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Evaluation of fundus first laparoscopic cholecystectomy in an obscured calot triangle: outcomes

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Abstract

Background: A fundus first laparoscopic cholecystectomy when performed by an experienced surgeon, provides the same level of safety and durability as an open cholecystectomy. When Calot's triangle cannot be safely dissected during laparoscopic cholecystectomy a rescue treatment is advised. Current revisions stress the importance of intraoperative observations in helping surgeons make a rescue decision and minimize additional harm.

Objective: To examines the fundus-first strategy in laparoscopic cholecystectomy in an indistinct Calot's triangle and the patient's clinical outcome.

Patients and Methods: This is a prospective study that was done in Rizgary Teaching Hospital from January 1st, 2020 to December 31st, 2022, on 68 cases who underwent laparoscopic cholecystectomy where Calot's triangle was difficult to distinguish during the operation. Fundus: first dissection of the gall bladder down to the infundibulum and after safe ligation of the gall bladder stump and good hemostasis of the liver bed, the gallbladder is removed via a 10-mm port. This research looked at the duration of operation, postoperative pain, rate of conversion to open surgery and duration of the hospital stay.

Results: Among 68 cases of fundus first laparoscopic cholecystectomy most of the patients were female 45(66.17%) and 23(33.82%) were male, majority of cases were between 31 and 50 years old, with a mean age of 39±10.44, and the majority of patients were complaining of inflammation with fibrosis at the site of the cystic duct. The duration of operation ranged from 45-60 minutes in 16(23.52%) and 60-80 minutes in 20(29.41%) cases and 130-140 minutes in 2(2.94%) cases. The majority of our cases remained in the hospital and ambulated on day 3-5, and the main hospital stay was 4.68±1.8 days. There was statistical significance in the age distribution with a P-value 0.04.

Conclusion: Fundus first laparoscopic cholecystectomy remains a feasible and safe procedure. Surgeon experience and judgement affects the operative time, conversion rate, morbidity and hospital stay in difficult and obscured Calot's triangle.

Keywords: Difficult Calot's, Fundus first laparoscopic cholecystectomy, Gall stones.

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Introduction

Laparoscopic cholecystectomy (LC) is now the gold standard for the management of symptomatic gallstones and acute cholecystitis unless there are major contraindications or patients with comorbidities. Biliary anatomy, as well as laparoscopic cholecystectomy's access and dissection procedures, may vary greatly. The fundus-first dissection method of open cholecystectomy was originally suggested by French surgeons. The current LC approach was developed in 1988, and it was available as an ambulatory option (1). Calot's triangle is the traditional starting point for LC, followed by porta hepatis structural identification and then dissection to the fundus (2). When at least half of patients have trouble dissecting because of fibrosis brought on by multiple inflammations or because their anatomy is different (3). A Common bile duct injury is the most dangerous complication of LC since it requires sophisticated operations to deal with such an injury and has substantial consequences for the patient's health (4,5).

When Calot's triangle is not possible to dissect first in cholecystectomy, and only the gall bladder's fundus is exposed, then a rescue treatment is advised (6,7). Current revisions stress the importance of intraoperative observations in helping surgeons make a rescue decision and minimize additional harm. When compared to open cholecystectomy, the safety and durability of fundus first laparoscopy for cholecystectomy (FFLC) are almost identical (8).

Previous reports from the United Kingdom quoted that cholelithiasis affects 10–15% of the adult population, with the vast majority displaying no symptoms (9). In the surgical management of symptomatic cholelithiasis, LC remains the gold standard. Indications include biliary colic, cholecystitis, common bile duct stones, and biliary dyskinesia (10). Severe complications may arise even during a routine cholecystectomy (11). Due to severe adhesions and fibrosis, difficulty distinguishing key anatomical structures from the critical view of safety increases surgical risk and is the most common reason for conversion to open cholecystectomy (12). In addition, technique conversion is associated with a significantly increased incidence of postoperative complications (13).

In the fundus-first (FF) approach, the dissection begins from the fundus of the GB to the infundibulum make identifying the structures within Calot's triangle simpler for the operating surgeon (14).

This study has the potential to help us minimize hospital burdens by shortening hospital stays, lowering bed occupancy rates, and speeding up surgical procedures (15,16). Junior surgeons lack open surgery expertise in the age of minimally invasive surgery.

This may cause an increase in the incidence of common bile duct (CBD) transection or resection (17).

Clipping or cutting any structure before unequivocal identification of the structure is a mandatory component of the safe LC procedure, as is using the safest surgical technique (not the fastest) that is currently available, such as the critical view technique of Strasberg et al. with the circumferential dissecting of GB at the infundibulum to mimic the retrograde laparoscopic cholecystectomy (RLC) technique of the open era (18).

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However, conversion is linked to higher costs and both short- and long-term morbidity, thus a low threshold for conversion is not always indicative of efficient practice (19) . Retrograde or "fundus first" dissection was often utilized by surgeons during the days of open surgery, however, some surgeons only used it as a defensive measure in really difficult situations (20).

In most cases, retrograde dissection is used to turn a laparoscopic procedure into an open surgery. In the beginning of LC, when only fundamental instruments were available, RLC may have been underutilized. However, with the widespread availability of laparoscopic liver retractors, it is now possible to mobilize the gallbladder fundus-first while the liver is supported by a retractor and prevent the liver from traction during the procedure otherwise it will be difficult to use the fundus-first approach in LC (21).

This study aims to perform the fundus-first strategy in laparoscopic cholecystectomy when the calot's triangle is obscured and assesses its impact on the patient's clinical outcome.

Patients and Methods

This prospective study was done at Rizgary Teaching Hospital from January 1st, 2020 to December 31st, 2022 on 68 cases who underwent laparoscopic cholecystectomy during which it was difficult to define Calot's triangle.

Patients who were diagnosed with cholelithiasis were required to meet the inclusion criteria .

The criteria for exclusion include the age group known as pediatrics, individuals who are unsuitable for receiving general anesthesia, individuals who are suffering from choledocholithiasis and easy accessible laparoscopic cholecystectomies.

Patients underwent a full history and clinical examinations to find out risk factors like obesity, diabetes, thyroid diseases, ischemic heart disease, and chronic obstructive lung disease. These patients were subjected to routine and special laboratory and radiological investigations including CT and MRI. After a full explanation of the procedure, informed consent was taken and recorded and these patients were operated on under general anaesthesia. An appropriate dose of prophylactic antibiotics, 3rd generation cephalosporin and Metronidazole, was administered 30 minutes prior to the first incision of the skin.

In cases where the calot's triangle was obscured during laparoscopic cholecystectomy, the choice to proceed with the fundus-first method was made, and the underlying causes were documented. Hemostasis was performed using cautery or suturing, if needed, and the gallbladder stump was handled via cutting or trans-fixation sutures. In each instance, a subhepatic drain was placed. Fundus-first laparoscopic cholecystectomy indications, intraoperative complications and management, conversion to open cholecystectomy and reasons for conversion, postoperative pain assessment (VAS scale), oral feeding initiation, drainage, drain removal, ambulation, and length of hospital stay were all recorded. Patient's stay in the hospital and discharged when bowel sound is positive, the fully mobilized and drains are removed.

Patients were asked to put a finger on a scale from 0 to 10 (0= no pain and 10= severe pain) to rate their level of pain after surgery and

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throughout follow-up, with a high score indicating more severe pain.

Surgical Technique

In the FFLC, with the four-port technique, a telescope and camera monitor were used as standard in all cases and underwent the operations. Intraoperatively when Calot's triangle is obscured the fundus is first approached by elevating the liver with a liver retractor (Nathenson retractor). Dissection was performed by first incising the visceral peritoneum with a hook from the infundibulum away from Calot's triangle down the gallbladder bed to the fundus, and then working backwards from the fundus to the infundibulum. This procedure resulted in the cystic artery and duct leaving the gallbladder in a pedunculated position. The duct and the artery of the gall bladder were identified and stapled. The gallbladder is removed from the abdomen via the 10-mm port after good hemostasis of the liver bed.

Statistical Analysis

The data were tabulated on a specially designed questionnaire, collected and entered into a computer via a Microsoft Excel worksheet (Excel 2016) and then analyzed using an appropriate data system which is called Statistical Package for Social Sciences (SPSS) version 28 were compared between patients with different variables and a P-value of $\leq$ 0.05 was considered statistically significance. The results are presented as rates, ratio, frequencies, percentages in tables and figures and analyzed using t-test, and Chi square tests.

Results

Among 68 cases the majority of patients who were candidates for fundus first laparoscopic cholecystectomy were female 45(66.17%) and 23(33.82%) were male. The majority of cases were between 31 and 50 years old, with a mean age of 39±10.44 as shown in Table (1).

Table (1): Age and Sex Distribution

Age / Year	Male	Female	Total (Percentage)
21-30	3	3	6 (8.82%)
31-40 *	9	19	28(41.17%)
41-50 *	7	16	23(33.82%)
51-60	2	4	6 (8.82%)
61-70	2	3	5 (7.35%)
Total	23(33.82%)	45(66.17%)	68(100%)

* Significant correlation between Age group 31-50 to genders P value 0.04

Regarding the indication of shifting to the fundus first technique the majority of patients had inflammation with fibrosis at the site of the cystic duct. as illustrated in Table (2).

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Table (2): Fundus first technique according to the indications

Indications	Number of patients	Percentage
Mild inflammations and fibrosis at the cystic duct pedicle	45	66.17%
Obscured (CVS) because of disfigured anatomy	6	8.82%
A large stone in Hartman's pouch , adherence with the dilated cystic duct	7	10.29%
Contracted gall bladder or fibrosis	6	8.82%
Mirizzi syndrome	4	5.88%

*No significant correlations found between these indications P vale 0.055

The Mean operation time was 96.74±18.23 minutes and the duration of operation ranged from 45-60 minutes in 16(23.52%) and 60-80 minutes in 20(29.41%) cases and 130-140 minutes in 2(2.94%) cases as shown in Figure (1).

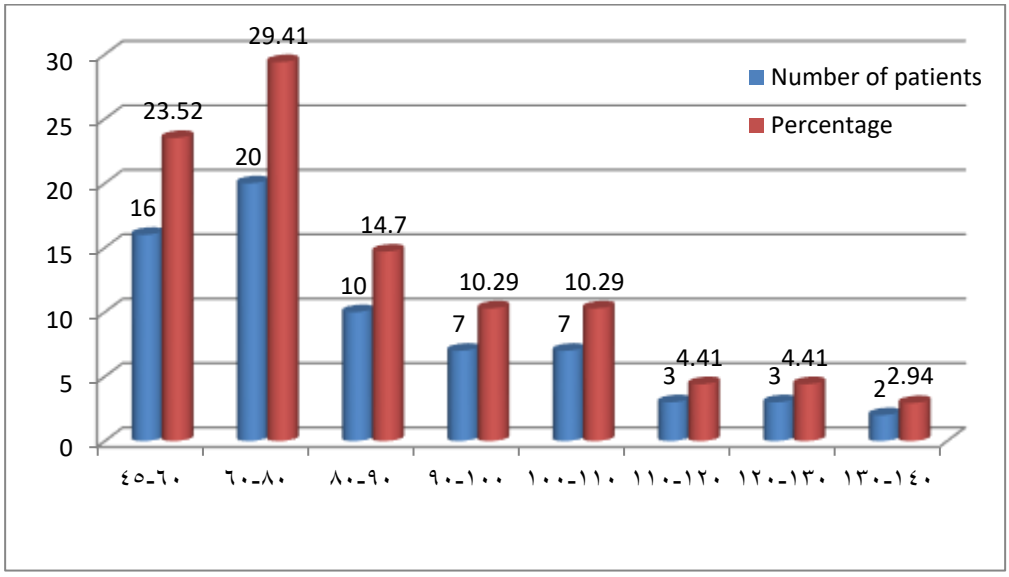

Figure (1): Distribution of Operation Times with Mean Duration

Twenty-six (38.23%) out of 68 cases were managed by subtotal cholecystectomy due to severe adhesions in the Calot's triangle or because of an acute attack of cholecystitis and three of them had Mirizzi syndrome. all these were done after we ensured that there was no stone in the remnant part of the gall bladder or the stump and their mucosa was cauterized by electrocautery. No cases of remnant stone in the stump, attacks of cholangitis, pancreatitis or stone in the biliary tree were not found during 6 monthly follow up of each patient.

In 4(5.88%) cases bile leakage was noted post operatively in the subhepatic drain that was left during the operation, 2 of them were stopped after 72 hours postoperatively and the remaining two cases needed ERCP and then bile leakage was stopped.

According to the visual analog scoring system, the majority of patients have experienced mild

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pain at rest, during mobility and during straining which is shown in Table (3).

Table (3): Arrangement of cases according to the pain perception on the 0th postoperative day following surgery

Visual analogue score	At rest	On Mobility	On straining
	Number of patients (Percentage)		
Mild (1-3)	49 (72)	38 (55.88)	34 (50.00)
Moderate (4-6)	17 (25)	23 (34.26)	25 (36.76)
Severe (7-10)	2 (2.94)	7 (10.29)	9 (13.24)
Total	68 (100)	68 (100)	68 (100)

*There is no association between the "Visual Analogue Score" and the different conditions. the p-value is 0.056

The majority of our cases remained in the hospital and ambulated at day 3-5, and the main hospital stay were 4.68±1.8 days as clarified in Table (4).

Table (4): Period of stay in hospital and ambulation

Hospital stays (Days)	Number of cases	Percentage
0-3	19	27.94
3-5	47	69.11
6-10	2	2.94
Total	68	100
Mean Hospital stay (days) ± SD	4.68±1.8	

Most of the cases were in difficulty category II and our conversion rate to open cholecystectomy was 7 (10.29%), in which 4 cases (2 male and 2 female) were in category IV level of difficulty. which is shown in Table (5).

Table (5): Difficulty category to sex distribution with conversion to open cholecystectomy

Difficulty level	Male	Female	Total(percentage)	Conversion (Percentage)
I	4	2	6 (8.82)	0
II	12	30	42 (61.76)	1 (1.47)
III	2	8	10 (14.7)	2 (2.94)
IV	5	5	10 (14.7)	4 (5.88)

* No significant correlations found between difficulty levels according to gendres to the conversion rates. P value was 0.055

There were major difficulties during surgery mainly in the form of bleeding, bile leakage and stone spillages to the peritoneal cavity. In 3(4.41%) cases of severe bleeding from the gall bladder bed in the liver, each required one pint of blood transfusion. The majority of gallbladder injuries and spillage were found in grade II as shown in Table (6).

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Table (6): Gall bladder injury and bile spillage according to grades of difficulty

Grades of difficulty	Number of cases	Gallbladder injury cases	Percentage
I	6	0	0
II	42	9	13.23
III	10	3	4.41
IV	10	0	0
Total	68	12	17.64

* No significant correlations found between Grades of difficulty to the gall bladder injuries. P value was 0.057

Discussion

Fundus first laparoscopic cholecystectomy has been successfully adapted in complicated cases when dense adhesions or fibroses and chronic inflammation of the Calot's triangle are observed. The fundus first approach is typically performed. As an alternative to reverting immediately to an open approach, fundus first (dome down) laparoscopic gall bladder removal allows for the completion of laparoscopic cholecystectomy without inflicting bile duct damage. Research has shown that taking a fundus-first approach can decrease both conversion and completion rates (22).

A fundus first cholecystectomy was performed in the following conditions; dense adhesions, impacted stones in Hartmann's pouch, a short dilated cystic duct, Mirizzi syndrome, a constricted gallbladder, and swelling and hardness at the junction of the common and cystic ducts (16,23,25).

According to this study, the gender and age distribution of patients were 66.17% female and 74 % of the age group of 30-50 respectively, which predicts an increase in difficulty in identifying the critical view of safety as in Mir et al about 73% female patients and 74% at the age of 30-50 years underwent fundus first laparoscopic cholecystectomy (24).

The degree of difficulty in cholecystectomy as classified by Orhan Bat into 4 classes, our results were: class I about 8.82%, class II about 61.76%, class III about 14.7% and class IV about 14.7%, this indicates a greater frequency of class II difficulty (adhesions of Calot's triangle resulting in the difficult dissection of the cystic artery and cystic duct) among the patients with laparoscopic cholecystectomy, which needs a fundus first approach, as its mimic Mishra BM et al. study about 71% in class II (25).

According to Neri, RLC cut down the period of operation and was simpler to carry out. They advocated for it to become the norm, rather than an exception made solely in exceptional circumstances (26).

The mean duration of the operative time in our study was about 96.74%± 18.23 while Cengiz et al reported a mean operation time of about 66.7 and a mean hospital stay of 4.68±1.8 the same as M. Kelly et al about 1/2 to 5 days (mean 2.2) due to the usage of a Ligasure shearing device in calot s triangle dissection (23,27).

In our study, the conversion rate from fundus first to open cholecystectomy was higher in grade IV, at 5.88%, Conversion to open

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cholecystectomy is necessary for several reasons, including impacted stones, Mirizzi syndrome, and bleeding that cannot be controlled laparoscopically. The rate at which patients required open surgery was reduced from 5.2% to 1.2% when the FF approach was used in the study by Mahmud (28).

