration of urine, often associated with liver or gallbladder disease, was noted in 6.3% of individuals. Clay-coloured stools, a potential sign of common bile duct obstruction, were reported by 4.2% of participants. Pruritis, or itching, was a less common but noteworthy symptom, observed in 1.3% of cases.

Diverse clinical presentations in gallstone disease. The clinical examination findings among participants diagnosed with gallstone disease were comprehensive, revealing several distinctive signs indicative of gallbladder and hepatobiliary complications (Table 3).

Table 3. Clinical signs

Clinical signs (N=238)	RUQ tenderness	Murphy's sign	Rebound/ Guarding	Hepatomegaly	Palpable GB	Ascites
Frequency	112	25	26	4	3	0
Percentage	46.67	10.42	10.83	1.67	1.25	0.00

Source: compiled by authors

RUQ tenderness was a prevalent clinical sign, observed in 46.67% of cases, highlighting the localised discomfort often associated with gallstone-related issues. Murphy's sign, a physical examination technique utilised to assess for gallbladder inflammation, was positive in 10.42% of individuals, providing further evidence of gallstone-related pathology. Rebound tenderness or guarding, indicative of peritoneal irritation, was noted in 10.83% of cases, suggesting the potential involvement of surrounding structures. Hepatomegaly, was observed in 1.67% of participants, while a palpable gallbladder, a less common but significant finding, was noted in 1.25% of cases. The absence of ascites further emphasised the localised nature of the clinical signs associated with gallstone disease.

Varying rates among gallstone patients. The majority of individuals, constituting 68.5% of the cohort (N=238), did not manifest any complications related to gallstones. Conversely, 19.7% of participants (N=238) experienced a single complication, underscoring the diversity in clinical presentations associated with gallstone disease (Table 4).

Table 4. Frequency and percentage of complications

Complication	Frequency	Percentage
No (N=238)	163	68.5
One (N=238)	47	19.7
More than One (N=238)	29	12.2
Two (N = 29)	21	72.4
Three (N = 29)	6	20.7
Four (N = 29)	0	0.0
Five (N = 29)	2	6.9

Source: compiled by authors

Furthermore, a subset of individuals, comprising 12.2% of the total cases (N=238), presented with more than one complication. Among those with multiple complications (N=29), a detailed breakdown revealed that 72.4% exhibited two complications, 20.7% had three complications, and 6.9% presented with five complications (Table 4). Notably, no individuals within this subset displayed four complications, highlighting the variability in the combinations and severity of complications associated with gallstone disease. In summary, this comprehensive categorization sheds light on the frequency and diversity of complications in individuals diagnosed with gallstone disease, providing valuable insights into the complexity of clinical presentations and the potential challenges in managing multifaceted cases.

Diverse issues in symptomatic gallstone disease cases. The study meticulously examined the prevalence of specific complications associated with gallstone disease, providing a detailed breakdown of individual complications and their corresponding frequencies. Acute cholecystitis was present in 26 individuals, accounting for 10.92% of the study population, while empyema was observed in 6 cases, representing 2.52% of the participants. Mucocele was documented in 14 individuals, constituting 5.88% of the cohort, and Common bile duct calculus (CBD calculus) was noted in 32 cases, indicating a prevalence of 13.45%. Cholangitis was identified in 6 individuals, making up 2.52% of the study population, and surgical obstructive jaundice (SOJ) was seen in 12 cases, with a prevalence of 5.04%. Gallstone Pancreatitis was present in 16 individuals, representing 6.72% of the cohort, while Mirrizi's syndrome was documented in 5 cases, accounting for 2.10% of the participants. Notably, gallstone ileus was not observed in any individuals within the study population, indicating a zero prevalence (Table 5).

Table 5. Complications associated with gallstone disease

Complication	Ac. cholecystitis	Empyema	Mucocele	CBD calculus	Cholangitis	SOJ	Gallstone pancreatitis	Mirrizi's syn	Gallstone ileus
Frequency	26	6	14	32	6	12	16	5	0
Prevalence / 100 (%)	10.92	2.52	5.88	13.45	2.52	5.04	6.72	2.10	0.0

Source: compiled by authors

These findings offer a comprehensive understanding of the distribution of specific complications associated with gallstone disease, shedding light on the varied clinical presentations, and highlighting the relative frequencies of each complication within the studied cohort.

Addressing gallstone disease complications effectively. In this study, all 238 patients were offered surgical treatment. All patients are offered either an upfront surgery or conservative management with or without ERCP followed by surgery (Fig. 1).

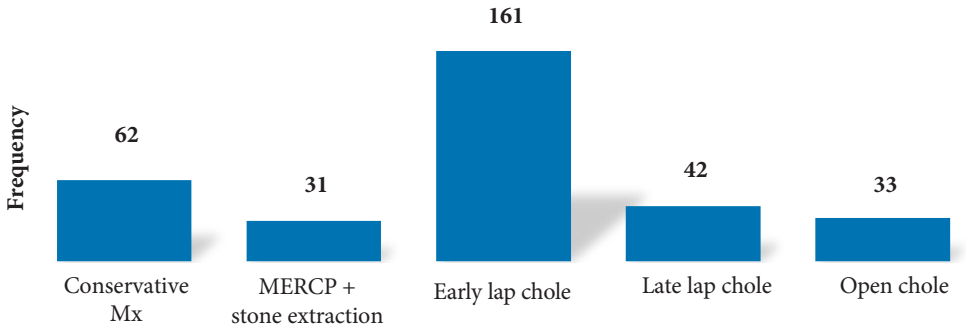

Figure 1. Management modalities

Source: compiled by authors

Out of 238 patients, 236 underwent cholecystectomies and 2 patients did not report back after conservative management. In patients who underwent surgery, 216 cases were taken up for laparoscopic cholecystectomy. Out of which, 203 cases (86%) successfully underwent laparoscopic cholecystectomy (LC) and 13 cases were converted to open cholecystectomy (OC) [conversion rates were 6%]. A total of 33 cases (14%) underwent open cholecystectomy. In the laparoscopic group, 161 cases (79.3%) underwent Laparoscopic cholecystectomy during the same admission. 42 cases (20.7%) underwent Laparoscopic cholecystectomy after a period of 4 weeks.

Acute cholecystitis. There were a total of 26 cases of acute cholecystitis in this study. All cases were managed conservatively, initially followed by surgery. Out of 26 cases, 20 cases (76.9%) underwent Lap cholecystectomy and 6 cases (23.1%) underwent open cholecystectomy (includes 2 cases of lap converted to open cholecystectomy).

Choledocholithiasis + acute cholangitis + obstructive jaundice. There were a total of 32 cases of CBD calculus in this study. Of 32 cases, 12 cases had associated obstructive jaundice and 6 cases had associated acute cholangitis. All cases were managed conservatively and subjected to ERCP. Out of this, 31 cases underwent Endoscopic papillotomy and stone extraction. The procedure was successful in 28 cases (90.3%) and failed in 3 cases (9.7%). All 32 cases underwent cholecystectomy, the distribution of which is mentioned in the Figure 2. 3 cases underwent early laparoscopic cholecystectomy, 17 cases underwent delayed laparoscopic cholecystectomy and 12 cases underwent open cholecystectomy with/without a drainage procedure.

