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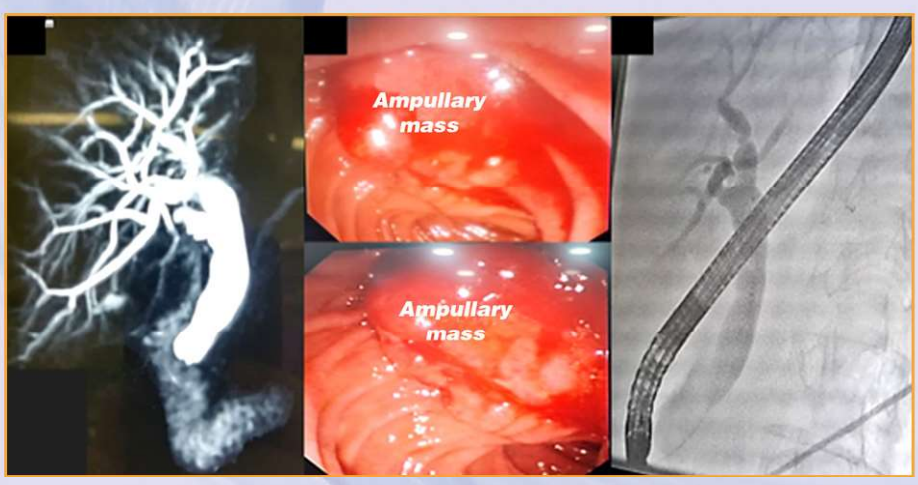

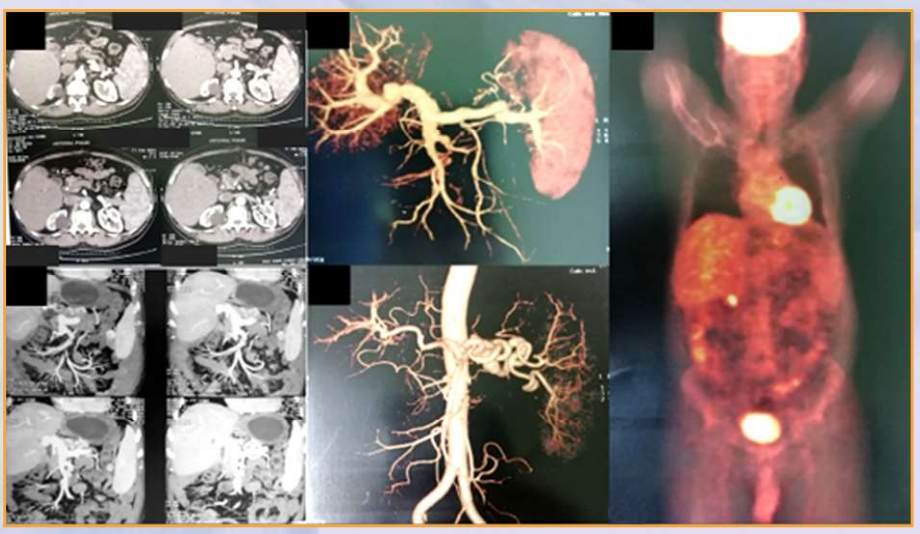

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REVIEW ARTICLE

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Characteristics of Toxic and Non Toxic Diffuse Goiter Sufferers with Hyperparathyroidism and SND ECG Features

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ABSTRACT

Background: Goitre, the second most prevalent endocrine disorder after diabetes, is followed in incidence rate. The most common source of hyperthyroidism is Graves' Disease. Graves' disease is responsible for around 60% to 80% of hyperthyroidism cases, with women aged 20 to 50 being more predominant than men. This autoimmune disorder is characterized by the presence of TSI and TSAb, which are secreted into the thyroid gland and bind to its TSH receptor. As a result, it stimulates the thyroid gland to produce thyroxine hormone under the influence of the TSH receptor. Prolonged TSAb stimulation leads to hyperthyroidism and thyroid enlargement. Hyperthyroidism causes the heart rate to weaken, and an overview of the ECG pattern shows atrial fibrillation with a fast RR pattern. Know Characteristics of Toxic and Non-Toxic Diffuse Struma sufferers with Hyperparathyroidism and ECG picture of RVR Atrial Fibrillation.
Method: This study employs the PRISMA approach, which involves a systematic execution of research steps and adherence to proper research protocols. Data sources were collected from both the PubMed and Google Scholar websites, encompassing journals published between 2017 and 2022. Subsequently, a screening process was conducted, resulting in the retrieval of 15,486 outcomes.
Result: Journal clustering was conducted, resulting in the acquisition of the count of journals indexed by Scopus in the Q2 category and journals indexed by Sinta in the S1 category. A total of eight journals were retrieved.
Conclusion: Most journals discuss age and lifestyle issue characteristics of Toxic and Non-Toxic Diffuse Goiter Patients with Hyperparathyroidism and ECG Atrial Fibrillation RVR.
Key words: Goiter, atrial fibrillation, toxic, non-toxic

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INTRODUCTION

The body's metabolic rate is regulated by thyroid hormones generated by the thyroid gland. These hormones have a direct impact on neurotransmitter function. In typical situations, thyroid hormone impacts tissue metabolism, oxidative processes in tissues, growth, and the synthesis of proteins (1). Disorders related to thyroid function can be detected through alterations in thyroid levels and variations in Thyroid Stimulating Hormone (TSH) levels in the bloodstream. The majority of these conditions arise from disruptions in the synthesis of thyroid hormones. Hyperthyroidism signifies an overactive thyroid gland in the production of thyroid hormones, consequently elevating metabolism within the body's tissues (2,3).

Alterations in thyroid function can lead to disruptions in cognitive abilities, behavior, and alterations in mood and anxiety levels. Approximately two-thirds of individuals suffering from thyroid-related conditions are documented to exhibit psychiatric issues, such as anxiety, depression, phobias, obsessive-compulsive disorder, and panic. The occurrence rate of anxiety disorders among those with thyrotoxicosis falls within the range of 33-61%, while hypothyroid patients typically grapple with problems like depression or bipolar disorder (4).

The thyroxine hormone, produced by the thyroid gland, plays a crucial role in regulating tissue metabolic rates to support normal cell function and overall bodily health. This hormone stimulates oxygen (O_2) consumption, protein synthesis, and gene transcription within cells. Inadequate thyroxine levels can lead to delays in development and hinder physical and mental growth processes. Conversely, an excessive amount of this hormone can result in an increased metabolism, leading to symptoms such as tremors, nervousness, and excessive heat production. Hyperthyroidism is the second most common endocrine disorder, following only diabetes in prevalence. Graves' Disease is the primary cause of hyperthyroidism, accounting for approximately 60% to 80% of cases. This condition is more frequently observed in women aged 20 to 50 compared to men (4,6).

A medical condition called diffuse goiter is identified by the generation of thyroid-stimulating immunoglobulin (TSI) or thyroid stimulating antibody (TSAb). These substances are discharged within the thyroid gland and bind to the thyroid stimulating hormone (TSH) receptor situated within the thyroid gland. Consequently, this activation prompts the thyroid gland to operate, generating the thyroxine hormone as a result of TSH receptor stimulation. Sustained TSAb stimulation leads to hyperthyroidism and the enlargement of the thyroid gland, a condition referred to as thyromegaly. Virtually all individuals diagnosed with Graves' disease exhibit the typical symptoms associated with hyperthyroidism (7). Common signs that manifest in young patients encompass temperature intolerance, perspiration, exhaustion, shedding pounds, palpitations, and trembling. In contrast, elderly individuals may exhibit more ambiguous and less defined symptoms, like weariness or weight reduction, often accompanied by extrathyroidal indications, such as ophthalmopathy, dermopathy, and osteopathy (5,8).

The test used to confirm diffuse goiter, especially in Graves' disease, is the calculation of TSAb (9). The TSH-level test is the initial laboratory examination used for diagnosis. In case of discovering low TSH levels, it is advisable to conduct the following tests: Free Thyroxine (FT4) and Free Triiodothyronine (FT3). If there is a concurrent decrease in TSH alongside increased levels of Total Thyroxine (T4) and triiodothyronine (T3), hyperthyroidism can be conclusively diagnosed. Graves's disease can be determined by considering historical data, conducting a physical examination, and performing fundamental laboratory tests. The existence of orbitopathy, enlargement of the thyroid gland, with or without the presence of bruits, and pretibial myxedema all offer substantial evidence for establishing the diagnosis. Nevertheless, if the signs and symptoms do not align with the typical presentation, a comprehensive examination is still recommended (10,11).

Hyperthyroidism leads to significant cardiovascular complications, such as coronary artery disease, ventricular arrhythmias, atrial fibrillation, atrioventricular block, myocardial systolic dysfunction, pericardial effusion, diminished cardiac output, and elevated blood pressure (12). Severe sick sinus syndrome (SSS) necessitating pacemaker intervention is seldom induced by hypothyroidism. Earlier research has indicated that mental disorders can also be triggered by hyperthyroidism (13).

Hence, the validity of utilizing atrial fibrillation electrocardiograms (ECGs) with Rapid Ventricular Response (RVR) to forecast the outcomes of both toxic and non-toxic diffuse goiter remains uncertain. In order to tackle this matter, we conducted a systematic review aimed at thoroughly assessing the predictive significance of ECG characteristics pertaining to sick sinus syndrome in predicting goiter prognosis.

METHOD

This research offers a Systematic Review that was carried out using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) approach. This approach entails a rigorous and systematic execution of the research process, adhering to established protocols. The systematic review process is highly organized and methodical, comprising several sequential stages: 1) the compilation of Background and Objectives, 2) formulation of Research Queries, 3) literature exploration, 4) establishment of Selection Criteria, 5) practical screening, 6) Quality Checklist and Procedures assessment, 7) Data Extraction Strategy, and 8) Data Synthesis Strategy. Data sources were collected from PubMed and Google Scholar, focusing on journal publications spanning from 2017 to 2022. Subsequently, a thorough screening procedure was employed, yielding a total of 15,486 results (*fig. 1*).

The literature search involved the selection of data in accordance with struma criteria derived from the Wayne index, which pertains to medical research and social health. Subsequently, a literature review was conducted regarding SND and Graves' disease. Research articles were sought through the PubMed and Google Scholar databases, focusing on articles pertinent to this study using keywords such as toxic and non-toxic diffuse goiter, Graves' disease, SND, and

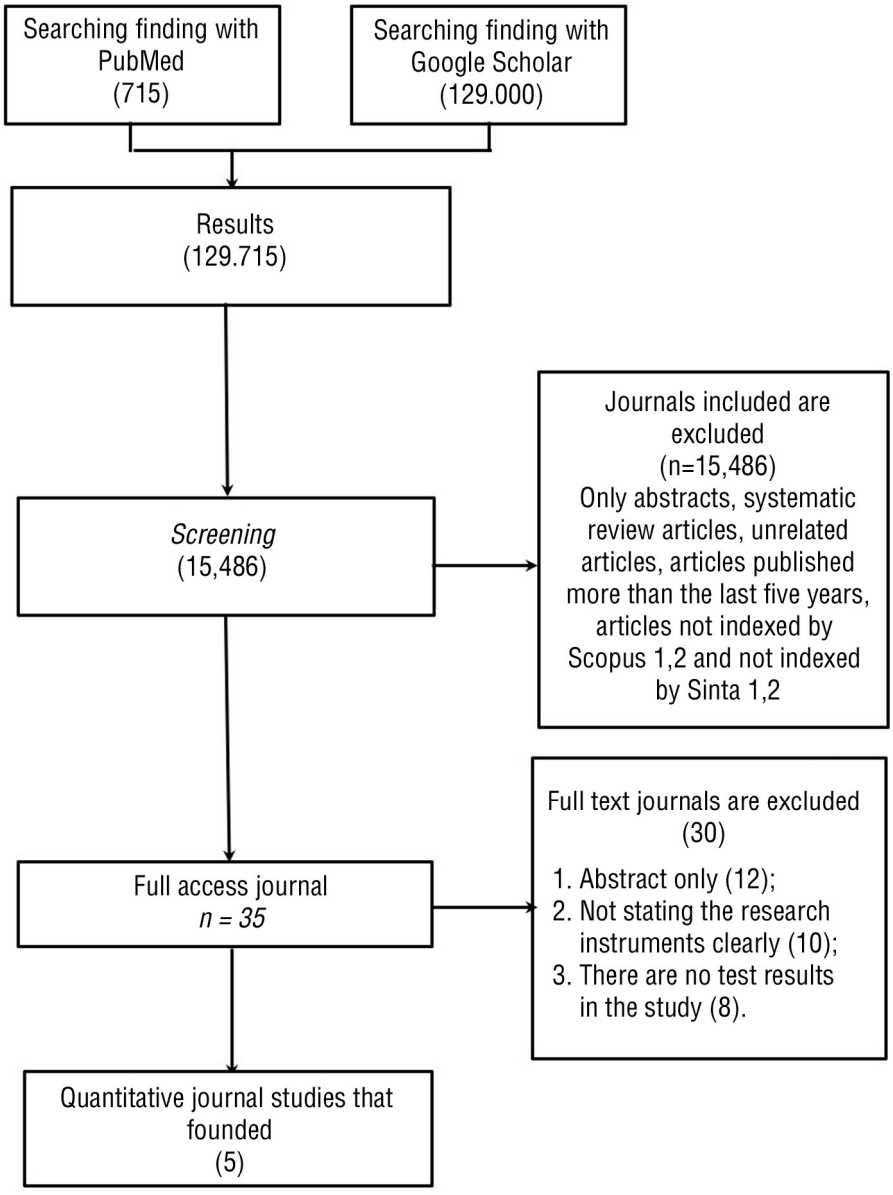

Figure 1 - PRISMA Diagram: stages systematic review

Graves' disease with the SND ECG. The chosen journals were those published between 2017 and 2022.

RESULTS

Clustering of journals was conducted, resulting in the acquisition of the number of journals included in Scopus Q2 and S1 journals listed in Sinta. Eight journals pertaining to the attributes of patients suffering from toxic and non-toxic diffuse goiter with ECG SND were identified. These journals were subsequently sifted through and compiled into a table to facilitate the elucidation of their contents. The selection of these journals was contingent upon their titles and abstracts, and they were subsequently evaluated against the inclusion criteria. Information extracted from the research encompassed the research title, author's name, publication year, research location, sample size, methodology, and findings (*table 1*).

DISCUSSION

Characteristics of Toxic and Non-Toxic Diffuse Struma Sufferers With an ECG SND Picture based on age and existing risk factors.

In individuals with hyperthyroidism as the research subjects, the predominant heart rhythm irregularities observed were as follows: fast-response atrial fibrillation was detected in six individuals, sinus tachycardia in four individuals, while normal-response atrial fibrillation and right bundle branch block (RBBB) were each found in three individuals. Two individuals exhibited benign ventricular ectopic beats (VES), and one person each experienced atrial flutter, supraventricular ectopic beats (SVES), and sinus tachycardia with RBBB.

Thyroid hormones, particularly T3, play a vital role in governing the expression of cardiac genes. These genes experience both positive and negative regulation (14). Increasing T3 that binds to TRs will induce positively regulated genes and suppress negatively regulated genes (15). These regulated genes include: Elevating T3 levels that interact with TRs will stimulate genes under positive regulation and inhibit genes under negative regulation (15). These affected genes encompass:

1. Alpha myosin heavy chain, known for its ability to enhance myocardial contractility (16);
2. The myocardium's electrochemical response is regulated by ion channels such as Na+-K+ ATPase and voltage-gated potassium ATPase (17). Alterations in the electrochemical performance of the myocardium have the potential to elevate systolic depolarization and diastolic repolarization, leading to a reduction in action potential duration. Such changes may lead to an augmentation in the Left Ventricular Mass (LVM) (18).

Research involving hypothyroidism, hyperthyroidism, and individuals with normal TSH levels has indicated that individuals with primary hyperthyroidism experience the highest degree of anxiety when compared to the other groups (19). Other research indicates that individuals with subclinical hyperthyroidism and subclinical hypothyroidism exhibit elevated levels of anxiety in contrast to euthyroid individuals (20). This viewpoint contrasts with the findings of other research, which assert that there is no correlation between thyroid disorders and mental health issues such as depression and anxiety (21).

Several studies have examined the connection between anxiety and thyroid function. In one particular study, it was discovered that individuals with subclinical hypothyroidism and subclinical hyperthyroidism exhibited elevated anxiety scores compared to those who had normal thyroid function (22). The results of this study are similar to this study. Namely, the anxiety score of people with thyroid disorders is higher than those with euthyroid. Another study with almost the same results stated that the symptoms of anxiety and depression were felt more severely by people with overt hypothyroidism and overt hyperthyroidism (23). Research on sufferers of hyperthyroidism also showed that the hyperthyroid sufferer group had higher anxiety and depression scores than the euthyroid group.

Research limitations & medical implications

In this research, the researcher encountered certain limitations. These limitations were identified as follows:

1. It was discovered that the researcher faced difficulties in regularly accessing full-text journals, leading to prolonged search efforts.
2. The researcher required additional time to gather relevant journals related to the research problem for appropriate referencing.
3. More time was needed by the author to comprehensively analyze and understand the journal contents and to compile journals or books relevant to the research problem for suitable reference sources.
4. The availability of journals pertaining to research variables concerning the characteristics of Graves' disease with an ECG SND picture was limited.
5. Researchers were able to find, at the very least, one journal that provided in-depth results on the

Table 1 - Journal analysis

No	Journal Title and Researcher Name	Objective	Population/ Sample	Instrument	Data Analysis / Research Methods	Results	Journal Clustering
1	Hyperthyroidism and Sick Sinus Syndrome, a Rare but Challenging Association: A Study of Three Cases M Tudoran, C Tudoran (2017)	This study looked at case reports aged 48 years, 63 years and 66 years	A female patient aged 48, 63, and 66 years was admitted to the emergency department by him relatives.	Analyzing case reports on three cases	Hyperthyroidism is typically linked to sinus tachycardia or supraventricular tachyarrhythmias, with infrequent occurrences of sinus node or conduction dysfunction disruption.	Hyperthyroidism and SSS rarely occur together, primarily found in individuals with Graves' disease, even during subclinical phases, which can lead to challenges in treatment when concurrent tachyarrhythmias are present. It generally improves in the majority of cases following the restoration of thyroid hormone levels and seldom necessitates the implantation of a pacemaker.	Q2
2	Graves' disease and mental disorders Atsushi Fukaoa, Junta Takamatsub, Takeshi Arishimac, Mika Tanakad, Toshio Kawaie, Yasuki Okamotof, Akira Miyauchic, Akihisa Imagawa (2020)	This study is to see whether graves disease and mental disorder are related to each other	Conduct a literature review of articles from 1985-2014	Analyzing journals on Pubmed, and Elsevier	Systemic review studies	Mental disorders, such as depression and anxiety, frequently occur alongside Gender Dysphoria (GD). Additionally, psychosocial elements encompass stress and an awareness of the condition, while biological elements, such as the impact of thyroid hormones, can affect the progression of the illness. Approaches involving both psychology and the body, like the use of antipsychotic medications and psychotherapy rooted in a bio-psycho-social framework, are considered viable treatments. Medical models are regarded as beneficial for individuals experiencing concurrent symptoms of mental health disorders and hyperthyroidism in the context of GD.	Q2
3	Digital Interventions for Generalized Anxiety Disorder (GAD): Systematic Review and Network Meta-Analysis Pedro Saramago (2021)	Generalized anxiety disorder is the most common mental health condition based on weekly prevalence. Digital interventions have been used as an alternative or as a supplement to conventional therapy to improven access, patient choice, and clinical results. Little is known about their comparative effectiveness for generalization anxiety disorders.	We included 21 randomized controlled trials with a total of 2350 participants of the general anxiety disorder population noneintervention.	We performed a systematic review and random network meta-analysis controlled trials comparing digital interventions with medication, non-digital interventions, non-therapeutic controls, and	The results obtained from the analysis of covariance and the ranking based on the cumulative rating curve indicated that antidepressant medication and group therapy had a greater likelihood of being considered the most effective interventions compared to digital interventions. It should be noted that supported digital interventions are not inherently superior to unsupported ones (pure self-help).	Because of the extensive confidence intervals, the outcomes of the network meta-analysis raise uncertainty regarding whether digital interventions are superior to no intervention or non-therapeutic active controls, or if they offer added advantages compared to standard therapy. Future research should involve comparisons between digital interventions and one-on-one therapy, as well as between digital interventions and non-digital self-help manuals. Additionally, including antidepressant medications as a treatment comparison and assessing their impact changes will be necessary.	Q2
4	Graves' disease and mental disorders Atsushi Fukao (2020)	Mental disorders are closely associated with thyroid disease. Due to its regulatory effect on serotonin andnoradrenaline, T3 has been closely linked to depression and anxiety	Literature review data study from 1998-2017	Literature review	Analysis of literature review	Mental disorders, such as depression and anxiety, frequently accompany Gender Dysphoria (GD). Psychosocial elements, such as stress and awareness of the condition, also play a role. Biological factors, including the impact of thyroid hormones, can affect the progression of GD. The psychosomatic approach incorporates the use of antipsychotic medications and psychotherapy grounded in a bio-psycho-social framework. Medical models are deemed beneficial for individuals experiencing simultaneous mental GD symptoms and hyperthyroidism.	Q2