Regarding gall bladder injury and bile, spillage depends on the degree of difficulty, but most bile injury and spillage was in grade II about 13%, while in the Cengiz study, was about 4% which explains the usage of ultrasonic devices rather than mechanical closure (23).

Conclusions

Fundus first laparoscopic cholecystectomy remains a feasible and safe procedure in the hands of experienced surgeons and the surgeon's judgment affects the operative time and need for conversion, which would subsequently impact the morbidity rate and hospital stay in difficult and obscured Calot's triangle.

Recommendations

We recommend to provide concise steps for the laparoscopic cholecystectomy, emphasize adherence to ethical guidelines, outline the four ports technique and specify concise step-by-step description of the fundus-first approach.

Source of funding: The current study was funded by our charges with no any other funding sources elsewhere.

Ethical clearance: The patient selection and data-gathering methods were authorized by the Ethical Committee of Hawler Medical University's College of Medicine. The patients provided written informed permission for the surgical operation, research participation, and publishing of the results and any accompanying photos. The study adhered to the ethical criteria set by the institutional and national research committees, as well as the 1964 Helsinki Declaration. (Document no. 2024AJN840).

Conflict of interest: Nil

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تقييم عملية استئصال المرارة بالناظور بدءاً من القاع في حال كون مثلث كالوت مبهماً: النتائج

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الملخص

خلفية الدراسة: عندما يُجرى استئصال المرارة بالمنظار مع التركيز على الجزء السفلي للمرارة أولاً، يوفر هذا المستوى نفس مستوى السلامة والمتانة كما في الجراحة المفتوحة عند إجرائها من قبل جراح متمرس. وعندما لا يمكن تمييز مثلث كالوت بأمان أثناء جراحة استئصال المرارة بالمنظار، يُنصح بإجراء علاج إنقاذ. تؤكد المراجعات الحالية على أهمية الملاحظات داخل الجراحة في مساعدة الجراحين على اتخاذ قرار الإنقاذ وتقليل الأذى الإضافي

اهداف الدراسة: تهدف هذه الدراسة إلى استكشاف استراتيجية التركيز على الجزء السفلي أولاً في استئصال المرارة بالمنظار في حالات عدم وضوح مثلث كالوت وتأثيرها على نتائج العلاج للمرضى.

المرضى والطرائق: هذه دراسة استطلاعية أُجريت في مستشفى رزكاري التعليمي من ١ يناير ٢٠٢٠ إلى ٣١ ديسمبر ٢٠٢٢ على (٦٨) حالة أجريت لها جراحة استئصال المرارة بالمنظار حيث كان من الصعب تمييز مثلث كالوت خلال العملية. يتم في هذا البحث تحليل تشريح الجزء السفلي للمرارة حتى القاعدة الجذعية وبعد ربط قاعدة المرارة بشكل آمن وضمان التوقف الجيد للنزف في الكبد، يتم إزالة المرارة عبر فتحة ١٠ ملم. درس هذا البحث مدة العملية، وآلام ما بعد العملية، ومعدل التحويل إلى جراحة مفتوحة، ومدة البقاء في المستشفى.

النتائج: من بين ٦٨ حالة تم إجراء استئصال المرارة بالمنظار مع التركيز على الجزء السفلي أولاً، كان معظم المرضى من الإناث ٤٥ (٦٦.١٧٪) و٢٣ (٣٣.٨٢٪) من الذكور، وكانت غالبية الحالات في الفترة العمرية بين ٣١ و٥٠ عامًا، مع متوسط عمر يبلغ ٣٩ ± ١٠.٤٤ عامًا، وكانت غالبية المرضى يشتكون من التهاب مع تليف في موقع القناة المرارية. تراوحت مدة العملية بين ٤٥-٦٠ دقيقة في ١٦ حالة (٢٣.٥٢٪) وبين ٦٠-٨٠ دقيقة في ٢٠ حالة (٢٩.٤١٪) وبين ١٣٠-١٤٠ دقيقة في ٢ حالة (٢.٩٤٪)، وبقيت غالبية حالاتنا في المستشفى وتم التنقل في اليوم الثالث إلى الخامس، وكانت مدة البقاء الرئيسية في المستشفى ٤.٦٨ ± ١.٨ أيام. كان هناك تفاوت إحصائي في توزيع الأعمار فقط قيمة P ٠و٠٤.

الاستنتاجات: يظل استئصال المرارة بالمنظار مع التركيز على الجزء السفلي أولاً إجراءً آمنًا وقابلاً للتطبيق. يؤثر خبرة الجراح وتقديره على مدة العملية، ومعدل التحويل، والمضاعفات، ومدة البقاء في المستشفى في حالات مثلثات كالوت الصعبة والمعتمة.

الكلمات المفتاحية: مثلث كالوت الصعب، استئصال المرارة بالمنظار مع التركيز على الجزء السفلي أولاً، حصوات المرارة.

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Association of Spexin Hormone Levels with Metabolic Disturbance in Women with Polycystic Ovarian Syndrome

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Abstract

Background: Polycystic ovarian syndrome is affecting around 5–15% of females. Spexin hormone, identified as neuropeptide Q, has been newly recognized by bioinformatics methods.

Objective: To evaluate the relationship concerning levels of spexin hormone with metabolic disruption in women with polycystic ovarian syndrome.

Patients and Methods: A case-control study carried out in the department of Obstetrics and Gynecology in Al-Imamain Al-Khademain medical city/Baghdad, Iraq, from Jan 1, 2022, to the end of Dec 31, 2022. The study sample comprises, 192 participants aged 18-45 years were joined and allocated into a case group (96 women with PCOS) and a control group (96 women without PCOS).

Results: Mean value of spexin hormone was (2.7±0.3 ng/mL) in the PCOS group, while it was (3.5±0.7 ng/mL) in the control group; fasting blood sugar shows significant association with a negative, weak correlation with Spexin in patients (P-value= 0.005), Insulin shows significant association with inverse correlation with Spexin in patients (P-value= 0.04), Homeostasis model valuation of insulin resistance (HOMA-IR) shows significant association with inverse correlation with Spexin in patients (P-value= 0.003). Spexin had a significant inverse correlation with LH, SHBG, testosterone, FAI, and Dehydroepiandrosterone.

Conclusion: Serum level of spexin hormone was meaningfully decreased in patients with PCOS than that in healthy women.

Keywords: Polycystic ovary syndrome, Spexin, Hormonal, Metabolic Disturbance.

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Introduction

Polycystic ovary syndrome (PCOS) is a mutual endocrine-reproductive-metabolic disorder in women which remains a significant cause of unproductiveness, disturbing around 5–15% of females global (1-6). The principal hormonal irregularities in PCOS are categorized by greater androgen and estrogen but lesser progesterone ranks; the occurrence of gestational diabetes, asthma, and repeated miscarriage is 3–7-fold, 10-fold, and 3–5-fold higher in females with PCOS than in the overall people, correspondingly (6-13). A latest work has revealed that a greater body mass index is connected with hypertriglyceridemia in PCOS women, which is ascribed to the obesity-induced variation of adipokines, comprising tumor necrosis factor-alpha (TNFα), interleukin (IL)-6, and adiponectin (7-9,12-16). PCOS is a complex and multifactorial disease, and not all investigators agree with the classifications (14,20-26). In Germany, Greece, and other countries, no significant differences in insulin resistance (IR), dyslipidemia, or BMI were observed (24,25-32). Spexin (SPX), also known as neuropeptide Q, has lately been recognized by bioinformatics procedures. SPX is a secreted 14-amino-acid peptide exceedingly preserved from fish to mammals. It is broadly conveyed in the central nervous system and outlying tissues such as the liver, gonad, and kidney in rodents, fish, and humans (33-41). Hence, SPX has been described to have a diversity of purposes, comprising roles in stomach tightening, adrenocortical cell propagation, cardiovascular and renal task, nociception, nourishing, and replica (42-44). A new revision stated that intracerebroventricular (icv) inoculation of SPX augmented hypothalamic mRNA ranks of leptin receptor and melanocortin four receptor in mice, signifying a possible part of SPX in the act of leptin in the hypothalamic center for dynamism homeostasis (45-48). Latest articles have emphasized SPX purposes in governing obesity and energy metabolism founded on the witnessed interactions amid SPX and obesity: the circulating level of SPX is little in fat people matched to their steady equivalents (44,48-52).

Patients and Methods

Design of the study

A case-control study, carried out in Al-Imamain Al-Khademain Medical City/Baghdad, from Jan 1, 2022, to Dec 31, 2022. This research was ethically accepted by the scientific congress of Obstetrics and Gynecology, the Iraqi Board for medical specialization, and the scientific committee of the hospital setting. As well as verbal consent from all patients, the objective and processes were clarified to all contributors, and they were specified the right to contribute or not; oral agreement was taken with assurance that the information would be reserved confidential. 192 participants aged between 18-45 years old were enrolled and allocated into two sets: Case group: 96 women with PCOS. Control group: 96 non-PCOS women healthy women coming to the hospital for checkup and follow up.

Identification of women with PCOS was established on the following

Clinical parameters:

BMI calculated according to Kg/m2

Waist circumference

Modified Ferriman-Gallwey score for hirsutism (women with FG >8 considered as hirsute)

Presence of acne. Menstrual irregularity (oligo anovulation)

U/S: (ovarian volume>10 ml without cyst or dominant follicle and appearance of more than 12 follicles was seen and 2-9 mm in diameter.

Hormonal parameters

Progesterone, LH/FSH, Free testosterone, DEHEA, SHBG, Estradiol, FAI, and Spexin.

Metabolic parameters

FBS, insulin level, and HbA1c

HOMA-IR hemostatic model assumes that IR

While the women in the control set were designated from those, who consult our department in the hospital for a routine check-up or from patients' relatives with no disorders (hirsutism, acne, and hyperandrogenism).

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The inclusion criteria used for recruitment of women with PCOS

PCOS women were identified agreeing to the 2003 Rotterdam criteria.

Range of age between 18-45 years old

Married and unmarried women.

Exclusion criteria

Patients aged more than 45 years and less than 18 years

Chronic disease

Congenital adrenal hyperplasia

Cushing syndrome

Androgen secreting tumor

Autoimmune disease

Thyroid disease

Matching criteria:

Age and BMI were matched for both groups in the study.

Methods

Blood samples from all participants were taken from antecubital veins during the initial follicular phase of the cycle (3-5 days) after the selection of the patients, and the blood sample was taken after 10 hours of fasting. Next, the researchers place the blood samples at room heat for at a minimum of 30 min to touch the coagulated form. Then, the coagulated models were centrifuged for 15 min. at 2000 X g for parting. Then, the serum samples were centrifuged and kept the separated pieces in aliquots at -80 C0 to analyze circulating spexin levels by ELISA test.

Insulin resistance (IR)

was evaluated by homeostasis model assessment of insulin resistance: HOMA-IR = fasting insulin (mU/mL) X fasting glucose (mg/dL)/405.

Statistical Exploration

Data were scrutinized by using the SPSS IBM program version 25 Statistics are offered as means ± variance matched using an unpaired t-test.

Chi-square or Fisher s exact ʾtests matched means and percentages when suitable.

Probability values < 0.05 were deliberated statistically noteworthy in all results.

Results

The mean age of the PCOS group was (29.9±5.84) years and (30.3±6.0) for the control group, mean BMI level in the PCOS group was (30.82±4.67) kg/m2 and (29.67±4.39) kg/m2 in the control group, mean Waist: Hip ratio level in PCOS group was (0.80±0.06) and (0.79±0.02) in the control group, mean FBS level in PCOS group was (85.20±12.33) and (84.8±11.79) in the control group, mean insulin level in PCOS group was (15.12±3.63) and (10.6±3.29) in the control group, and mean HOMA-IR level in PCOS group was (3.15±0.09) and (2.07±0.08) in control group. There was no substantial variance between PCOS and control (p-value ≥ 0.5) concerning age, BMI, Waist: Hip ratio, and FBS. At the same time, Insulin and HOMA-IR were meaningfully greater in PCOS matched to the control (p-value < 0.001), as illustrated in table1.

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Table 1: Characteristic parameters of PCOS* and control set

Group	PCOS	Control	*P-value*
Number	96	96	
Age (years), mean ± SD	29.9±5.84	30.3±6.0	0.6
BMI (kg/m^2), mean ± SD	30.82±4.67	29.67±4.39	0.08
Midriff: hip ratio, mean ± SD	0.80±0.06	0.79±0.02	0.1
FBS (mg/dL), mean ± SD	85.20±12.33	84.8±11.79	0.8
Insulin (mU/mL), mean ± SD	15.12±3.63	10.6±3.29	<0.001
HOMA-IR, mean ± SD	3.15±0.09	2.07±0.08	<0.001

The mean FSH level was (8.07±4.12 IU/L) in the PCOS group and (9.35±3.53 IU/L) in the control set. The mean LH level was (17.29±8.56 mIU/ml) in the PCOS group and (6.66±2.99 mIU/ml) in the control group, mean Progesterone level was (1.03±0.04ng/ml) in the PCOS group and (1.04±0.07ng/ml) in the control group, mean Estradiol level was (53.82±5.71 pg/dl) in PCOS group and (52.87±4.92 pg/dl) in control group, mean Testosterone level was (2.03±0.39 nml/L) in PCOS group and (1.71±0.32 nml/L) in control group, mean Androgen level was (7.86 ± 1.85) in PCOS group and (2.41 ± 0.31) in control group, mean SHBG level was (34.40±12.33 nmol/l,) in PCOS group and (55.62±17.15 nmol/l,) in the control group, mean DEHEA level was (169.27±64.18 **µ**g/dl) in PCOS group and (151.87±41.69 **µ**g/dl) in the control group. No important dissimilarity among both clusters in the study among FSH and Estradiol (P≥0.05). At the same time, significant differences were found among (LH, progesterone, TT, FAI, SHBG, and DEHEA, as illustrated in Table 2.

Table 2: Comparison between mean hormonal assay in the studied groups

Group	PCOS	Control	p-value
Number	96	96	-
FSH (IU/L), mean ± SD	8.07±4.12	9.35±3.53	0.36
LH (mIU/ml), mean ± SD	17.29±8.56	6.66±2.99	0.001
Progesterone (ng/ml), mean ± SD	1.03±0.04	1.04±0.07	0.02
Estradiol,(pg/dl) mean ± SD	53.82±5.71	52.87±4.92	0.1
Testosterone (nml/L), mean ± SD	2.03±0.39	1.71±0.32	<0.001
Free Androgen index, mean ± SD	7.86 ± 1.85	2.41 ± 0.31	<0.001
SHBG nmol/l, mean ± SD	34.40±12.33	55.62±17.15	<0.001
DEHEA **µ**g/dl, mean ± SD	169.27±64.18	151.87±41.69	0.02

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The mean level of LDL was (133.42±29.65 mg/dL) in the PCOS group while (130.32±27.13 mg/dL) in the control cluster, the mean level of HDL was (44.16±8.43 mg/dL) in the PCOS group, and (54.12±11.09mg/dL) in the control group, mean TG level was (141.01±22.57 mg/dL) in PCOS while (94.87±16.03 mg/dL) in the control group, and mean level of cholesterol was (162.70±15.13 mg/dL) in PCOS group and (161.20±13.23 mg/dL) in control group. No major variance between two clusters regarding LDL and serum cholesterol (P≥0.05. At the same time, HDL and TG were significantly different in PCOS compared to control, as illustrated in Table 3.

Table 3: Lipid profile of PCOS cases and control group

Group	PCOS	Control	*P-value*
Number	96	96	-
LDL (mg/dL), mean ± SD	133.42±29.65	130.32±27.13	0.4
HDL (mg/dL), mean ± SD	44.16±8.43	54.12±11.09	<0.001
TG (mg/dL), mean ± SD	141.01±22.57	94.87±16.03	<0.001
Cholesterol (mg/dL), mean ± SD	162.70±15.13	161.20±13.23	0.4 Ns

The Mean value of Spexin was (2.7±0.3 ng/mL) in the PCOS group, while it was (3.5±0.7 ng/mL) in the control cluster; this level showed that there was considerably decreased in PCOS compared to control, as illustrated in Fig.1.