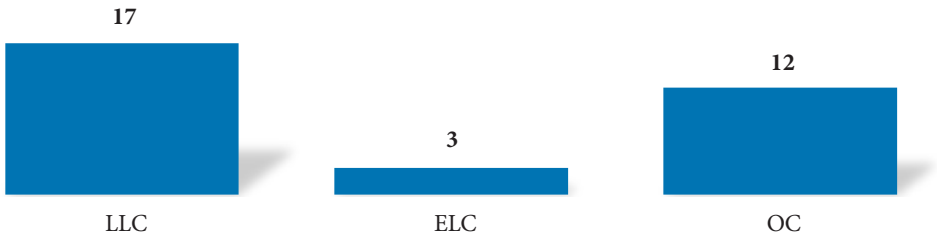

Figure 2. Surgery in CBD calculus

Source: compiled by authors

Gallstone pancreatitis. In this study, there were a total of 16 cases of gallstone pancreatitis. All cases underwent conservative management followed by one of the surgical procedures. Out of 16 cases, 12 cases underwent delayed laparoscopic cholecystectomy, 2 cases underwent open cholecystectomy and 2 cases did not report back to this centre after conservative management.

Mirizzi syndrome. In this study, there were 5 cases of Mirizzi syndrome, out of which 3 patients underwent laparoscopic cholecystectomy, and 2 patients underwent open cholecystectomy.

Empyema. There were a total of 6 cases (2.52%) of empyema in this study. Most of the cases underwent early lap cholecystectomy (83%) and one case underwent open cholecystectomy.

Mucocele. A total of 14 cases of mucocele had been observed in this study. 50% of the cases (7) underwent early lap cholecystectomy and 50% (7) underwent late lap cholecystectomy.

Imaging findings: comprehensive insights into gallstone disease complications. In this study, all 238 patients had undergone Imaging in form of ultrasound abdomen after the initial assessment and clinical diagnosis. This was followed by CECT abdomen/MRCP/ERCP as per the ultrasound findings and requirement of the case. In 85.3% of cases (N=203), the clinical diagnosis had been confirmed by imaging diagnosis. In the rest, 14.7% of cases (N=35), the imaging diagnosis differed from the clinical diagnosis.

The study, involving 238 patients with gallstone disease complications in Western Maharashtra, revealed a diverse demographic, with the majority aged 31 to 60. Abdominal pain was the predominant symptom, while clinical signs such as RUQ tenderness and Murphy's sign varied. Complication prevalence highlighted the complexity of cases, with 68.5% exhibiting no complications and 12.2% presenting with more than one. Specific complications, including acute cholecystitis and CBD calculus, were prevalent, while imaging methods confirmed clinical diagnoses in 85.3% of cases. In terms of management, all patients were offered surgical treatment, with laparoscopic cholecystectomy emerging as the primary surgical approach. These findings underscore the multifaceted nature of gallstone disease and provide essential insights into patient characteristics and treatment methods, bridging the gap between clinical and instrumental diagnostic approaches.

Discussion

The study aligns with the emphasis put by S. Mukai *et al.* [1] on the centrality of pain in the abdomen (87.4%) in diagnosing gallstone-related conditions, highlighting the consistency and reliability of this symptom. The study is consistent with the opinion of M. Lodha *et al.* [6], reinforcing the significance of pain in the abdomen in diagnosing gallstone-related conditions. Both studies contribute to the understanding of clinical profiles and outcomes in symptomatic gallstone disease. The study contrasts with the advocacy provided by N.Y. Cho *et al.* [5] for early intervention within 72 hours. The discordance emphasises the influence of institutional factors and patient profiles on treatment decisions, highlighting the need for a personalised approach in gallstone disease management.

The study supports Mendelian randomization study by Q. Zhu *et al.* [3], emphasizing the strong correlation between metabolically-abnormal obesity and gallstone disease. Both studies contribute to the understanding of the multifaceted nature of gallstone development. This study is consistent with the findings by P.Y. Su *et al.* [8] and W. von Schönfels [9], adding insights into the association between metabolic factors and gallstone pathogenesis. However, this study did not address the postoperative complications in patients with metabolic abnormalities and their management, as highlighted by A. Paro *et al.* [10].

The study aligns with the focus of F. Roesch-Dietlen *et al.* [11] on the safety of laparoscopic subtotal cholecystectomy, providing insights into the surgical approach. Both studies contribute valuable information on surgical considerations [7]. However, the study contrasts with the advocacy by K. Okamoto *et al.* [12] and N.Y. Cho *et al.* [5] for early intervention within 72 hours, indicating the diversity in approaches and the complexity of decisions in gallstone disease management.

The results of the study mirror the report by C. Zhang *et al.* [13] and S.M. Staubli *et al.* [14] on the efficacy of endoscopic management in the treatment of cholecystolithiasis. The high success rate in this study reaffirms the role of endoscopic procedures in managing gallstone-related complications. This study aligns with the exploration by G.A. Bass *et al.* [15] and S.B. Kim *et al.* [16] of long-term outcomes of acute acalculous cholecystitis and in patients over 65 years of age treated by non-surgical management. Both studies contribute insights into the management of gallstone-related complications. The investigation aligns with the assessment of G. Janjic *et al.* [17] of early vs. delayed laparoscopic cholecystectomy for acute cholecystitis, contributing to understanding the optimal timing of surgical interventions.

This study does not provide specific details on the comparison between ERCP vs. Surgery for choledocholithiasis and clinical application of enhanced recovery after surgery in the treatment of choledocholithiasis. Additional information on this could have facilitated a meaningful comparison [16, 17]. In this study, ERCP is done predominantly for all CBD calculus, whereas the study performed by F.C. Schacher *et al.* [18] did not find any difference in outcomes of patients who underwent ERCP or lap interventions. This study participants underwent laparoscopic cholecystectomy as the commonly performed procedure, but the study did not follow the enhanced recovery after surgery protocol (ERAS) which could have added more information on its impact on surgical outcomes. Y. Zhang *et al.* [19] documented better outcomes of patients following ERAS before surgery. Further, this study did not contribute much to the aetiology of acute pancreatitis and its endoscopic management and timing of surgery, areas explored by P. Szatmary *et al.* [20]. The role of safe anaesthesia and infection control practices during cholangioscopy and pancreatoscopy was not discussed in detailed as documented by Sanders et al. where the necessity of routine duodenoscopy, endoscopic ultrasound and propofol as a safe anaesthetic agent was documented [20].

The results of this study align with the systematic review and meta-analysis by D.J. Sanders *et al.* [21] and with the study by W.K. Peng *et al.* [22], and the study by M. Johnstone [23], contributing to the understanding of the role of laparoscopic cholecystectomy in the management of gallstone-related complications, the timing of surgery, and postoperative outcomes. All these studies add valuable insights into surgical approaches. The study successfully elucidated key demographic patterns, predominant clinical presentations, and prevalent complications associated with gallstone disease. Notably, these findings revealed a higher prevalence of gallstones in females, aligning with global literature trends [21, 22]. Choledocholithiasis emerged as

the most common complication, underscoring the clinical significance of secondary bile duct stones in gallstone patients [22, 23]. The imaging-based approach, including ultrasound and additional modalities as needed, provided a reliable confirmation of clinical diagnoses in the majority (85.3%) of cases. Furthermore, the study shed light on the treatment patterns, with laparoscopic cholecystectomy being the preferred approach, complemented by timely interventions for specific complications like choledocholithiasis.

Conclusions

In conclusion, this qualitative study was conducted at a tertiary care centre in Western Maharashtra with the primary aim to comprehensively explore the spectrum of complications in gallstone disease. The study successfully achieved its objectives by analysing the incidence of complications, comparing clinical and imaging diagnoses, and examining various management modalities.