Table 1 - Journal analysis (continuation)

No	Journal Title and Researcher Name	Objective	Population/ Sample	Instrument	Data Analysis / Research Methods	Results	Journal Clustering
5	The Role of Cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4) Gene, Thyroid Stimulating Hormone Receptor (TSHR) Gene and Regulatory T-cells as Risk Factors for Relapse in Patients with Graves Disease Fatima Eliana (2017)	Graves' disease (GD) is a condition commonly found in thyrotoxicosis. The management of GD begins with administration of antithyroid drugs, although the patient needs time time to achieve recovery or remission.	Compared 72 subjects with relapse and 72 subjects without relapse at 12 months after discontinuation of antithyroid treatment	Case control study	Genetic polymorphism analysis was conducted through PCR-RFLP. The quantification of Regulatory T cells was performed using flow cytometry analysis and ELISA for TRAb measurement. Logistic regression was employed due to the categorical nature of the dependent variable.	Genetic polymorphism at nucleotide 49 in codon 17 in exon 1 of the CTLA-4 gene, the SNP rs2268458 in intron 1 of the TSHR gene, combined with the levels of Regulatory T cells and TRAb, constitute risk factors for relapse in patients with Graves' disease.	S1
6	Long Term Antithyroid Drug Treatment: Systematic Review and Meta Analysis Azizi (2017)	Some studies have reported inconsistent findings regarding advantages and disadvantages long-term treatment with antithyroid drugs (ATD). A systematic review and meta-analysis was carried out to clarify various aspects of long-term treatment with ATD	Medline and the Cochrane Library for trials published between 1950 and May 2016 were searched systematic.	Literature review	Studies that included data on the extended treatment of TB for more than 24 months were incorporated. A summary was generated using a random effect model to calculate pooled prevalence estimates, odds ratios, and weighted mean differences.	Among the 587 related articles uncovered, six satisfied the inclusion criteria. Prolonged OAT therapy resulted in a remission rate of 57% (with a confidence interval (CI) ranging from 45% to 68%), with a higher rate observed in adults compared to non-adults (61% vs. 53%). The complication rate stood at 19.1% (CI 9.6–30.9%), of which only 1.5% constituted major complications. Each year of treatment saw an annual remission rate of 16% (CI 10–27%), which was more pronounced in adults versus non-adults (19% vs. 14%). Nonetheless, it's worth noting that this doesn't represent a true linear correlation, although a positive relationship between time and remission rates can be inferred. Meta-regression analysis unveiled that smoking had a notably adverse impact on remission rates. In conclusion, Long-term OAT treatment demonstrates efficacy and safety, particularly in adults, suggesting its consideration as an alternative therapy for Graves' disease.	Q2
7	Sick sinus syndrome and hyperthyroidism: A rare phenomenon Nitesh Kumar, Diwakar Verma, Kapil Gupta, Madhu Kiran, Prakarti Yadav, Shatrughan Pareek (2021)	This study is to look at case reports that are 70 years old	A 70 year old female patient was brought in to the emergency department by him relatives. He have a history of that feeling dizziness and light headedness. He is a known case of diabetes mellitus, hyperthyroidism, hypertension, and atrium fibrillation with controlled ventricular rate.	Analyzing case reports	Analyzing rare case reports	Hyperthyroidism and SSS are uncommon occurrences, particularly in individuals diagnosed with Graves' disease. SSS/SA/AV node block can be rectified through the treatment of hyperthyroidism to restore euthyroidism, potentially obviating the requirement for a pacemaker. This instance underscores the identification of SSS in hyperthyroidism, subsequent to the pacemaker implantation. Achieving control over hyperthyroidism eventually led to the restoration of a regular rhythm and the eventual removal of the pacemaker.	Q2

Table 1 - Journal analysis (continuation)

No	Journal Title and Researcher Name	Objective	Population/ Sample	Instrument	Data Analysis / Research Methods	Results	Journal Clustering
8	An Adolescent Patient with Sick Sinus Syndrome Complicated by Hypothyroidism Carrying a Case Report of the SCN5A A Variant Hiroaki Yamane, Mitsuru Seki, Takahiro Ikeda, Ayumi Matsumoto, Sadahiro Furui, Tomoyuki Sato, Kazuhiro Muramatsu, Toshihiro Tajima, Takanori Yamagata (2022)	This study is to see case report that is 13 years old	An old girlA 13 year old was referred to our hospital for bradycardia, as revealed by the school's electrocardiography (ECG) screening. There were no ECG abnormalities been observed during school screening 3 previous year. He has had no episodes of syncope, he reported noticing facial and lower leg edema as well as quickly tired over the past 2 years. An analysis its growth curve is also revealingIt's true that he experienced a growth slowdown during this 2 year period. No family history of arrhythmia, sudden death, or congenital heart disease	Analyzing case reports	Analyzing case reports	In this report, we've outlined the instances of a 13-year-old girl diagnosed with SSS who possesses the SCN5A variant and has additionally experienced the onset of hypothyroidism. The current case underscores the significance of genetic analysis, particularly for the SCN5A variant, among individuals dealing with hypothyroidism complicated by SSS or cardiac conduction disorders.	Q2

characteristics of Graves' disease with an ECG SND picture.

The study's findings suggest a connection between Graves' disease and the occurrence of an ECG picture of Sick Sinus Syndrome (SSS). Based on these study results, it is anticipated that healthcare professionals will gain a better understanding of the characteristics of individuals with anxiety disorders in Graves' disease who exhibit an ECG picture of Sick Sinus Syndrome (SSS).

CONCLUSION

After going through a sequence of procedures and considering research outcomes from Scopus and Sinta indexed journals that focus on the characteristics of systematic reviews in patients with diffuse toxic and non-toxic goiter displaying an ECG pattern of SND, we can draw the conclusion that the majority of these journals address the correlation between age and gender as risk factors for Graves' disease.

From the subsections examined, it is evident that the risk factors for Graves' disease are established based on age, gender, and lifestyle. Additionally, Graves' disease is linked to anxiety disorders and the presence of an SND ECG pattern.

Authors' contributions

The author acknowledges exclusive accountability for the subsequent tasks: conceptualization and design of the study, gathering of data, analysis and result interpretation, as well as the preparation of the manuscript. The final manuscript was reviewed and endorsed by all authors.

Conflicts of interest

The authors confirm that there are no conflicts of interest involving any financial organizations in relation to the content discussed in the manuscript.

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ORIGINAL PAPER

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Esophageal Malignancy – Endoscopic and Clinicopathologic Patterns Study and Their Outcome in a Tertiary Hospital in South India

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ABSTRACT

Objectives: The aim of this study is to define epidemiological, clinicopathological and prognostic factors in patients with esophageal cancer.
Methods: This study was conducted in JSS Medical college & Hospital, Mysuru and the study period was from January 2020 to January 2023. All the patients who were diagnosed to have carcinoma esophagus were included in study. These patients were allowed to undergo necessary diagnostic work up and treatment. They were called for follow up at regular intervals. Data thus collected were analyzed and studied for understanding the pattern of the disease presentation, efficacy of the diagnostic modalities and management which includes Surgery, chemotherapy and radiotherapy.
Results: 71 patients with esophageal cancer were included. The mean age of esophageal malignancy was 62 years. Males were more than females (56 % v/s 44%). In our study,chronic smokers were 51%. Twenty three percent patients were alcoholics. Upper third of esophagus was found to be most common site. 82 % of patients had squamous cell carcinoma while 18% had adenocarcinoma. Out of 71 patients, surgery was done as therapy for 5(7%) patients. 60% underwent combination Chemoradiotherapy. The longest duration of follow-up was one and a half years in a post-operative patient. Among surgical patients two patients were alive at 1 and 1.5 years. The remaining were in their 2nd to 8th postoperative months and were still on follow-up and all are keeping well.
Conclusion: Carcinoma esophagus is one of the common gastrointestinal cancer in our hospital. Early diagnosis offers the only chance of cure in these patients. Unfortunately, 50 % of patients with this disease are already in advanced stage at presentation, so prognosis continues to be very poor. Chemoradiation therapy has made a real impact on current management strategies and improved survival with low morbidity in carefully selected patients.
Key words: adenocarcinoma, chemotherapy, surgery

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INTRODUCTION

Cancer of the esophagus ranks twelfth among the major cancers and seventh in the number of cancer death. Its high mortality rate makes it a major concern. Overall survival rate is 62.5% at 1 year, 42.4% at 2 years, 30% at 5 years (1).

Early stages of the disease are only found serendipitously or during screening of precursor lesion. As a result, the typical patient presents with locally advanced disease with lymph node involvement (2).

Esophageal malignancies are diagnosed by UPPER GI ENDOSCOPY with multiple biopsies. CT scan is needed to identify lung and abdominal metastases. It also helps in assessing the local invasion of the growth by delineating the invasion into meditational structures and for assessment of response to neoadjuvant therapy in patients with esophageal cancer. FDG PET seems to be a promising noninvasive tool for assessment of neoadjuvant therapy in patients with esophageal malignancy (3).

Surgery remains the best option for these patients providing the only chance of cure (4). Combined modality therapy including radiotherapy and chemotherapy has raised hope for improvement of survival with promising preliminary data.

Finally, for palliation of dysphagia in those patients with advanced disease endoscopic management remains standard of choice.

MATERIAL AND METHODS

It is a longitudinal study conducted in the Department of Medical Gastroenterology, JSS Medical College and Hospital, Mysuru, Karnataka – a tertiary care hospital. Study duration was from January 2020 till January 2023. A total of 71 patients who were diagnosed with Esophageal malignancy were included in the study. They were called for follow up at regular intervals.

Inclusion criteria

Patients of all ages, sex or occupation primarily diagnosed in out patients/in patients department and later confirmed by radiological/histopathological reports were included in the study.

Exclusion criteria

Patients excluded from study were;

1. Where multiple concurrent tumors were found on CT scan in other parts of GIT.
2. Patients who were bound to be lost in follow up.
3. Patients insisting on having treatment from other hospital, other city and abroad.

Statistical analysis

Data was collected and entered in Microsoft excel worksheet and analysed using SPSS V21 software.

RESULTS

Total number of patients included in our study were 71 (*table 1*). Peak incidence of carcinoma esophagus occurred in the 5th and 6th decade of life. 29.6 % each in 5th & 6th decade (*fig. 1*). The mean age of esophageal malignancy was 62 years. Males were more than females (56 % v/s 44%) (*table 2, fig. 2*). In our study, chronic smoker was defined as a person who smokes more than 1 pack / day for at least 10 years (*table 4*). Among 40 men with the disease, 22 were smokers while women had the habit of tobacco chewing (*figs. 3, 4*). A patient was considered an alcoholic if he consumed 80gm of alcohol per week for atleast 5 years. Twenty three percent of patients were alcoholics. The average symptom duration was 8 weeks. Dysphagia was more to Solids & liquids than solids alone (94% v/s 6%) (*table 3*). Apart from dysphagia, loss of weight and appetite were the most prominent symptoms of the disease. Vomiting was present in 35% patients. Cough was associated in 9 % patients. Chest pain in 3%. Hoarseness of voice in 2 patients. On general examination, almost 60% patients had pallor. Except for general features like pallor and cachexia, the systemic examination was grossly normal in most of the patients.

Table 1 - Distribution of study subjects based on age group

		N	%
Age Group	Between 51 to 60 years	21	29.6%
	Between 61 to 70 years	21	29.6%
	Less than 50 years	13	18.3%
	More than 70 Years	16	22.5%

Figure 1 - Graph wise distribution of study subjects based on age group

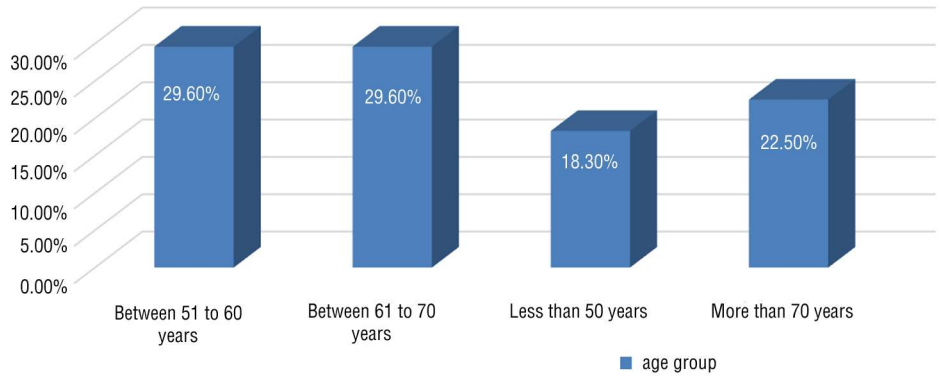

Table 2 - Distribution of study subjects based on gender

		N	%
Sex	Female	31	43.7%
	Male	40	56.3%

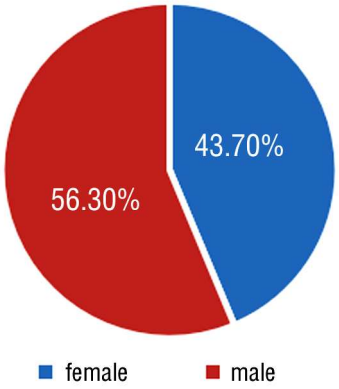

Figure 2 - Graph wise distribution of study subjects based on gender

Table 3 - Distribution of study subjects based on dysphagia

		N	%
Dysphagia	Both	28	39.4%
	Solids	4	5.6%
	Solids>Liquids	39	54.9%

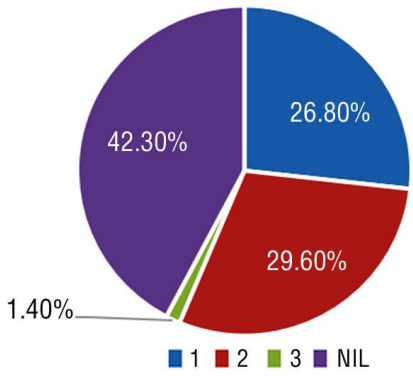

Figure 4 - Graph wise distribution of study subjects based on pack of cigarettes

Table 4 - Distribution of study subjects based on smoking risk factor

		N	%
Smoking	No	36	50.7%
	Yes	35	49.3%

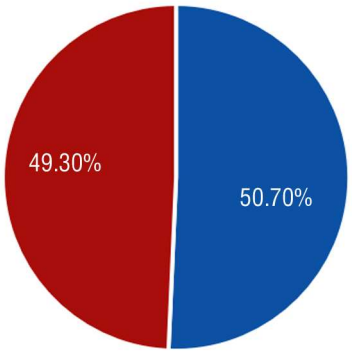

Figure 3 - Graph wise distribution of study subjects based on smoking risk factor

Diagnosis and management

Upper GI scopy was performed in all seventy one patients in our study. Three gross types of growths were identified in endoscopy. Ulcero-proliferative, Exophytic mass, Stricture (*table 6, fig. 5*). Upper third esophageal malignancy was found in 68% of patients (*table 7, fig. 6*). As noted in (*fig. 7, table 8*), 81.7% of patients had squamous variety of carcinoma while 18.3% of patients had adenocarcinoma.

Table 5 - Distribution of study subjects based on pack of cigarettes

		N	%
Packs of Cigarettes	1	19	26.8%
	2	21	29.6%
	3	1	1.4%
	NIL	30	42.3%

Table 6 - Distribution of study subjects based on endoscopic findings

		N	%
Endoscopy	Ulcero-Proliferative Growth in Upper Esophagus	18	25.4%
	Ulcero-Proliferative Growth in Lower Esophagus	15	21.1%
	Post Cricoid Growth	11	15.5%
	Mid Esophageal Growth	10	14.1%
	Upper Esophageal Stricture	6	8.4%
	Stricture In Mid Esophagus	4	5.6%
	Postcricoid Growth	3	4.2%
	Lower Esophageal Stricture	2	2.8%
	Post Cricoid Growth With Fistula	1	1.4%
	Mass With Sloughed Mucosa & Whitish Exudate In Pyriform Fossa	1	1.4%

Table 8 - Distribution of study subjects based on type of tumour

		Count	Column N %
TYPE	Adenocarninoma	13	18.3%
	Squamous Cell carcinoma	58	81.7%

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Clinical staging

For accurate staging of early as well as locally advanced tumors according the current AJCC criteria, the role of endoscopic ultrasound is indispensable. Our patients had financial limitations and hence we had to strongly rely on CT scan for assessing tumor (T) characteristics like depth of invasion into the esophageal wall and infiltration into adjacent structures. Also for assessing mediastinal and abdominal adenopathy, CT scan was relied upon which does not have very good sensitivity and specificity. Hence our staging may be inaccurate and a proper staging evaluation may take the number of cases to higher stages (*table 9*).

Figure 5 - Graph wise distribution of study subjects based on endoscopic findings

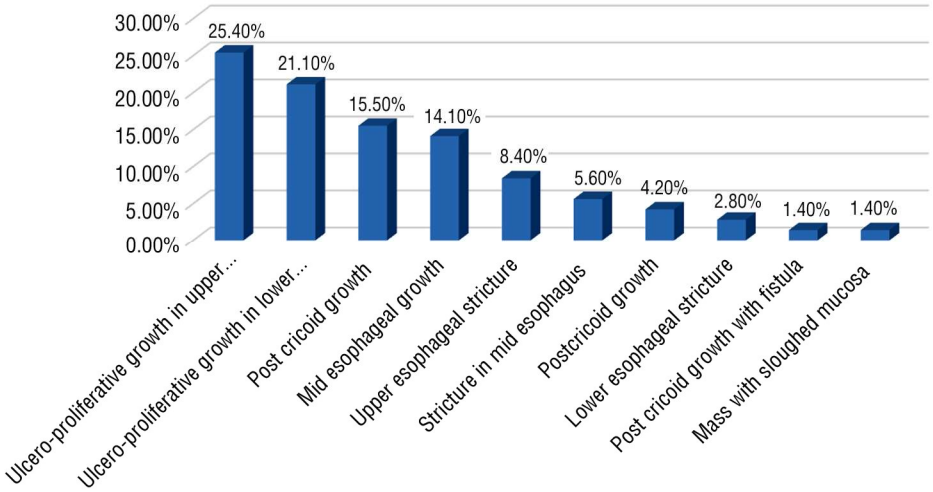
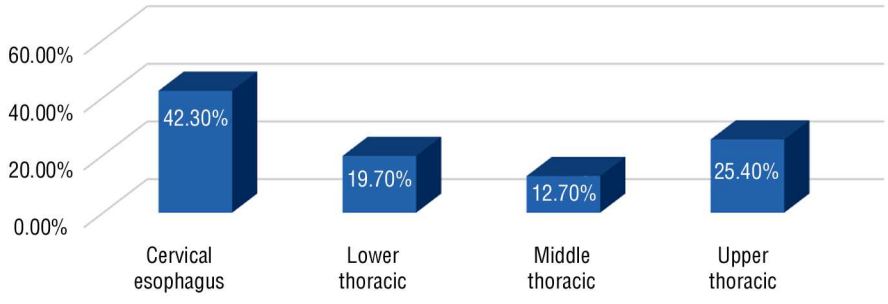


Figure 6 - Graph wise distribution of study subjects based on Location of tumour



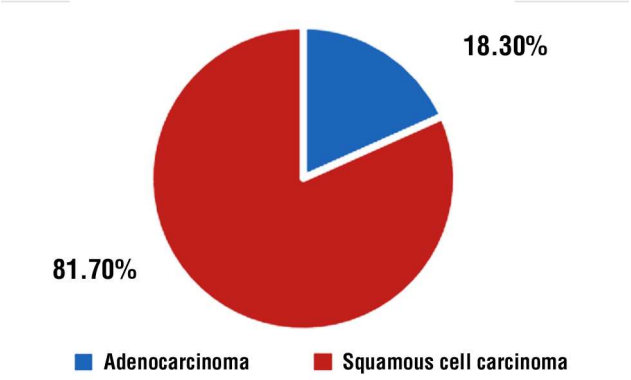


Figure 7 - Graph wise distribution of study subjects based on type of tumour

Table 9 - Distribution of study subjects based on staging of tumour

		N	%
Staging	IA (T1N0M0)	1	1.4%
	IB (T2N0M0)	8	11.3%
	II A (T3N0M0)	4	5.6%
	IIB (T1N1M0)	1	1.4%
	IIB (T2N1M0)	20	28.0%
	III (T3N1M0)	2	2.8%
	III (T4N1M0)	1	1.4%
	IIIA (T4aN0M0)	12	16.9%
	IIIB (T4aN1M0)	8	11.3%
	IV	13	18.3%
	IVA(T3N2M0)	1	1.4%

Treatment

The three main modalities of treatment offered in our hospital for cancer esophagus patients are surgery, chemotherapy and radiotherapy, often in combination. Patients are initially evaluated for operability. Surgery was the first treatment of choice in our hospital. In patients who are not fit or refuse surgery, radiotherapy was used.