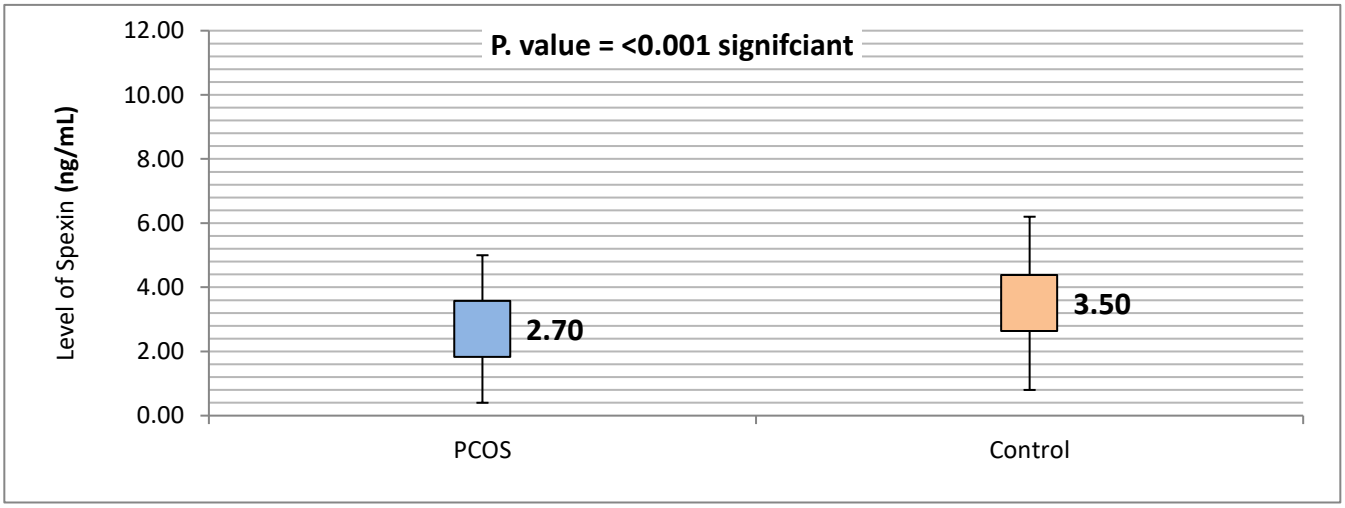

Figure 1: Distribution of serum levels of Spexin (ng/ml) in both PCOS patients & controls

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There was no significant association between spexin hormone with age (P-value= 0.210), While inverse significant correlation with BMI (P-value =0.027),moreover waist: hip ratio shows considerable association with spexin level in patients group (P-value= 0.027), FBS shows significant association with negative, weak correlation with spexin in patients (P-value= 0.005), Insulin shows significant association with negative, weak correlation with Spexin in patients (P-value= 0.04), while HOMA-IR shows significant association with negative, weak correlation with Spexin in patients (P-value= 0.003).and there is no association between Spexin with LDL, HDL, TG, and cholesterol. All these are shown in Table 5.

Table 5: Correlation between spexin hormone and metabolic assay in the PCOS group

Variables	Spexin	
	PCOS	
	(r)	*P-value*
Age (years)	0.190	0.210
BMI (kg/m^2)	-0.252	0.027
Waist: hip ratio	-0.237	0.020
FBS (mg/dL)	-0.231	0.005
Insulin	-0.338	0.04
HOMA-IR	-0.294	0.003
LDL (mg/dL)	-0.088	0.565
HDL (mg/dL)	0.268	0.3
TG (mg/dL)	-0.141	0.38
Cholesterol (mg/dL)	-0.143	0.349

Table 6 showed no significant correlation between Spexin and hormonal assay (FSH, E2, and progesterone) in patients with PCOS. At the same time, Spexin had a significant correlation with LH, SHBG, testosterone, FAI, and DEHEA but with a negative, weak correlation (r <0.4) except for SHBG, with a weak positive correlation.

Table 6: The correlation between Spexin with the hormonal assay in PCOS

Variables	Spexin	
	PCOS	
	(r)	*P-value*
FSH	0.06	0.121
LH	-0.202	0.03
Estradiol	-0.117	0.8
Progesterone	0.17	0.36
SHBG	0.147	0.03
Testosterone	-0.342	0.004
FAI	-0.199	0.02
DEHEA	-113	0.05

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Discussion

New biochemical markers are identified in patients with PCOS. In a study carried out by Ehrmann DA et al., 2006 in which Twenty-six (6.6%) subjects had diabetes; among the 368 nondiabetics, it mentioned that Hypothalamic-pituitary-ovarian axis dysfunction plays a crucial part in the progress of the disease, however the specific mechanical character is not entirely agreed so far (13). This alliance is chiefly controlled via reaction contrivances by gonadal steroids. It is understood that spexin shows a part in regulating the hypothalamic-pituitary-ovarian axis via the downregulation of Luteinizing hormone excretion (43). We found the mean insulin level in the PCOS set was (15.12±3.63) and (10.6±3.29) in the control cluster, and the mean HOMA-IR level in the PCOS cluster was (3.15±0.09) and (2.07±0.08) in the control cluster, Insulin and HOMA-IR were expressively greater in PCOS matched to controller (p-value < 0.001). This finding is in agreement with Behboudi-Gandevani et al., 2016 in a cohort of 754 reproductive-aged females, comprising 704 eumenorrheic non-hirsute patients and 50 PCOS ladies choose agreeing to the national institutions of health's (NIH) principles in which HOMA-IR (2.22 vs. 1.74, p-value = 0.017) (44). Moreover, Temur et al., 2016 when Fifty-two women with PCOS and 55 well females were involved in the study, accorded for oldness and body mass index (45). A significant difference was found in HOMA-IR between the studied groups (2.40±1.44 vs 1.37±1.10, p-value = 0.001). Also, this is in agreement with Ates et al., 2018 Subjects (n = 77) were categorized into two sets: oligomenorrhea (O) and clinical and biochemical hyperandrogenism (HA) (n = 38), without PCO and O + HA with PCO (n = 39). The control set comprised of 33 age-matched pubescent with HOMA-IR (3.54 ± 2.72 vs 5.02 .025, p-value = 0.011) [46], and These studies and the current findings indicate that PCOS is related to insulin resistance (IR) and an increased IR is present in PCOS. In the present study, all lipid parameters (TG and HDL) were expressively variance in POCS, and HDL was considerably lower in PCOS matched to control; these findings are consistent with several studies such as González A et al. study in 2011 in which a total of 117 subjects were enrolled. Of these, 93 females with IR were compared against 24 females without IR. Raised TGL/HDL ratio was noticed in 89 (61.4%) and 12 (38.6%) subjects with and without IR, correspondingly. The high TGL/HDL ratio was considerably linked to IR (OR 2.64, 95% CI = 1.12-6.29) (47). The most critical finding in this study was a important decrease in levels of spexin in the PCOS cluster than in the control cluster. This is the same as that mentioned by Ilhan GA 2018 in a Turkish study; 120 females with PCOS and 50 age and body mass index (BMI) harmonized healthy panels were joined. Clinical, hormonal, and metabolic considerations and serum spexin levels were matched between the clusters. This study was carried out to demonstrate the levels of spexin in females suffering from PCOS. And he revealed a significant decrease in Spexin levels in the patient's set paralleled with the average healthy respondents in the control group, with no differences in baseline criteria, lipid profile (except for triglyceride levels), HOMA-IR, and unrestricted androgen index in both groups. But in Ilhan GA 2018 study, significant differences were found according to Waist to hip ratio and triglyceride levels. Spexin levels were clearly interrelated with HDL and depressingly interrelated with HOMA-IR in women with PCOS (50,51,52). Moreover, in Beyazit F et al (49), in their study determined 91 women with PCOS and 86 well controls found that spexin concentration did not differ significantly between patients and controls. It is of pronounced worth since there is no study in literature describing the part of spexin in

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PCOS patients. Also, Beyazit F et al. do not agree with this study as they cannot detect any link between flowing spexin and other metabolic or hormonal features, comprising body structure or IR (49). Chen et al. 2019, considered the ranks of serum SPX in 40 fat and 32 average-weight adolescent children and found that Spexin levels were considerably diminished in fat teen-agers matched to controls. Additionally, serum SPX ranks were lesser in IR-fat individuals than in non-IR-fat individuals. Serum SPX amounts connected deleteriously and considerably with triglycerides, systolic blood pressure, diastolic blood pressure, fasting insulin level, HOMA-IR, insulinogenic index, and HOMA-β levels in fat kids (50). Similarly Al-Daghri et al found in their study which comprised 124 contributors Established that small serum ranks of the marker are somewhat correlated with parts of metabolic disorder (51). Further analysis of spexin in PCOS patients with baseline characteristics and metabolic assay shows a significant correlation with BMI. In contrast, for Waist: hip ratio, FBS, Insulin, and HOMA-IR show substantial association with a negative, weak correlation with spexin in patients. This result was comparable to a recent study by Guler A, 2021 when 160 women were joined in the case-control study, 80 PCOS women, and 80 age- and body mass index (BMI) accorded topics with regular menstrual cycles. The selected women were between 18- and 45-year-old; they revealed a significant decrease of markers in the case cluster than that in the control cluster in addition to converse link between spexin and insulin resistance, BMI, while for Waist: hip ratio, FBS, Insulin, and HOMA-IR in females with PCOS (52). In addition to that, Ilhan GA concluded that women with polycystic ovaries have Spexin levels confidently associated with HDL levels and deleteriously with HOMA-IR (48).

Conclusion

Serum level of Spexin hormone was considerably decreased in ladies with PCOS than in non-PCOS women with an inverse significant correlation with BMI, Waist: hip ratio, FBS, Insulin, and HOMA-IR. While no association was found between spexin with LDL, HDL, TG, and cholesterol. Spexin has a significant correlation with LH, SHBG, testosterone, FAI, and DEHEA.

Recommendations

A multicenter study may be recommended with investigations to identify the effect and relationship between spexin and PCOS

As well as follow up the patients and reevaluate Spexin level after treatment of PCOS.

Source of funding

No source of funding

Ethical clearance

Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023RFS786).

Conflict of interest

The author acknowledges no conflict of interest in this study

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علاقة مستويات سبيكسين مع الاضطرابات الهرمونية والتمثيل الغذائي لدى النساء المصابات بمتلازمة المبيض المتعدد التكيس

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الملخص

الخلفية الدراسية: متلازمة المبيض المتعدد التكيس تصيب حوالي ٥-١٥٪ من الإناث. تم التعرف حديثًا على سبيكسين، الذي تم تحديده على أنه neuropeptide Q، من خلال طرق المعلوماتية الحيوية.

الهدف من الدراسة: تقييم العلاقة بين مستويات سبيكسين والاضطرابات الهرمونية والتمثيل الغذائي لدى النساء المصابات بمتلازمة المبيض المتعدد الكيسات.

طرق العمل: دراسة الحالات والشواهد التي أجريت في قسم أمراض النساء والتوليد في مدينة الإمامين الخادمين الطبية / بغداد، من ١ كانون الثاني (يناير) ٢٠٢٢ إلى ٣١ كانون الأول (ديسمبر) ٢٠٢٢. في الدراسة الحالية، ١٩٢ مشاركاً تتراوح أعمارهم بين ١٨- تم ضم ٤٥ عامًا وتخصيصها لمجموعة حالة (٩٦ امرأة مصابة بمتلازمة تكيس المبايض) ومجموعة مراقبة (٩٦ امرأة بدون متلازمة تكيس المبايض).

النتائج: متوسط قيمة سبيكسين كان (٢,٧±٠,٣ نانوجرام/مل) في مجموعة متلازمة تكيس المبايض، بينما كان (٣,٥±٠,٧ نانوجرام/مل) في مجموعة التحكم. يُظهر سكر الدم الصائم ارتباطًا كبيرًا مع ارتباط سلبي ضعيف مع سبيكسين في المرضى (قيمة P= 0.005)، ويظهر الأنسولين ارتباطًا كبيرًا مع ارتباط عكسي مع سبيكسين في المرضى (قيمة P= 0.04)، وتقييم نموذج التوازن لمقاومة الأنسولين (يُظهر HOMA-IR) ارتباطًا كبيرًا مع الارتباط العكسي مع سبيكسين في المرضى (القيمة P = 0.003). كان لدى سبيكسين علاقة عكسية كبيرة مع LH، SHBG، التستوستيرون، FAI، و.Dehydroepiandrosterone

الاستنتاجات: انخفض مستوى سبيكسين في الدم بشكل ملحوظ لدى المرضى الذين يعانون من متلازمة تكيس المبايض مقارنة بالنساء الأصحاء.

الكلمات المفتاحية: متلازمة تكيس المبايض، سبيكسين، هرموني، اضطراب التمثيل الغذائي.

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Influence of lymphovascular invasion on outcome of colon cancer

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Abstract

Background: Colon cancer is the third most common type of cancer. High lymphovascular levels are linked to a number of cancers, including colon cancer, while lymph vascular invasion levels as a predictor of outcome are not well understood.

Objective: Determine the influence of lymphovascular invasion on the recurrence of colon cancer.

Patients and Methods: it was collected 126 colon cancer patients who had surgery and additional chemotherapy. The patients attended in the Baquba teaching hospital oncology centre and the Al Jawad oncology centre of Alkadhemiya hospital.

Results: it was shown in this study that the high percentage ages of colon cancer patients was between 55-60 years, and there were more in women (57 %) than in men (43 %). The most common stage of the tumours was stage 3 (42.9 %), and in grade 2 (76.2 %). In terms of return, in this study, 71.4 % of people who had lymphovascular invasion positive and had a return of cancer in a percentage 73.3% of colon cancer patients.

Conclusion: LVI plays an essential role for increasing recurrence of colon cancer, and there were a strong link between them.

Keywords: Colon cancer, Lymphovascular invasion, Cancer recurrence, Cancer differentiation.

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Introduction

Colon cancer is the most common type of cancer in the world, with about 14,000,000 new cases and 700,000 deaths each year. In the United States, it is the second most common type of cancer that causes death (1). It was the cause of 10% of cancer deaths in 2010. Random colon tumors become much more common in people over the age of 45 to 50, regardless of age. This effect is stronger than any other factor. In almost every country, age-standardized incidence rates are lower for women than for men. However, while the general incidence has gone down, likely because of more aggressive screening of people over 50, there has been a huge rise in cases younger than 50 years old (3). From 2011 to 2015, the Iraqi Cancer Registry (ICR) showed an incidence rate of 3.22 to 4.4 per 100,000 people. A comparison study of the ICR over 30 years, from 1965 to 1994, showed that the incidence rate rose from 25% to 50% in Iraq. It happens about 2.6% of the time in Iraq, compared to 6.1% to 13.3% in developed countries and 17.1% to 51.1% in industrialized countries. It is the sixth most common cancer in Iraq (4). The GLOBOCAN 2018 report on the top 5 cancers in the world lists breast, lung, leukaemia, bladder, and colorectal cancers. Furthermore, it is advised by the most recent guidelines to check for nodal evolution in at least 12 lymph nodes (LNs) (5). For nodal staging to be accurate, the specimen must have adequate LN retrieval (6). A lower pN stage or a false-negative result could occur from a poor lymph node (ELN) examination (7). The presence of cancer cells in lymphatics or blood arteries is known as lymphovascular invasion (LVI), and it is thought to be an initial step to lymph node metastasis (8). According to numerous research, LVI positive (LVI+) is a crucial prognostic factor for a number of malignancies, such as gastric, bladder, and breast cancers (9,10,11). The prevalence of LVI in CRC ranges from 4.1 to 89.5%, according to reports (12). It was showed that LVI is linked to higher tumour grade, greater pre-CEA levels, and more advanced T and N categories (13). In addition, it was found that LVI is associated with a number of characteristics in patients with advanced colorectal cancer, such as distant metastases, greater size, more advanced T stage, and LN involvement (14). In addition, LVI is substantially linked to a higher elevated tumour differentiation, advanced tumour stage, and CEA level (8). In individuals with colorectal cancer, LVI is a strong predictor of advanced stage and is strikingly associated with a worse prognosis. Clinicians may find it easier to effectively strategies treatment options for patients with colorectal cancer if they use the survival nomogram that incorporates LVI (15). In addition, it was showed that LVI is a strong predictive indicators for colon cancer staging (16). Thus, it is important to determine the relationship between colon cancer and LVI to reduce the risk factors for cancer recurrence and increase the awareness for these factors. Therefore, this study aims to protrude the correlation between LVI and recurrence of colon cancer.

Patients and Methods

It was collected 126 patients in this study in total. The results for the study were gathered from the Baquba teaching hospital oncology centre and the Al-Jawad oncology centre from October 2023 to March 2024. There were recorded other factors in the study that have an effect on colon cancer return, but their effects on recurrence were left out. The inclusion criteria of the patients including, patient completed surgery and chemotherapy and regular follow-up. The exclusion criteria of the patients including, the following character, de novo metastasis colon cancer, comorbidity –patient suffering from severed comorbid disease that have effect on survival of patients like diabetes mellitus and thyroid disease, strict diet for any cause or anorexia, inoperable patients or patients refuse surgery for any cause, discontinue adjuvant chemotherapy, second or more primary cancers,

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and family history of colon cancer.

Study design

All the patients in this study had LVI measured by histopathology during surgery or biopsy to find out how lymphovascular invasion affected the return of cancer.

The information of the patients was collected included:

1-Gender and age

2-Date of diagnoses of colon cancer

3-Date and type of surgery

4-Date of first chemotherapy

5- Performance state and bowel obstruction or perforation at presentation

6-Tumour location and pathological macroscopically feature of malignancy

7-Differentiation and depth of penetration and lymph node status of tumors

8- Recurrence if present and time from diagnoses to recurrence.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 25 was used to look at the data. The results were shown as a percentages of cancer patients.