The predominant age group was 31 to 60, with abdominal pain identified as the leading symptom. 12.2 % of study participants had specific complications, including acute cholecystitis, CBD calculus, and gallstone pancreatitis, demonstrated varying prevalence rates. The study emphasised the multifaceted nature of gallstone disease, with a majority of patients not exhibiting complications up to 65%, but a subset presenting with multiple complications. The confirmation rate of clinical diagnoses through imaging is 85 %, emphasizing the crucial role of imaging modalities in enhancing diagnostic accuracy and guiding appropriate treatment strategies. Laparoscopic cholecystectomy emerged as the predominant surgical intervention, conducted in 86% of cases, highlighting its widespread acceptance and efficacy in managing gallstone-related complications. However, 6% of laparoscopic cholecystectomies required conversion to open cholecystectomy, indicating challenges encountered during the procedure. Long-term follow-up data and regional variations can be incorporated for a more comprehensive understanding of gallstone disease.

Moving forward, the prospects for further research include expanding the study to a more diverse and larger population to enhance generalizability. Additionally, future research could delve into refining diagnostic and management strategies, contributing to ongoing efforts to optimise patient care.

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None.

Conflict of Interest

The authors declare no conflict of interest.

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Спостережне дослідження спектру ускладнень у хворих на жовчнокам'яну хворобу в Західній Махараштрі

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Анотація. Вивчення поширеності каменів у жовчному міхурі сприяло виявленню значних регіональних розбіжностей, що впливають на громадське здоров'я. Дане дослідження було спрямовано на оцінку частоти ускладнень у діагностованих випадках каменів у жовчному міхурі з використанням проспективного спостережного підходу. Методи включали комплексне збирання анамнезу, клінічні обстеження, обстеження та аналіз біохімічних маркерів. У цьому експерименті, що охоплював 238 випадків симптоматичних каменів у жовчному міхурі, комплексний аналіз показав, що 31,9 % пацієнтів мали ускладнення. З них найбільш поширеним ускладненням був холедохолітіаз, який виявлявся у 13,45 % випадків. Гострі жовчнокам'яні холецистит та панкреатит також були значними ускладненнями, які виявлялися у 10,9 % та 6,7 % випадків відповідно. Важливою є послідовність між клінічними діагнозами та результатами обстежень, що підкреслює точність і надійність діагностичного процесу. Щодо дослідження методів лікування, дані продемонстрували лапароскопічну холецистектомію як переважне хірургічне втручання. Часто виконувалися як ранні, так і відстрочені лапароскопічні холецистектомії, що відображає універсальність цього підходу у лікуванні симптоматичних випадків жовчнокам'яної хвороби. Однак важливо зазначити, що загальний коефіцієнт конверсії від лапароскопічної до відкритої холецистектомії становив 6 %, що підкреслює важливість адаптивності в хірургічних стратегіях. Ці результати не лише допомагають глибше зрозуміти поширеність та ускладнення, пов'язані з симптоматичними каменями у жовчному міхурі, але й підкреслюють значення точних діагностичних заходів та необхідність хірургічної гнучкості у вирішенні цих випадків. Представлені в цьому дослідженні результати надають цінні висновки, які можуть бути корисними для клінічного прийняття рішень та покращенні ведення пацієнтів із симптоматичними каменями у жовчному міхурі

Ключові слова: лапароскопічна холецистектомія; холедохолітіаз; камені жовчного міхура; відкрита холецистектомія; гострий холецистит

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Cytological study of different thyroid lesions and its correlation with thyroid function test

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Abstract. The research relevance of the combined use of fine needle aspiration cytology, sonography, and thyroid function tests is determined by accurate diagnostics of thyroid enlargement in both adults and children. The study aimed to analyse thyroid lesions through cytological analysis and their correlation with thyroid function test results. This cross-sectional study enrolled 100 patients with suspected thyroid disorders and nodules. Comprehensive assessments included clinic demographics, fine needle aspiration cytology procedures, and thyroid hormone profiles. Based on the Bethesda system, cytological diagnoses were correlated with thyroid function test results using the chemiluminescent microparticle immunoassay method. Non-tumour thyroid lesions were found to be the most common (95%), with colloidal goitre being the most common. Neoplastic cases mainly included papillary and follicular carcinoma. Most thyroid lesions occurred among the 21-30 age group, non-neoplastic cases were more frequent among the 10-20 age group, and neoplastic cases were more common in those aged 21-40. All patients had neck swelling. Most cases were euthyroid (76%), predominantly classified as Category 2. A strong correlation between cytological diagnoses and thyroid hormone levels (p=0.04) was observed. Fine needle aspiration cytology demonstrated good sensitivity (80%) and high specificity (98.46%), with an 80% positive predictive value and 98.46% negative predictive value, resulting in a diagnostic accuracy of 97.14%. The study highlights the valuable role of fine needle aspiration cytology, when coupled with thyroid function tests, in effectively guiding the management of patients with thyroid lesions, owing to its impressive accuracy, sensitivity, and specificity

Keywords: fine needle aspiration cytology; Bethesda system; thyroid; cytologyhistopathology

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Introduction

Thyroid enlargement, or goitre, is a common disease, affecting 4-7% of adults and 0.2-1.8% of children. In India, 42 million people have thyroid disorders, with thyroid cancer being relatively rare [1, 2]. The absolute rates of thyroid carcinoma in females were four times those diagnosed in males. However, the thyroid cancer-specific mortality rate has remained stable [3]. Most swellings are benign, but 10-20% can be malignant. R.A. McPherson & M.R. Pincus [1] reported that detection of thyroid nodules is crucial, as 7-15% of cases may be cancerous, depending on various factors. Thyroid diseases are categorised as hyperthyroid, hypothyroid, or euthyroid based on clinical features and hormone profiles. Subtle symptoms often necessitate biochemical testing and cytological evaluation for diagnosis [4]. Iodine deficiency, affecting a third of the global population, causes goitre and, in severe cases, congenital hypothyroidism, as noted by A. Hatch-McChesney & H.R. Lieberman [5]. Thyroid cancer accounts for 2% of all cancers and 95% of endocrine cancers, with an increasing incidence, primarily due to small papillary thyroid cancers (≤2 cm) [6]. The thyroid parenchyma consists of two major cell types, the thyroid follicular cells that cause differentiated thyroid cancer (DTC) and the parafollicular or C-cells that are genesis to medullary thyroid carcinoma. DTC includes papillary thyroid cancer, follicular thyroid cancer and Hurthle cell cancer, accounting for 90-95% of all thyroid malignancies. Medullary thyroid carcinoma accounts for around 1 to 2%, and anaplastic thyroid carcinoma accounts for less than 1% of all thyroid cancers. From 1998-2012, the incidence of papillary thyroid cancer increased worldwide, mostly due to early detection and advanced imaging technology with the risk of overdetection [6]. Fine needle aspiration cytology (FNAC) is the gold standard for evaluating thyroid nodules, with high sensitivity and positive predictive value. FNAC is a minimally invasive, accurate, and cost-effective screening test. It bridges the gap between clinical evaluation and surgical diagnosis, reducing unnecessary surgeries [7]. FNAC should be used with thyroid hormone status assessment, including serum thyroid function tests (TSH) levels. P. Petranović Ovčaričeк *et al.* [8] determined that higher TSH levels, even within the upper reference range, indicate an increased risk of malignancy and advanced thyroid cancer. V. Jain *et al.* [9] reported that FNAC, alongside thyroid function test, can be used for early and accurate diagnosis of various thyroid lesions, and reduces unnecessary intervention. Routine FNAC screening has reduced unnecessary thyroidectomies for benign thyroid diseases [10]. H.E. Yazdaan *et al.* [11] reported that thyroid function tests are essential in evaluating risk and prognosis, specifically thyroid nodules, and thyroid cancer. Furthermore, S.K.C. Mishra *et al.* [12] demonstrated that the euthyroid state was more common than hypothyroid and hyperthyroid states for both non-neoplastic and neoplastic conditions. A clear interpretation of FNAC results is crucial. The National Cancer Institute's "The Bethesda System for Reporting Thyroid Cytopathology" (TBSRTC) provides a useful reporting system for thyroid fine needle aspirates and management guidelines for follow-up or surgery [10]. FNAC in conjunction with the thyroid hormonal profile helps assess the disease stage and determine the treatment option for the patient. This study aimed to assess the cytological findings of palpable thyroid nodules in conjunction with the thyroid hormonal profile of the patient.