Radiotherapy was used as a primary modality of therapy in patients with mediastinal invasion and for palliation of dysphagia. In a significant minority of patients who had widely disseminated disease and who were too sick for any form of anti-cancer therapy, supportive therapy Was given.

Out of 71 patients, surgery was done as therapy for 5 patients (*table 10, fig. 8*). Actually, 13 patients were taken for surgery during the study. The remaining 8 patients had intraoperative findings that precluded resection. After postoperative recovery, Nine received combination chemotherapy and four received radiotherapy. Six patients had mucositis & three patients developed pulmonary complications, which were managed conservatively (*table 11*).

Table 10 - Distribution of study subjects based on treatment

		Count	Column N %
Treatment	CT + RT	29	40.6%
	RT	23	32.4%
	Surgery + FJ + CT	4	5.6%
	Endoscopic dilatation + CT + RT	7	10%
	Endoscopic -Sems + CT + RT	7	10%
	Esophagectomy+CT	1	1.4

Figure 8 - Graph wise distribution of study subjects based on treatment

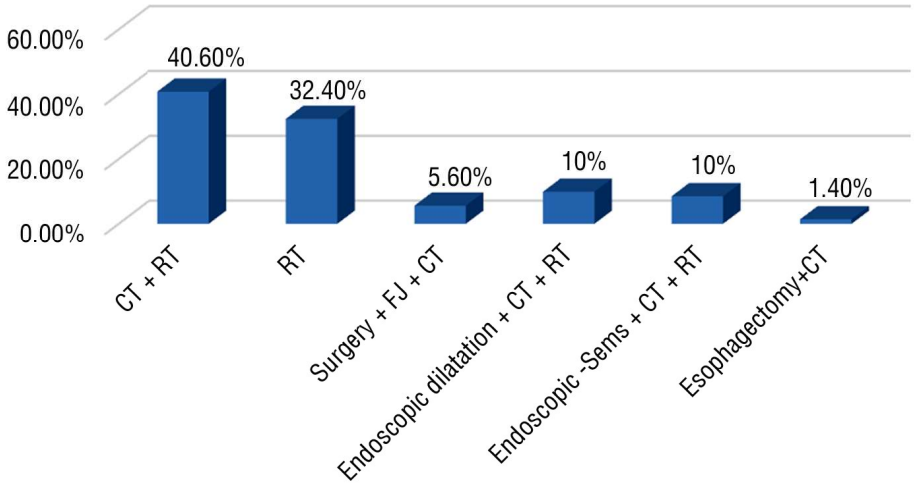


Table 11 - Distribution of study subjects based on treatment related complications

		N	%
Treatment related complications	Mucositis	6	8.5%
	Nil	62	87.3%
	Pulmonary complications	3	4.2%

Follow-up & outcome

The mean duration of follow-up was 5.24 + 7 - 2.12 months. The longest duration of follow-up was one and a half years in a post-operative patient. Among surgical patients two patients were alive at 1 and 1.5 years. The remaining were in their 2nd to 8th postoperative months and were still on follow-up and all are keeping well. The patients who were found inoperable on table died on an average between 2 and 6 months following treatment.

Three out of 23 patients survived beyond one year. The remaining patients were lost to follow-up. Only one out of 29 patients who received chemotherapy as their primary therapy was surviving at the end of I year. Thirty-two percent expired at the end of 3 months while 56% died between 3-6 months (*table 12*). Ten percent did not survive beyond 6 to 12 months. Of the patients who were not treated by any modality, none survived beyond 6 weeks. Patients with poorly-differentiated cancers did not survive beyond 6 months.

DISCUSSION

Carcinoma esophagus is one of the most common gastrointestinal tract malignancies. The male: female ratio in our study was 1.4:1. Worldwide, esophageal cancer is much more common in males compared to females. The maximum occurrence of this malignancy in our study was found in the fifth and sixth decade of life which was similar to the nationwide incidence as reported by Pennathur et al (5).

Population-based studies demonstrate that tobacco and alcohol use are independent risk factors and their effects are multiplicative, as evidenced by the association of the highest risk of developing esophageal cancer with heavy use of both agents. Cigarette smoking is also a risk factor in the development of carcinoma of the esophagus. Ninety percent of patients with adenocarcinoma in our study were heavy smokers. Although tobacco smoke contains known or putative carcinogens such as nitrosamines, 2-naphthylamine, benzopyrene and benzene, causative agents and their mechanisms of action for esophageal cancer have not been elucidated.

The consumption of alcoholic beverages is a major contributing factor in the increased risk of esophageal squamous cell carcinoma in Western countries. Although specific carcinogens may be present in a variety of alcoholic beverages, in all likelihood it is alcohol itself, either as a mechanical irritant, promoter of dietary deficiency, or contributor to susceptibility to other carcinogens, that leads to carcinogenesis. In our study, 16.0% of patients were alcoholics.

Gastroesophageal reflux disease has been implicated as one of the strongest risk factors for the development of adenocarcinoma of the esophagus. Chronic reflux is associated with Barrett's esophagus, the premalignant precursor of esophageal adenocarcinoma. Although no patients had documentation of either GERD or Barrett's esophagus in our study, 6 out of 13 adenocarcinoma patients had history that was strongly suggestive of GERD (6).

The overwhelming majority of esophageal malignancies may be classified as either squamous cell carcinomas or adenocarcinomas. Squamous cell carcinomas account for the vast majority of cancers arising in high-incidence areas throughout the world (7). Eighty two percent of our patients had squamous cell cancer while 18% had adenocarcinoma which is in sharp contrast to United States where only 40% were squamous variety. This reflects the difference in epidemiology and the fact that adenocarcinoma is not rising in incidence in less well-developed nations like ours compared to the West (8).

The symptoms most commonly associated with esophageal cancer are dysphagia and weight loss. Unfortunately, in most instances dysphagia signifies locally advanced disease or distant metastases or both.

Table 12 - Distribution of study subjects based on outcome

		TYPE			
		ADENOCA		SCC	
		Count	Column N %	Count	Column N %
Out come	Discharged	8	61.5%	40	69.0%
	Mortality	5	38.5%	18	31.0%

Chi Square = 0.267 p= 0.60

At presentation, patients usually describe progressive dysphagia, with difficulty initially in swallowing solids then liquids and in most extreme circumstances, their own saliva. In our study, all but one patient had dysphagia.

Substantial weight loss accompanying dysphagia is seen in approximately 90% of patients with squamous cell carcinoma. In our study, 75% had significant weight loss. Approximately 20% of patients experience odynophagia (painful swallowing).

Esophagogastroscopy allows precise evaluation of the extent of esophageal and gastric involvement and can precisely measure the distance of the tumor from the incisors to appropriately categorize the tumor's locationm (9). This is limited by the fact that negotiation into the stomach and duodenum will not always be possible because of totally occluding growths. In this study, 27% failure rate in negotiation into stomach was observed. Upper endoscopy also allows identification of "skip" lesions or second primaries as well as indicating the presence and extent of Barrett's esophagus (10).

On completion of the initial diagnostic workup and after a tissue diagnosis of esophageal cancer, pretreatment staging procedures are essential to accurately determine the depth of esophageal wall penetration, the status of regional lymph node basins, and the presence or absence of distant metastases so that patients can be guided to the appropriate treatment options and provided with prognostic information (11). All patients should undergo a computed tomography (CT) scan of the chest, abdomen, and pelvis as the initial evaluation for extent of disease. CT scans are highly accurate (approaching 100%) in detecting liver or lung metastases and suggesting peritoneal carcinomatosis (ascites, omental infiltration, peritoneal tumor studding etc) (12). Accuracy for detecting aortic involvement or tracheobronchial invasion exceeds 90% (13).

CT is inaccurate in determining T stage, because it cannot define individual layers of the esophageal wall and will miss small Tl and T2 tumors (14). CT assessment of regional or distant lymph nodes is hindered by relatively low sensitivity (50% to 70%) due to its reliance on size criteria (larger than 1 cm) alone. Because lymph node involvement is frequently seen in small or normal-size lymph nodes, the false-negative rate is high, and despite a reasonable specificity of 85%, accuracy in determining lymph node involvement is limited (approximately 60%) (15).

The staging was done using TNM system according to the latest AJCC (16).

The goal of treatment for esophageal carcinoma remains cure of the neoplasm for early stage, improvement of the disease-free and overall survival in advanced disease, relief from dysphagia, and improvement of quality of life for patients with metastatic disease and with minimal morbidity (17).

The following guidelines seem to be generally accepted:

- T1 or T2 tumors with no evidence of lymphatic metastases at endosonography (NO) or CT scan: surgical resection seems to be the treatment of first choice.
- T3 or T4 with nodal involvement (N +): inclusion into trials, surgical resection after preoperative radiochemotherapy may be preferable. Currently available data suggest that resection of the residual mass in responding patients are required for adequate tumor control (18-20).
- Patients with significant comorbidity considered unfit for major surgery should be treated by radiochemotherapy.
- Metastatic disease: palliative treatment only.

In our study, after initial endoscopic diagnosis, patients were assessed for operability. If ultrasound or clinical examination reveals metastatic disease, only palliative therapy was given. Following this resectability is assessed by CT scan of thorax and abdomen and patients are taken up for surgery if there is no invasion into major mediastinal structures.

CONCLUSION

Early diagnosis offers the only chance of cure in these patients. Unfortunately, 50 % of patients with this disease are already in advanced stage at their presentation, and so the prognosis continues to be very poor. Also, early diagnosis itself is difficult as dysphagia which is the cardinal symptom occurs relatively late in the course of the disease. Primary endoscopic screening is also impossible in our country as the cost benefit ratio of undertaking will not be acceptable (21).

However, advances have been made in the management of esophageal carcinoma; the key is to select the most appropriate combination for individual patients. Surgeons play a central role in direction treatment of this disease by advising on how best to integrate surgical resection with non operative programs. Our study shows very good survival rate in patients who underwent surgical resection which partly may be due to the stage at their presentation. Still, it is highly recommended to aim at improving the results further, so that low mortality rates for resections are used to compare with seemingly safer therapies (22).

Chemo radiation therapy has made a real impact on current management strategies and our study shows low morbidity in carefully selected patients. Distant metastasis remains a major problem even in the best centers and search is on for more effective systemic drugs. The challenge for future for us is to identify esophageal cancer at early stage & critically test our strategies in a scientific, unbiased manner and to explore other innovative treatment option.

Conflicts of interest

None declared.

Funding

None declared.

Ethical statement

Informed Consent taken, as well as Ethical Committee Approval.

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ORIGINAL PAPER

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Can Celiac Disease Affect Liver Enzymes in Patients with Gallstones? A Comparative Study

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ABSTRACT

Background: Gallstone disease is growth of a pebble-like substance as gallstones. Celiac disease is an autoimmune disease in genetically susceptible patients. The aim of the study is to investigate the liver enzymes among patients with gallstones in the presence of celiac disease once and the absence of disease again.
Methods: A comparative study was conducted on 280 people, 134 of them had gallstone disease, 6 patients who had celiac and gallstones disease, 12 asymptomatic celiac patients and 128 healthy persons were involved. All of participants had subjected to immunological investigations via Enzyme Linked Immunosorbent Assay technique. Biochemical investigations (Liver Function Test) were performed to check liver enzymes parameters fluctuations.
Results: The gallstones disease and active celiac disease cases mean age was 41.01 years. Six patients revealed a positive ultrasonography exam for having gallstones as well as a positive immunological test including anti-gliadin IgA, IgG and anti-transglutaminase IgA (greater than 10U/ml). Asymptomatic or silent celiac disease group comprised of 12 healthy persons with a seropositive immunological result and still with silent symptoms of celiac disease with positive anti-gliadin IgA and IgG only (greater than 10U/ml). Furthermore, the present research revealed that these two diseases together seemed to have a substantial or relatively significant influence on ALT, AST and ALP.
Conclusion: Active celiac disease produces disturbances in the AST liver enzyme, which have been related to both of the disorders that were investigated in this research, although Gallstones Disease alone had a possible influence on biliary system specific enzymes.
Key words: celiac disease, gallstones disease, Cholelithiasis, Cholecystokinin, liver enzymes

INTRODUCTION

Celiac disease (CD) is an autoimmune enteropathy defined by a lifelong sensitivity to eating gluten in people who are genetically predisposed to it (1). CD prevalence may approximately reach to affect one person every 100 persons worldwide and varies by gender, age, and geography (2). Inflammation and tissue injuries throughout the small intestine are caused by an abnormal immune response to gluten and the symptoms are diverse and can affect both intestinal and extra-intestinal locations (3).

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Respectively, Gallstones or (Cholelithiasis) are a pebble-like material that develop inside the gallbladder (GB), hepatic bile duct (HBD) and common bile duct (CBD). It is considered as one of the most common gastroenterological conditions (4). GSD is a major burden on healthcare systems across the world, and it is one of the most prevalent illnesses among people who arrive at emergency departments with abdominal pain (5). Gallstone disease has an estimated frequency of 5 to 22%, depending on risk factors (6). Although many gallstones remain asymptomatic, around one-third of them eventually produce symptoms and complications (7).

Fraquelli et al, stated the impact of CD on gallstone formation via reduced postprandial enteric peptide secretions and increased gallbladder volume (8). GB motility has been investigated in untreated celiac patients and the result confirms that decreased CCK secretion will affect intestinal and gallbladder motility (8). Diet with low-calorie content possibly induces GB stasis and consequently a reduction in GB stimulation (9). Fat intake plays a crucial role to induce GB contraction, this idea has been introduced by Gebhard et al (10). Additionally, GB stasis promotes the conversion of cholesterol into cholesteryl esters for deposition in the GB wall, exacerbating the already poor GB motor function. More specifically, a lengthy retention period of cholesterol supersaturated bile inside the biliary lumen commonly results in rapid cholesterol crystal development, crystallization, and aggregation as microlithiasis, and subsequently macroscopic gall stones, not just in CD patients but also in non- celiac individuals (11). Most importantly, in celiac patients, biliary cholesterol synthesis and secretion are substantially doubled, indicating increase biliary cholesterol secretion is a crucial component in the formation of supersaturated bile (12). Liver enzymes were not significantly linked with gallstone development, but may be changed dramatically as an impact of CD with Gallstones on the liver organ (5-12).

METHODS

Study participants

This comparative study has conducted on 280 participants (aged ≥ 15 years) in Basrah teaching hospital from December 2021 to August 2022. Totally, 140 patients were admitted into the surgical word, diagnosed, examined, investigated and followed up in outpatient clinic, all of those patients underwent to abdominal ultrasonography and the results indicated that they are diagnosed with gallstones and have prepared to performing laparoscopic cholecystectomy. Six patients among them who had celiac as well as gallstones disease. They have seropositive tests results of anti-gliadin autoantibodies IgA, IgG and anti-transglutaminase autoantibodies IgA. About 140 healthy control subjects were chosen randomly from the outpatient clinic of Basrah teaching hospital, those who visited the outpatient clinic for general health checkup. All of them were checked by ultrasonography consultant to exclude gallstones disease (GSD). Twelve patients among them had immunological seropositive biomarkers result and clinical presentations indicated the patients was asymptomatic celiac patients. All the 280 participants were subjected to a liver function test.

Ethical commitment

The study has conducted after obtaining the written consent of the participants, taking into account medical ethics.

Design of study

Patients and healthy control have assessed by questionnaire. All collected blood samples in this study were obtained from fasting patients for 12 hours at least. A fresh vein blood sample of 4 ml was taken by a laboratory technician using a sterilized syringe. Collected blood samples were putted into specific GEL tube (acid citrate dextrose) that helps the blood sample to coagulate rapidly and enhances the separation of the sample into two phases after centrifuging them. After 20 minutes, the Centrifuge process was conducted by an electrical centrifuge instrument for 5 minutes at speed of 4000 rpm. Beyond centrifuging process, we obtain serum sample using a micro pipette putting them into Eppendorf tubes, each tube containing (0.5 ml) and make ready for preservation. Serum samples were used to achieve the celiac biomarkers: (anti-tissue transglutaminase T/IgA and T/IgG, anti-gliadin-A, and anti-gliadin-G) and liver function tests. The samples were stored immediately in a sterile Eppendorf tube, then transported directly into a deep-freezing instrument at the BASRA BIOBANK to prevent serum sample damage. Samples were kept at -50°C that ensure the biomarkers and serum protein content were still undegraded and kept these contents active for 6 months (13). Serum samples were used to achieve the celiac biomarkers: (anti-tissue transglutaminase T/IgA and T/IgG, anti-gliadin-A IgA, and anti-gliadin-G IgG) and liver function test.

Immunological markers of CD

Anti-gliadin markers IgA and IgG were detected via indirect ELISA (Demeditec Diagnostic GmbH (Germany), cut off value for both isotypes markers were (10 U/ml) (14,15). Anti-tissue transglutaminase markers IgA and IgG were detected via indirect ELISA (Demeditec Diagnostic GmbH (Germany), cut off value for IgA isotypes markers were (10 U/ml) and for IgG isotypes markers were (7 U/ml) (16,17).

For a quantitative examination, the absorbances of both the standards as well as controls are graphed versus their levels. The level values for each specimen can then be obtained from the resulting reference curve in relation to their absorption spectra. It is also feasible to employ computer applications that run automatically (10-13).

Biochemical markers of LFT

Using a commercial kit from Sigma-Aldrich – USA, serum samples were tested for liver function test, liver enzymes Alanine aminotransferase enzyme (ALT) (references values for adults at 37°C up to (40 U/L) (0.67 kat/L) and 30°C up to (25 U/L) (0.42 kat/L), for plasma or serum) (18), Aspartate aminotransferase enzyme (AST) (references values for adults at 37°C up to (40 U/L) (0.67 kat/L) and at 30°C up to (25 U/L) (0.42 kat/L), for plasma or serum) (19) and Alkaline phosphatase enzyme (ALP) (references values for Serum or plasma in adults) (20). All of these tests depend on measured absorbance (A) of both the samples and standard compared to reagent blank.

Statistical analysis

The data were analyzed using the statistical software, SPSS-26.0 (SPSS Inc, Chicago, IL). Quantitative data were represented using basic measurements of mean and standard deviation. The significance of differences between means was assessed using the ANOVA test for differences between more than two independent means, followed by the Tukey test. Chi2 was used to investigate any association between qualitative variables. Statistical significance was regarded when the P value was less than 0.05 and highly significant when it was less than 0.01.