Results

The total number of study patients were 126 that were diagnosed with colon cancer. The Figures 1 and 2 demonstrated distribution of patients according to their ages and gender, respectively. It was shown that the most dangerous ages for colon cancer are between 55-60 years and it was found in the female (57 %) more than in male (43 %).

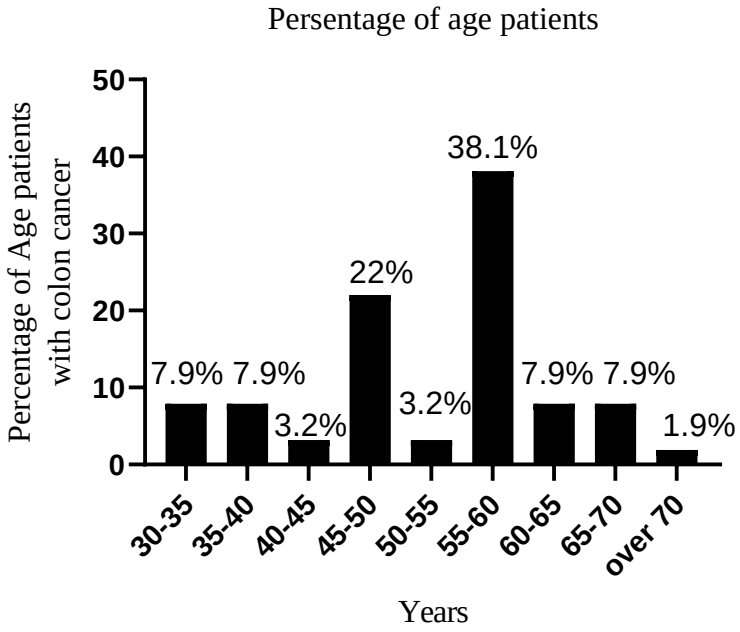

Figure 1. Distribution of patients according to their ages.

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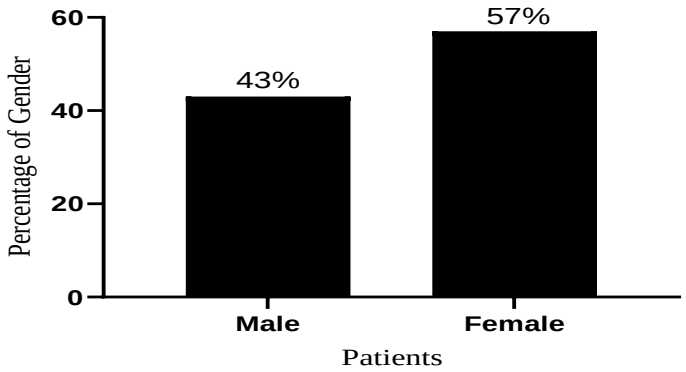

Figure 2. Distribution of patients according to their gender.

The tumor characteristics including grade and stage were obtained in this study and showed in figure 3 and 4, respectively. It was demonstrated that 76.2 % of the colon cancer cases were in grade 2 and 23.8% in the grade 3. Interestingly, it was shown that there are not found any case in the grade 1 and 4 in this study. In addition, it found that 42.9% and 33.3 % of the cases in the stage 3 and 2, respectively. However, the stages 1 and 4 appeared in 4.8% and 19% of the colon cancer cases.

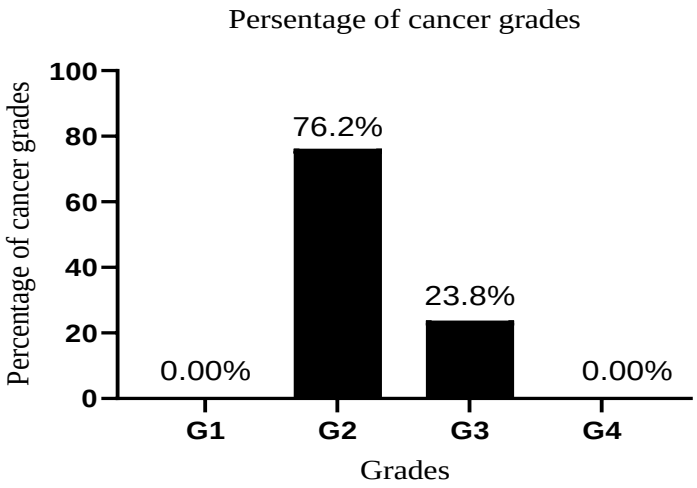

Figure 3. Distribution of patients by tumor grades.

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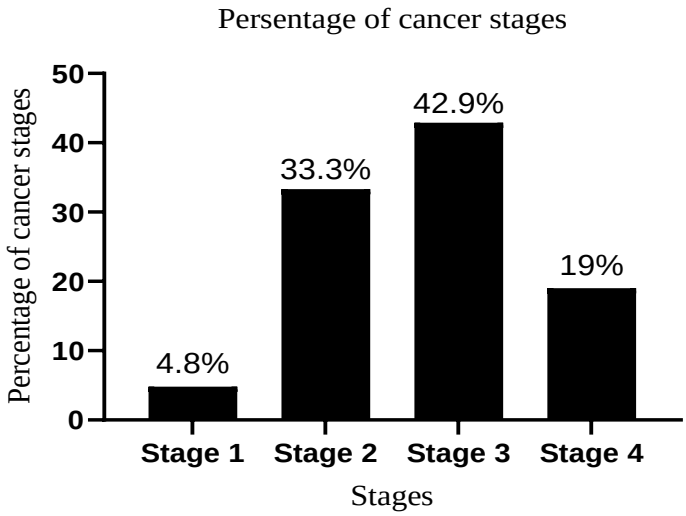

Figure 4. Distribution of patients according to cancer stages.

It was noticed that 71.4 % of study patients have lymphovascular invasion Positive and 28.6 % appeared Negative for lymphovascular invasion (Figure 5).

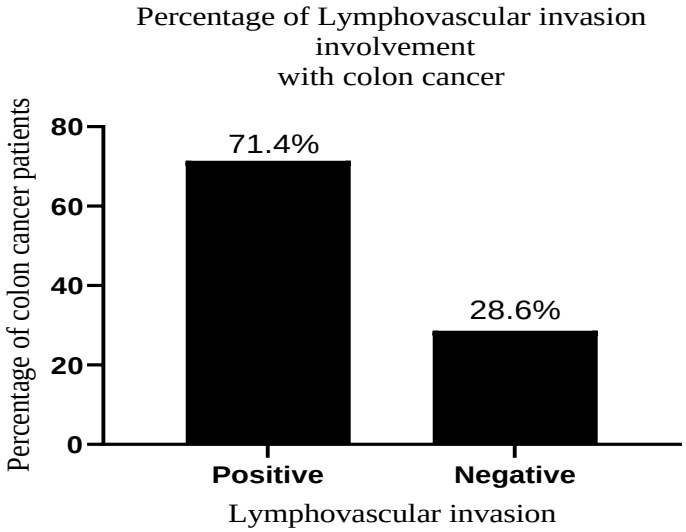

Figure 5. The percentages of lymphovascular invasion in the colon cancer patients.

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It was shown in Figure 6 that the association between prevalence of recurrence of malignancy and lymphovascular invasion (LVI). In this study, 94.4% of patients with lympho-vascular invasion negative were not appeared recurrence colon cancer. However, 73.3% of patients with lymphovascular invasion positive were complained from recurrence of malignancy. In addition, it was shown that 5.6% of LVI Negative were suffering from recurrence colon cancer and 26.7% of patients with positive LVI were not appeared recurrence colon cancer (Figure 6).

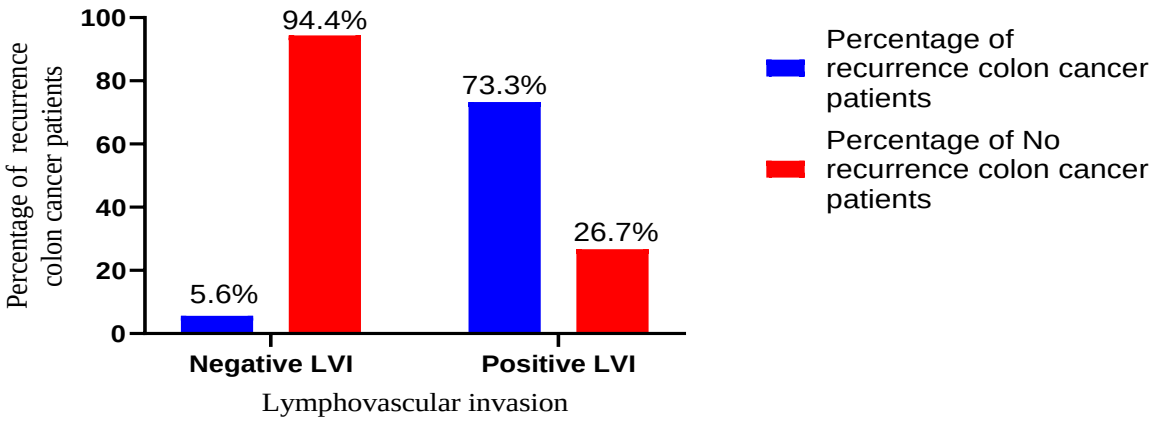

Figure 6. The percentage of recurrence colon cancer patient's camper with lymphovascular invasion.

Discussion

In this study, it was demonstrated the role of lymphovascular invasion on the result (recurrence) of colon cancer. It was shown that high percentage ages of colon cancer patients were between 55-60 years and high percentage of patients from women. In addition, it was found that the colon cancer grade two is the higher percentage of cancer occur in the patients, and stage three was the highest percentage grade that effected most patients. Furthermore, it was shown that most colon cancer had lymphovascular invasion positive. In the current study, most common patients had a return of cancer, high percentage of those who did had lymphovascular invasion positive. This fits with the results of the 2017 study by Bandamiri et al., which found that the overall five-year recurrence rate was 56.8%. However, it seems higher than what Aghili and colleagues found in 2010 in Iran, where they found that 30% of all recurrences happened recently (17,18). The research done by Fatemi and colleagues in 2015 showed that neither gender nor age was significantly linked to CRC coming back after surgery (19). In addition, in the 2015 study by Micu et al., there was no statistically significant difference between the ages of patients with cancer recurrence and those who did not have a recurrence (p=0.08). There was also no statistically significant difference between the genders of the two groups (p=0.4). In the Micu et al. study, the level of differentiation had a statistically significant effect on the disease-free period, with grade four (G4) being significantly linked to cancer coming back (20). Bandamiri found in 2017 that patients with colon cancer recurrence were older than those who did not have a recurrence (P=0.035). It was reported that women had a much lower chance of recurrence (43.5%) than men (56.5%) (P=0.041) (17). This result fits with what other studies have found: older

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patients have a much higher chance of getting CRC again, as seen in the Aghili et al. study from 2010 and the Westberg et al. study from 2015 (18,21,22). In this study, it was appeared that high percentage of patients with lymphovascular invasion had their cancer come back. There was a strong link between the rate of cancer coming back and lymphovascular invasion. They found that lymphovascular invasion happened much less often in patients who did not have a recurrence than in patients who did have a recurrence. In a 2018 study by Yamano that looked at 3039 people with colon cancer who had surgery that was successful, the results showed that lymphavascular invasion, venous invasion, and clinical stage were all significantly linked to return (23). There were no strong links ($P \geq 0.05$) between the frequency of return and pathological traits, tumour site, differentiation, tumour status, lymph nodes, or stage of the tumour. Our results are different from what Micu and colleagues found in their study in 2015. They said that people with colon cancer who have more lymph nodes involved have a worse outlook and a higher chance of the cancer coming back (20). It was explain by Ooki et al.'s study from 2017 found that having more lymph nodes involved was strongly linked to CRC coming back (24). Additionally, Yamano et al.'s 2018 study found that male sex, emergency surgery, vascular and perineural invasion, and problems after surgery were all linked to a higher chance of recurrence (23).

Conclusion

for lowering body weight may lower the risk of colon cancer and make it possible for people to live longer without getting worse. Moreover, it should be screening schemes for people to find colon cancer early to reduce the number of cases of LVI.

Recommendations

It was found in this study, it was need more studies with large sample sizes and different centres. In addition, it was recommended that keep the people for lowering body weight may lower the risk of colon cancer and make it possible for people to live longer without getting worse. Moreover, it should be screening schemes for people to find colon cancer early to reduce the number of cases of LVI.

Source of funding

This research received no specific grant from any funding agency in the public, commercial, or not for profit sectors (the author received no financial support for the research, authorship, and or publication of article) and it was done by using self-funding.

Ethical clearance

Consents documents of patients will be catchup this research with full information about patients colon cancer were mentioned. The patients were informed about this study and accepted orally to be enrolled and the approval of this study was obtained from two hospitals (Baquaba teaching hospital oncology centre and the Al Jawad oncology centre of Alkadhemiya hospital) for including its patients in this study. Thus, every patient received inquiry form comprised full information about disease status in relation to this study (Document no. 2024AHM826).

Conflict of interest

The author acknowledges no conflict of interest in this study.

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Diyala Journal of Medicine

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تأثير الغزو اللمفاوي الوعائي على نتيجة سرطان القولون

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الملخص

الخلفية الدراسية: سرطان القولون هو ثالث أكثر أنواع السرطان شيوعًا. ترتبط المستويات اللمفاوية الوعائية العالية بعدد من أنواع السرطان، بما في ذلك سرطان القولون، في حين أن دور مستويات الغزو اللمفاوية الوعائية كمؤشر على مدى عوده السرطان ليست مفهومة جيدًا.

الهدف من الدراسة: تحديد تأثير الغزو اللمفاوي الوعائي على تكرار سرطان القولون.

المرضى والطرق: تم جمع ١٢٦ مريضًا بسرطان القولون الذين خضعوا للجراحة والعلاج الكيميائي الإضافي. حضر المرضى مركز الأورام في مستشفى بعقوبة التعليمي ومركز أورام الجواد في مستشفى الكاظمية.

النتائج: أظهرت هذه الدراسة أن النسبة المئوية العالية لأعمار مرضى سرطان القولون كانت بين ٥٥-٦٠ عامًا، وكان هناك المزيد لدى النساء (٥٧٪) مقارنة بالرجال (٤٣٪). كانت المرحلة الأكثر شيوعًا للأورام هي المرحلة ٣ (٤٢,٩٪)، وفي الدرجة ٢ (٧٦,٢٪). من حيث العودة، في هذه الدراسة، ٧١,٤٪ من الأشخاص الذين لديهم غزو وعائي لمفي إيجابي وكان لديهم عودة السرطان بنسبة ٧٣,٣٪ من مرضى سرطان القولون.

الاستنتاجات: يلعب LVI دورًا أساسيًا في زيادة تكرار سرطان القولون، وكان هناك ارتباط قوي بينهما.

الكلمات المفتاحية: سرطان القولون، الغزو الوعائي اللمفي، عودة السرطان، تمايز السرطان.

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The Association between Vitamin D3 Deficiency and Cataract Formation in Baghdad Al-Karkh

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Abstract

Background: Visual impairment is a global issue that is particularly problematic for poor nations. It is linked to diminished physical activity, social isolation, reliance on everyday tasks, and even death. The clouding of the lens inside the eye is called a cataract. It is one of the main causes of blindness and visual impairment in the world. Because of its anti-inflammatory and antioxidant properties, vitamin D, a prohormone in the blood, is crucial to the pathophysiology of many ocular illnesses. Given that oxidative stress and inflammation are significant contributors to the development of cataracts, a number of research have evaluated the relationship between vitamin D3 deficiency and cataract formation.

Objective: Determine whether a vitamin D3 deficiency and cataracts are related.

Patients and Methods: A cross-sectional study that was carried out included a total of 100 cataract patients who are 60 years of age or younger from September 2023 to March 2024 in the Ophthalmology Department of Imamein Kadhimein Medical City, Baghdad, Iraq. Questionnaire form was used which consist of sociodemographic information, socioeconomic status, dietary sources of vitamin D3, sun exposure, anthropometric measures and ophthalmic examination. Vitamin D3 level had been investigated in laboratory of the hospital.