Materials and Methods

In this cross-sectional study, conducted at the Department of Pathology, patients seeking FNAC for thyroid lesions at the Department of Ear, Nose, and Throat (ENT) at Nehru Chikitsalay, B.R.D Medical College, were examined from July 2020 to June 2021. Ethical clearance and informed consent were obtained. This study enrolled 100 patients with clinical suspicion of thyroid disorders and thyroid nodules, excluding those with inadequate samples. Demographic information for all participants was documented, a process that involved participants disclosing their demographic details involved a questionnaire or during an initial consultation with healthcare professionals participating in the study. An exhaustive medical history was then compiled, encompassing details of participants' illnesses, including symptoms and their duration. Participants were queried regarding any prior thyroid-related ailments or pertinent medical conditions, as well as familial history of thyroid disorders. A comprehensive physical examination was conducted before FNAC to evaluate factors such as nodule size, mobility, consistency, and the presence of cervical lymph nodes. This examination entailed an assessment of each participant's thyroid gland and its adjacent structures. Additionally, healthcare providers palpated the thyroid gland to discern any tenderness or nodularity. The findings from this examination provided clinical insights into the nature and attributes of thyroid lesions in each participant. These procedures provided information on participants' demographic profiles, clinical manifestations, and physical examination outcomes, all of which are indispensable for precise diagnosis and effective management of thyroid disorders.

Routine investigations and serum triiodothyronine (T3), serum thyroxine (T4), and TSH levels were noted. FNAC procedures were performed using aspiration and non-aspiration techniques with a 23/24-gauge needle and a 10 mL syringe. Multiple smears were prepared from 2-6 sites within the lesion and stained using haematoxylin and eosin (H&E) and May-Grunwald Geimsa (MGG) techniques. In the H&E staining process, slides were first immersed in haematoxylin solution to impart a blue-purple hue to the cellular nuclei. This was followed by a brief rinse in acidic alcohol to differentiate nuclei from other cellular components. Subsequently, slides were counterstained with eosin, which imparted a pink colouration to the cytoplasm, facilitating the identification of cellular structures and abnormalities. Concurrently, MGG staining was employed to enhance the contrast and resolution of cellular components. This multi-step staining method

involved successive immersion of slides in May-Grünwald stain, Giemsa stain, and buffer solutions. May-Grünwald stain was used to fix cellular components and impart an initial staining, while Giemsa stain further enhanced cellular details by selectively staining components such as nuclei, cytoplasm, and cellular inclusions. Once stained, the slides were thoroughly rinsed, air-dried, and covered slipped for microscopic examination. The dual staining approach provided comprehensive visualization of cellular morphology and accurate identification and characterization of various thyroid lesions. This cytological processing protocol, incorporating both H&E and MGG staining techniques, ensured high-quality cytological evaluations crucial for correlating with thyroid function tests and guiding effective patient management strategies. In the case of cystic lesions, fluid was first aspirated, followed by nodule re-aspiration. In the case of cystic swellings, the aspirated fluid was centrifuged, and sediment smears were prepared. Experienced pathologists examined all slides at various magnifications. Final FNAC diagnoses were made, and the cytology slides were reported using the Bethesda system [13]. Hormone profile samples, including serum TSH, T4, and T3, were obtained and analysed using the chemiluminescent microparticle immunoassay (CMIA) method. CMIA is an advanced variation of the enzyme-linked immunosorbent assay (ELISA). Reference ranges for the study were as follows: TSH: 0.3-4.9 uIU/mL; T4: 4.8-11.7 ug/dL; T3: 0.3-4.9 ng/mL.

The study involving human subjects adhered to ethical principles outlined in the Declaration of Helsinki [14] and applicable national and institutional guidelines. Informed consent was obtained from all participants, detailing the study purpose, procedures, potential risks, and benefits. Patient confidentiality and data protection were strictly maintained throughout the experiment. The study received ethical approval from the Institutional Ethical Review Board.

Statistical Analysis:

Cytomorphological details, FNAC diagnoses, and TFT results were recorded in Microsoft Excel 2016, and statistical analysis was conducted using SPSS 27. This study collected all relevant data and applied appropriate statistical methods for analysis, including data sorting, tabulation, and visual representation through pie diagrams and histograms. Statistical techniques, such as p-value calculation and the chi-square test, were used to assess the study's significance. Initially, data collection procedures were implemented to retrieve cytologic and histopathological information. Subsequently, cases were classified into true positive (TP), true negative (TN), false positive (FP), and false negative (FN) categories based on the agreement or discrepancy between cytologic and histopathological diagnoses. A professional statistician was consulted to interpret the results, and a significance threshold of $p<0.05$ was established.

Results

In a recent study, 100 cases with thyroid swelling underwent cytological evaluation, with diagnoses aligned with the Standard Nomenclature of the Bethesda System. The average patient age was 32.76 years, with the highest incidence of thyroid lesions in the 21-30 age group (27%). Table 1 demonstrates the prevalence of non-neoplastic cases over neoplastic cases. Within the non-neoplastic category, the 10-20 age group had the highest percentage (27.37%), followed by the 21-30 and 31-40 age groups. Conversely, neoplastic cases were primarily concentrated in the 21-40 age group, representing 60% of such cases, while the 41-60 and 61-80 age groups contributed 20% each. Gender-wise, females demonstrated a higher incidence of cases, constituting 88% of the total, compared to males who made up the remaining 12%. Lastly, examining the residence distribution, the majority of cases (78%) were reported in urban areas, with rural areas accounting for the remaining 22%. The comprehensive analysis of the table provided valuable insights into the demographic characteristics of the cases, offering a foundation for further investigation and public health planning.

The non-neoplastic thyroid lesions accounted for the majority at 95%. In comparison, 5% were categorised as neoplastic (Fig. 1).

Table 1. Demographic parameters of enrolled patients (N=100)

Age (years) (all cases)	N	%
10-20	26	26
21-30	27	27
31-40	19	19
41-50	14	14
51-60	9	9
61-70	4	4
71-80	1	1
Non-neoplastic cases		
10-20	26	27.37
21-30	25	26.31
31-40	18	18.95
41-50	14	14.74
51-60	8	8.42
61-70	3	3.16
71-80	1	1.05

Continued Table 1

Age (years) (all cases)	N	%
Neoplastic cases		
0-20	0	0
21-40	3	60
41-60	1	20
61-80	1	20
Gender		
Male	12	12
Female	88	88
Total	100	100
Residence		
Rural	22	22
Urban	78	78

Source: compiled by the authors

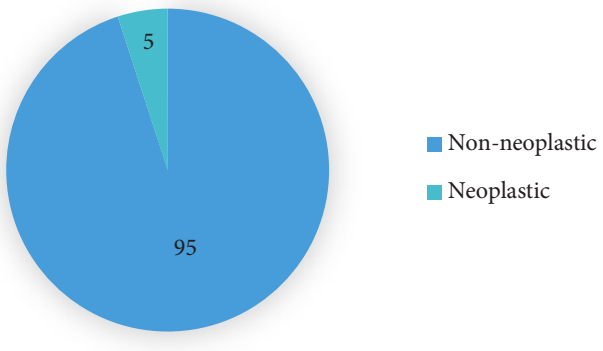

Figure 1. Distribution of cases based on neoplastic and non-neoplastic lesions
Source: compiled by the authors

According to the Bethesda classification, the data revealed that Category 1 (non-diagnostic) had no instances, constituting 0% of the cases. Category 2 (benign) comprised the majority, accounting for 95% of the cases, suggesting a prevalent benign nature of the observed conditions. Category 3 (atypia of undetermined significance) and Category 5 (suspicious for malignancy) both showed no occurrences, representing 0% in the past data. Within the Bethesda system, Category 4 (follicular neoplasm) constituted 2% of the cases, indicating a relatively low but existing prevalence of follicular neoplasms. Category 6 (malignant) had a presence in 3% of the cases, indicating instances where malignant conditions were identified cytologically. This comprehensive analysis of the past data according to Bethesda categories provides valuable insights into the distribution of cytological findings, aiding in understanding the nature of thyroid lesions and guiding further clinical management and investigation (Table 2).