RESULTS

The demographic findings of participants enrolled in this study showed 134 patients (14 male and 120 female) with GSD only without CD of ages range (19-85 years) with a mean value (41.01) who have claimed clinical features of gallstones, 6 female patients of ages range (15-52) years with a mean of (34.33) revealed seropositivity of anti-gliadin and anti-transglutaminase autoimmune antibodies in a varying degree and appeared as overt CD in addition to GSD. 128 healthy control persons (14 male and 114 female) who didn't complain of any disease, age range (16-76) years with a mean of (40.99). 12 healthy female persons with a seropositive immunological result and still with silent symptoms of CD, ages range (17-68) years with a mean of (39.83), (*fig. 1*). Statistical analysis didn't show a significant association between age among study groups (P>0.05).

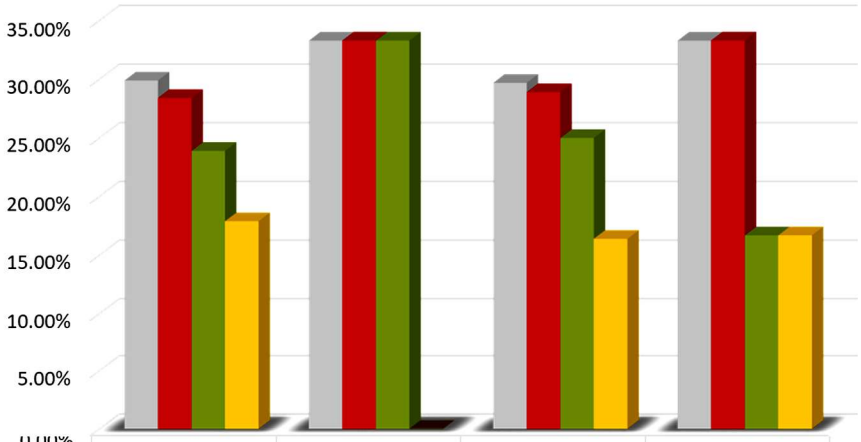
Our study has showed the female/male ratio for gallstone prevalence was 9:1. Residence distribution of study groups indicated that most of the patients and healthy control were of urban residence and the little percentage were of rural residence. The residence of patients in GSD group was distributed as (120, 89.6%) urban and (14, 10.4%) rural. The residence of patients in dual disease group was distributed as (6, 100%) urban. The distribution of residence in healthy control group was (106, 82.8%) urban and (22, 17.2%) rural and finally the distribution of residence in asymptomatic Celiac disease group was (7, 58.3%) urban and (5, 41.7%) rural (*table 1*).

Gliadin autoantibody G/IgA

Results showed a highly significant differences in gliadin autoantibody G/IgA titers (P<0.01) among study groups. Dual disease group showed the highest mean value (85.5833 U/ml ± 128.05484) greater than upper limits (≥10 U/ml), indicating the peoples in this group have CD with GSD. Healthy control group revealed the lowest mean value (2.3539 U/ml ± 1.39199). GSD group showed G/IgA with a mean value (2.6373 U/ml ± 1.57917) and the mean value of CD group is (17.4 U/ml ± 8.74) (*fig. 2a*).

Gliadin specific immune marker (G/IgG) results indicated a substantial variation (P<0.01) between research groups. Dual disease group showed mean value (36.9167 U/ml ± 20.87165) greater than upper limits (≥10 U/ml), indicating that these patients have celiac disease (CD) with Gallstone disease (GSD). GSD group showed G/IgG with a mean value of (2.6873 U/ml ±1.65309), healthy control group revealed the lowest mean value (2.3789 U/ml ±1.56), and CD group showed mean value (13.7583 U/ml ±11.06) with a slight elevation more than upper limits (≥10 U/ml), (*fig. 2b*).

Figure 1 - Study groups stratified by age



	Gallstone	Celiac disease+ Gallstone	Control	Celiac disease
Age group (Year) 15-29	29.90%	33.30%	29.70%	33.30%
Age group (Year) 30-44	28.40%	33.30%	28.90%	33.30%
Age group (Year) 45-59	23.90%	33.30%	25.00%	16.70%
Age group (Year) 60-85	17.90%	0.00%	16.40%	16.70%

Age group (Year) 15-29 Age group (Year) 30-44 Age group (Year) 45-59 Age group (Year) 60-85

Table 1 - Study groups stratified by sex and residence

		Category				Total
		Gallstone disease	Silent Celiac disease	Celiac disease + Gallstone	Control	
Sex	Male	14 10.4%	0 0	0 0	14 10.9%	28 10.0%
	Female	120 89.6%	12 100.0%	6 100.0%	114 89.1%	252 90.0%
Residence	Urban	120 89.6%	7 58.3%	6 100.0%	106 82.8%	239 85.4%
	Rural	14 10.4%	5 41.7%	0 0	22 17.2%	41 14.6%
Total		134 100.0%	12 100.0%	6 100.0%	128 100.0%	280 100.0 %

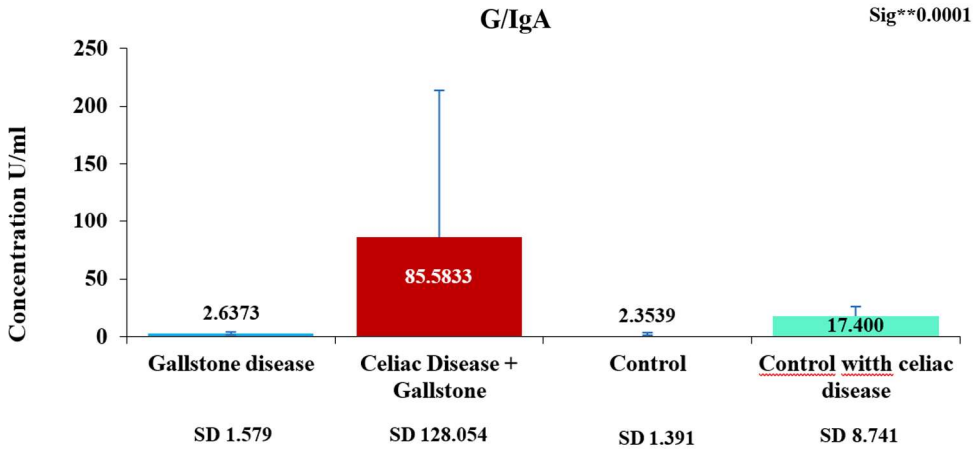


Figure 2 a - Level of G/IgA (U/ml) among study groups Gliadin autoantibody G/IgG

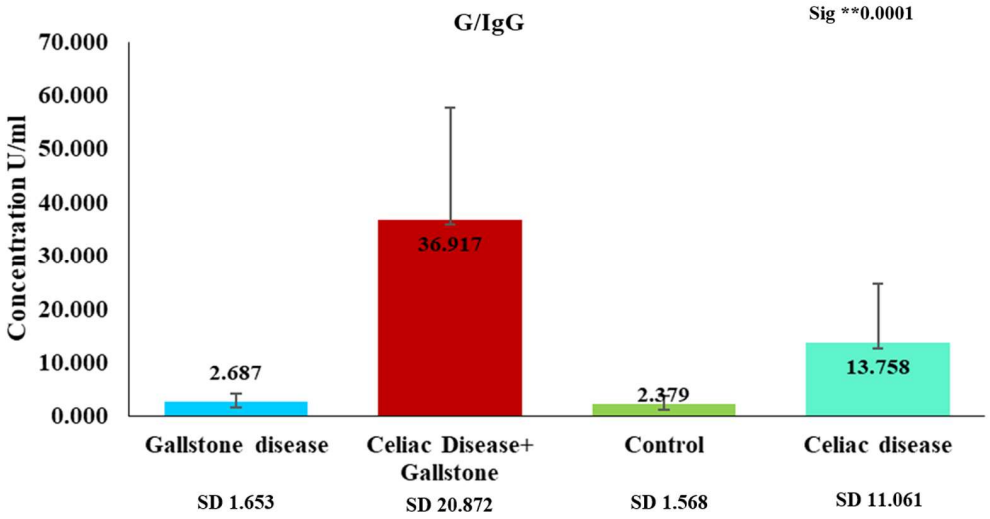


Figure 2 b - Level of G/IgG (U/ml) among study groups

Transglutaminase autoantibody T/IgA

Transglutaminase specific antibody marker (T/IgA) results revealed highly significant difference (P<0.01) between study groups. Dual disease group showed the highest mean value (74.85 U/ml ± 148.55) greater than upper limits (≥10 U/ml), indicating the people in this group have CD with GSD. GSD group showed the lowest mean value of tTG/IgA (2.05 U/ml ± 1.40) and silent CD group showed mean value of (8.73 U/ml ± 8.09), subsequently, healthy control group showed mean value of (2.46 U/ml ± 1.46) which are stay below upper limits of normal values (*fig. 3a*).

Transglutaminase autoantibody T/IgG

The results of (T/IgG) transglutaminase specific antibody markers revealed a highly significant difference (P<0.01) between study groups. Dual disease group showed a mean range greater than 7 U/ml, indicating that the T/IgG titer is slightly elevated more than the normal range below 7 U/ml (35). GSD group revealed T/IgG with a mean value of (2.06 U/ml ±1.34), dual disease group showed a mean value (8.61 U/ml ± 10.30), the control subjects group showed mean value (2.36 U/ml ±1.45), and asymptomatic Celiac disease group revealed mean value (6.40 U/ml ±8.36). Also,

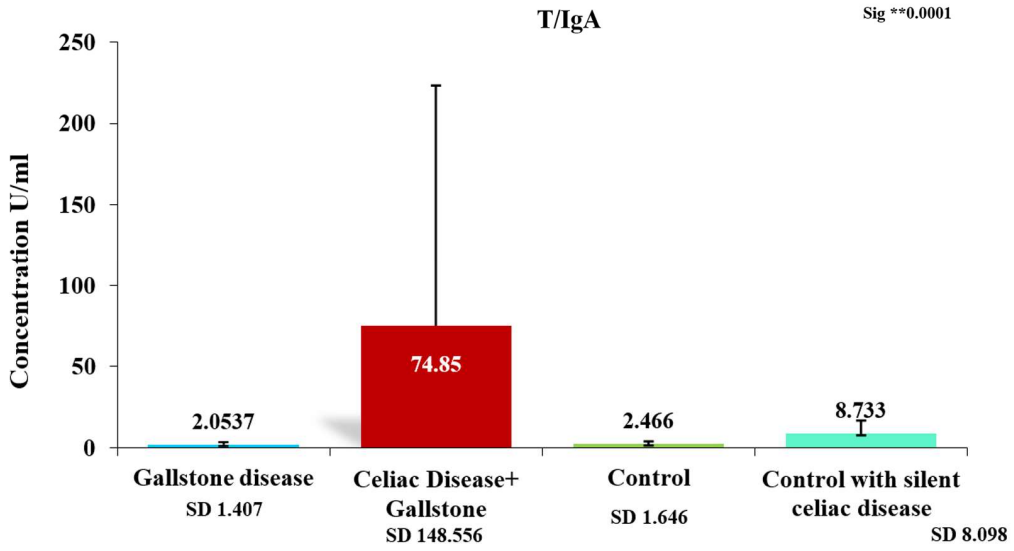


Figure 3 a - Level of T/IgA (U/ml) among study groups

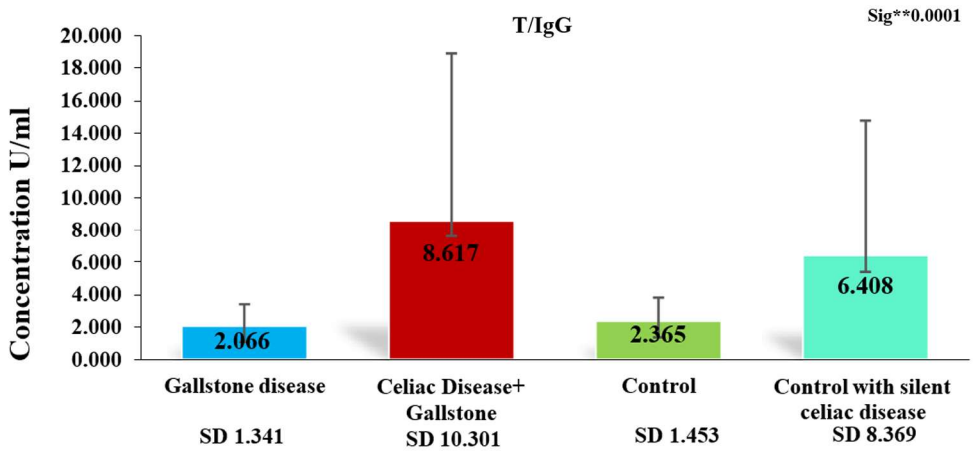


Figure 3 b - Level of T/IgG (U/ml) among study groups

dual disease group showed the highest mean value (8.61 U/ml ±10.30) while GSD group revealed the lowest mean value (2.06 U/ml ±1.34) (*fig. 3b*). Also, dual disease group showed the highest mean value (8.6167 U/ml ± 10.30134) while GSD group revealed the lowest mean value (2.0664 U/ml ± 1.34063).

Alanine aminotransferase enzyme (ALT)

Gallstones disease (GSD) group revealed Alanine aminotransferase enzyme (ALT) enzyme with a lowest mean value of (25.4552 U/L ± 29.30488), dual disease group showed a highest mean value (30.1667 U/L ± 13.57080), healthy control group showed a mean value (26.1016 U/L ± 13.26818), finally asymptomatic CD group revealed a mean value (29.25 U/L ± 20.66233). There was a very significant difference (P<0.01) between the research groups. The ALT enzyme was found to be within normal levels in all research groups, with really no evidence of an increase, (*fig. 4 a*).

Aspartate aminotransferase enzyme (AST)

The Gallstones disease group seemed to have an AST mean value of (31.9776 U/L ± 45.85929), the dual disease group seemed to have a mean value of (54.3333 U/L ± 50.85928), the control subjects' group had a mean value of (23.6563 U/L ± 12.84090), as well as the silent celiac disease group had an average value of (26.0 U/L ± 11.64630).

Collected data that explained in *fig. 4 b* was demonstrated insignificant differences (P>0.05) by comparison between study groups together. All study groups showed that AST enzyme have be within normal value and no one of them showed elevation except dual disease group that showed a slight elevation.

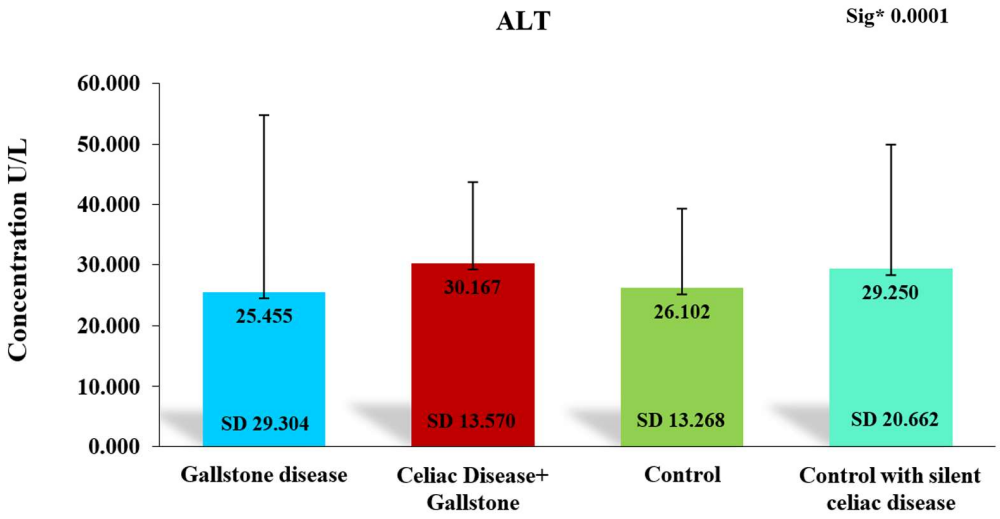


Figure 4 a - Level of ALT (U/L) among study groups

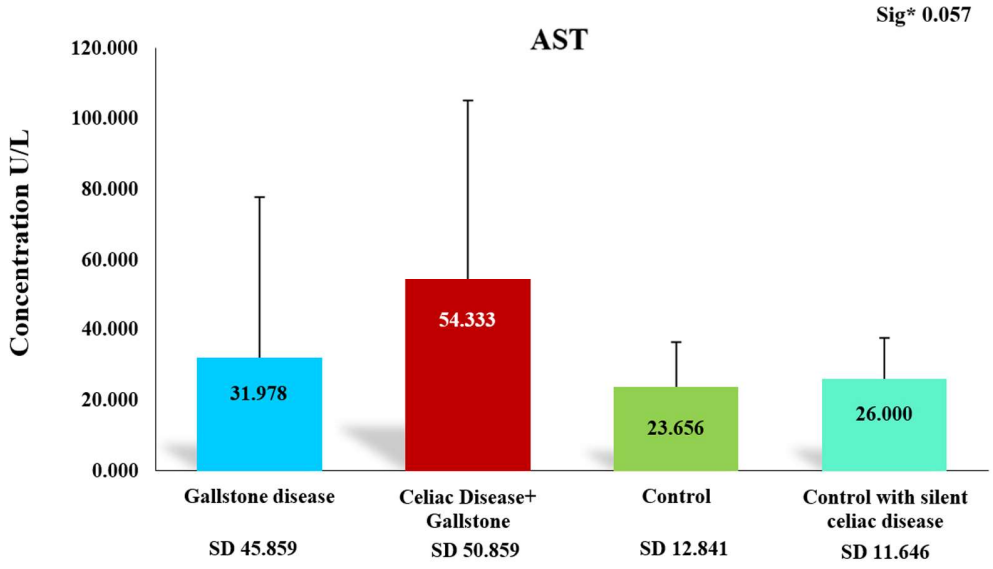


Figure 4 b - Level of AST (U/L) among study groups

Alkaline phosphatase enzyme (ALP)

The data obtained, as described in *fig. 4c*, showed statistically significant variations among research groups (P<0.01). Gallstones disease group had an ALP with a greatest mean value of (263.8134 U/L ± 123.91976), the dual disease group seemed to have a mean of (214.3333 U/L ± 69.54.327), the control patients' group seemed to have a mean of (136.6719 U/L ± 82.61705), and the silent celiac disease group seemed to have the lowest mean of (135.2500 U/L ± 71.64448), (*fig. 4c*). All study groups showed that ALP enzyme have be within normal value and no one of them showed elevation except GSD group that showed a light elevation. ALP enzyme elevation indicated biliary system injury.

DISCUSSION

According to Celiac disease-specific antibodies, a significant number of patients appear having atypical symptoms (asymptomatic CD) or even without symptoms (potential CD) (21).

It is clear that the age is considered as a predisposing

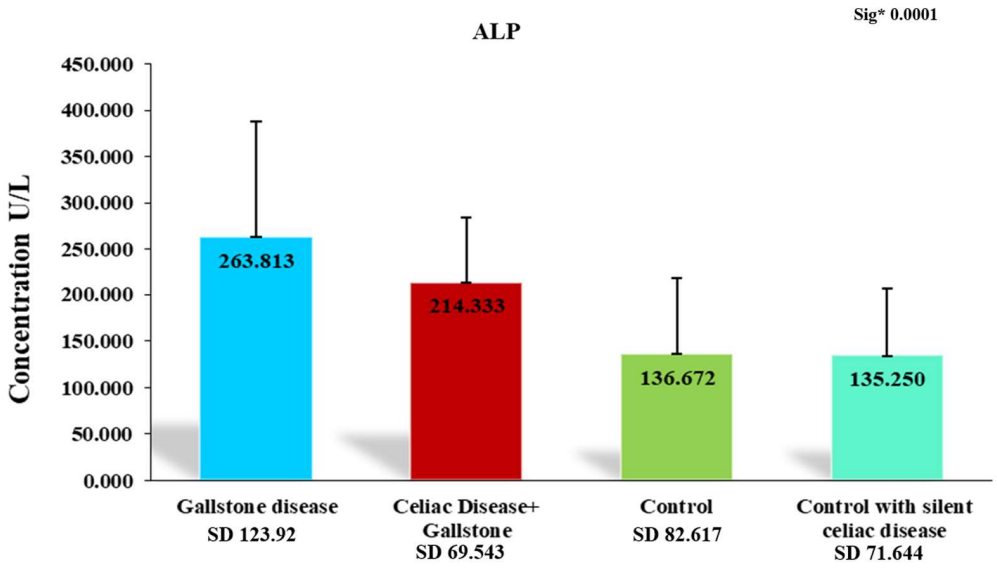


Figure 4 c - Level of ALP (U/L) among study groups

factor to the risk of gallstones and celiac disease incidence (22,23). The results of present study revealed age is closely related to gallstones disease (GSD) occurrence and show high frequency at patients younger than 50 years and the number of patients decreased in older age, but we noticed in our study, all patients have equal chance to get Celiac disease (CD) regardless the age. This may be related to the small population of CD group (24-28).