Results: Thirty percent of patients had cortical cataracts, 57% had nuclear cataracts, and 13% had posterior subcapsular cataracts. Sixty-nine percent of patients had a vitamin D3 level that is less than 20 ng/ml. Of the patients, 13% had a vitamin D3 level between 20 and 30 ng/ml, while 18% had a level greater than 30 ng/ml. There is a significant association between the level of vitamin D3 and the type of cataract (p-value = 0.013). Sixty-nine percent of patients with deficient vitamin D3 levels had 9% posterior subcapsular cataracts, 36% cortical cataracts, and 55% nuclear cataracts. Patients with insufficient vitamin D3 levels had 8% posterior subcapsular cataracts, 8% cortical cataracts, and 84% nuclear cataracts. While patients with sufficient vitamin D3 levels had 33% posterior subcapsular cataracts, 22% cortical cataracts, and 45% nuclear cataracts. The body mass index and vitamin D3 level were significantly associated (p-value = 0.003). Patients with a vitamin D3 level less than 20 ng/ml comprised 31% overweight patients, 26% class I obese patients, 26% class II obese

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patients, and 4% class III obese patients. Thirteen percent of these patients had normal weights. Patients with a vitamin D3 level 20-30 ng/ml comprised 46% overweight patients, 23% class II obese patients, and 31% with normal weight. While patients with a vitamin D3 level more than 30 ng/ml comprised 33% normal weight patients and 67% overweight.
Conclusion: Vitamin D3 deficiency has a significant association with cataract formation, especially nuclear and cortical types, sun exposure, educational level, socioeconomic status, and obesity.
Keywords: Visual impairment, Cataract, Vitamin D3.

Introduction

Visual impairment is a global issue, particularly in developing nations (1). Age has been found to be a significant non-modifiable risk factor for cataract disease, which is a complex condition (1). It is prevalent in older adults (2), and it has been linked to decreased physical activity, social isolation, dependence on daily tasks, and even death (3). Opacification of the lens within the eye is known as a cataract (4, 5). It is the primary cause of blindness and loss of usable vision globally, accounting for half of all cases of blindness (16 million cataract cases were reported globally) (4, 5, 6). Although it can occur at any age, it usually manifests itself in later life (1, 4, 5). As the world's population ages, especially in developed nations, the prevalence of this disorder is rising quickly (6). According to studies, the visually significant cataract reduces visual acuity to roughly below the 20/40 level in 2.5% of cases in people ages 40–49, 6.8% in people ages 50–59, 20% in people ages 60–69, 42.8% in people ages 70–79, and 68.3% in people ages 80 and above (4,7). When cataracts occur in young children, they are typically linked to other disorders. For example, diabetes has been shown to increase the likelihood of cataract formation by two to five times (4, 5, 8). When compared to the general population under 40 years of age, the prevalence in diabetic patients may rise to 15–25 times higher (4, 5, 8, 9). Atopic dermatitis, neurofibromatosis, Down syndrome, myotonic dystrophy, and hypoparathyroidism are additional conditions linked to the early development of cataracts (5). In addition to steroid usage, ocular diseases such as uveitis, extreme myopia, retinitis pigmentosa, and blunt and penetrating ocular trauma are among the causes of early cataract formation (5). One controllable risk factor that raises oxidative stress and inflammation is malnutrition (1). As of right now, lens extraction is the only treatment for cataracts (6). Although there are many different kinds of cataracts, the most prevalent ones are cortical, nuclear, and sub-capsular (anterior and posterior) cataracts (10, 11). Depending on the cataract's maturity, it can be categorized as Morgagni an, hyper mature, mature, or immature (10, 11). As a prohormone in the bloodstream, vitamin D is essential for maintaining calcium homeostasis. It is produced in the skin endogenously by exposure to sunlight and diet (4, 12- 14). Vitamin D comes in two different forms: D3 and D2 (4,14). In reality, the skin produces calcitriol, often known as vitamin D3, when it is exposed to ultraviolet Blight. It possesses two metabolic conversions that are necessary for the activation of vitamin D: 1-α hydroxylation in the kidney and 25-α hydroxylation in the liver (4, 12-14). Dietary food intake originating from plants provides the D2 form (4, 14). A number of visual disorders, including glaucoma and diabetic retinopathy, are influenced by vitamin D (15). By preventing the overstimulation of cytotoxic T cells and by blocking the release of pro-inflammatory cytokines and increasing the release of anti-inflammatory cytokines, vitamin D has an anti-inflammatory impact (4, 14, 16, 17, 18). One of the antioxidant vitamins, vitamin D is known to reduce oxidative stress through controlling the expression of genes that are linked to antioxidant defenses (4,14,17,18,19). According to recommendations from the Institute of Medicine, a plasma vitamin D level of ≥30 ng/mL is considered normal, whereas a level of ≥21–30 ng/ml indicates insufficiency, and <20 ng/ml indicates vitamin D deficiency (4, 11, 20, 21). Recent research indicates that vitamin D3 insufficiency is linked to systemic and ocular disorders (1, 4). Given that oxidative stress and inflammation are significant contributors to the development of cataracts, several researches had evaluated the relationship between vitamin D3 deficiency and cataract formation (1, 4, 22).

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In our study, we hope to identify a relationship between the existence of cataract in patients aged 60 years or younger and their serum vitamin D3 level. Previous studies have focused on the link between senile cataract formation and vitamin D3 deficiency (4, 7).

Patients and Methods

The Department of Ophthalmology of Imamein Kadhimein Medical City, Baghdad, Iraq was the site of the current cross-sectional study, for 6 months duration of data collection from 1st of September 2023 to 1st of March 2024. One-hundred cataract patients were collected from outpatient in ophthalmology department of this hospital; Patients were only included if they met our inclusion criteria. Patients who are 60 years of age or younger meet the inclusion criteria, cortical, nuclear and posterior sub capsular cataract. Exclusion criteria are: ocular (surgery, disease, medications, glaucoma, congenital cataract and trauma), complicated cataract, post ocular or systemic cause, steroid use, high myopia, alcohol, smoking, atopic dermatitis, hyperthyroidism, neurofibromatosis, myotonic dystrophy, use of osteoporosis drugs or calcium supplements, diabetes, autoimmune diseases or skin cancer disorders, diagnoses of cancer, or cardiopulmonary diseases.

Questionnaire form

was used in current study and consist of sociodemographic information, socioeconomic status, dietary sources of vitamin D3, sun exposure, anthropometric measures and ophthalmic examination.

1- Sociodemographic information consist of age, sex, education, smoking, alcohol consumption, history of drug use, history of chronic diseases and family history.

2- Socioeconomic status was determined based on standard equation: Education + Occupation + house ownership ×0.5 +car ownership × 0.1 (23).

3- Dietary sources of vitamin D3: fish, salmon, tuna, almond, brazilnut, pumpkin seed, sesame seed, avocado, mushroom, spinach, collard green, egg yolk, beef liver, cheese, yogurt, fortified milk, fortified cereal, fortified juice, dark green vegetables and dark chocolate (24).

4- Sun exposure: is classified into no sun exposure, 10-30 minutes of midday sunshine per day, multiple times / weeks. Individuals with darker skin tones might want slightly more (21).

5- Anthropometric measures: A stadiometer is a portable medical equipment was used to measure body weight and height for all patients, and the formula used to determine body mass index (BMI) was weight in kilograms divided by square height in meters. Class I obesity (BMI 30-34.9), class II obesity (BMI 35-39.9), class III obesity (BMI ≥ 40), underweight (BMI < 18.5), normal weight (BMI = 18.5 -24.9), and overweight (BMI = 25-29.9) were the BMI classifications assigned to the patients (25).

6- Ophthalmic examination: All patients were examined by senior ophthalmologist using slit-lamp bio microscopy for:

a-Anterior segment examination (Cornea. Anterior chamber, pupil, lens and anterior chamber angle) to exclude any abnormalities.

b- Posterior segment (vitreous and retina) examination to exclude any retinal abnormalities.

Slit-lamp retro illumination bio microscopy was used by senior ophthalmologist to classify types of cataract (nuclear, cortical and posterior subcapsular).

Assessment of vitamin D3 level

Vitamin D3 level had been investigated in laboratory of Imamein Kadhimein Medical City. Samples were collected from peripheral blood. To measure the serum vitamin D3 level, 1-2 milliliters of blood were drawn from 100 participants in a sterile tube. Vitamin D3 level was estimated on a FinecareTM FIA Meter II plus SE system using Finecare kits. An immunofluorescent technique was used to estimate vitamin D3 level. The Institute of Medicine has classified vitamin D3 levels based on reference ranges. A plasma level of ≥30 ng/mL is regarded normal, a level of 21–30 ng/ml is considered insufficiency, and a level <20 ng/ml is termed vitamin D3 deficiency (4, 11, 20, 21).

The Statistical analysis

Data input and analysis were performed using the Statistical Package for Social Sciences, version 24 (SPSS 24) program. Simple frequency and percentage measures were used to display the data. The chi square test was used to determine the significance of the association between the

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variables, and a p value of 0.05 or less was deemed statistically significant.

Ethical approval

Imamein Kadhimein Medical City and the Arabic Council of Medical Specialization had granted their official approval. After informing the patients about the purpose and goals of the study, assuring their privacy, and ensuring that the questionnaires were completed anonymously, the patients gave their informed consent. (Document no. 2024HRS863).

Results

The study comprised 100 cataract patients who were 60 years of age or younger. Forty five percent of patients with age group (50-59) years, 36% of them with age 60 years, while patients with age group (40-49) were 15% and 4% of them with age group (30-39) years. Male patients made up 39% of the total, while female patients made up 61%. In 30% of cases, cortical cataracts are present, 57% nuclear cataract and 13% posterior subcapsular cataract. Sixty nine percent of patients have vitamin D3 level less than 20 ng/ml, 13% have a level of 20-30 ng/ml, and 18% have a level greater than 30 ng/ml as shown in table 1. Table 1 also shows that 54% of patient with low socioeconomic status and percentage of medium socioeconomic status was 46% and there is no high socioeconomic status in our study. Class I obesity was 18%, class II obesity was 21%, class III obesity was 3%, and normal weight was 19%. Overweight was 39%. The educational level of patients was 42% illiterate, primary education 24%, secondary education 31% and high education 3%. The percentage of patients who has no sun exposure 49%, daily sun exposure 36%, once /week sun exposure 6% and more than once/week sun exposure 9%.

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Table 1: Frequency distribution of study variables in participant patients

Variables		Frequency	Percent
Age	30-39 year	4	4.0
	40-49 year	15	15.0
	50-59 year	45	45.0
	60 year	36	36.0
Sex	Male	39	39.0
	Female	61	61.0
Socioeconomic status	Low	54	54.0
	Medium	46	46.0
Body mass index	Normal weight	19	19.0
	Overweight	39	39.0
	Obesity class I	18	18.0
	Obesity class II	21	21.0
	Obesity class III	3	3.0
Education	illiterate	42	42.0
	primary	24	24.0
	Secondary	31	31.0
	High	3	3.0
Sun exposure	No sun exposure	49	49.0
	Daily	36	36.0
	Once /week	6	6.0
	> once /week	9	9.0
Type of cataract	Cortical Cataract	30	30.0
	Nuclear Cataract	57	57.0
	Posterior Sub-capsular Cataract	13	13.0
Vitamin D3 level	<20 ng/ml deficient	69	69.0
	20-30 ng/ml insufficient	13	13.0
	> 30 ng/ml sufficient	18	18.0
	Total	100	100.0

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Table 2 shows that Sun exposure and vitamin D3 levels had significant association (p-value = 0.001), Sixty nine percent of patients had vitamin D3 level <20 ng/ml, 52% of them with no sun exposure, 39% with daily 10-30 min sun exposure, 9% with 10-30 min sun exposure once/week. Thirteen percent of patients had insufficient vitamin D3 level, 31% of them with no sun exposure, 46% with daily exposure and 23% with 10-30 min sun exposure once/week. Eighteen percent of patients had sufficient vitamin D3 level, 50% of them with no sun exposure, 17% with daily exposure and 33% with 10-30 min sun exposure once/week.

Table 2: Relationship between sun exposure and vitamin D3

Vitamin D3 level		Sun exposures				Total	P value
		No sun exposure	Daily	Once /week	> once /week		
<20 ng/ml deficient	No.	36	27	6	0	69	0.001
	%	52	39	9	0	100	
20-30 ng/ml insufficient	No.	4	6	0	3	13	
	%	31	46	0	23	100	
> 30 ng/ml sufficient	No.	9	3	0	6	18	
	%	50	17	0	33	100	

Table 3 shows that the level of vitamin D3 and educational attainment are significantly associated, with a p-value of 0.01. Forty eight percent of patients with deficient vitamin D3 level were illiterate and 26%, 22%, 4% had primary, secondary and high educational level respectively. While 46% of patients with insufficient vitamin D3 level were illiterate and 46%, 8%, 4% had primary, secondary educational level respectively. Seventeen percent of patients with sufficient vitamin D3 level were illiterate and 83% of them were with secondary level of education.

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Table 3: Association between Vitamin D3 and Education level

Vitamin D3 level		Education level				Total	P value
		Illiterate	primary	secondary	High		
<20 ng/ml deficient	No.	33	18	15	3	69	0.01
	%	48	26	22	4	100	
20-30 ng/ml insufficient	No.	6	6	1	0	13	
	%	46	46	8	0	100	
> 30 ng/ml sufficient	No.	3	0	15	0	18	
	%	17	0	83	0	100	

Table 4 shows the level of vitamin D3 and socioeconomic status are significantly associated (p-value = 0.001). Sixty five percent of patients with low socioeconomic status had deficient vitamin D3 level (less than 20ng/ml) and 35% of them with medium socioeconomic status. Patients with insufficient vitamin D3 level were 46% low socioeconomic and 54 % medium socioeconomic status. While patients with sufficient vitamin D3 level (> 30 ng/ml) had 17% and 83% with low and medium socioeconomic status respectively.

Table 4: Association between Vitamin D3 and socioeconomic status

Vitamin D3 level		Socioeconomic status		Total	P value
		Low	Medium		
<20 ng/ml Deficient	No.	45	24	69	0.01
	%	65	35		
20-30 ng/ml Insufficient	No.	6	7	13	
	%	46	54		
> 30 ng/ml Sufficient	No.	3	15	18	
	%	17	83		

Table 5 shows that the body mass index and vitamin D3 level are significantly associated (p-value = 0.003). Patients with a vitamin D3 level less than 20 ng/ml comprised 31% overweight patients, 26% class I obese patients, 26% class II obese patients, 4% class III obese patients and 13% with normal weight. Patients with a vitamin D3 level 20-30 ng/ml comprised 46% overweight patients, 23% class II obese patients, and 31% with normal weight. While patients with a vitamin D3 level more than 30 ng/ml comprised 33% normal weight patients and 67% overweight.

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Table 5: Association between Vitamin D3 and body mass index.

Vitamin D3 level		body mass index					Total	P value
		Normal weight	Over weight	Obesity Class I	Obesity Class II	Obesity Class III		
<20 ng/ml deficient	No.	9	21	18	18	3	69	0.003
	%	13	31	26	26	4	100	
20-30 ng/ml insufficient	No.	4	6	0	3	0	13	
	%	31	46	0	23	0	100	
> 30 ng/ml sufficient	No.	6	12	0	0	0	18	
	%	33	67	0	0	0	100	

Table 6 shows that the type of cataract and vitamin D3 level are significantly associated (p-value = 0.013). Sixty-nine percent of patients with deficient vitamin D3 levels (<20 ng/ml) had 55% nuclear cataracts, 36% cortical cataracts and 9% posterior subcapsular cataracts. Patients with insufficient vitamin D3 levels (20-30 ng/ml) had 84% nuclear cataracts, 8% cortical cataracts and 8% posterior subcapsular cataracts. While patients with sufficient vitamin D3 levels (> 30ng/ml) had 45% nuclear cataracts, 22% cortical cataracts and 33% posterior subcapsular cataracts.