Table 2. Distribution of thyroid lesions according to the Bethesda classification system

Bethesda category	N	%
Category 1 (non-diagnostic)	00	0
Category 2 (benign)	95	95
Category 3 (atypia of undetermined significance)	00	0
Category 4 (follicular neoplasm)	02	2
Category 5 (suspicious for malignancy)	00	0
Category 6 (malignant)	03	3

Source: compiled by the authors

Among the non-neoplastic lesions, Colloid Goitre was the most prevalent, constituting 72% of the cases. Autoimmune Thyroiditis accounted for 16%, while Lymphocytic Thyroiditis, Hyperplastic Nodule, and Colloid Cyst each contributed 3% and 2% to the cases, respectively.

Within the neoplastic lesions category, Follicular Neoplasm and Papillary Carcinoma each represented 2% of the cases. Medullary Carcinoma had a presence in 1% of the cases. This highlights the diverse spectrum of thyroid lesions encountered, emphasizing the prominence of

non-neoplastic lesions such as Colloid Goitre and providing insights into the relative occurrence of various neoplastic entities, including Follicular Neoplasm, Papillary Carcinoma, and Medullary Carcinoma.

This is crucial for clinicians and researchers to understand the prevalence and distribution of thyroid lesions for effective diagnostic and therapeutic strategies (Table 3).

Table 3. Distribution of various thyroid lesions by the conventional method

Thyroid lesions	N	%
Non-Neoplastic lesion		
Colloid Goitre	72	72
Autoimmune Thyroiditis	16	16
Lymphocytic Thyroiditis	3	3
Hyperplastic Nodule	2	2
Colloid Cyst	2	2
Neoplastic lesion		
Follicular Neoplasm	2	2
Papillary Carcinoma	2	2
Medullary Carcinoma	1	1

Source: compiled by the authors

All patients had neck swelling, suggesting a high prevalence of conditions or disorders characterised by neck swelling within the studied population. Other symptoms included weight loss, weight gain, palpation and anxiety, fever, cold intolerance, dysphagia, or difficulty in swallowing, change in voice, and neck pain contributing to 3%, 4%, 1%, 2%, 9%, 3%, 4%, 5%, and 6% of the cases, respectively. These findings highlight the diversity of symptoms experienced by the individuals under consideration, with a spectrum of manifestations ranging from physical signs, such as exophthalmos, to more subjective symptoms such as palpation and anxiety. Understanding the prevalence and distribution of these symptoms is crucial for healthcare professionals in diagnosing and managing the underlying conditions, and it forms the basis for further clinical investigation and intervention (Fig. 2).

Among the cases, 36% had diffuse thyroid swelling, while 64% had nodular thyroid swelling (Fig. 3).

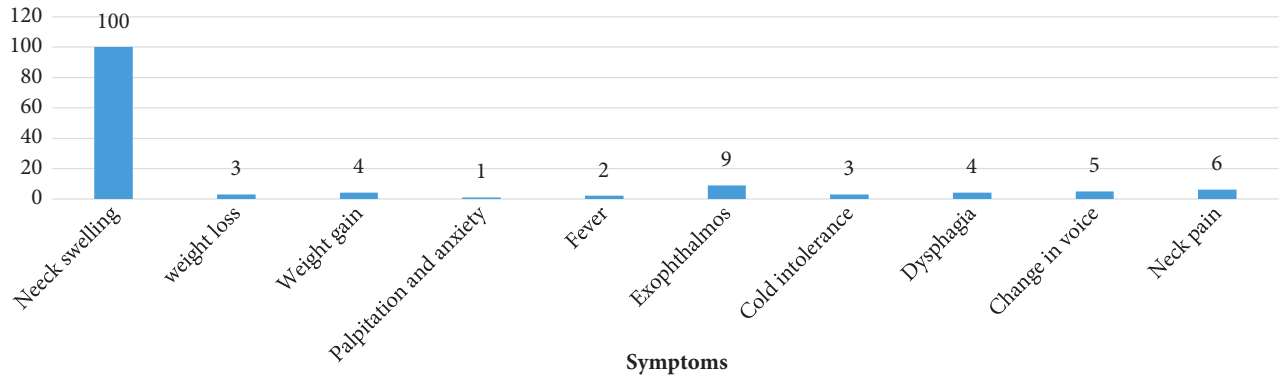

Figure 2. Presenting symptoms of the enrolled cases

Source: compiled by the authors

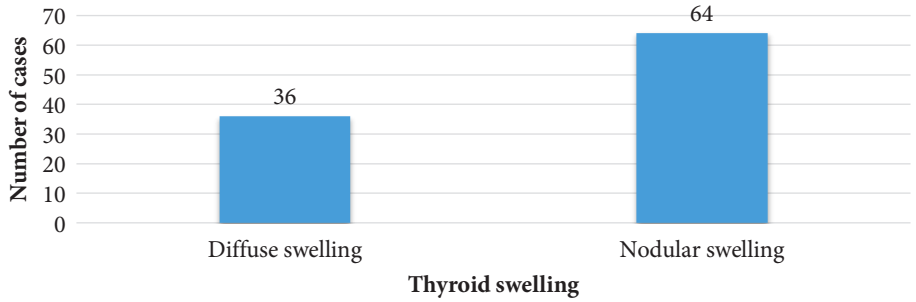

Figure 3. Type of thyroid swelling among the enrolled cases

Source: compiled by the authors

The most prevalent lesion was Colloid Goitre, constituting 75.79% of the total cases. This suggests a significant predominance of Colloid Goitre within the cohort, indicating a prevalent non-neoplastic thyroid condition characterised by the enlargement of thyroid tissue. Autoimmune Thyroiditis was the second most common lesion, representing 16.85% of the cases. This finding underscores the presence of autoimmune-mediated inflammation of the thyroid gland within the studied population. Lymphocytic Thyroiditis, Hyperplastic Nodule, and Colloid Cyst contributed to 3.16%, 2.10%, and 2.10% of the cases, respectively, highlighting the diversity of thyroid lesions observed. In total, the combined percentage of cases accounted for 100% of the studied cohort, providing a comprehensive overview of the prevalence and distribution of different thyroid lesions (Fig. 4).