Some studies have proven different results, the prevalence of disease increase with age especially more than 60 years old with a Positive association between GSD trend and age has been revealed (29).

Age as a risk factor in population has a little effect on CD incidence; however, children population showed a significant disease occurrence relatively to adults (30, 31). In the present study, all age groups have equal chance to get CD and no correlation between age and disease, consequently, the effect of age may be related to metabolic disorder which synergized with CD. Moreover, CD occurred equally in all age groups approximately and decreased or not detected in old ages more than 60 years old.

Demographic parameters represented by the sex variation, the commonest sex that prone to have Gallstones disease (GSD) is female and the incidence in female more than male due to increasing bile cholesterol excretion and endogenous synthesis via female reproductive hormones that can induce gallstone development, as demonstrated by animal research and recently, testosterone has been linked to gallstone production in men. Number of births can increase the chance to get gallstones (32,33). This is in acceptance with our findings.

As a consequence, estrogens may increase the likelihood of GSD by increasing hepatic biliary cholesterol synthesis, which raises bile cholesterol saturation (34,35). Undiagnosed CD is more common in women than in men and increased risk of CD for female participants compared to male people involved is greater in children than in adults (36). By reviewing the previous results, we noticed sex as a predisposing factor plays a crucial role in GSD incidence and the sex effect on CD it is difficult to admit because of the number in this group was only 6 patients and healthy control group give rise only 12 asymptomatic patients. The ratio of female/male in healthy group was selected according to the ratio of female/male in GSD group.

By rechecking the residence findings in demographic results in this figure, 13 patients with CD, 7 patients (58.3%) from celiac group and 6 patients from dual disease group are residing in urban regions versus only 5(41.7%) patients are residing in rural regions. Also 126 patients with GSD, 120 patients (89.6%) from GSD group and 6 patients (100%) from dual disease group are residing in urban regions versus only 14 patients (10.4%) are residing in rural regions.

Patients with GSD in rural locations are frequently underserved and could not have the same access as their urban counterparts particularly health care (37). It was proposed that greater engagement to a Modern lifestyle, particularly increasing saturated fat with decreased fiber consumption, might be a potential factor for this. Increased BMI, in conjunction with increased urbanization, appears to be a significant potential factor in the genesis of GSD (37).

Rural populations have more disparities in health care because it has been founded that individuals who live in rural regions would be less likely to have healthy meal retail outlets and grocery stores, so it may be a requirement that comes with rural regions and is therefore not as widely reported as a restriction for such areas compared to urban areas (38).

The effect of residence on the disease was reviewed by previous studies (37,38) and these were in agreement with our study findings, it could reflect the impact of environment, nature of life, may be nature of nutrition and the level of education via the direct influence of these factors on disease discovering or progressing.

The findings of G/IgA indicated the patients in dual disease group have CD, while, asymptomatic CD group showed false seropositive result of gliadin autoantibody G/IgA due to negative result of T/IgA and this explained why patients in this group was asymptomatic. Another explanation for asymptomatic Celiac group they have slightly elevated titer and still asymptomatic, patients in this group may have the disease recently and need more time for titer elevation or they have gluten sensitivity without symptoms. By focusing on the mentioned results, elevation of anti-gliadin antibodies G/IgA, Multifoods more than its upper limits may precipitate GSD as a complication of CD.

Deamidated gliadin peptide-IgG (DGP-IgG) test is frequently used for CD screening. Tissue transglutaminase-IgA antibody is more sensitive and selective than DGP-IgG antibody (39). DGP-IgG is a sensitive method for CD discovering, especially in IgA deficient people. A positive DGP-IgG with presence of a negative T/IgA seems to have a low diagnostic accuracy for CD in children, although it can be increased in a number of non-celiac gastrointestinal diseases for unknown causes. Conjunction with digestive problems or biochemical signs of malabsorption or

inflammation (39). Positive G/IgG is difficult to be interpreted especially with negative T/IgA, Endoscopic duodenal biopsy was performed on forty individuals who tested positive for gliadin peptide G/IgG but negative for T/IgA, only one of those patients had CD verified by biopsy and this patient lacked IgA antibodies. Regarding separated G/IgG positive serology, this results in a positive predictive value about 2.5% (40). These studies were in agreement with our study findings.

The G/IgG assay had no effect on the diagnostic performance of the T/IgA test. The serology of T/IgA was favorably linked both for IgG and IgA gliadin peptide antibodies, with significant agreement with T/IgA and G/IgG and moderate correlation with G/IgA. G/IgG, but not IgA, was equivalent to T/IgA, indicating that it might be used as a reliable option for CD diagnosis and follow-up in case of T/IgA was positive (15).

Silent CD group showed insignificant difference with a slightly elevation of G/IgG titer with negative T/IgA that confirmed they are free of CD and they have either gluten sensitivity with non-inflammatory changes or patients have recently the disease without enteropathy or intestinal damage and no presence of histological modification like villous atrophy and crypt hyperplasia. It needs more time for titer elevation and induce bowel damage and make the symptoms obviously to appear in these group. Previous researches (39,40) that explored the association between anti-gliadin IgA and IgG with gallstones occurrence revealed a negligible correlation between them. Many studies included GIT and liver disorders such as IBS but did not include this correlation (41). Anti-gliadin autoantibodies (AGA) might be detected in non-celiac gluten sensitivity cases and considered as indicator of gluten sensitivity without giving any imagine about intestinal damage and enteropathy. GSD occurrence is closely related to intestinal dysmotility, intestinal enteropathy and villous atrophy as a result of CD and CCK neuropeptide secretion disturbance (41).

ALT level within dual disease group demonstrated insignificant difference and this pointing to a slightly effect of CD on aminotransamine enzyme. These findings contradicted previous research (42-44) that examined the effect of CD on aminotransamine enzymes. Gallstones effect is almost non-existent on ALT enzyme due to GSD group didn't show a significant difference with dual disease group and control group.

Obviously, hypertransaminemia refer to the elevation of hepatic transamine enzymes in multiple illness cases such as CD, sclerosing cholangitis and autoimmune hepatitis that may be associated with CD (44). Transaminase enzymes levels are higher in 9-42% of adult persons with CD and 24-40% of children with CD, according to studies. Furthermore, the incidence of unknown aminotransferase height in adults is proven to be 4% and 1.8% in kids. Increased liver enzymes could be the only result in Celiac disease; this could combine with non-alcoholic fatty liver disease (NAFLD), non-specific hepatitis, immunologic illness, and cholestatic liver problems (42). Elevated transaminases owing to CD are described as gluten-induced liver abnormalities hat often revert to baseline after 12 months of rigorous gluten-free eating (44). The liver is influenced to varying degrees in CD. Due to increased liver enzymes are remarkably common at the time of CD diagnosis, all clinically diagnosed cases with CD should be evaluated for hypertransaminemia (42).

When these patients were given a gluten-free diet (GFD), their ALT levels recovered to normal in (2.7%) of patients. After liver histopathology, hepatic cells didn't show pathognomonic findings rather than nonspecific or mild changes observed. Previous study conducted on 149 children of newly diagnosed with CD, liver pathological changes was found in 17 children and only 10 children had ALT enzyme elevation. Hepatic pathology represented as steatosis or liver enlargement that was detected at 12 patients. This study has documented there is a significant relation between IgA autoantibody against Transglutaminase 2 TG2 and ALT serum level (43).

Elevated value of ALP in the serum predicts the presence of stones, whereas elevated levels of liver testing process do not demonstrate disease because ALP is unique to the biliary system (44). Alkaline phosphatase (ALP) values might be normal or high in 4-20% of Celiac patients (45). ALP enzyme may be closely related to vitamin D level and parathyroid hormone PTH, since it inversely related to them and our study didn't asses vitamin D and PTH (46). The biliary system, in additional to the liver, can be significantly disrupted among CD patients; in addition, gallbladder function might vary in these individuals (47).

It is noticeable that ALP levels within the dual disease group revealed a significant correlation with CD, suggesting that CD has a little influence on enzyme levels and that gallstones have a direct effect on the biliary system.

CONCLUSION

Gallstones Disease had a potential effect on biliary system specific enzyme (ALP). Liver enzymes disturbances can be observed which associated with one of

diseases or both. We can distinguish between celiac and non-celiac gluten sensitivity by exclusion the immunological test. Anti-Gliadin test give an indication of gluten sensitivity and not for intestinal damage, also it has 95% sensitivity for CD and low specificity due to overlapping with another autoimmune disease.

Conflict of interests

The authors declare no conflict of interests.

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Predictive Value of Rectal Cancer Alarm Symptoms: Sudanese Population-Based Study

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ABSTRACT

Background: Rectal cancer is the most frequent malignancy of the gastrointestinal tract. However, statistical data are scarce regarding colonic tumor prevalence, location, or racial distribution in Sudan. Therefore, the main objective of this study is to identify the pattern of rectal cancer in Sudanese patients and to evaluate the symptoms or combination of symptoms that have a more significant prediction of rectal cancer.
Methods: A descriptive cross-sectional hospital-based study with a total of 200 patients was confirmed to have rectal cancer in the period between December 2013 and February 2016.
Results: A total of 200 patients were included. The number of males was 113(56.3%), and the mean age of patients in this study was 48 (±6.7). Rectal bleeding was found in 91.5% of the patients (n=183). The mean duration of rectal bleeding before seeking medical advice was 12 months ± 4 months. Half of the patients had rectal bleeding mixed with stool, 50.3% (n=100). Tenesmus (difficulty to pass stool) was found in 60.8% (n=121), and mucus discharge was found in 72.4% (n =144). The rectal bleeding and change in bowel habits, when combined, were found in 80.9% (n=161) (P value=0.04). When mucous discharge is added, the percentage jumps to 82.6 % (P value=0.01). Patients who had palpable rectal tumors were 78.9% (n=157). The location of the tumor, rectum, 64.3% (n=128).
Conclusion: Rectal bleeding, blood mixed with stool, change in bowel habits, tenesmus, and mucus discharge were the most typical presenting symptoms for rectal cancer. The combination of these symptoms has a higher prediction for rectal cancer.
Key words: rectal cancer; Sudanese patients; prediction; symptomatology; rectal bleeding.

INTRODUCTION

Colorectal cancer (CRC) is seen more in developed countries with a Western culture, where it is a significant source of morbidity and mortality worldwide (1-2). The highest CRC incidence rates are seen in New Zealand and Australia, then in the Americas, Europe, and Eastern Asia (3-5). In 2018, it is anticipated that 1,096,000 new cases of colon cancer will be diagnosed, compared to 704,000 new cases of rectal cancer (6). These represent 1.8 million new cases of CRC collectively. In 10 of the 191 countries throughout the world, CRC is the

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most common cancer among men to be diagnosed (7). Although colon cancer represented 5.4% of all new cases in Sudan in 2018, it has gotten less attention despite being the fourth most prevalent cancer overall due to less available data about incidence, demographic, clinical, and pathological features (8-9). Due to its more significant burden, breast cancer has received the majority of government attention in the fight against cancer in our country's strategies. The disease stage at diagnosis has a significant impact on the CRC prognosis (10). For CRC patients with localized stage disease, the 5-year survival rate is 90%, while for those with distant metastases is 10% (11-12). Consequently, improvements in screening and treatment have contributed to a decrease in disease-related deaths among the global population (1,13). Many countries have developed cancer screening guidelines and fast-track endoscopy for patients with alarm symptoms suggestive of CRC, like rectal bleeding, weight loss, and change in bowel habits in those more than 40 years of age, to accelerate early diagnosis and improve survival rates (14-15). The range of symptoms experienced by patients with colonic tumors is broad, ranging from very healthy patients with minor symptoms to those in danger of fecal peritonitis and bowel obstruction, which can be fatal (16-17). All studies available locally addressed the symptoms and signs of colorectal cancer in general. Furthermore, there is no clear hospital-based or population-based rectal cancer registry in our country. Therefore, epidemiologic hospital-based studies are of imperative importance since they may assist in planning wide-scale population-based studies. In addition, such studies can provide better insight and awareness of the changing nature and symptoms of tumors and differentiate them from benign colorectal conditions as early as possible (11,18). GPs have difficulty distinguishing symptoms that need an urgent professional evaluation from those that do not, such as those that could indicate colorectal cancer or other benign illnesses (19). Although frequently nonspecific, lower gastrointestinal symptoms are widespread in the general population and general practice. The issue is made more difficult by infectious disease signs on our side of the globe. Therefore, the main objective of this study is to identify the pattern of rectal cancer in Sudanese patients and to evaluate the symptoms or combination of symptoms that have a more significant prediction of rectal cancer (20).

MATERIALS AND METHODS

This cross-sectional descriptive hospital-based study on predictive symptoms of rectal cancer was carried out at Soba University Hospital, which has a high-volume center for overseas patients and referred oncological patients to colorectal surgeons in Sudan. The data covers all patients with rectal cancer who attended Soba University Hospital between December 2013 and February 2016, all patients with a histologically confirmed diagnosis of rectal cancer, and all patients who were diagnosed with carcinoma rectum attended the referring clinic, endoscopy unit, and surgical ward between December 2013 and February 2016. In addition, the data includes patients with no precise established pathological diagnosis of rectal cancer, patients with rectal cancer but cannot respond to questions, and patients with other colonic tumors. To collect data, the questionnaire's Arabic version was translated from its original English version. Cronbach's alpha was used to evaluate internal consistency, and kappa statistics was used to determine test-retest reliability for each item between the first and final surveys. To be considered internally consistent, our questionnaire required a Cronbach's value of >0.7. The English version was then translated into Arabic by a specialist fluent in both languages. Finally, a second independent translator, unaware of the original English version, reverse-translated the Arabic version into English. The principal investigator compared the primary translator and the back-translated version of the questionnaire. Data regarding their presenting symptoms and signs (i.e., perianal pain, discharge, itching, swelling, abdominal pain, diarrhea, constipation, tenesmus, weight loss, and anorexia), bedside examination, endoscopy results, and histopathology investigation were also recorded. patients' demographic data (i.e., age and gender), as well as the clinical (i.e., rectal bleeding amount, duration, and color) and histopathological (i.e., location, distance of tumor from anus and histology) features were evaluated. Microsoft Excel (Microsoft Corporation, Redmond, WA) was used to record all of the responses that were collected accurately. The responses were then coded and imported into the IBM Statistical Package for Social Sciences, Version 23 (SPSS Inc., Chicago, IL, USA) for data analysis. An impartial bio-statistician conducted the data analysis. Categorical data were represented using descriptive statistics in the form of frequencies and percentages utilizing appropriate tables and figures. The association between categorical variables was tested using Pearson's chi-square, and a p-value of 0.05 was considered statistically significant.

RESULTS

In this study, a total of 200 patients were included. The number of males was 113(56.3%) and females 87(43.7%), with a ratio of male to female 1.3:1. The mean age of the patients was 48 (±6.7) with 6% less than 25 (n=12), see *table 1*, with the majority of patients found between the age group of 45 to 65 years 41.2% (n=82).

Rectal bleeding was found in 91.5% of the patients (n=183). The mean duration of rectal bleeding before seeking medical advice was 12 months ± 4 months. It was bright red in 64.8% (n=129) and melaena in 24.1% (n=48). The amount of bleeding was categorized; 36.7 (n=73) described their bleeding as moderate in amount, 28.6% was small (n=57), and 21.6% (n=43) was a significant amount.

In half of the patients with rectal bleeding, the bleeding was mixed with stool at 50.3% (n=100). In addition, 23.6% have related bleeding to stool but not mixed with it (n=47), and 15.1% had rectal bleeding not related to stool (n=30).

Perianal symptoms: perianal pain was found in 68.8 % of patients (n= 137). Mucus discharge was reported in 72.4% (n =144), and Perianal itching was found in 16.1% (n=32).

Change in bowel habits was found in 87.9% of the patients (n=175). Tenesmus was found in 60.8% (n=121). Constipation alone was found in 48.7% (n=97), diarrhea only in 27.1% (n=54), and alternating diarrhea with constipation was found in 14.1% (n=28). The sensation of incomplete evacuation was mentioned by 40.7% (n=81).

Table 1 - Demographic characteristics

	Variables	Patients (%)
Age	15-25	12 (6)
	26-35	34 (17.1)
	36-45	41 (20.6)
	46-55	46 (23.1)
	56-65	36 (18.1)
	>65	30 (15.1)
Gender	Male	113 (56.3)
	Female	87 (43.7)

The rectal bleeding and change in bowel habits, when combined, were found in 80.9% (n=161) with a P value of 0. 004, see *fig. 1*. When mucous discharge was combined with rectal bleeding and a change in bowel habits, the percentage increased to 82.6 % (P value=0.001), see *fig. 2*. Abdominal pain was found in 74.9% of the patients (n=149), and all the patients described it as lower quadrant pain. Anorexia was found in 58.8% (n=117), while weight loss in 68.3% (n=136).

The patients with a previous diagnosis (misdiagnosis) for the same symptoms were 40.7%. They were diagnosed with dysentery (n=81) and 27.1 % with irritable bowel syndrome (IBS) (n=57). Only 14.1% of the patients have a positive family history of colorectal cancer (n=28). Digital rectal examination was done for all patients by inspection; 20.1% had perianal swelling (n=40), and the patients had palpable rectal mass 78.9% (n=157). The location of the tumor was as follows: rectum 64.3% (n=128), rectosigmoid 10.6% (n=21), anorectum 9% (n=18), and only 4% at the anus (n=8), see *table 2*.

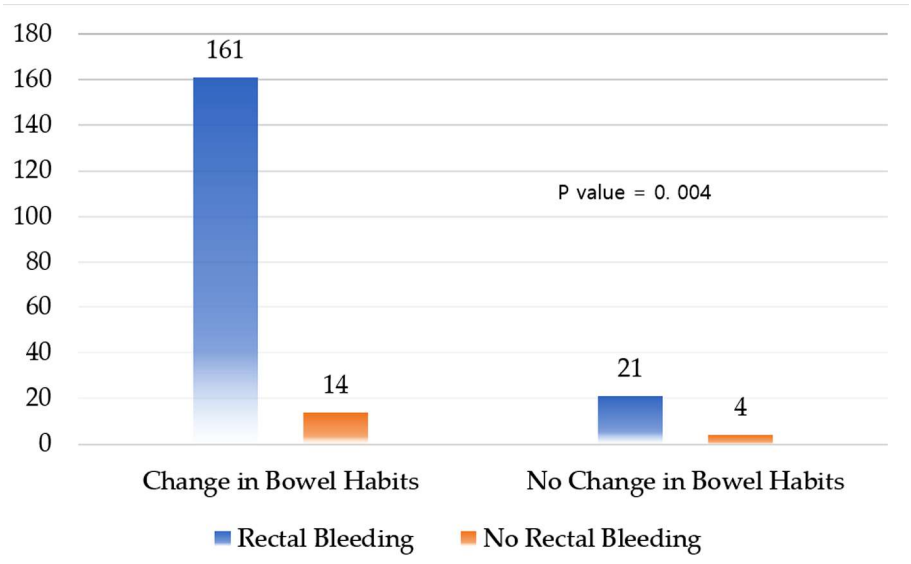
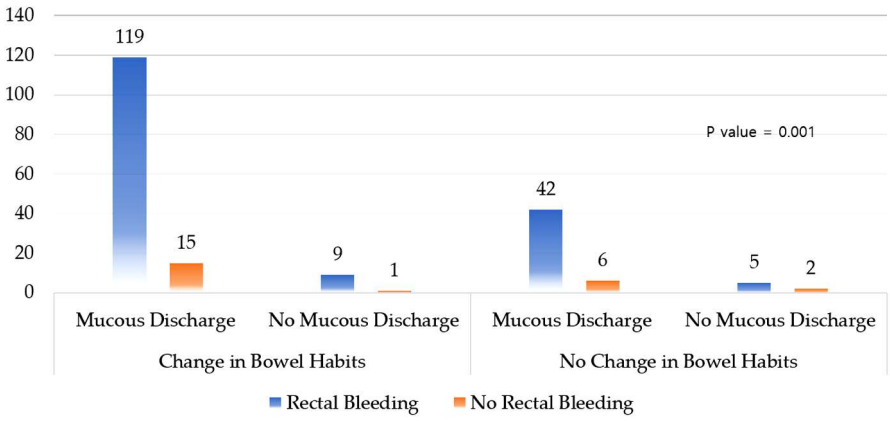


Figure 1 - Combined symptoms of rectal bleeding and change in bowel habits

Figure 2 - Combined symptoms of rectal bleeding, change in bowel habits, and mucous discharge



The digital rectal examination was done in all patients; the palpable tumor was found in 39.7% (n=79) up to 5 cm and more than 6 cm in 34.6% (n=69).