Table 6: Association of vitamin D3 level and type of cataract

Vitamin D3 level		Types of cataract			Total	P value
		Cortical	Nuclear	Posterior Subcapsular		
<20 ng/ml Deficient	No.	25	38	6	69	0.013
	%	36	55	9	100	
20-30 ng/ml insufficient	No.	1	11	1	13	
	%	8	84	8	100	
> 30 ng/ml sufficient	No.	4	8	6	18	
	%	22	45	33	100	

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Discussion

One of the main issues with public health is the lack of vitamin D3 (26, 27, 28), and it is now recognized as a pandemic (27). Numerous factors, including decreased sun exposure, poor consumption of vitamin D-rich foods, skin tone, garment selections, obesity, impaired vitamin D synthesis and metabolism and malabsorption syndromes, can contribute to it (26,- 36). The cutaneous generation of vitamin D3 is affected by the following factors: glass, age, skin pigmentation, latitude, time of day, and season (37). In the current study, A strong relationship was found between vitamin D3 level and sun exposure (p-value = 0.001); 69% of patients had a vitamin D3 level <20 ng/ml, 13% had a level 20–30 ng/ml, and 18% had a level > 30 ng/ml. UVB is more common in the spring, summer, and fall between the hours of 10 a.m. and 3 p.m. For light-skinned people, 10 to 15 minutes of sun exposure (over the arms and face, or the arms and legs/hands) is sufficient to produce adequate vitamin D. For people with darker skin, however, further exposure is necessary to manufacture enough cutaneous vitamin D from their melanin. Africans may need six to ten times more sun exposure than Caucasians, whereas Asians from the Indian subcontinent are thought to need three times as much (21). With a p-value of 0.003, this study demonstrates a strong inverse relationship between vitamin D3 levels and obesity. Research has indicated that obesity and being overweight with little sun exposure are linked to a higher risk of vitamin D deficiency, and that there is a inverse relationship between vitamin D levels and obesity (38 - 44) which are agree with the result of current study. Vitamin D shortage and insufficiency in obese people are associated with the sequestration of vitamin D into adipose tissue (44, 45). Research has indicated a noteworthy association between BMI classes and the observation of vitamin D deficiency (40, 46- 48). Vitamin D regulates the expression of genes linked to the process of adipogenesis, inflammation, oxidative stress, and metabolism in adult adipocytes (48). A complex condition, cataracts are one of the main causes of blindness and useful vision loss in the globe (4, 6). In industrialized nations especially, age has been found to be a significant non-modifiable risk factor for the development of cataracts (1, 4, 5, 6, 49). Due to its anti-inflammatory and antioxidant properties (4, 16, 17, 18, 42), vitamin D3 plays a significant role in lens metabolism (50). The results of the current study indicate a significant inverse association (p-value = 0.013) between vitamin D3 level and cataract. Sixty nine percent of patients had deficient vitamin D3 level with different types of cataract, 36% cortical cataract, 55% nuclear cataract and 9% posterior sub capsular cataract. Studies conducted in Iran, South Korea, Turkey, and Egypt showed that serum vitamin D3 levels were inversely associated with nuclear cataract and cortical cataract and not associated with posterior sub-capsular cataract, higher serum vitamin D3 level may be associated with lower risk of cataract. (1, 4, 51, 52, 53, 54, 55), while studies conducted in the United States and Turkey indicated that vitamin D3 deficiency was linked to posterior sub capsular cataract, indicating that increasing vitamin D level intake may lower its incidence (56, 57) the result of current study are agree with previous studies. According to our research, there is a significant association (p-value = 0.001) between vitamin D3 levels and educational attainment. Forty eight percent of patients with deficient vitamin D3 level were illiterate and 26%, 22%, 4% had primary, secondary and high educational level respectively. The explanation of these results may be attributed to that patient had insufficient

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information about the benefit of sun exposure and rich sources of vitamin D3 in the food. The amount of vitamin D3 and socioeconomic status was significantly associated in this study (p-value = 0.001). Sixty five percent of patients with low socioeconomic status had deficient vitamin D3 level (less than 20ng/ml) and 35% of them with medium socioeconomic status. These results may be related to unemployment, poverty and expensiveness of food rich with vitamin D3. Research has indicated that those with a lower socioeconomic class get less vitamin D from their food and spend less time in the sun (58,59)

which are agree with the result of current study.

Conclusion

Vitamin D3 deficiency has significant association with cataract formation especially nuclear and cortical types, sun exposure, educational level, socioeconomic status and obesity.

Source of funding

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Conflict of interest

The author acknowledges no conflict of interest in this study

Recommendation

1- Appropriate sun exposure.

2- Encourage weight reduction.

3- Suggested daily consumption of vitamin D rich food.

4- Vitamin D3 level assessment for early detection of vitamin D3 deficiency

5- Routine ophthalmic examination.

Limitations:

1- Limited time.

2- Overcrowded of ophthalmology outpatients.

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العلاقة بين نقص فيتامين د٣ وتشكيل اعتام عدسة العين في بغداد الكرخ

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الملخص

الخلفية الدراسية: يعد ضعف البصر مشكلة عالمية، خاصة بالنسبة للبلدان النامية ويرتبط بالاعتماد على الأنشطة اليومية وانخفاض النشاط البدني والعزلة الاجتماعية وحتى الوفيات. إعتام عدسة العين هو عتامة العدسة داخل العين. وهو أحد الأسباب الرئيسية لفقدان البصر والعمى في جميع أنحاء العالم. فيتامين د هو هرمون في الدورة الدموية ويلعب دورا هاما في التسبب في أمراض العين المختلفة من خلال آثاره المضادة للالتهابات ومضادات الأكسدة. قامت دراسات مختلفة بتقييم العلاقة بين نقص فيتامين د٣ وتكوين إعتام عدسة العين اعتمادًا على حقيقة أن الإجهاد التأكسدي والالتهاب هما عاملان مهمان في تكوين إعتام عدسة العين.

الهدف من الدراسة: تحديد العلاقة بين نقص فيتامين د٣ وإعتام عدسة العين.

الحالات والمنهجية: تضمنت دراسة مستعرضة اجمالي ١٠٠ مريض أعمارهم ٦٠ سنة واقل يعانون من إعتام عدسة العين أجريت في الفترة من ايلول ٢٠٢٣ إلى اذار ٢٠٢٤ في قسم طب العيون في مدينة الإمامين الكاظمين (ع) الطبية، بغداد، العراق. تم استخدام قائمة الاستبيانات التي تتكون من المعلومات الاجتماعية والديموغرافية، الحالة الاجتماعية والاقتصادية، المصادر الغذائية لفيتامين د ، التعرض لأشعة الشمس، القياسات البشرية، وفحص العيون. تم فحص مستوى فيتامين د٣ في مختبر المستشفى.

النتائج: في هذه الدراسة، كان ٣٠٪ من المرضى مصابين بإعتام عدسة العين القشري، و٥٧٪ مصابين بإعتام عدسة العين النووي، و١٣٪ مصابين بإعتام عدسة العين الخلفي تحت المحفظة. تسعة وستون بالمائة من المرضى لديهم مستوى فيتامين د٣ أقل من ٢٠ نانوجرام/مل. من بين المرضى، كان لدى ١٣٪ مستوى فيتامين د٣ بين ٢٠ و٣٠ نانوغرام/مل، في حين أن ١٨٪ لديهم مستوى أكبر من ٣٠ نانوغرام/مل. هناك ترابط معتد به احصائيا بين مستوى فيتامين د٣ ونوع إعتام عدسة العين (القيمة الاحتمالية = ٠,٠١٣). تسعة وستون في المائة من المرضى الذين يعانون من نقص مستويات فيتامين د٣ لديهم ٩٪ إعتام عدسة العين الخلفي تحت المحفظة، و٣٦٪ إعتام عدسة العين القشرية، و٥٥٪ إعتام عدسة العين النووي. كان لدى المرضى الذين يعانون من نقص مستويات فيتامين د٣ ٨٪ إعتام عدسة العين الخلفي تحت المحفظة، و٨٪ إعتام عدسة العين القشري، و٨٤٪ إعتام عدسة العين النووي. في حين أن المرضى الذين لديهم مستويات كافية من فيتامين د٣ كان لديهم ٣٣٪ إعتام عدسة العين الخلفي تحت المحفظة، و٢٢٪ إعتام عدسة العين القشري، و٤٥٪ إعتام عدسة العين النووي. هناك ترابط معتد به احصائيا بين مؤشر كتلة الجسم ومستوى فيتامين د٣ (قيمة p = 0.003). المرضى الذين لديهم مستوى فيتامين د٣ أقل من ٢٠ نانوجرام/مل هم ٣١٪ من المرضى الذين يعانون من زيادة الوزن، و٢٦٪ من المرضى الذين يعانون من السمنة المفرطة من الدرجة الأولى، و٢٦٪ من المرضى الذين يعانون من السمنة المفرطة من الدرجة الثانية، و٤٪ من المرضى الذين يعانون من السمنة المفرطة من الدرجة الثالثة. ثلاثة عشر في المئة من هؤلاء المرضى لديهم أوزان طبيعية. كان المرضى الذين لديهم مستوى فيتامين د٣ ٢٠-٣٠ نانوجرام/مل ٤٦٪ من المرضى الذين يعانون من زيادة الوزن، و٢٣٪ من المرضى الذين يعانون من السمنة المفرطة من الدرجة الثانية، و٣١٪ من ذوي الوزن الطبيعي. في حين أن المرضى الذين لديهم مستوى فيتامين د٣ أكثر من ٣٠ نانوجرام/مل يشكلون ٣٣٪ من المرضى ذوي الوزن الطبيعي و٦٧٪ من المرضى الذين يعانون من زيادة الوزن.

الاستنتاجات: نقص فيتامين د٣ له علاقة كبيرة بإعتام عدسة العين وخاصة النووية والقشرية، والتعرض لأشعة الشمس، والمستوى التعليمي، والحالة الاجتماعية والاقتصادية والسمنة.

الكلمات المفتاحية: ضعف البصر، إعتام عدسة العين، فيتامين د٣.

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Early Childhood Cholestasis, Causes & Associated Factors in Children

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Abstract

Background: Newborn cholestasis is explained as a persisted rise of the serum conjugated bilirubin outside the first two weeks of life. There are many etiologies of newborn cholestasis that must be differentiated since immediate interference may give a better outcome.

Objective: Newborn cholestasis is explained as a persisted rise of the serum conjugated bilirubin outside the first two weeks of life. There are many etiologies of newborn cholestasis that must be differentiated since immediate interference may give a better outcome.

Patients and Methods: A cross-sectional research of forty-eight children consulting the Childhood Wellbeing Teaching Hospital in Baghdad/Medical City from 1st of November 2018 to the 30th of November 2021, complete evaluation by full history, physical checkup and laboratory studies. Cholestasis was demarcated as an extended raise of the levels of conjugated bilirubin outside the 1st 2 weeks of age above 1.0mg/dl(17.1µmol/l) if the whole serum bilirubin(TSB) is <5.0 mg/dL or above 20% of the TSB if the TSB is >5.0 mg/dl.

Results: Out of 48 children involved in the study ,62.5% resided in Baghdad, and the remainder was belonged to other districts. The mean age of children was 11.1 months. The males constituted 58.3% of them. Eleven cases (22.9%) were caused by congenital infection, nine 18.8% had no cause detected, while 16.7% caused by biliary atresia and 16.7% had unidentified etiology, however 10.4% was related to sepsis. Biliary atresia was more frequent in boys in 62.5% compared to 37.5% in females. Family history was positive only in11.1% of idiopathic neonatal hepatitis. It was found that 81% of cholestatic jaundice were caused by congenital infection. In comparison, 62.5% caused by biliary atresia and 60% caused by sepsis appeared on the second week of the child's age, and this difference was significant statistically P-value 0.01.

Conclusion: Innate infections are the most frequent source, where CMV contagion is the most commonly detected. Clinical findings included clay colored stool & elevated alkaline phosphatase concentrations observed primarily on biliary atresia. There are no specific test to identify the etiology of newborn cholestasis.

Keywords: Cholestasis, children, causes, associated factor

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Introduction

Newborn Cholestasis is demarcated as continued raise of the concentrations of conjugated bilirubin outside the initial 2 weeks of life more than 1mg/dl (17.1micromol/l) if the whole serum bilirubin is <5 mg/dL (85.5 µmol/l) or more than 20 % of the total serum bilirubin if the total serum bilirubin is >5 mg/dl (85.5 µmole/L). Neonates with jaundice outside two weeks after birth should be assessed for conjugated hyperbilirubinemia. (1-5). Conjugated hyperbilirubinemia occurs in approximately 1 / 2500 infants and is less common than unconjugated hyperbilirubinemia. (6-9). There are various etiologies of neonatal cholestasis, and essential to be differentiated since immediate interference, the outcomes will be better. Furthermore, other treatable illnesses such as (tyrosinemia, galactosemia, hypothyroidism, and infectious etiologies) initiate early effective therapy. (10-15). If jaundice continues, detection of whole and direct serum bilirubin might be done. (3,16-18). The most frequent etiologies of cholestasis in babies are biliary atresia (BA) (extra & intrahepatic) and neonatal hepatitis (NH), a diagnosis that is imparted to broad-based liver disorders, which occurs secondary to various causes comprising intrauterine infection, endocrine illnesses and inherited error of metabolism (17-23). A hepatic biopsy is the only best absolute analysis in assessing neonatal cholestasis. In numerous center searches, identification of biliary atresia was accurately implied by hepatic biopsy histologic results in 90 to 95 % of circumstances. (24-28). Management is supportive and directed toward promoting development and growth and handling the problems of prolonged cholestasis, such as malabsorption, nutritional deficiencies, pruritis, as well as portal hypertension (29-32). The Kasai portoenterostomy used for biliary atresia at age of 6-8 weeks of age which may be curative (33-38). For children with late hepatic disorder, liver transplant has an accomplishment rate of >85% [6, 20,39-42]. The natural history of cholestatic syndromes in childhood remains unclarified, mainly due to insufficient data in our country. This study aimed to determine the possible causes and some associated factors of neonatal cholestasis in patients consulting the childhood's Wellbeing Teaching Hospital/Baghdad

Patients and Methods

A cross-sectional study of forty-eight babies consulting the Childhood Wellbeing Teaching Hospital in Baghdad/Medical City from 1st of November 2018 to the 30th of November2021. The patients were assessed by full history, exam and laboratory tests. Cholestasis was demarcated as an extended raise of the levels of conjugated bilirubin outside the 1st 2 weeks of age above 1.0mg/dl(17.1µmol/l) if the whole serum bilirubin(TSB) is <5.0 mg/dL (85.5 µmole/l) or above 20 per cent of the TSB if the TSB is >5.0 mg/dl (85.5 µmole/L). (5,9). The evaluation included a history that includes [maturity, gender, weight at birth, blood group and mother and baby, age, onset of jaundice, the color of feces, household similar history or any hepatic or long-lasting illness, history of miscarriage or baby death. Full physical examination, and any significant systemic signs or findings were taken into consideration. Laboratory tests which included liver enzymes (alanine transferase, aspartate transferase, alkaline phosphate) conjugated and unconjugated bilirubin level, prothrombin time (PT), partial thromboplastin time(PPT), kidney function tests. Full blood count and blood picture, CRP, blood culture, general urine examination, urine culture, abdominal ultrasound, and specific tests were done for most of the children as needed, which included TORCH screen, thyroid gland tests (T3, T4, TSH), metabolic screen we depended on (MS/MS) and liver biopsy for selected patients. The scientific council of the Arab Board of

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Pediatrics approved the study protocol. approval of the hospital director was taken, as well as verbal permission from patients families (parents or other relatives). Patients' information was remained confidential (electronic) and not revealed to non-legal individuals. Statistical analysis: SPSS version 21 was applied for information entrance and scrutiny, results were displayed as count and percent, mean and standard deviancy were used, and appropriate statistical tests were used for data analysis.

Results

The mean age of children was 11.1 months±12.4 SD, and girls were 20(41.7%), and boys were 28 (58.3%), (30) 62.5% came from the capitol, and the others were from other districts of the report group. The results showed that 11(22.9%) were caused by inborn infection (Cytomegalovirus infection 10 cases (91%) was the most typical cause of intrauterine infections and 9 (18.8%) of conditions were no etiology found, 8(16.7%) instigated by biliary atresia, 8(16.7%) of unidentified source, as seen in table.1

Table 1. Etiology of cholestasis in patients group

The Etiology	Frequency	Per cent
Congenital infections	11	22.9
INH	9	18.8
Biliary atresia	8	16.7
Sepsis	5	10.4
Progressive familial intrahepatic cholestasis	2	4.2
Alagille syndrome	1	2.1
Choledochal Cyst	1	2.1
Galactosaemia	1	2.1
Hypothyroidism	1	2.1
Tyrosinemia	1	2.1
Unspecified	8	16.7
Total	48	100.0

There was considerable correlation between the etiologic cause and timing of beginning of jaundice, where 81% of cholestatic jaundice were caused by congenital infection. In comparison, 62.5% caused by biliary atresia and 60% caused by sepsis appeared on the second week of the child's age, and this difference was significant statistically (P-value 0.01), as seen in the table.2

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Table 2. Relationship between etiology of the disease and time of appearance of jaundice after birth.

Diagnoses		Time of onset of jaundice				
		<1 week		≥1 week		
	Total No.	No.	%	No.	%	P-value
Congenital infection	11	9	81.8%	2	18.2%	0.01
Idiopathic neonatal hepatitis	9	7	77.8%	2	22.2%	
Biliary atresia	8	3	37.5%	5	62.5%	
Sepsis	5	2	40.0%	3	60.0%	

The highest percentage of jaundice triggered by inborn infection and idiopathic neonatal hepatitis (63.6%, and 55.6%, respectively) were presented with intermittent clay color feces. In contrast, all that was triggered by biliary atresia manifested with continuing clay-colored feces and altogether that were produced by septicemia were presented with standard colored feces, with a difference statistically significant as seen in table.3.

Table 3. Relationship between etiology of the disease and stool color of patients with jaundice

Diagnoses	Feces color									p-value
	Clay stool			intermittent clay			Normal			
	Count	Row N %	Column N %	Count	Row N %	Column N %	Count	Row N %	Column N %	
Congenital infection	0	0.0	0.0	7	63.6%	58.3%	4	36.4%	36.4%	0.01
Idiopathic neonatal hepatitis	2	22.2%	20.0%	5	55.6%	41.7%	2	22.2%	18.2%	
Biliary atresia	8	100.0%	80.0%	0	0.0	0.0	0	0.0	0.0	
Sepsis	0	0.0	0.0	0	0.0	0.0	5	100.0%	45.5%	

No significant difference was detected (Pvalue≥0.05 for altogether) with respects to the level of liver enzymes, TSB and direct bilirubin amongst babies owing to diverse etiologies, and only substantial variance was seen with Alkaline phosphatase concentration (p=0.01) as shown in the table.4

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Table 4. The different Lab. tests matching with etiological factors.