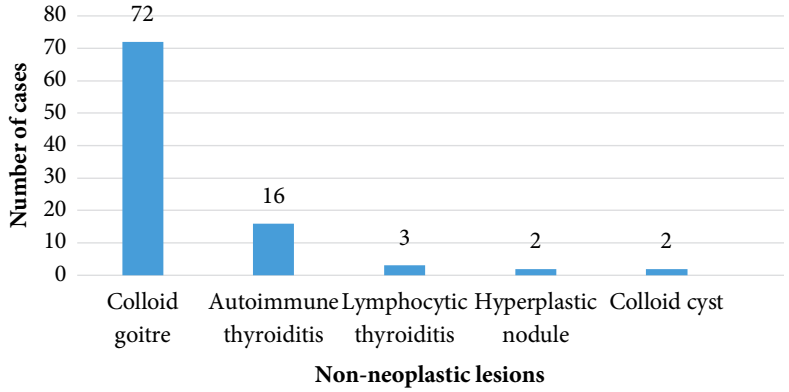

Figure 4. Type of non-neoplastic lesions among the enrolled cases
Source: compiled by the authors

Among the observed cases, Papillary Carcinoma and Follicular Neoplasm were equally prevalent, each constituting 40% of the total cases. This suggests a notable occurrence of these two neoplastic lesions within the studied population, highlighting the significance of both Papillary Carcinoma and Follicular Neoplasm as contributors to thyroid pathology. Medullary Carcinoma, while less frequent, represented 20% of the cases. This indicates a proportion of individuals within the cohort presenting with this specific type of thyroid carcinoma (Fig. 5).

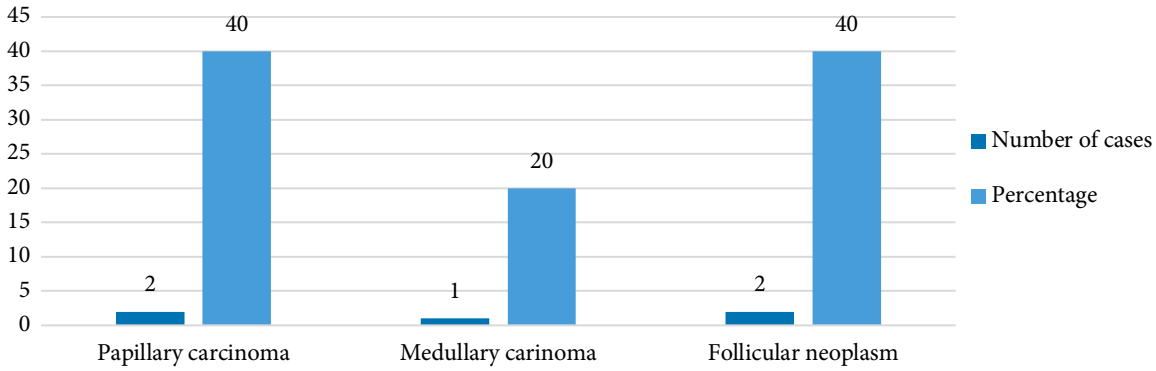

Figure 5. Type of neoplastic lesions among the enrolled cases
Source: compiled by the authors

In terms of thyroid hormone profiles, the majority of cases were classified as Euthyroid, constituting 76% of the group. This indicates a prevalent state of normal thyroid function within the studied population, where the thyroid gland is functioning within the normal range, and hormone levels are balanced. Hypothyroid cases accounted for 20%, reflecting individuals with an underactive thyroid, a condition characterised by insufficient thyroid hormone production. On the other hand, Hyperthyroid cases represented 4% of the total, suggesting a minority of individuals with an overactive thyroid gland, leading to an excess of thyroid hormones. Comprehension of the prevalence of different thyroid statuses is crucial for healthcare professionals in diagnosing and managing thyroid disorders, as it helps determine appropriate treatment strategies based on the specific thyroid status of individuals within a given group (Fig. 6).

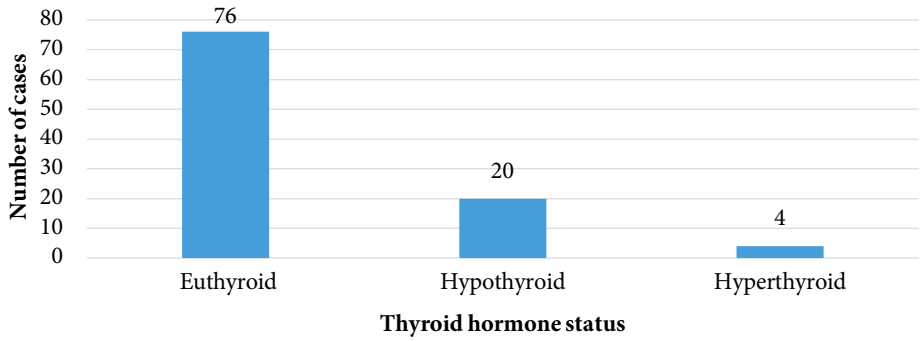

Figure 6. Thyroid hormone status among the enrolled cases
Source: compiled by the authors

Among the 95 cases classified as non-neoplastic lesions, the distribution of thyroid statuses varied significantly across different lesion types. For Colloid Goitre, the majority of cases were Euthyroid (60 cases), with 9 cases classified as Hypothyroid and 3 as Hyperthyroid. The Chi-squared test revealed a prominent relation between Colloid Goitre and thyroid status (p=0.04), suggesting that the thyroid status of individuals with Colloid Goitre differed significantly from the expected distribution. Similarly, for Autoimmune Thyroiditis, the majority of cases were Hypothyroid (10 cases), with 5 Euthyroid and 1 Hyperthyroid case. Lymphocytic Thyroiditis and Hyperplastic Nodules showed a predominantly Euthyroid distribution. The neoplastic lesions, including Follicular Neoplasm, Papillary Thyroid Carcinoma, and Medullary Carcinoma, were all associated with Euthyroid status (Table 4).

Table 4. Correlation between thyroid lesions and hormone profiles

Non-Neoplastic lesions (N=95)	Euthyroid	Hypothyroid	Hyperthyroid	p-value
Colloid Goitre	60	9	3	
Autoimmune Thyroiditis	5	10	1	
Lymphocytic Thyroiditis	2	1	0	
Hyperplastic Nodule	2	0	0	
Colloid Cyst	2	0	0	Chi^2 =24.67 p= 0.04
Neoplastic lesions (N=5)				
Follicular Neoplasm	2	0	0	
Papillary Thyroid Carcinoma	2	0	0	
Medullary Carcinoma	1	0	0	

Notes: Chi^2 = 24.67 (p = 0.04) indicates a strong association between thyroid lesion type and thyroid status
Source: compiled by the authors

Histopathological examination was available for 70 cases. Among non-neoplastic lesions, 61 cases initially diagnosed as Colloid Goitre on FNAC were histopathologically examined, with 60 cases confirming benign status and 1 indicating malignancy. Hyperplastic Nodule and Colloid Cyst, both benign lesions, demonstrated complete concordance between cytological and histopathological evaluations, with all cases being consistently classified as benign. Follicular Neoplasm exhibited a more complex pattern, with two cases initially classified as benign cytologically later revealing malignancy upon histopathological examination. Papillary Carcinoma and Medullary Carcinoma, malignant lesions, showed concordance between the two diagnostic methods, with all cases being consistently identified as malignant. These findings highlight the importance of combining both cytological and histopathological assessments for accurate diagnosis and subsequent management of thyroid lesions. The discrepancies observed in certain cases highlight the challenges in accurately characterizing lesions based on cytological evaluation alone, emphasizing the need for a comprehensive approach to ensure optimal clinical decision-making and patient care (Table 5).