Table 2 - Clinical characteristics

Variables		Patients (%)
Rectal Bleeding		183 (91.5)
Duration (Year)		
	≤ 1	115 (62.8)
	1 >, ≤5	67 (36.6)
	5 >, ≤10	1 (0.6)
Amount		
	Large	43 (21.6)
	Moderate	73 (36.7)
	Small	57 (28.6)
Color		
	Bright red	129 (64.8)
	Melaena	48 (24.1)
Associated Symptoms		
Relation to Stool		
	Non	21 (10.6)
	Not related	30 (15.1)
	Mixed	100 (50.3)
	Related but not mixed	47 (23.6)
Perianal pain		137 (68.8)
Perianal discharge		144 (72.4)
Perianal swelling		40 (20.1)
Perianal itching		32 (16.1)
Change in bowel habits		175 (87.9)
Mainly diarrhea		54 (27.1)
Constipation		97 (48.7)
Alternating diarrhea		28 (14.1)
Tenesmus		121 (60.8)
Sensation of incomplete emptying		81 (40.7)
Abdominal pain		149 (74.9)
Anorexia		117 (58.8)
Weight loss		136 (68.3)
Dysentery		81 (40.7)
IBS		54 (27.1)
Family history of colorectal disease		28 (14.1)

Regarding the histopathology subtypes of cells, the result was as follows: well-differentiated adenocarcinoma in 28.1% (n=56), moderately differentiated adenocarcinoma found in 45.7% (n=91), poorly differentiated adenocarcinoma 10.1% (n=20), the mucinous adenocarcinoma 13.1%(n=26), and only 3% had small cell carcinoma (n=6), see *table 3*.

DISCUSSION

Colorectal cancer in Sudan is a dilemma. Although most previously published local and even international papers address the symptoms of colorectal cancer as all one disease, few works of literature focus on the symptoms of rectal cancer as a separate entity (3,8). In this study, we addressed the symptoms that have a high prediction of rectal cancer and studied the combination of these symptoms. The main difficulties facing our study were collecting data regarding the details of the symptoms and their duration before

Table 3 - Histopathology characteristics

Variables		Patients (%)
Histology		
	Well	56 (28.1)
	Moderate	91 (45.7)
	Poor	20 (10.1)
	Mucinous	26 (13.1)
	Small Cell	6 (3)
Palpable rectal mass		157 (78.9)
Site of Tumor		
	Rectum	128 (64.3)
	Anus	8 (4)
	Anorectal	18 (9)
	Rectosigmoid	21 (10.6)
Distance of Tumor (cm)		
	≤ 5	79 (39.7)
	6>, ≤ 10	69 (34.7)
	>10	21 (10.6)

patients sought medical advice.

The total number of patients diagnosed with rectal cancer included in this study was 200 patients who attended Soba University Hospital in the last three years. This number of patients is considered significant when compared to a previous study done by Suliman et al. at the same hospital between 2004 and 2009. They reported 138 patients of colorectal cancer, 63.8% of them at the rectum (9). The increase in the number of patients is due to the establishment of a colorectal unit and team with a new development in the hospital theatre and the increase in the capacity of the refer clinic and endoscopy unit. The rise in number is also due to the increased number of patients referred from all over the country.

The male-to-female ratio is 1.3:1. It is similar to the previous two studies done by Mutaz et al. at Ibn Sina Hospital (Khartoum) (8) and Husam et al. at Wad Madni Hospital (Gazira state) (3). According to Wu et al., in 28 population-based central cancer registries around the world that included 134 724 cases of colorectal cancer, the male-to-female ratios increased over time as people became older, and the ratios of proximal-to-distal CRC also increased over time (21). A second study by Saltzstein and Behling, using data from the California Cancer Registry and 213 383 cases, reached the same conclusion (22-23). They also claim that the left-to-right shift is stronger in Whites than in other racial/ethnic groups.

The age group in this study was between 15 years and 70 years. The mean of this age group is 48±6.7, with 6% of the patients less than 25 (n=12). Most patients are between 46 to 65 years, 41.2% (n=82). Several studies searched the age distribution among colorectal patients. According to Svensson et al., who conducted an age-period-cohort survey of 32 981 and 32 812 cases, respectively, for men and women, the age distribution varies for subsites and between the genders. Women are more likely to get proximal colon cancers than men are to develop distal colon and rectal cancers (24-25).

In the Middle East, a study from Egypt done by Gado et al. concluded that CRC rates among individuals under the age of 40 are relatively higher than those reported in the West (26). Locally, Ahmed et al. at the University of Gazira studied the pattern of colorectal cancer in Gazira state and noted that Sudanese patients were shown to be more likely to develop colorectal cancer at younger ages, with a peak frequency occurring in the fifth and sixth decades (27).

The most typical symptom in this study was rectal bleeding, which is a common symptom of colorectal cancer in general. In this study, 91.5% (n=183) of the patients had rectal bleeding. We study the rectal bleeding characteristics and duration before attending primary care. The duration of rectal bleeding was 12 months ± 4 months, which is a relatively long period. The patients reported the bleeding was bright red in 64.8% and dark in color in 24.1%. The amount of bleeding was also studied and categorized as large, moderate, or small. 36.7% described it as moderate bleeding, 28.6% as small, and 21.6% as significant.

There was 50.3% of patients had blood mixed with stool, 23.1% related but not mixed, and 15.1% had bleeding not related. In Wad Medani Hospital in Gazira state, Ahmed et al. described rectal bleeding as the main presenting symptom in 97.2%, as in this study (27).

A study conducted in Edinburgh by Roma et al. about predicting the risk of CRC in patients with rectal bleeding studied 604 patients referred to an access sigmoidoscopy clinic. They found that 22 patients have CRC, and they reported that rectal bleeding has low prediction in the primary care population, but when the blood is mixed with stool, there is a significant prediction for CRC (28). They also stated that the bright red bleeding not mixed with stool has a lower prediction for CRC, mainly when the hemorrhoid is found, but did not eliminate it; cancer was present in 2% of patients with these symptoms (28). In addition, a large meta-analysis conducted by Jellema et al. about the value of symptoms and another diagnostic test for predicting CRC in primary care found rectal bleeding in 13 studies from 47 primary diagnostic studies (19). According to a comparison of those with positive test results to those with negative test results, individuals with rectal bleeding and/or patients who have blood mixed with their stool have a slightly increased risk of developing colorectal cancer than those without. Additionally, it was noted that people with dark blood have a noticeably higher risk than those with normal blood (29). The above literature supports our findings that half the patients with bleeding had mixed with stool.

The change in bowel habit was reported in 87.9%, tenesmus was found in 60.8% of the patients, constipation in 48.7%, diarrhea in 27.1%, alternating diarrhea with constipation in 14.1%, and feeling of incomplete evacuation in 40.7%. Muatz et al. studied the presentation in IbnSina Hospital, and they found that 90.5% of 63 patients have a change in bowel habits and address it as the first symptom, more than rectal bleeding (8), while Ahmed et al. reported that rectal bleeding is more common than the change in bowel habit. Jellema et al., in their meta-analysis of 47 papers, 18 indicated a

high risk of CRC in patients with a change in bowel habits. Tenesmus is the most common symptom of the change in bowel habits in our study. This is the same for Mutaz et al., who found 63.5% of the patients with tenesmus (8). Furthermore, Ahmed et al. reported tenesmus in 77.8% of patients with rectal cancer (27).

In this study, mucous discharge was found in 72.4%. The perianal symptoms were also addressed in detail in this study. Anorectal pain is found in 68.8%, while perianal itching in 16.1%. Mutaz et al. reported mucus discharge in 77.8% of patients (8). He also reported perianal pain in 42.9%. In addition, five studies reported by Jellema studied the perianal symptoms. They categorize it into perianal itching, anal protrusion, and anal eczema (perianal changes due to itching and infection). These have a lower risk for CRC alone, but when eczema is found, the risk is high. Although mucous discharge is a common and essential symptom of rectal cancer, they reported mucus discharge as an informative significant risk for CRC (29).

Abdominal pain was reported in 75% of the patients, and all have lower abdominal pain. Mutaz et al. reported abdominal pain in 54.0% of the patients (8). They include both the left and right colon. Jellema et al. claimed that abdominal pain has lower sensitivity and specificity for CRC (29).

We also include anorexia as a symptom of cancer in general. We found it in 58.8% of the patients. We reported it early in the course of the disease before they started the neoadjuvant treatment. Weight loss was found in 68.3% of the patients. Ahmed et al. reported it to 26% of their patients (27). Family history for CRC was found positive in 14.1% of the patients. Ahmed et al. found it positive in 11.1% of the patients (8). Li et al. studied CRC as three distinct entities and revealed that the familial types varied. The two main familial types of CRC, FAP and HNPCC, indicate a propensity for proximal and distal locations, respectively (30).

The few investigations in the evaluation by Jellema et al. that included data on family history produced inconsistent diagnostic performance (29). To conclusively demonstrate the diagnostic performance of family history in a symptomatic patient, a precise definition of "positive family history" that details the number, age, and severity of afflicted family members is required (29).

In this study, as most patients presented late during the disease, we asked them if they had any medical consultation before primary care. We found that 40.7% of the patients were diagnosed as having dysentery, and 27.1% had irritable bowel syndrome (IBS). In addition, Roma et al. reported that IBS has a lower risk of colorectal cancer (28), though the patients in our study may have missed diagnoses.

A digital rectal examination was done for all patients. Palpable mass was found in 78.9% of patients; 39.7% of the tumor was below 5 cm, and 34.7% was above 6 cm. This stated that about half of the tumors could be detected by examination. This is an important fact that warns the doctor at the primary care level about the crucial role of digital rectal examination for any patient with lower abdominal symptoms. In addition, regarding the tumor's location, the rectum was found in 64.3%, rectosigmoid in 10.6%, anorectal in 9%, and anus in 4%. Suliman et al. reported in their study that 63.8% of the CRC tumor at the rectum and rectosigmoid. *Figs. 3* and *4* display the tumor location through colonoscopy and radiology evaluation (31). Also, Mutaz et al. reported that 54.1% of tumors were found in the rectum. This all supports that rectal tumors are the most common tumors. However, Ahmed et al. found rectal tumors in 29.0% of the patients (8).

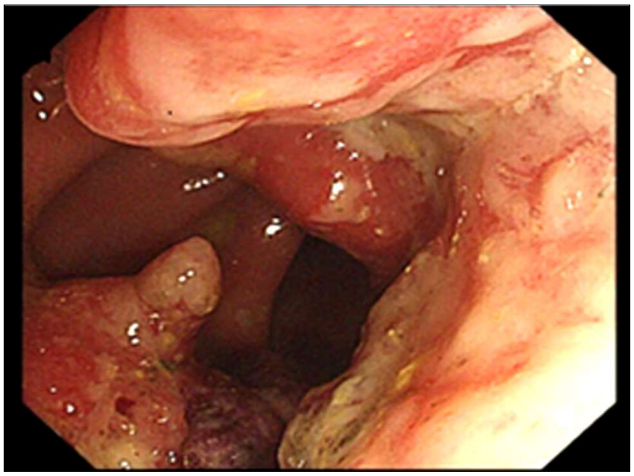


Figure 3 - The mass at rectosigmoid colon through colonoscopy (31)

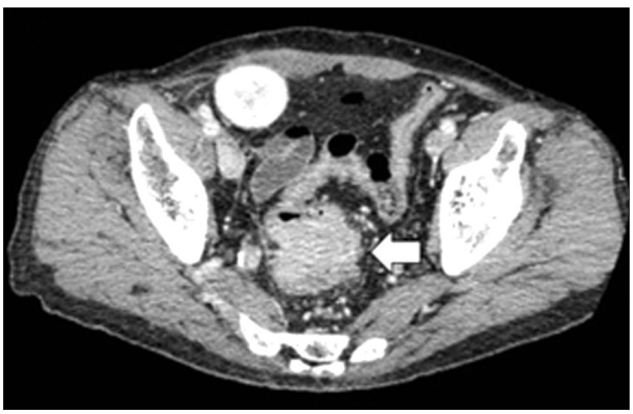


Figure 4 - The mass at the rectosigmoid colon through computerized tomography (31)

In addition, the most commonly diagnosed histopathology subtype is moderately differentiated adenocarcinoma at 45.7%, followed by well-differentiated adenocarcinoma at 28.1%, poorly differentiated adenocarcinoma at 10.1%, mucinous at 13.1%, and small cell in only 3%. Ahmed et al. found that well-differentiated adenocarcinoma is commonest (27).

In this study, we study the percentage of patients with combined symptoms. We found that of patients who had rectal bleeding, 92.0% of them had a change in bowel habits. The patients with two combined symptoms account for 80.9% of the total patients in the study (n=200). Roma et al. reported that the only symptoms connected to a higher risk of colorectal cancer were black blood, blood mixed with stool, or both of these (28). He also reported further that a mixture of dark blood and mixed blood with stool showed a higher positive likelihood for colorectal cancer. Roma et al. added further that alteration in bowel habits is another typical sign of colorectal cancer, but sensitivity and specificity are not high (28).

Several studies focused on patients diagnosed by their GP with rectal bleeding exhibit that the changes in bowel habits have been strongly linked to a diagnosis of colorectal cancer (28). In addition, Hamilton and Sharp concluded that rectal bleeding and changes in bowel habits have a substantial predictive value for colorectal cancer (29), (18). Thompson et al. also reported that when rectal bleeding is associated with a change in bowel habits, the probability of colorectal cancer rises from 6% to 12% (29).

In this study, we found that 93.1% of patients with a change in bowel habits and rectal bleeding had a mucous discharge. They account for 82.9% of the total (P values ‹0.005). According to Thompson et al., the probability rose to 20% when more details about perianal symptoms were gathered. However, the risk of colorectal cancer dropped from 6% to 1% when perianal symptoms were accompanied by rectal bleeding but not by a change in bowel habits.

Despite the limited diagnostic performance of individual signs and symptoms, Jellema et al. showed that because combinations of symptoms are frequent in primary care, they increase sensitivity at the expense of specificity. This also supports our results (29).

In conclusion, rectal bleeding is the primary symptom that colorectal cancer patients in Sudan most frequently experience, particularly those who are between the ages of 45 and 65. Furthermore, due to the great variety of symptoms, colorectal cancer is frequently misdiagnosed. Therefore, it is recommended that all physicians be made more aware of the potential for rectal cancer in this age range. Furthermore, more investigation is required to establish a connection between rectal bleeding in young people and rectal cancer.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Pancreaticoduodenectomy for De Novo Tumor of Ampulla of Vater Nine Years after Living-donor Liver Transplantation: A Case Report

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ABSTRACT

Background: De novo tumors after liver transplantation are recognized as a major cause of long-term mortalities. Ampulla of Vater tumor is a relatively uncommon tumor among all periampullary tumors. In the current report, we describe a rare case of successful resection of De Novo tumor of the ampulla of Vater nine years after living-donor liver transplantation (LDLT).
Case report: 57 years male patient underwent LDLT utilizing right hemi-liver graft nine years ago for hepatitis C virus related liver cirrhosis. He developed recent onset diabetes mellitus and abnormal elevation of serum liver functions. After detailed work up, endoscopic retrograde cholangio-pancreatography (ERCP) was performed and showed an ampullary mass that was biopsied. Endoscopic biopsy result was poorly differentiated adenocarcinoma of the Ampulla of Vater. The patient was discussed in multi-disciplinary meeting and the decision was to proceed for exploration for potential resection. Pancreaticoduodenectomy (PD) was performed with adequate lymph nodes dissection. Reconstruction was performed by pancreatico-gastrostmy over an internal stent, retrocolic choledocho-jejunostomy, and antecolic gastro-jejunostomy. The patient developed grade B postoperative pancreatic fistula that required ultrasound guided tube drainage for abdominal collection. The patient was discharged from hospital for regular follow up.
Conclusion: Liver transplant recipients are at high risk for the development of De novo tumors. Here, we presented a rare case of successful PD for De novo adenocarcinoma of the Ampulla of Vater nine years after LDLT. The current case supports the feasibility and eligibility of performing such major pancreatic resection among recipients after LDLT.
Key words: living-donor liver transplantation, De Novo tumors, Ampullary tumor, pancreatico-duodenectomy

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INTRODUCTION

De novo tumors after liver transplantation have been well recognized as a

major cause of long-term mortalities following cardiovascular complications (1,2). The incidence of de novo tumors after liver transplantation has been heterogenous among different studies. This is related to several factors including patient demographics, the underlying aetiology of liver transplantation, the immunosuppression protocol utilized, and the duration of follow up after liver transplantation (3,4). We previously reported that the incidence of de novo tumors among Egyptian patients after living-donor liver transplantation (LDLT) was 2.3% after a mean follow-up period of 41.2 ± 25.8 months, in area where hepatitis C viral infection (genotype 4) is the main underlying cause of liver cirrhosis (5).

Previous studies had identified a wide variety of de novo malignancies after solid organ transplantation. The most reported de novo malignancies after liver transplantation include post-transplantation lymphoproliferative disorders (PTLDs), and cutaneous cancers. Other malignancies were also reported including head and neck tumors, gynecological malignancies, Kaposi sarcoma, genitourinary tumors, and gastrointestinal tumors (6-8).

Periampullary neoplasms are recognized among the most lethal tumors worldwide. They represent the seventh leading cause of cancer-related mortality worldwide with mortality rate of almost 7.7 per 100,000 population in European countries and almost 7.6 per 100,000 population in North American countries (9,10). Ampulla of Vater tumor is a relatively uncommon tumor, accounting for almost 6% of all periampullary tumors (11). In most series, a high resectability rate has been reported, and the prognosis is more favorable than with other malignant tumors of the periampullary region after curative resection (11,12).

Pancreaticoduodenectomy (PD) for De novo periampullary tumors following living-donor liver transplantation had been addressed in few previous reports (13,14). To the best of our knowledge, PD for De novo tumors of ampulla of Vater after LDLT had been rarely reported (15).

In the current report, we describe a rare case of successful PD for De Novo tumor of ampulla of Vater nine years after LDLT. This work has been reported in line with the SCARE criteria (16).

CASE PRESENTATION

57 years male patient underwent LDLT utilizing right hemi-liver graft nine years ago for hepatitis C virus related liver cirrhosis. The actual graft weight was 1100 g and graft weight to recipient weight ratio (GRWR) was 1.33. The surgical technique regarding LDLT had been described previously (17). He had smooth postoperative course and was under routine follow up in outpatient clinic. He was maintained on a single agent immunosuppressive regimen (Tacrolimus). He developed recent onset diabetes mellitus (two months ago) that was controlled with regular insulin therapy.