Lab Tests	Etiology	N	Mean	Std. Deviation	p-value
ALT(U/L)	Congenital infection	11	144.1	70.7	0.5
	INH	9	56.7	34.9	
	Biliary atresia	8	139.0	258.3	
	PFIC	2	78.5	14.8	
AST(U/L)	Congenital infection	11	201.2	117.2	0.8
	INH	9	130.6	145.2	
	Biliary atresia	8	200.1	186.8	
	PFIC	2	102.0	19.7	
Alkaline Phosphatase (U/L)	Congenital infection	11	277.5	203.4	0.01
	INH	9	151.7	140.9	
	BA	8	692.5	312.1	
	PFIC	2	1183.5	426.1	
TSB(mg/dl)	Congenital infection	11	8.1	203.4	0.08
	INH	11	7.6	3.1	
	Biliary atresia	9	12.6	3.4	
	PFIC	2	13.5	5.0	
Direct(mg/dl)	Congenital infection	11	6.5	3.2	0.3
	INH	9	6.2	3.2	
	Biliary atresia	8	8.6	2.9	
	PFIC	2	10.9	12.7	

Ultrasound scanning of the abdomen found that 19(39%) of patients showed enlarged liver, 29.1% was normal, 7(14.6%) enlarged liver with signs of biliary atresia, 7(14.6%) enlarged liver and spleen and just one choledochal cyst as shown in the table.5

Table.5. Abdominal ultrasound findings for the studied 48 patients.

Ultrasound findings	Frequency	Per cent
Enlarged liver	19	39.6
Enlarged liver with signs of Biliary atresia	7	14.6
Enlarged liver and spleen	7	14.6
Choledochal Cyst	1	2.1
Normal	14	29.1
Total	48	100.0

The enlarged liver was more evident in patients with BA, INH, and congenital infections, 87.5% of biliary atresia cases had characteristics signs by ultrasound test, which is a significant finding P value 0.001. The typical ultrasound finding was found in all cases of sepsis, as seen in the table.6

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Table 6. Relationship of ultrasound finding and etiological factors.

Etiology		Abdominal US				p-value
		enlarged liver with signs of Biliary atresia	enlarged liver	enlarged liver &spleen	Normal	
Congenital infection	No.	0	6	2	3	0.001
	% within etiology	0.0	54.5%	18.2%	27.3%	
Idiopathic neonatal hepatitis (INH)	No.	0	5	2	2	
	% within etiology	0.0	55.6%	22.2%	22.2%	
Biliary atresia(BA)	No.	7	0	1	0	
	% within etiology	87.5%	0.0%	12.5%	0.0	
progressive familial intrahepatic cholestasis(PFIC)	No.	0	1	1	0	
	% within etiology	0.0	50.0%	50.0%	0.0	
Sepsis	No.	0	0	0	5	
	% within etiology	0.0	0.0	0.0	100.0%	

Of 13 patients with liver biopsy, it was found that 9(18.8%) of them showed idiopathic neonatal hepatitis characteristics,4.2% showed PFIC characteristics,2% biliary atresia characteristics and 2% of nonspecific findings, as seen in the table.7.

Table.7. Finding of liver biopsy of 13 studied patients

	Frequency	Per cent
Idiopathic neonatal hepatitis	9	69.21
PFIC	2	15.38
Biliary atresia	1	7.69
Nonspecific findings	1	7.69
Total	13	100.0

The study revealed a significant association (P value 0.02) between etiological factors and the family history of patients, which should withdraw the attention toward the etiology of cholestasis, as seen in the table.8.

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Table 8. Relationship between the most common causes of cholestasis & family history of cholestasis

			Family history		p-value
			N-ve	P+ve	
Etiology	Congenital infection	Count	10	1	0.02
		% within etiology	90.9%	9.1%	
	Idiopathic neonatal hepatitis	Count	8	1	
		% within etiology	88.9%	11.1%	
	Biliary atresia	Count	8	0	
		% within etiology	100.0%	0.0%	
	Sepsis	Count	5	0	
		% within etiology	100.0%	0.0%	

There was no significant relationship between gender of the children and the etiological factors P value0.7 , as seen in table 9.

Table 9. Relationship of etiological factors and gender of 48 patients.

Diagnoses		Gender		
		Male	female	*P value*
Congenital infection	Count =11	6	5	0.7
	% within Diagnoses	54.5%	45.5%	
Idiopathic neonatal hepatitis	Count =9	7	2	
	% within Diagnoses	77.8%	22.2%	
Biliary atresia	Count =8	5	3	
	% within Diagnoses	62.5%	37.5%	
Sepsis	Count =5	3	2	
	% within Diagnoses	60.0%	40.0%	

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Discussion

Hyperbilirubinemia is a usual symptom in the first 14 days of life, which can be physiological or due to breast milk. Nonetheless, if it continues for over 14 days, it implies a crucial reserve (28-30). The cholestasis analysis has been a big task for pediatricians, and the prompt verdict is critical since the efficacy of therapy is more in early identification. For instance, various studies revealed that detecting biliary atresia in the first two months of life is much better for the efficiency of operation than in three months (31-33). Even if an exact therapy is unavailable, an early opinion can lead to quickly reassuring therapy to decrease the problems of cholestasis, like hemorrhage caused by vitamin K defect. (28,42,43) . We found that, the most common cause was a congenital infection, 22.9%, followed by idiopathic neonatal hepatitis, 18.8%., while one patient 2.1% was related to each of the following etiologies: Alagille syndrome, choledochal cyst, galactosemia, hypothyroidism plus tyrosinemia ,however 16.7%) were of unknown origin, this is in agreement with Matthai J, et al. and other studies (25,34), and from 14(38.8%) with neonatal hepatitis, 16.2% were related to CMV, and 5.4%) were positive for herpes virus which suggests that 21.6% due to congenital infections as the most common cause. BA was seen in 7(18.9%), NH in six cases 16.2%), five patients had metabolic etiologies, one with hypothyroidism, these findings disagrees with previous studies (35,44-48), which revealed that BA was the commonest etiology of cholestatic jaundice. Moreover this study disagrees with most recent studies (36,49-51). This disagreement may be due to declines in antenatal care and maternal health in the last years in our country as well as clinical awareness about the etiology of the problem. Also, a small number of patients underwent liver biopsies, where 8 cases (16.7%) of unknown etiology, and this decreased the percentage of both BA and INH. We found CMV infection in ten cases 91% which is the most frequent agent of intrauterine infections, followed by toxoplasmosis infection and this is in agreement with other studies (35,42,43,50). Moreover, our finding agrees with Matthai J, Paul S. et al. (32). Genetic and metabolic diseases were detected in 8.2%, progressive familial intrahepatic cholestasis in 4.1% of patients. These findings are like Dehghani SM et al. study (36). Due to the lack of facilities for metabolic and genetic testing in our center as well as many patients did not have a liver biopsy; which may be due to postponements in cases referral, abnormal PT, PTT, family rejection and the fact that absence of liver transplant center, eight patients (16.7%) considered as having unknown cause, as in Dehghani SM et al. study (36). Moreover, in Al-azzawi study (35), in Baghdad 9 patients (18%), had no obvious etiology to be uncovered. The current study showed that INH was more frequent in 7 boys (77.8%) than in two females (22.2%), which agree with. WongsawasdiL et al. study (37), in Chiang Mai University, in which the male was 13 cases and female was 10 cases, also B. A was more frequent in males, with 5 (62.5%) as compared with 3 (37.5%) in females, which disagree with that study, which show 14 cases and 17 cases, and this is due to that in our studied patients, males constitute 28(58.3%) which were higher as compared with females 20 (41.7%).also, this study matches with Dehghani SM et al. study (36) , in which INH was detected in 20 males, and 10 cases were females, while BA had 13 cases were male, and 17 cases were female, which disagrees with our study; this is because the study took a large sample(122 cases), while our sample was only 48 cases; moreover our community paid more attention to males than females. In this study, the persistent clay-color stool was more frequent in all patients with BA, while in Wongsawasdi study INH, had more intermittent clay feces, and this agrees with Dehghani SM et al. study (36) and similar to Wongsawasdi L et al. study (37) in

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Turkey, alcoholic stool was observed in all patients in the BA group but only in 10 cases (37%) in the non-B.A group [38]. Our finding also agrees with the Sinha CK et al. study and others (39,42,43), in which all patients with BA present with changing levels of obstructive jaundice and light non-pigmented feces. In this study, the onset of jaundice in INH is more in the initial seven days of life, while in BA, mainly after the initial 7 days of life, and this helped identify the etiology of the disease, Which disagrees with the Dehghani SM et al. study (36), in which there was no substantial relationship between the age of jaundice commencement and the etiology of Cholestasis. This study revealed that B. A cases did not correlate with family history, and 11.1% of INH cases had a household record of a alike disorder, as in Ağın M et al. study (38), in Turkey in which none of the BA cases had a family history of a similar disease. In this research, the alkaline phosphatase concentration shows a significant alteration, largely between the BA and INH had high S.ALP levels in preference of BA. In contrast, the total and direct serum bilirubin levels and both S.ALT S.AST show no significant difference, and this agrees with Al-azzawi S et al. study (35), in Baghdad in which the biochemical profile showed that S.ALP level was increased in BA patients rather than in NH and total serum bilirubin transaminases levels have no influence on the differential diagnosis, since both of them may similar enzymes changes. In the Dehghani SM et al. study (36), the parallel of liver function tests in various etiologies of cholestasis does not help determine the causes of cholestasis, and this agrees with our study. In contrast, the ALP in our study was significant finding, which is different from that study. Furthermore, this study disagrees with other studies (39,40,41) in which transaminases were definite in discriminating biliary atresia from neonatal hepatitis or other etiologies of cholestasis. This study revealed that 39.6% of cases had hepatomegaly, and 14.6% had hepatomegaly with the signs of BA and 14.6%had hepatosplenomegaly, which means collectively that 66.8% of cases had hepatomegaly and 14.6% had splenomegaly which is in agreement with Dehghani SM et al. study [36]. In this study, all the cases of B. A had hepatomegaly, and 12.5% had splenomegaly. In comparison, in INH, 77.8% had hepatomegaly, and 22.2 % had splenomegaly, which agrees with the Dehghani SM et al. study (36), in which there was no relationship between the etiologies of cholestasis and the presence of hepatomegaly and splenomegaly, and in comparison, with Deghady AM et al. study (40), in Alexandria, in which 94.2% of BA cases had hepatomegaly is slightly lower than our study, and 96.6% of INH cases had hepatomegaly, which is higher than our study; splenomegaly was found in 29.4% of BA cases and in 69% of INH cases in that study, which is higher than our study. Moreover our findings are similar to Al-azzawi S et al. report (35) in Baghdad in which enlarged liver was also discovered in all patients with BA. The limitations of this study are lack of family compliance and delayed cases referral, and the necessity for teaching of practitioners and pediatricians about the etiologies of cholestasis and its identification, and the lack of electron microscopy and immunohistochemical study by liver biopsy, the need for further investigations like hepatobiliary scintigraphy, and the limitation of facilities that needed for the diagnosis of genetic and metabolic disorders.

Conclusion

inborn infections are the most frequent etiology in this study, in which CMV infection was the utmost frequent etiology of intrauterine infections. Constant mud color feces, high alkaline phosphatase concentration mainly observed in BA. There was no specific procedure to identify the etiology of newborn with cholestasis. Certainly, the identification may only be proved utilizing all existing procedures.

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Ethical clearance

Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023AHI808).

Conflict of interest

The author acknowledges no conflict of interest in this study

Recommendations

Good maternal and antenatal care to control and reduce the risk of congenital infections. A significant number of cholestasis in this study has unknown etiology, so we recommend to establish center or units in children hospitals for metabolic diseases screening.

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اسباب الركود الصفراوي لحديثي الولادة في مستشفى حماية الاطفال التعليمي

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الملخص

الخلفية الدراسية: يعرف الركود الصفراوي عند الأطفال حديثي الولادة على أنه ارتفاع مستمر في البيليروبين المترافق في الدم بعد الأسبوعين الأولين من الحياة. هناك العديد من مسببات الركود الصفراوي عند الأطفال حديثي الولادة والتي يجب التمييز بينها لأن التداخل الفوري قد يعطي نتيجة أفضل.

الهدف من الدراسة: الكشف عن أسباب الركود الصفراوي في مرحلة الطفولة المبكرة ودراسة بعض العوامل المرتبطة به.

طرق العمل: بحث مقطعي لثمانية وأربعين طفلاً يراجعون مستشفى صحة الطفولة التعليمي في بغداد / المدينة الطبية في الفترة من ١ نوفمبر ٢٠١٨ إلى ٣٠ نوفمبر ٢٠٢١، التقييم الكامل عن طريق التاريخ الكامل والفحص البدني والدراسات المخبرية. تم تحديد الركود الصفراوي على أنه زيادة ممتدة في مستويات البيليروبين المترافق بعد الأسبوعين الأولين من العمر فوق ١ ملجم / ديسيلتر) إذا كان البيليروبين في المصل بأكمله (TSB) أقل من ٥ ملجم / ديسيلتر أو أعلى من ٢٠٪ من TSB إذا كان TSB أكبر من ٥ ملجم/ديسيلتر.

النتائج: من بين ٤٨ طفلاً مشاركاً في الدراسة، كان ٦٢,٥٪ يقيمون في بغداد، والباقي ينتمي إلى مناطق أخرى. وكان متوسط عمر الأطفال ١١,١ شهرا. وشكل الذكور ٥٨,٣٪ منهم. إحدى عشرة حالة (٢٢,٩٪) كانت ناجمة عن عدوى خلقية، وتسع حالات (١٨,٨٪) لم يتم اكتشاف سبب لها، في حين أن ١٦,٧٪ كانت ناجمة عن رتق القناة الصفراوية و١٦,٧٪ كانت مسبباتها غير محددة، ولكن ١٠,٤٪ كانت مرتبطة بالإنتان. وكان رتق القناة الصفراوية أكثر شيوعاً عند الأولاد بنسبة ٦٢,٥٪ مقارنة بـ ٣٧,٥٪ عند الإناث. كان تاريخ العائلة إيجابيًا فقط في ١١,١٪ من حالات التهاب الكبد الوليدي مجهول السبب. وقد وجد أن ٨١٪ من حالات اليرقان الركودي كانت بسبب عدوى خلقية. بالمقارنة، ٦٢,٥٪ ناجمة عن رتق القناة الصفراوية و٦٠٪ ناجمة عن الإنتان ظهرت في الأسبوع الثاني من عمر الطفل، وكان هذا الفرق ذو دلالة إحصائية بقيمة P-0.01.

الاستنتاجات: تعد العدوى الفطرية المصدر الأكثر شيوعًا، حيث تكون عدوى الفيروس المضخم للخلايا (CMV) هي الأكثر شيوعًا. وشملت النتائج السريرية البراز ذو اللون الطيني وارتفاع تراكيز الفوسفاتيز القلوية التي لوحظت في المقام الأول على رتق القناة الصفراوية. لا يوجد اختبار محدد لتحديد مسببات الركود الصفراوي عند الأطفال حديثي الولادة.

الكلمات المفتاحية: الركود الصفراوي، الأطفال، الأسباب، العوامل المرتبطة به .

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Compare nasal endoscopy with Computed Tomography scans for chronic rhinosinusitis detection in adult Iraqi patients

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Abstract

Background: Chronic rhinosinusitis (CRS) is often diagnosed based on clinical features. Assurance in this context is based on the finding of inflammatory features during nasal endoscopy and computed tomography (CT) scans of the paranasal sinuses. While a CT scan is considered the most reliable method, research has shown that nasal endoscopy is also valuable and can sometimes provide additional information to supplement the CT scan in diagnosing CRS.

Objective: The study goal was to demonstrate the comparative reliability of nasal endoscopy and computed tomography scans in diagnosing chronic rhinosinusitis in adult patients treated at Baqubah Teaching Hospital.

Patients and Methods: The study sample consisted of consecutive adult participants clinically diagnosed with chronic rhinosinusitis. Patients who had a computed tomography scan of the paranasal sinuses and a nasal endoscopy during three months were the subjects of this investigation; the outcomes were linked.

Results: Study results exhibit that the most prevalent symptoms seen in the study participants were nasal discharge and nasal obstruction, reported by 95% and 90%, respectively; the most prevailing observation during nasal endoscopy was middle meatus purulent discharge, noticed in 58% of the patients. Maxillary sinus was most often affected, seen in 65% of the patients on a CT scan, and 40% had obstruction of the osteomeatal complex on CT imaging. The nasal endoscopy had a sensitivity of 73.3%, specificity of 85.3%, positive predictive value of 92.7%, and negative predictive value of 55.8%. The research also found no significant differences in positive predictive value (PPV) between nasal endoscopy and CT scan. In contrast, the sensitivity of nasal endoscopy was significantly greater than that of CT scan.