Table 5. Cyto-histopathological correlation of lesions of thyroid

Lesions	Cytology	Histopathology	
		Benign	Malignant
Colloid Goitre	61	60	1
Hyperplastic nodule	2	2	0
Colloid cyst	2	2	0
Follicular neoplasm	2	1	1
Papillary carcinoma	2	0	2
Medullary carcinoma	1	0	1

Source: compiled by the authors

Among the cases classified as cytologically benign, most of the 64 cases were consistent with histopathology (true negative), indicating accurate identification of benign lesions. However, one case was falsely classified as benign cytologically but revealed malignancy upon histopathological examination (false negative). For cytologically malignant cases, four cases were consistent with histopathology (true positive), accurately identifying malignant lesions. However, there was one case classified as malignant cytologically that was later determined to be benign upon histopathological examination (false positive). In total, out of the 70 cases, 68 were consistent with histopathology, showcasing the reliability of cytological diagnoses, while 2 cases showed inconsistencies between cytology and histopathology (Table 6).

Table 6. Relation between cytologic and histopathological diagnosis

Lesion	Consistent with histopathology	Inconsistent it histopathology	Total
Cytologically benign	64 (True negative)	1 (False negative)	65
Cytologically malignant	4 (True positive)	1 (False positive)	5
Total	68	2	70

Source: compiled by the authors

In the study of 100 cases of thyroid swelling, the 21-30 age group had a 27% prevalence, predominantly affecting females. Most cases were non-neoplastic, with Colloid Goitre being the most common. Neoplastic cases were mostly dominant within the 21-40 age group. Bethesda's classification revealed a benign nature, thus being categorised as Category 2 (benign). All patients had neck swelling, along with other symptoms. Cytological-histopathological concordance occurred in 68/70 cases, highlighting the importance of a comprehensive diagnostic approach. The study provides valuable insights into the demographic characteristics, prevalence, and distribution of thyroid lesions, guiding clinical understanding and public health planning. The dominance of non-neoplastic lesions, particularly Colloid Goitre, underscores the need for accurate diagnostic methods. The cytological-histopathological concordance supports the reliability of cytological diagnoses, reinforcing the significance of combined assessments for optimal patient care.

Discussion

The age spectrum of patients with thyroid lesions in this study ranged widely from 10 to 77 years, demonstrating an average age of 32.76 years. Notably, a substantial proportion (46%) of thyroid lesions were within the 21-40 age group, underscoring a demographic predilection. Comparative insights from V. Jain *et al.* [9] emphasised a similar trend, with a focal point in the 31-40 age bracket, where the average age of the population was 41.3 ± 12.4 years. In contrast, T. Thakor *et al.* [15] determined the predominance in the 41-50 age group, with an average age of 39.64 years.

The gender dynamics within the present study group demonstrated female predominance, constituting 84% of cases compared to males at 16%. This trend aligns with previous research by D.S. Bhadouria *et al.* [16], confirming a prevalence of thyroid lesions among females. The urban-rural distribution disclosed a distinct inclination toward urban areas in the present study, with a ratio of 3.45:1. This urban dominance echoes the findings reported by D. Asmelash *et al.* [17]. Moreover, female dominance remained a consistent pattern, with 88% females and 12% males, illustrating a striking female-to-male ratio of 7.3:1. This gender disproportionality resonates with the findings of earlier studies by V. Jain *et al.* [9] and T. Thakor *et al.* [15], as well as the study conducted by C.B. Patel *et al.* [18], which reported a male-to-female ratio of 1:4.8. Observed ratios in the present study are in concordance with those reported by T. Thakor *et al.* [15] and V. Jain *et al.* [9], highlighting the recurrent theme of thyroid lesions exhibiting a higher prevalence among females.

In the context of the present study, a substantial majority, accounting for 95% of the cases, exhibited non-neoplastic thyroid lesions, contrasting with 5% of cases characterised as neoplastic. These proportions align closely with findings from S. Ranabhat *et al.* [19], who reported an 88%

prevalence of non-neoplastic lesions and a 12% incidence of neoplastic lesions. This consistent pattern is also reflected in the investigation by V. Jain *et al.* [9], where non-neoplastic lesions were more prevalent. The symptomatic presentation within the present study unveiled neck swelling as the most prevalent complaint, constituting a chief concern in all cases. Further analysis disclosed a nodular manifestation in 64% of cases, while 36% exhibited diffuse swelling. Accompanying symptoms included weight gain in 4% of cases, cold intolerance in 3%, and weight loss in 3%. Additional complaints, such as anxiety, palpitation, and fever, were less frequent, reported by 1% and 2% of patients, respectively. Exophthalmos was observed in 9% of cases, while dysphagia and a change in voice were reported by 4% and 5% of patients, respectively. This corroborates the consistent emphasis on neck swelling as the primary patient-reported symptom in studies by V. Jain *et al.* [9] and M.N. Haque *et al.* [20].

Bethesda system for cytological classification revealed a substantial predominance of cases within the benign spectrum, specifically categorised as Category 2, constituting 95% of the cases. Interestingly, only 2 cases were designated as Category 4 (FN/SFN), and 3 cases were classified under Category 6 (malignant). Remarkably, the present study did not encounter any cases falling within Category 1, 3, or 5. This distribution aligns with the observations of V. Jain *et al.* [9], who noted a similar prevalence of lesions in Category 2 (69.1%) within the Bethesda System. A corroborating study by M. Syed *et al.* [21] demonstrated the majority of their patients also belonging to Category 2, with a prevalence of 33.3%. These consistent findings underscore the robustness and reliability of the Bethesda system categorization across diverse studies. Exploring the spectrum of thyroid lesions, the present study uncovered a notable prevalence of non-neoplastic cases, with Colloid Goitre emerging as the predominant lesion, constituting 72% of the total non-neoplastic cases. Hashimoto Thyroiditis and Lymphocytic Thyroiditis followed, contributing 16% and 3%, respectively, to the non-neoplastic category. In the neoplastic lesions, both Papillary Carcinoma and Follicular Neoplasm were observed in 2% of each of the cases. Comparable patterns were identified in the study conducted by V. Jain *et al.* [9], wherein Colloid Goitre predominated among non-neoplastic lesions, accounting for 40.6% of the cases. In their evaluation of neoplastic lesions, Follicular Neoplasm took precedence, reflecting a consistency of findings across studies. C.B. Patel *et al.* [18] further supported these observations, reporting Colloid Goitre as the prevalent lesion in the majority of their cases (65.1%). These collective findings underscore the recurring prominence of specific thyroid lesions, providing valuable insights into the relative distribution of these lesions across different studies.

Histopathological confirmation was available for 70 cases in the present study, shedding light on the concordance between cytological and histological assessments. Among the non-neoplastic cases, 60 out of 61 cases initially diagnosed as Colloid Goitre cytologically were corroborated as Colloid Goitre upon histological examination. However, a singular case initially identified as Nodular Goitre cytologically was histopathologically determined to be Papillary Carcinoma, highlighting the challenges in accurately diagnosing Papillary Carcinoma, especially in the presence of cysts or co-existing with nodular colloid goitre without cystic changes. These diagnostic intricacies align with the observations made by M.N. Haque *et al.* [20], who reported Multinodular Goitre as the predominant non-neoplastic lesion in 55.76% of their cases, followed by Papillary Thyroid Carcinoma at 25%. D.S. Bhadouria *et al.* [16] also emphasised the prevalence of Multinodular Goiter (MNG) in the majority of their cases (55%), supporting the diverse distribution of thyroid lesions. The need for a meticulous examination of nuclear features, particularly in longstanding goitre cases, becomes imperative to ensure accurate and timely diagnosis, thereby guiding appropriate clinical management. In evaluating the diagnostic performance of FNAC in the present study, a sensitivity of 80%, specificity of 98.46%, positive predictive value (PPV) of 80%, negative predictive value (NPV) of 98.46%, and an overall diagnostic accuracy of 97.14% was recorded. These values affirm the effectiveness of FNAC in diagnosing thyroid lesions, providing reliable results. Comparable studies conducted by A. Jamaiyar & K. Yogesh [7] reported a sensitivity of 90.91% and specificity of 94.12%, further reinforcing the robustness of FNAC in accurately identifying thyroid abnormalities. M. Syed *et al.* [21] demonstrated sensitivity and specificity of 82.3% and 64.3%, respectively, along with PPV and NPV of 73.6% and 75%. Despite differences in specificity, these findings align with the present study's observations and underscore the consistent utility of FNAC across diverse studies. Additionally, prior investigations by various researchers [22, 23] reported sensitivity, specificity, and diagnostic accuracy ranging from 85.7% to 98.6%, 72.5% to 97.7%, and 83.5% to 92.2%, respectively. This collective evidence highlights the reliability and reproducibility of FNAC as a valuable diagnostic modality in the assessment of thyroid lesions, emphasizing its significance in clinical practice.