The patient showed abnormal elevation of serum liver functions on follow up visit in the form of elevated serum total bilirubin 3.3 mg/dl, serum direct bilirubin 3 mg/dl, serum alkaline phosphatase 22 KAU, serum gamma glutamyl transferase 228, serum alanine aminotransferase 70 IU/ml and serum aspartate aminotransferase 92 IU/ml. Abdominal ultrasound showed healthy liver graft with mild dilatation of intrahepatic biliary radicals (IHBRs) and dilated common bile duct (CBD) up to 12 mm. Magnetic resonance cholangiopancreatography (MRCP) was ordered and showed dilatation of IHBRs, CBD (16 mm) down to a periampullary mass (*fig. 1 a*). Endoscopic retrograde cholangio-pancreatography (ERCP) was performed and showed an ampullary mass that was biopsied, and a stent was placed inside the CBD (*fig. 1 b,c*). Endoscopic biopsy result was poorly differentiated adenocarcinoma of the Ampulla of Vater.

Abdominal computed tomography (CT) was ordered average sized liver graft with uniform parenchyma with no focal lesions of abnormal enhancement. Mild enlarged spleen with normal density and enhancement. The biliary tree showed mild dilatation of IHBRs, dilated CBD up to 16 mm with stent inside down to ampullary mass measuring 2 × 2.2 cm without any vascular invasion (*fig. 2 a,b*). CT portography showed a normal course and contrast filling of the main portal vein with mild decrease caliber at the anastomotic site without stenosis (*fig. 2 c*). CT angiography showed normal course and contrast filling of hepatic arteries till the liver graft (*fig. 2 d*).

Positron emission tomography (PET-CT) study was ordered to rule out the presence of metastatic deposits. PET-CT showed glucose avid periampullary mass 2.4 × 2.8 cm with SUVmax of 32 (active tumor biology) without any nearby organ invasion. Few enlarged paraduodenal lymph nodes up to 1 cm in size eliciting increased tracer uptake with SUVmax of 5.5. No other metabolically active lesions were detected in the liver graft and other body organs (*fig. 2 e*).

The patient condition was discussed in multidisciplinary meeting and the decision was to proceed for exploration for potential resection of the ampullary lesion. Surgical exploration was done which showed

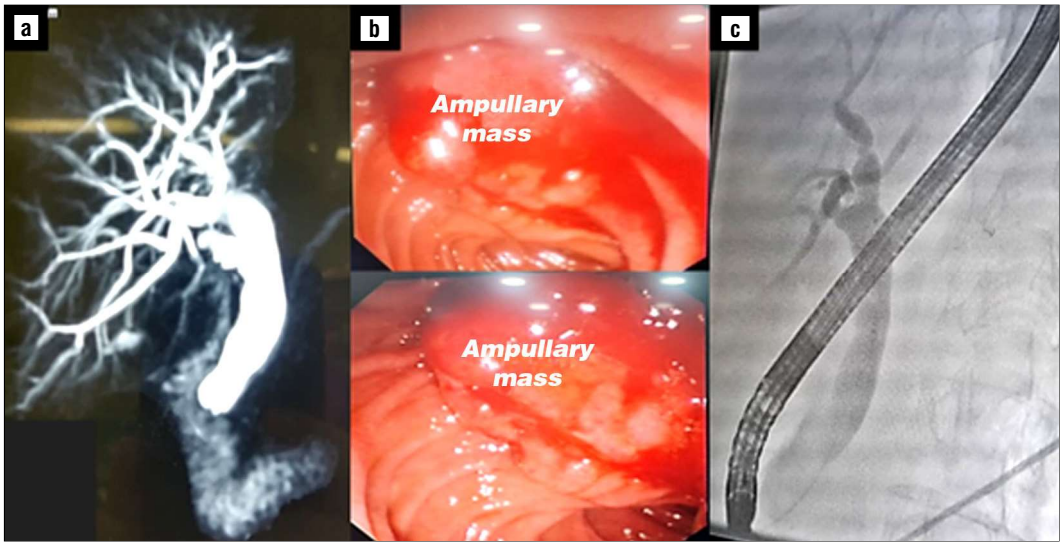

Figure 1 - (a) Preoperative magnetic resonance cholangio-pancreatography showing dilatation dilated intrahepatic biliary radicles and common bile duct down to a distal stricture. (b) - Endoscopic view during endoscopic retrograde cholangio-pancreatography showing a friable ampullary mass. (c) - Endoscopic retrograde cholangiography dilated intrahepatic biliary radicles and common bile duct down to a distal stricture.

moderate perihepatic adhesions that were completely dissected. After Kocher maneuver of the duodenum, an ampullary lesion about 2 cm in size was identified with no local vascular invasion or distant abdominal metastasis. Pancreaticoduodenectomy was performed with adequate lymph nodes dissection (*fig. 3 a*). Reconstruction was performed by pancreatico-gastrostomy in two layers utilizing Vicryl 3/0 interrupted sutures over an internal stent. Choledocho-jejunostomy was performed in end-to-side fashion utilizing PDS 5/0 continuous sutures. We utilized the recipient remnant bile duct because of adequate bleeding from cut end of the bile duct denoting adequate vascularity. Finally, antecolic gastro-jejunostomy was performed in side-to-side fashion utilizing Vicryl 3/0 continuous sutures (*fig. 3 b*). Total operation time was 4 hours. Operative blood loss was about 600 cc and one unit of red blood cells was transfused to the patient.

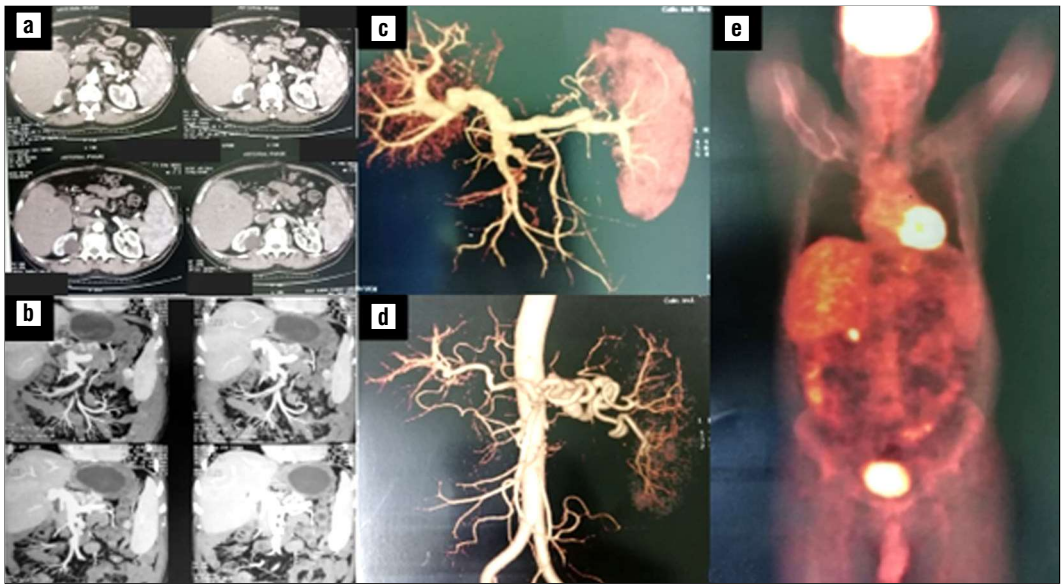

Figure 2 - (a,b) - Abdominal computed tomography (CT) showing an ampullary mass 2 X 2.2 cm. (c) - Preoperative CT portography. (d) - Preoperative CT angiography. (e) - Preoperative positron emission tomography showing glucose avid periampullary mass without other metabolically active lesions.

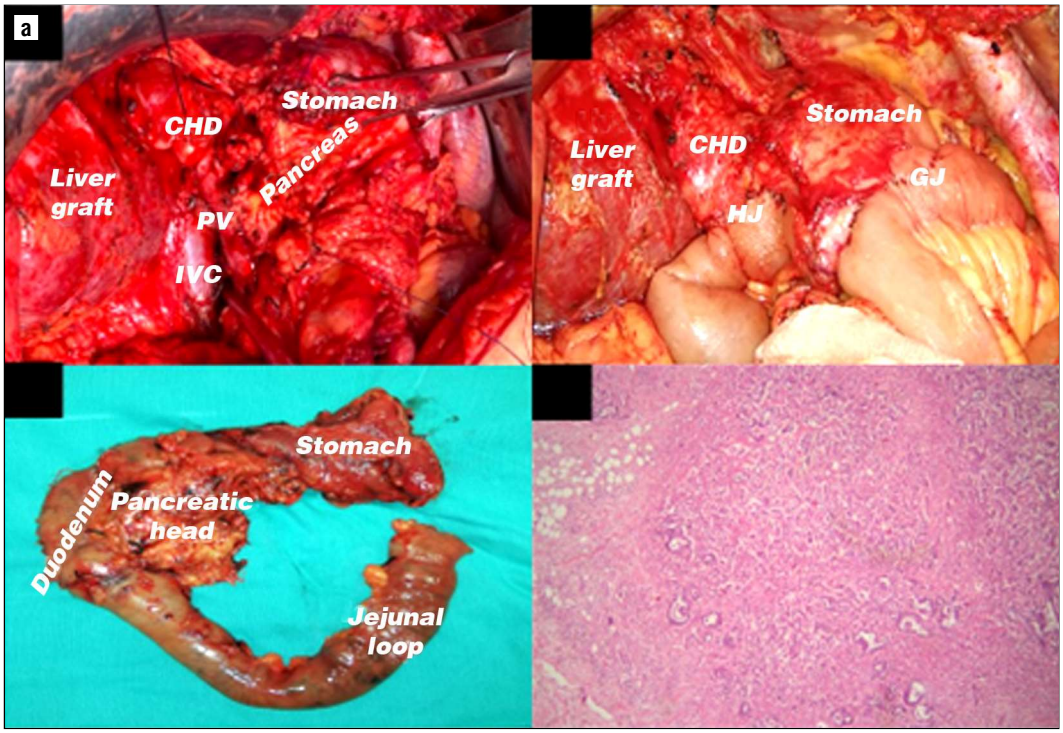

Figure 3 - (a) - Operative field after completing pancreatico-duodenectomy. (b) - Operative photo after completing reconstruction. (c) - Gross picture of the surgical specimen after completing pancreatico-duodenectomy. (d) - Microscopic examination of the specimen showing a moderately differentiated ampullary adenocarcinoma (H&E X40) (CHD, common hepatic duct; PV, portal vein; IVC, inferior vena cava; HJ, hepatico-jejunostomy; GJ, gastro-jejunostomy).

After surgery, the patient was transferred to the intensive care unit for monitoring of vital signs and abdominal drains. Afterwards, the patient was transferred for the ward for routine care till discharge. The patient developed grade B postoperative pancreatic fistula that required ultrasound guided tube drainage for abdominal collection. The patient was discharged from hospital for regular follow up. The patient was shifted from Tacrolimus monotherapy to Everolimus monotherapy afterwards. Postoperative pathological examination revealed a moderately differentiated ampullary adenocarcinoma infiltrating all the duodenal wall and encroaching pancreatic tissue (*fig. 3 d*). All surgical resection margins were free from tumor tissue. All dissected lymph nodes were free from tumor tissue. The tumor showed perivascular and perineural emboli.

DISCUSSION

Adenocarcinoma of the Ampulla of Vater is the second most common periampullary neoplasm. It one of the uncommon tumors and accounts for almost 0.2% of all gastrointestinal tract tumors (11). In the setting of post-LDLT De novo tumors, Ampulla of Vater adenocarcinoma is very rarely reported (15). In the current report, we describe a rare case of De novo adenocarcinoma of the Ampulla of Vater after LDLT that could be successfully managed with radical surgical excision.

Many challenges remain concerning the diagnosis and management of the Ampulla of Vater tumors. The diagnosis is mainly dependent on endoscopic biopsy. However, endoscopic biopsy fails to identify the presence of malignant tumor foci in about 12% to 40% of ampullary tumors. Also, the pathologic examination of the resected surgical specimens demonstrated concomitant adenomas in up to 80% of ampullary carcinomas (18,19). In the current case, our patient presented with laboratory abnormalities of early biliary obstruction allowing early endoscopic intervention by ERCP. Endoscopic biopsies confirmed the presence of adenocarcinoma of the Ampulla of Vater.

Major pancreatic resections for periampullary tumors after LDLT had been rarely reported in the literature (13-15). Major pancreatic operations, especially PD, after LDLT are always complex and technically demanding. This is attributed to the extensive postoperative surgical adhesions especially around the hepatoduodenal ligament. Also, the associated risks of accidental injuries to essential hepatic vascular structures like the portal vein and

hepatic artery (15). In the current study, performing PD for De novo adenocarcinoma of the Ampulla of Vater after LDLT was challenging. The tissues around the area of the hepatoduodenal ligament, the pancreatic head, and the porto-mesentric junction were soft and friable compared to the routine PD patients owing to the impact of the immunosuppressive medications. Meticulous dissection was performed with acceptable blood loss during the dissection stage and the patient required transfusion of only one unit of red blood cells.

Another important point to be clarified is the biliary reconstruction in PD after LDLT with duct-to-duct anastomosis. In this situation, it is not safe to remove the whole recipient extrahepatic bile duct till the hepatic hilum. So, division of the distal part of the recipient common bile duct is performed away from the site of previous duct-to-duct anastomosis. The vascularity of this segment of recipient bile duct remains a matter of debate. This issue had been raised by Na et al. in a previous report from ASAN Medical Center, Korea. They worried about the blood supply of the interposed portion of recipient bile between the graft bile duct and jejunal bowel loop. They recommended checking of retrograde arterial blood flow of this interposed portion of the common bile duct from the graft side. If the retrograde arterial blood flow is adequate, thus choledocho-jejunostomy could be safely performed (15). In the current report, we performed the same procedure and checked the retrograde arterial bleeding from the divided recipient bile duct. The vascularity of the recipient bile duct was adequate and allowed choledocho-jejunostomy to be performed safely. The patient did not suffer from biliary leakage after the operation.

Finally, the association between the development of De novo tumors and recurrent rejection episodes after solid organ transplantation is well demonstrated in previous studies (20-22). The development of rejection episodes will require higher doses of immunosuppression medications or addition of other anti-rejection therapies to transplant recipients. On the other hand, other studies did not find any significant difference in the incidence of De novo tumors among liver transplant recipients with and without rejection episodes (23). We previously reported the strong association of rejection episodes and the development of De novo tumors among liver transplant recipients (5). However, in the current study, the patient did not suffer from any clinically significant rejection episodes during the follow up period.

The patient was shifted from calcineurin inhibitor, as a primary immunosuppressant agent, to a mammalian target of rapamycin (mTOR) inhibitor owing to the expectation of anti-tumor effect of the mTOR inhibitor.

CONCLUSION

Liver transplant recipients are at high risk for the development of De novo tumors which are a leading cause of their long-term mortality. Here, we presented a rare case of successful PD for De novo adenocarcinoma of the Ampulla of Vater nine years after LDLT. The current case supports the feasibility and eligibility of performing such major pancreatic resection among recipients after LDLT.

Conflicts of interest / Competing interest

All authors declare no conflicts of interest.

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Consent to participate

Written informed consent was obtained from the patient of this case report.

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Rare Cause of Peritonitis - Perforated Duodenum Diverticulum

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ABSTRACT

Introduction: Perforated duodenum diverticulum is a rare, but life-threatening condition, and there are not well-established guidelines in the management of this disease. Worldwide, there are less than 200 reported cases of perforated duodenum diverticulum and its management has changed from immediate surgery to conservative treatment, in selected cases.
Case report: We present a case of a female patient treated in our department for duodenal (D2) diverticulum perforation. A diverticulectomy and duodenal suture with omental flap was performed, the patient had a favorable postoperative course, and she was discharged on the 7th day.
Discussions: Prevalence of duodenum diverticulum can be as high as 22%. Complications are rare and include inflammation, jaundice, pain, hemorrhage, or perforation. The symptoms and signs of perforation are not specific. In selected cases non-operative treatment was also used, but the standard management consists of surgery (diverticulectomy, duodenopancreatectomy).
Conclusions: When peritoneal irritation and generalized abdominal symptoms are present, surgery remains the elective treatment modality for perforated duodenum diverticulum.
Key words: perforated duodenum diverticulum, diverticulectomy, duodenopancreatectomy

INTRODUCTION

The duodenum is a common site for diverticula formation. Based on cadaveric studies, the prevalence of duodenal diverticula is estimated at 22% of the population, and this percentage increases with age, without differences being observed between the sexes. Most duodenal diverticula are asymptomatic and are discovered accidentally during investigations, such as upper digestive endoscopy or imaging investigations. 1-5% of duodenal diverticula present symptoms during life: pain, hemorrhage, inflammation, jaundice, cholangitis or perforation. Duodenal diverticulum perforation is a rare, but potentially fatal complication for the patient. In these cases, the treatment of choice is surgical intervention (1,2,3).

Perforation of the duodenal diverticulum is the rarest, but also the most severe complication, with an increased mortality rate: 3-30%. Until 2012, a total of 162 cases were reported worldwide (4,5,6).

Due to the low prevalence of perforation, it is often omitted in the diag-

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nostic process, and its symptoms are confused with another cause of acute abdomen. In some selected cases, the treatment can be non-surgical, or we can talk about a double surgical and endoscopic approach (5,7,8).

CASE REPORT

We present the case of a 82 years old female patient known to have essential arterial hypertension under treatment, varicose veins of the lower limb, kidney stones, osteoporosis, and nodules of the thyroid gland. She presented at the Emergency Department with a 5-hour history of epigastric pain and abdominal flatulence. The patient's blood pressure was 171/81 mmHg, pulse was 87 and saturation 97%. On physical examination abdominal distension and diffuse abdominal pain were revealed, with signs of peritoneal irritation. The lab test results showed a mildly increased white blood cell level. *Table 1* shows the results of the blood tests.

Table 1 - Initial blood test

Blood test	Results
Hemoglobin	11.9 g/dL
Hematocrit	37.2%
White blood cells	15.0 10^3/uL
Neutrophils	92.6%
Lymphocytes	1.63%
Monocytes	5.11%
Eosinophils	0.038%
Basophils	0.00%
Platelets	252.000/mm³
Amylase	154 U/L
Urea	47.08 mg/dL
Creatinine	0.87 mg/dL
Glucose	110 mg/dL
SGPT	10 U/L
SGOT	25 U/L
INR	1.04
Sodium	140 mmol/L
Kalium	4.92 mmol/L

Abbreviations: SGPT - serum glutamic pyruvic transaminase, SGOT - serum glutamic oxaloacetic transaminase, INR - international normalizes ratio

The abdominal and pelvic computed tomography showed a small amount of pneumoperitoneum around the gall bladder and on the side of duodenum, a thin blade of liquid around the liver and the right colon, and a few hydro aerial levels on the ileum and the coecum (*fig. 1*).

The preliminary diagnosis was perforated duodenal ulcer and we decided to do a laparotomy. After opening the peritoneum free liquid and peritoneal soiling were found, but without a perforated duodenal or gastric ulcer. We decided to insert methylene blue substance on the naso-gastric tube and examine the duodenum (*fig. 2*). After performing the Kocher maneuver, a perforated duodenum diverticulum was identified, at level D2, which measured around 3x3 cm (*fig. 3*).

The decision of manual diverticulectomy and duodenal suture, with omental flap was made (*fig. 4*). A drain tube was inserted around the duodenal suture and another drain in the rectouterine pouch.