In alignment with the established guidelines of the American Thyroid Association (ATA), the present study not only delved into cytological assessments but also considered the crucial aspect of thyroid hormone status, particularly focusing on serum TSH levels as an integral component of the initial evaluation for thyroid lesions. The diverse aetiology of thyroid lesions contributes to variations in thyroid hormone statuses, a factor contingent upon the disease's stage and extent. Within the present study group, a majority of patients exhibited a euthyroid state (76%). Analysing the relationship between thyroid disease and hormonal status, a significant proportion of individuals with colloid goitre (83.33%) maintained euthyroid status. This was consistent with the findings of S. Ranabhat *et al.* [19]. Additionally, V. Jain *et al.* [9] reported a predominant euthyroid status in their patient population (69.1%), followed

by hypothyroid (18.8%) and hyperthyroid (12.1%) cases. These observations underscore the intricate interplay between thyroid lesions and hormonal equilibrium.

Goitre, characterised by the enlargement of the thyroid gland, often arises from impaired thyroid hormone synthesis, frequently attributed to dietary iodine deficiency. This deficiency triggers an elevation in TSH levels, prompting compensatory hypertrophy and hyperplasia of thyroid follicular cells, ultimately culminating in glandular enlargement. The consequential goitre causes elevated hormonal levels, resulting in the attainment of euthyroid status among affected patients [24]. The present study further substantiates these insights, emphasizing the intricate relationship between iodine deficiency, TSH elevation, and subsequent thyroid gland alterations. In the context of specific thyroid disorders, the present study's findings align with previous studies. In patients with Hashimoto's thyroiditis, a substantial majority (62.5%) exhibited hypothyroidism, underscoring the impact of autoimmune inflammation on thyroid function. Conversely, among cases of lymphocytic thyroiditis, 66.67% maintained euthyroid status, consistent with the expected resolution of thyroid dysfunction post-inflammation subsidence within six to eight weeks [24]. Cytologically, the present study's observations revealed distinctive features in Hashimoto's or lymphocytic thyroiditis, including thyroid follicular cells intricately entwined with lymphocytes, oxyphil cells, a polymorphous population of lymphocytes, multinucleated giant cells, and scant or absent colloid. Furthermore, the present study reinforces the correlation between cytological findings and thyroid function in neoplastic cases. All instances of follicular neoplasm, papillary carcinoma, and medullary carcinoma were associated with euthyroid status, aligning with similar trends observed in prior studies [19]. This defines FNAC as a valuable tool for early and accurate diagnosis, particularly when complemented by clinical assessments and thyroid function tests. This integrated diagnostic approach significantly reduces the necessity for surgical interventions, offering a comprehensive strategy for the effective management of diverse thyroid lesions [9, 18, 25]. The recognition of such correlations provides clinicians with essential insights, facilitating optimal decision-making in the management of thyroid disorders.

Conclusions

Examination and analysis of thyroid abnormalities via cytological assessment and their association with TFT outcomes highlighted the significant utility of FNAC. When integrated with TFT results, FNAC is a powerful tool for guiding the treatment of individuals with thyroid irregularities, given its remarkable precision, sensitivity, and specificity. The recent study involving 100 cases of thyroid swelling yielded valuable insights into the demographics and characteristics of thyroid lesions. With an average patient age of 32.76 years, the highest incidence of thyroid lesions occurred in the 21-30 age group (27%), predominantly affecting females (88%). Non-neoplastic cases outweighed neoplastic ones (95% vs. 5%), with Colloid Goitre emerging as the most prevalent lesion (72%). Neoplastic cases were concentrated in the 21-40 age group (60%). Bethesda classification indicated a predominantly benign nature, with Category 2 (benign) accounting for 95% of cases. A sensitivity of 80%, specificity of 98.46%, PPV of 80%, NPV of 98.46%, and an overall diagnostic accuracy of 97.14% was recorded. The study highlights the practical significance of these findings in guiding clinical decisions, especially with the prominence of Colloid Goitre and the high reliability of cytological diagnoses. Numerical indicators, such as demographic percentages and lesion prevalences, provide a clear quantitative overview of the study outcomes. Further research should include exploring molecular aspects of prevalent thyroid lesions, conducting longitudinal studies, and investigating targeted therapeutic approaches based on specific lesion types.

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Conflict of Interest

The authors declare no conflict of interest.

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Цитологічне дослідження різних уражень щитовидної залози та його взаємозв'язок з оцінкою функції щитовидної залози

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Анотація. Вивчення комбінованого використання тонкоголкової аспіраційної цитології, сонографії та функціональних тестів щитовидної залози має вирішальне значення для точної діагностики збільшення щитовидної залози як у дорослих, так і у дітей. Дана робота була спрямована на вивчення уражень щитовидної залози за допомогою цитологічного аналізу та їх кореляції з результатами тестів функції щитовидної залози. У цьому перехресному дослідженні взяли участь 100 пацієнтів із підозрою на захворювання щитоподібної залози та утворення вузлів. Комплексна оцінка включала демографічні показники клініки, процедури тонкоголкової аспіраційної цитології та профілі гормонів щитовидної залози. На основі системи Bethesda, цитологічні діагнози корелювали з результатами аналізів функції щитоподібної залози методом хемілюмінесцентного імуноферментного аналізу з мікрочастинками. Було встановлено, що найбільш поширеними виявилися непухлинні ураження щитовидної залози (95 %), причому найчастіше зустрічався колоїдний зоб. Неопластичні випадки в основному включали папілярну та фолікулярну карциному. Більшість уражень щитоподібної залози спостерігалися у віковій групі 21-30 років, непухлинні ураження частіше зустрічалися у віці 10-20 років, а неопластичні – у віці 21-40 років. У всіх пацієнтів спостерігалося збільшення щитоподібної залози. Більшість випадків були еутироїдними (76 %), переважно належали до категорії 2. Була відмічена сильна кореляція між цитологічними діагнозами та рівнем тиреоїдних гормонів (p=0,04). Тонкоголкова аспіраційна біопсія показала високу чутливість (80 %) та специфічність (98,46 %), з позитивною прогностичною цінністю 80 % та негативною прогностичною цінністю 98,46 %, що призвело до діагностичної точності 97,14 %. Дослідження підкреслює важливу роль тонкоголкової аспіраційної біопсії у поєднанні з оцінкою функції щитоподібної залози для ефективного ведення пацієнтів з ураженнями щитоподібної залози завдяки її високій точності, чутливості та специфічності

Ключові слова: тонкоголкова аспіраційна цитологія; система Bethesda; щитовидна залоза; цитологія; гістопатологія

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