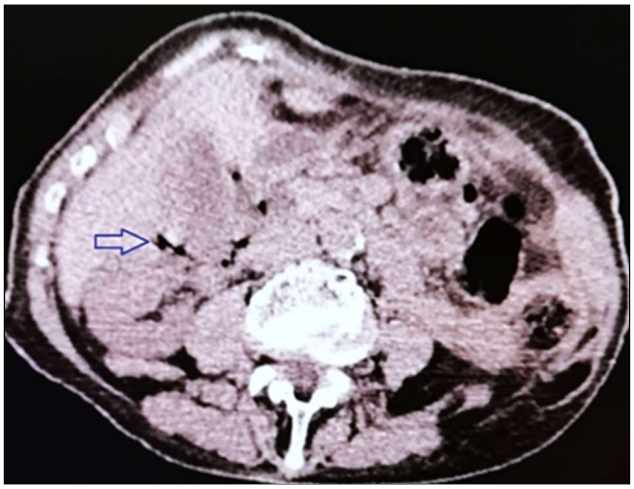

Figure 1 - Abdominal CT scan: pneumoperitoneum on the side of duodenum (marked with errow)

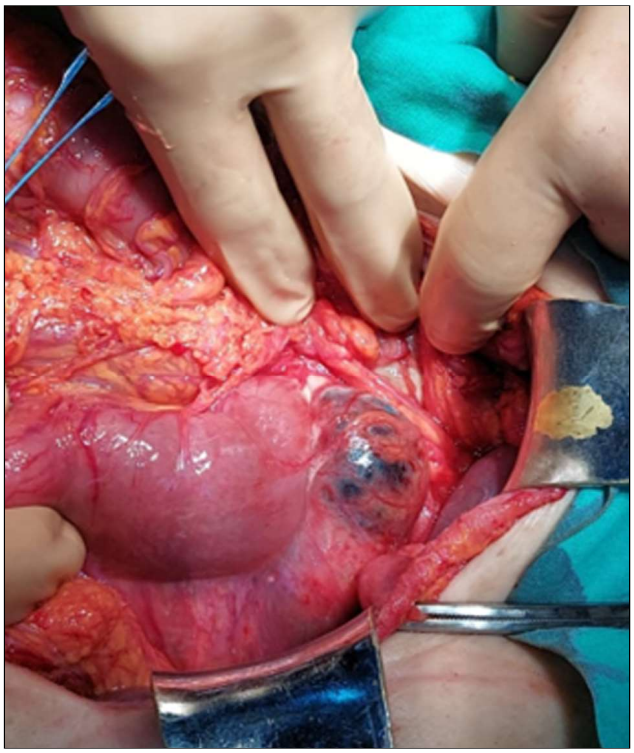

Figure 2 - The methylene blue substance externalized in the retroperitoneal space

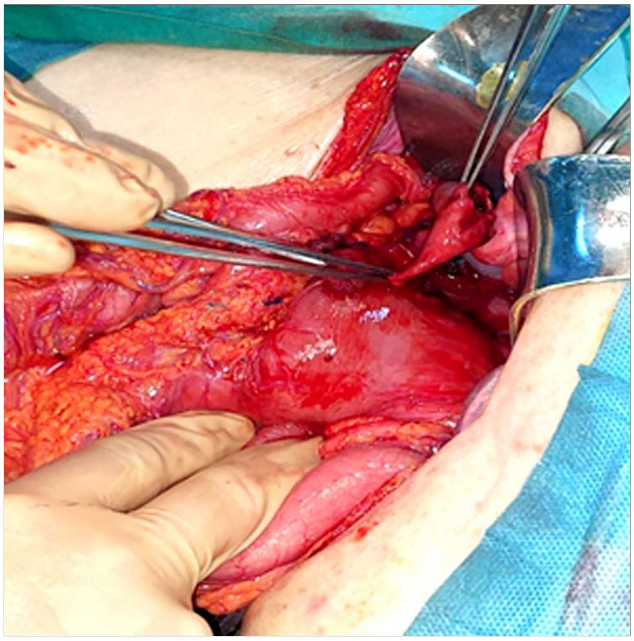

Figure 3 - Duodenum (D2) diverticulum

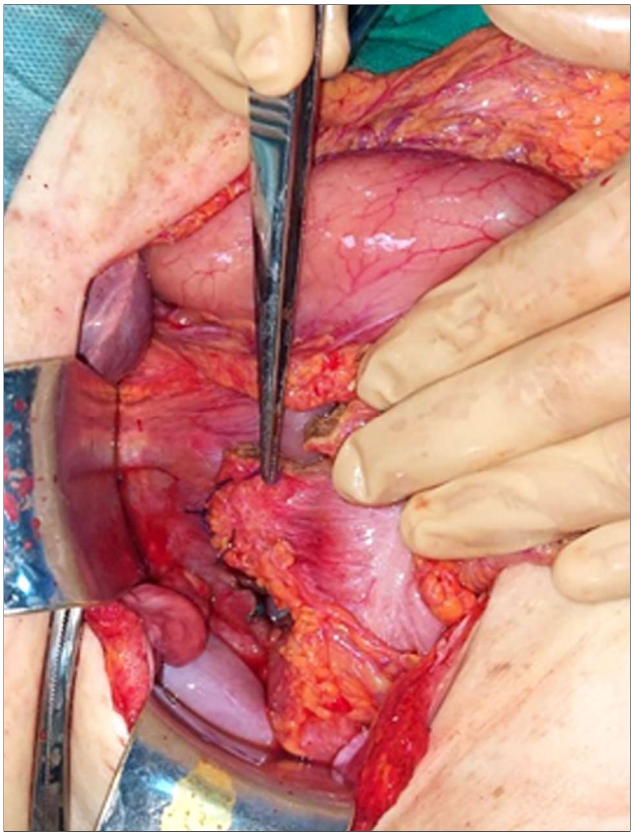

Figure 4 - Duodenal suture with omental flap

The naso-gastric tube was removed on the 4th post-operative day. The postoperative period was uneventful, the patient was discharged on the 7th day.

DISCUSSIONS

The duodenum is described as the second most common location for diverticula, followed by the colon. As far as the duodenum is concerned, the most frequent diverticula are localized in the second segment (D2), on the medial wall, around the ampulla of Vater. Their prevalence increases with age and no gender differences have been described. 85-90% of diverticula are solitary. Based on the described cases, the most common causes of perforation are diverticulitis (62%), enterolithiasis (10%), iatrogenic cause (5%), ulceration (5%), trauma (4%) and foreign body.

Regarding symptomatology, it is usually not pathognomonic. In most cases, the patient goes to the doctor because of abdominal pain. If it is an intra-peritoneal perforation, the pain will be in the epigastrium or in the right hypochondrium, but some patients may complain of back pain, especially if the perforation is retroperitoneal. Other possible symptoms can be fever, nausea, vomiting. In some cases, patients may report the presence of some signs and symptoms related to the presence of a duodenal diverticulum, for a longer period before the acute episode, such as weight loss, jaundice, or a feeling of satiety (9).

Symptoms can easily be attributed to other causes of acute abdomen, such as cholecystitis, biliary or pancreatic obstruction, pancreatitis, peptic ulcer, retro-cecal appendicitis, neoplasia, pancreatic pseudocyst, or colitis. Practically, it is impossible to differentiate pre-operatively between a duodenal ulcer and a perforated duodenal diverticulum, although the ulcer usually affects the bulb, and the diverticulum occurs more often in the second part of the duodenum (10).

In the diagnostic process, laboratory investigations are suggestive, but non-specific. Usually, the number of leukocytes increases, with neutrophilia. The level of inflammatory markers can help us in the positive diagnosis of the perforation, respectively in the post-operative follow-up.

Imaging investigations are necessary in the diagnostic process of patients with acute abdomen, and they can help us establish the indication for emergency surgical intervention. Native abdominal radiography and abdominal ultrasound can highlight the presence of free air in the subdiaphragmatic region in only 10% of cases. The most important imaging investigation in the case of perforation of the duodenal diverticulum is the abdominal CT, which can reveal small amounts of air or liquid in the abdominal

cavity, thinning of the intestinal walls, fatty infiltration, or the presence of abscesses, all of which may be present in the case of perforation of the duodenal diverticulum (1,12).

Until recently, the only treatment option in the case of perforation was surgical intervention, due to the high mortality rate. Several types of surgical interventions have been described, depending on the severity of the situation, respectively the location of the diverticulum and the perforation: diverticulectomy with mechanical or manual suture, in a single plane or double plane, with or without the use of omental flap, segmental and duodenal duodenectomy - jejunostomy, duodenal occlusion and biliary diversion, Whipple procedure with preservation of the pylorus (11).

The procedure chosen by us, diverticulectomy with double plan suture, can also have complications: damage to the common bile duct, the common pancreatic duct, duodenal fistula, sepsis, intra-abdominal abscess, or pancreatitis (12).

Being a rare complication, no conclusions can be drawn regarding the advantages or disadvantages of one surgical procedure, compared to others, and no consensus can be reached regarding surgical treatment. However, studying the literature and the meta-analyses done on this topic, one can observe a tendency towards conservative treatment, in well-selected cases. Kapp et al developed an algorithm, based on their study, which can be used in clinical practice, in the classification and stratification of the optimal treatment of patients with perforated duodenal diverticulum (5).

To summarize, the perforation of a duodenal diverticulum is a serious, potentially fatal complication. In the diagnostic process and treatment planning, the most important investigation is the abdominal CT with oral or intravenous contrast. In cases with signs and symptoms of peritonitis or pneumoperitoneum, the treatment of choice remains surgical intervention. A patient with a small perforation, located retro-peritoneally, with the local formation of a small abscess, without significant comorbidities or signs of septicemia, may be a candidate for conservative management. The treatment method must be individualized and chosen not only according to the listed criteria, but also according to the equipment of the health unit, respectively the experience of the surgeon and the presence of an interventional radiologist.

CONCLUSIONS

As numerous other studies conclude, it would be necessary to create a classification of perforation of the duodenal diverticulum, depending on the severity, to help the clinician in choosing the correct treatment method.

Conflict of interests

The authors declare no conflict of interest.

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Ethical statement

Written informed consent was obtained from the patient of this case report.

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A Case of Incarcerated Rectal Prolabsus due to an Unspecified Sigmoid Colon Tumor: Emergency Surgical Approach

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ABSTRACT

Rectal prolapse (RP) is a rare cause of anorectal emergencies. The etiology of RP is not clear. Many theories have been presented. Colorectal masses are uncommon causes of RP. Patients with high sphincter tonus may develop incarceration and strangulation which may require surgical intervention. If an undiagnosed mass is found in the prolapsed segment, pathologic evaluation is recommended. In cases where there is no pathologic diagnosis and urgent surgery is required, the surgical technique should be chosen considering the possibility of malignancy of the mass.
Key words: rectal prolapse, colon tumor, incarceration, strangulation

INTRODUCTION

Full-thickness prolapse of the rectum from the anus is called RP. Pain, incomplete defecation, rectal bleeding, mucous stools, and rarely strangulation may be observed with the prolapsed bowel segment from the anal canal. The annual incidence of rectal prolapse is 2.5 per 100 000 population (1). Although it is seen at any age, it is more common in women and especially in the elderly. The ratio of female to male is around 6-10/1 (2). There are studies reporting that it is more common in men in the young population as opposed to the elderly population (3). Rectal prolabsus is a disease of unclear etiology. Many theories have been proposed and it has also been tried to be explained by anatomical differences in the pelvic region. First Moschowitz developed the theory of sliding herniation from the pelvic floor in 1912 and performed the Moschowitz procedure accordingly (2). Genetic factors also affect rectal prolapse. Failure in fixation of the rectum to the sacrum, excessive straining habit, pelvic floor pathologies that occur with aging, sphincter weakness as a result of pudental nerve damage, long sigmoid colon, mobile mesorectum, relaxation of lateral ligaments, colorectal masses may cause rectal prolapse (2,3). Rectosigmoid colon tumors are rare causes of rectal prolapse. In patients with high sphincter tension, strangulation may occur with incarceration and urgent surgical treatment may be required.

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RP is diagnosed by clinical evaluation. The most common complaint is intermittent protrusion of the rectum from the anal canal. It is typical to see rings of the rectum in the prolapsed segment. The patient should be examined by straining. Colonoscopy, MRI defacography, barium enema, fluoroscopy, urodynamic tests can be used selectively to support the diagnosis and to identify associated pathologies. Especially in elderly patients, RP may be accompanied by a tumor and preoperative colonoscopy would be useful.

There is no standardized classification for RP. It is clinically divided into 3 groups (4)

- Full-thickness rectal prolapse; true prolapse;
- Rectal mucosal prolapse; only the mucosa is prolapsed;
- Rectal invagination is not a true prolapse. The rectum does not protrude from the anal verge.

CASE REPORT

Seventy-two-year-old female patient. She presented to the emergency department with rectal prolapse with an undiagnosed mass at the tip that could not be reduced for three days. Approximately 25 cm segment of the colon was prolapsed (*fig. 1*). On presentation, edema and occasional bleeding were seen in the prolapsed part. In the absence of necrosis, manual reduction was attempted under emergency conditions but was not successful. Because of pain and edema, it was planned to be reduced under anesthesia and taken to the operating room. Since the patient could not be reduced under any condition, anterior resection was planned. Reduction could not be achieved laparoscopically. On laparotomy, there was a 4 times diameter difference between the invaginated distal portion and the normal proximal colon segment (*fig. 2*). The incarcerated portion could be reduced into the abdomen by colotomy. Considering the diameter difference and the clinical condition of the patient, the patient underwent sigmoid colon resection and hartman procedure. The pathologic diagnosis was reported as well-differentiated adenocarcinoma on the basis of villous adenoma. The tumor had invaded the muscularis propria. One metastatic lymph node was detected in 19 lymph nodes (T2N1M0). Postoperative regimen was started on the 1st day and the patient was discharged on the 5th day. Colostomy was closed on the 3rd month. The patient who did not receive oncologic treatment voluntarily did not have any problem in the 48-month follow-up.

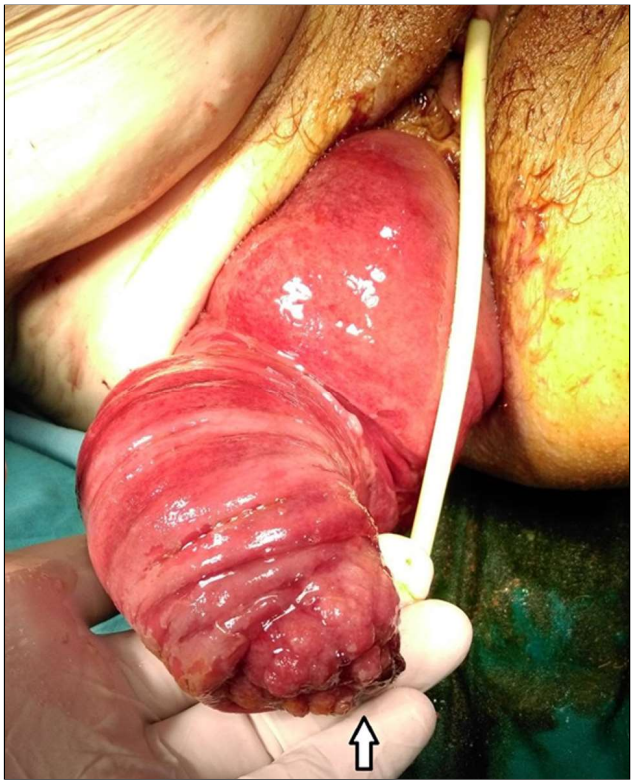

Figure 1 - Undiagnosed sigmoid colon mass causing RP by forming a leading point (white arrow)

DISCUSSION

Although rectal prolapse is benign, it is a disease that reduces the patient's quality of life. The clinical situation varies. The rectum may prolapse with or without defecation. The rectal mucosa is usually edematous and fragile. Small ulcerated areas and bleeding may be seen. Spontaneous reduction may occur in some patients, but manual reduction is required in others. It should be kept in mind that

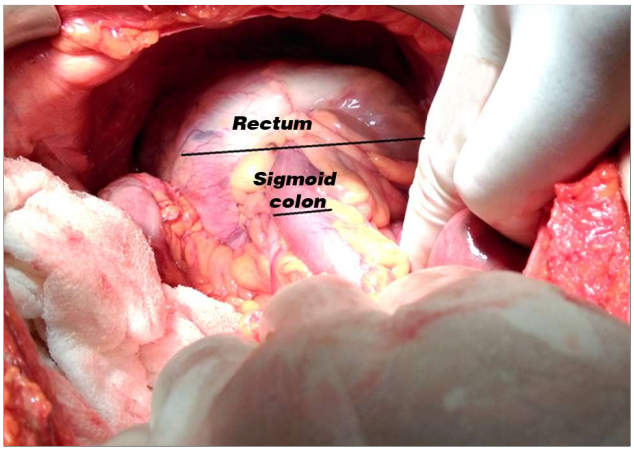

Figure 2 - Difference in diameter between two intestinal segments

recurrent episodes of prolapse may cause relaxation of the anal sphincter and fecal incontinence.

The etiology of rectal prolapse has been attributed to anatomical, mechanical, mental and neurologic causes but has not been fully explained. The most accepted theory is that an anatomical defect causes the disease with the effect of some predisposing factors (5). In their study, Sun et al. reported that the most common cause of rectal prolapse in the young population was the long rectosigmoid colon with 61% (5). After the development of prolapse, the idea that the increasing depth of anatomical problems (elongation of the mesocolon, deepening of the Douglas space, weakening of the pelvic floor muscles) is not the cause of prolapse but the result of prolapse has started to be accepted (2,6,7). As an opposing view, Attaallah et al. put forward the thesis that rectum length is the cause of prolapse, not the result of prolapse. In the study, patients with RP were compared with patients who underwent laparotomy for reasons other than RP and RP was significantly more common in patients with longer rectum length (8). Intussusception due to colon tumor is a rare but important condition. Sun et al. in their study of 44 patients, no rectosigmoid cancer was observed in any patient with rectal prolapse, while Rashid et al. in a retrospective study of 70 patients found a 5.7% association of rectosigmoid cancer in the etiology of rectal prolapse (5,9). In addition, the risk of colorectal cancer was found to be 4.2 times higher in patients with rectal prolapse compared to the control group (9). In case reports, the majority of patients with RP due to colorectal cancer were women like our patient (10). In our case, the pelvic floor was quite deepened and the sigmoid colon was elongated. It can be thought that the tumor in the sigmoid colon creates a leading point and causes intussusception with siphon effect, elongation of the mesocolon and sigmoid colon, and deepening of the pelvic floor. Progressive intussusception with the effect of constipation, peristalsis and straining develops prolapse.

Rectal prolapse is very rare in anorectal emergencies. Reduction by gentle manipulations with sedation and analgesia is recommended in patients who are not strangulated but cannot be reduced (11). Incarcerated or strangulated rectal prolapse is seen in 2-4% of cases (12). Strangule RP cases present with pain and bleeding. Necrosis and perforation may develop in cases without early intervention. In our case, the strangulated intestinal segment was edematous, hemorrhagic and painful. Intussusception had dragged the tumoral structure, which was the leading point, to the end of the prolapsed colon segment.Increasing edema and pain made reduction impossible. Although it could not be reduced even under anesthesia, necrosis and perforation were not seen. The RP could be reduced after laparotomy by performing colotomy proximal to the tumor site. Treatment of irreduced rectal prolapse is controversial. Sugar administration and simple reduction may be considered in conservative treatment approach. Surgical approach [rectopexy, resection by laparotomy, Delorme's procedure, perineal resection (Altemeiers' operation)] usually gives good results (13). The choice of surgical technique depends on the patient's clinic and the surgeon's experience and preference. We planned sigmoid colon resection in our case without a pathological diagnosis because of a suspicious tumoral mass in order to perform adequate mesenteric and lymphoid tissue excision (Emergency pathological evaluation could not be performed for the mass during the surgical procedure). Sülü et al. changed their decision of perineal approach and performed anterior resection in a similar case with a pathological diagnosis of adenocarcinoma (14). In the postoperative paraffin section examination, the mass was reported as adenocarcinoma, supporting the surgical procedure we performed. Colo-rectal anastamosis was considered risky in this case because of the 4 times diameter difference between the distal and proximal segments and the distal segment was edematous. In high-risk incarcerated RP cases who underwent perineal rectosigmoidectomy, 25% anastamotic leakage was observed (15). This supports our decision of colostomy.

CONCLUSION

Rectal prolapse is rare in anorectal emergencies. A review of the literature reveals a limited number of cases of RP due to sigmoid colon tumour. It should be kept in mind that one of the causes of rectal prolapse may be a colon tumour as in our case. Total colonoscopy and biopsy should be performed in cases of rectal prolapse caused by colorectal masses. Which surgical procedure to choose depends on the patient's clinic, time of presentation, the cause of RP (such as rectosigmoid cancer) and the hospital's facilities. In patients with RP due to a mass, without a pathologic diagnosis and presenting urgently, we believe that the mass should be considered malignant and oncologic surgery should be performed.

Conflict of interest

All authors declare that they have no conflict of interest.

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Ethical statement

Written informed consent was obtained from the patient of this case report.

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