Conclusion: The study found that nasal endoscopic findings for patients with positive clinical features were purulent (cream-colored) discharge and middle meatus polyps, which is sufficient for diagnosing chronic rhinosinusitis; the study showed that Nasal endoscopy is almost as accurate as CT scans and CT scan findings are well correlates with sinus endoscopy, due to its precision, cheap cost, and radiation dosage.

Keywords: chronic rhinosinusitis, nasal endoscopy, Computed Tomography Scan, Baqubah Teaching Hospital.

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Introduction

Chronic rhinosinusitis (CRS) is one of the most common chronic health conditions, and its incidence is increasing worldwide. CRS affects about 1 in 7 adults in the US population (prevalence rate of 12.5%). CRS significantly reduces the patients' quality of life and causes functional and emotional impairment Various conditions contribute to the pathophysiology of CRS. The etiology of CRS may be inflammatory, such as viral, bacterial, and fungal infections, allergy and asthma, and polyposis, or noninflammatory, such as neural dysfunction, nociceptive dysfunction, and gastroesophageal reflux (1). The Chronic rhinosinusitis (CRS) is distinguished by continuous inflammation of the mucous membranes of the nose and paranasal sinuses, lasting for 12 weeks or more (2), Due to its high sensitivity and specificity, standard computed tomography (CT) scanning is the gold standard method for CRS diagnosis, Despite the high accuracy of conventional CT scanning, its high costs and high radiation doses have limited its application (1). Endoscopy of the paranasal sinuses allows the observation of anatomical areas and the evaluation of sino nasal lesions and their relationship with endonasal structures. Diagnostic sinus endoscopy is an invasive and costly method for the assessment of CRS that needs local or general anesthesia. In addition, it cannot be applied to all patients, may be difficult or impossible in children, and may be associated with severe complications. Regarding these limitations, finding an alternative diagnostic modality is beneficial (1). The diagnostic criteria for chronic rhinosinusitis (CRS) submitted by (AAO)– (HNS) Foundation depend on the existence of profitable clinical characteristics, as well as evidence of inflammation noticed during paranasal sinuses CT scan and nasal endoscopy (1, 3). The primary and secondary CRS symptoms were minimized to less than five distinguishable symptoms, and inflammation of the middle meatus was formed in the diagnostic criteria for CRS to improve diagnosis accuracy via objective data (1, 4) A duration of 12 or more needs to exhibit more than two manifestations, such as mucopurulent drainage, nasal blockage, pain-pressure-fullness of the Face, and hyposmia (1, 5).

A nasal endoscopy is inspected by illuminating and magnifying the nasal cavity, meatus, and nasopharynx (6, 7), yet a CT scan delivers specific and vast details on the inside architecture of the nose and sinuses and any current abnormalities or illnesses. Divergent results have been reported concerning the link between the finding of nasal endoscopy and CT scan of the sinus in persons with chronic rhinosinusitis (CRS). (8, 9). Finding out how nasal endoscopy stacks up against CT scans in our setting in terms of sensitivity, specificity, (PPV), (and NPV) is crucial from an economic viewpoint for our patients. Specially for patients with restricted finances, the results will help direct the selection of study in CRS patients. Consequently, various research was achieved to evaluate endoscopy accuracy corresponding to CT scans for diagnosing CRS (4, 10, 11). Studies have demonstrated that nasal endoscopy improves the accuracy of diagnosing chronic rhinosinusitis (CRS) in individuals who fulfill the symptom criteria outlined in the recommendations. Diagnostic nasal endoscopy permits lessening the demand for CT scans, lowering costs, and minimizing radiation exposure (12). Previous studies have not shown a relation between endoscopy and CT scan accuracy in diagnosing CRS among Iraqi society, especially patients from Baqubah City. Our study explores this correlation between endoscopy and CT scans as diagnostic tools for CRS, in particular, Baqubah City patients.

Patients and Methods

Study population

The investigation was performed in the (ENT) Department outpatient clinic at Baqubah Teaching Hospital, located in the Diyala government, Iraq. It was a prospective study.

We chose 100 adults at random from a pool of 134 cases; individuals with a clinical diagnosis of CRS and a terminated permission form were Participants aged 18 to 63. The enrollment period was three months, from October 2023 to January 2024. Participants had CT scans and nasal endoscopies of the paranasal sinuses as part of the research. Chronic rhinosinusitis (CRS) diagnosis was confined to utilizing the clinical practice guidelines for adult rhinosinusitis patients authorized by (AAO–HNSF). (Table 1) (1).

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Patient data, medical history, and physical examination outcomes were acquired by employing a standardized questionnaire.

Excluded criteria

People under the age of 18, patients with (who had sino nasal surgery, sino nasal tumor, immunocompromised, cystic fibrosis, and who refused to give consent). They were removed from the sample population. Participants could not receive a CT scan of the paranasal sinuses simultaneously with a nasal endoscopy or if there was more than a three-month gap between the two procedures.

Investigation

A Senior Resident Doctor performed a nasal endoscopy in the clinic employing a zero-degree and thirty-degree Medtronic 4-millimeter rigid endoscope while the patient was under topical anesthesia. Disc documentation of endoscopic findings was done. An Otorhinolaryngology specialist assessed and estimated a grade to this. The expected notable observations showed purulent discharge (creamy color), meatal or ethmoidal mucosal edema, and polyps in the middle meatal region or nasal cavity. After twelve weeks of the nasal endoscopy, a CT scan of the paranasal sinuses was performed. A consultant radiologist documented this data. The important predicted findings possessed sinus mucosal thickening, sinus opacification (OMC) obstruction, and polyps. Manifestation of polyps possesses thickening of bone trabeculae, spherical lumps within the nasal cavity, an enlarged sinus or parts of the nasal cavity, and enlarged sinus ostia. The thickening of two or more sinus walls was employed to demonstrate mucosal thickening of the sinus, whereas sinus opacification was indicated as partial or complete opacification. Right or left pansinusitis involves all four sinuses on one side. Bilateral pansinusitis concerns all four sinuses on both sides. Sinus opacification was categorized as entire or partial. The Philips Brilliance 64-slice CT employed in this investigation was a 2007 model—hospital CT scan machine. Coronal, sagittal, and axial images were taken utilizing 2 mm incisions.

Ethical approval

The University approved the study of Diyala's Baqubah medical faculty. The data for the questionnaire was obtained with the patient's permission. (Document no. 2024ALS841).

Statistical analysis

The data were scrutinized employing IBM version 23 of (SPSS). The numeric variables, standard deviation, and standard error were estimated ($P \leq 0.05$). Nasal endoscopy corresponded to paranasal sinus CT images. Nasal endoscopy sensitivity, specificity, PPV, and NPV were compared to CT scan findings table 1. (13, 14).

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Table (1): Criteria for CRS diagnosis seen in Nasal Endoscopic or CT scans the Purulent middle meatus/anterior ethmoid mucus can see in Nasal Endoscopic, the Paranasal sinus inflammation more Diagnoses by CT, SCAN

	Findings	
Manifestation	**Nasal Endoscopic**	**CT scan**
Front/back nasal mucopurulent drainage, Congestion/obstructed nose, Face pain/pressure/fullness, hyposmia	**Purulent middle meatus/anterior ethmoid mucus/edema, Nasal/middle meatus polyps**	**Paranasal sinus inflammation**
Two or more symptoms and signs, together with one or more inflammatory abnormalities on endoscopic or CT scans, must be present for 12 weeks in order to diagnose CRS.		

Results

One hundred thirty-four adult patients were recognized with chronic rhinosinusitis (CRS) over a three-month study course spanning from October 2023 to January 2024 in the outpatient unit of (ENT) clinic. One hundred individuals were consecutively recruited in the experiment. Out of all the patients, 74.6% were qualified for the trial, while the remaining 25.3% were disqualified because they could not have both nasal endoscopy and CT scan within a 3-month; the study included individuals aged 18 to 65, with 41% being male and 59% being female. Individuals between the ages of 25 and 44 comprised 53% of the total population. Patients' CRS symptoms and frequencies are shown in Table (2).

Table (2): Diagnostic criteria for chronic rhinosinusitis in the study population. Show the rhinorrhea occur in 95 % ,he of study population and nasal obstruction occur in 90% the headache pressure, Pain,fullness of the face hyposmia/anosmia , excessive sneezing occur in 65%,50%45%,44% respectively

Diagnostic characteristics of CRS	Patients number
Rhinorrhea	**95**
nasal obstruction	**90**
headache	**65**
pressure, Pain, the fullness of the face	**50**
hyposmia/anosmia	**45**
excessive sneezing	**44**
nose, throat, and ear itching	**42**
cough	**34**
epistaxis	**32**
halitosis	**30**
dental pain	**17**
SD	**20.437**
SE	**6.463**
P- value	**0.0001***
*** Significant (P ≤ 0.05)/ n=100**	

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Purulent (cream-colored) middle meatus discharge was the most prevalent symptom on nasal endoscopy (58%). Subjects had 39% middle meatal edema and 30% nasal polyps. table (3).

Table (3): Nasal endoscopy findings indicate middle meatal discharge at 58%, middle meatal mucosal edema at 39%, and nasal polyps at 30%.

Nasal endoscopy findings	Patients number
Middle meatal discharge	58
Middle meatal mucosal oedema	39
Nasal Polyps	30
SD	6.364
SE	4.500
P- value	0.083
* Significant (P ≤ 0.05)/ n=100	

On the other side, CT scan findings demonstrated, Middle meatal oedema was (27 %), and nasal polyps were (20 %), Obstruction of osteomeatal complex was (40 %), sinuses Anatomic variations was (43 %) and Sinuses inflammation was (83 %) were noted of the subjects. table (4)

Table (4): nasal CT scan finding Middle meatal mucosal edema was observed in 27% of cases. Obstruction of the osteomeatal complex was noted in 40% of cases. Nasal polyps were present in 20% of cases. Sinus inflammation was detected in 83% of cases. - Anatomic variations were identified in 43% of cases.

Sinus pathology identified by computed tomography	Patients number
Middle meatal mucosal edema	27
Obstruction of osteomeatal complex	40
Nasal Polyps	20
Sinuses inflammation	83
Anatomic variations	43
SD	26.382
SE	13.194
P- value	0.039*
* Significant (P ≤ 0.05)	

The maxillary sinus had the highest prevalence of inflammation among the 65 individuals. In 30 individuals, the Sphenoid sinus was the least affected. Mucosal thickening was predominantly observed in the maxillary sinus, affecting 55 patients. Conversely, the Sphenoid sinus showed the least amount of mucosal thickening, affecting only 16 patients. On the other hand, opacification was mostly observed in the maxillary sinus, affecting 42 patients. The Sphenoid sinus had less opacification, observed in 18 patients. Based on CT scan findings related to sinus morphology, the most commonly affected sinus is the maxillary sinus, with 65% of cases showing involvement. This includes 42% with sinus opacification and 55% with mucosal thickening. The ethmoid sinus is affected in 53% of cases, with 25% showing sinus opacification and 30% showing mucosal thickening. The frontal sinus is involved in 30% of cases, with 20% exhibiting sinus opacification and

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10% showing mucosal thickening. The sphenoid sinus is affected in 25% of cases, with 15% showing sinus opacification and 10% showing mucosal thickening. In cases of pansinusitis, mucosal thickening and opacification occur in 10% of instances. Figure (1):

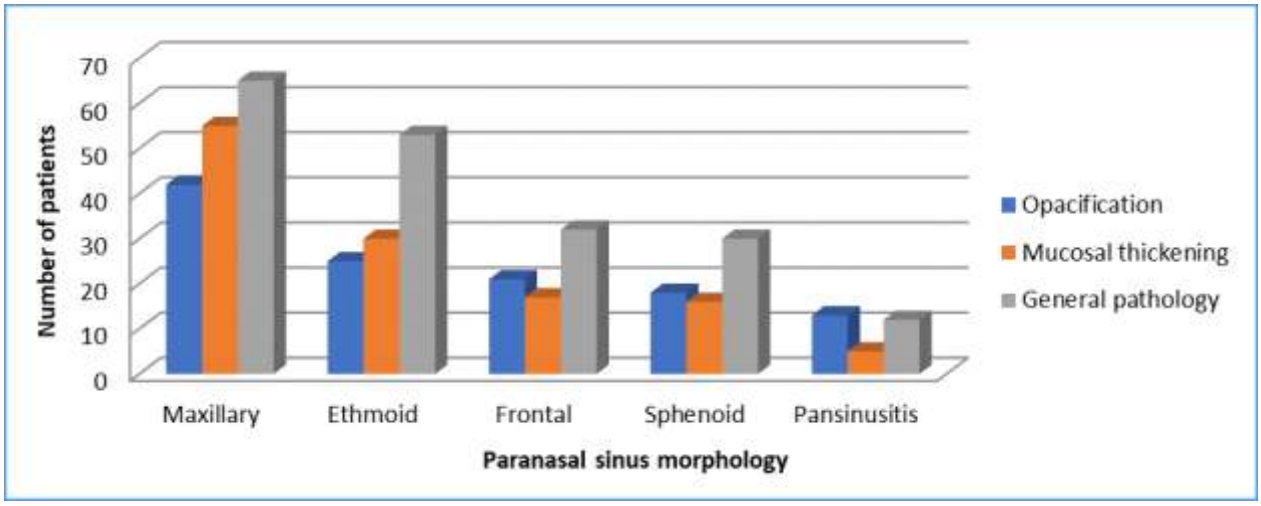

Figure (1): CT scan finding based on the morphology of sinus

Discussion

The investigation outcomes revealed a predominance of females among the study participants, which may be associated with women encountering more significant problems with postnasal drainage; our finding is compatible with previous studies, which have also shown that females had a more significant occurrence of CRS (in the presence and absence of nasal polyps). (15)

The study also revealed that the considerable prevalent manifestations of CRS were rhinorrhea and nasal blockage. These results are compatible with previous studies examining similar clinical presentations (3, 16, 17), In addition to nasal blockage and rhinorrhea, other common symptoms prevalent among the study patient population were headache, facial pain, facial pressure, and anosmia. These findings were consistent with earlier studies showing that the most prevalent CRS symptoms were nasal blockage, congestion, rhinorrhea, weariness, headache, face pressure, and loss of smell (18). The nasal endoscopy findings in our research indicated that the most prevalent observation was the existence of middle meatus discharge. Additionally, there was evidence of mucosal edema in the middle meatus and the subsequent presence of nasal polyps; these findings were consistent with another research that demonstrated middle meatus purulent discharge as the most prevalent observation during nasal endoscopy (19), While The other had nasal endoscopy-reported middle meatus mucosa edema. (4). Conversely, separate research shows nasal polyps were a prevalent observation during nasal endoscopy (20). The results of our research indicate the presence of edema in the middle meatal mucosa and blockage of the stomatal complex, as shown in the CT scan. This result was consistent with previous research, which found that blockage of the stomatal complex was the most frequent observation on CT scans of individuals with (CRS) (21). According to another study, a CT scan showed that the sinuses most affected were the maxillary, ethmoidal, and sphenoid (22), These outcomes were compatible with the results of our study. These results may be attributed to the fact that the study sample group consisted of adult patients. Our study CT scan showed more opacification compared to mucosal thickness in the case of Pansinusitis; this fact illustrates the high severity of the disease if Pansinusitis is involved. The research found that the identification of nasal polyps by CT scan was lower linked to nasal endoscopy (23),

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Which may correlate to the capacity of nasal endoscopy to detect middle meatus polyps of smaller dimensions corresponding to CT scans. In contrast to CT scans, nasal polyps exhibit different features when seen using nasal endoscopy (20). The study's results show that a correct diagnosis of CRS using positive symptoms by the AAO-HNS guidelines and endoscopy, in comparison to CT results, which are considered the gold standard; findings exhibit that nasal endoscopy is more specific than CT scan findings. Additionally, PPV is similar to endoscopy and CT scans. These outcomes align with an earlier study, which shows that integrating endoscopy into symptom-based diagnosis improves accuracy, PPV, NPV, and specificity from (42.8% to 69.1%), (39.9% to 66.0%), (62.5% to 70.3%), and (12% to 84.1%) respectively. Endoscopy substantially improves diagnostic accuracy for CRS in patient's symptom patients, and it may assist in lessening CT utilization in particular patients for whom endoscopy is conducted in order to diagnose CRS (24). One study saw that endoscopy and CT scores are extremely correlated when diagnosing individuals with CRS. Furthermore, abnormal endoscopic outcomes may reliably predict the presence of CT opacification, therefore confirming the significance of endoscopy in the process of clinical decision-making. Nevertheless, the negative predictive value of endoscopy is much smaller, meaning that a normal endoscopy does not guarantee a normal CT scan. Therefore, symptoms, endoscopy, and CT scans are mutually beneficial in assessing patients with post-ESS CRS (25). An additional study was performed to evaluate the correlation between symptom-based criteria and distinct mucopurulence findings on endoscopy and CT results in CRS. In comparison to CT, subjective symptom demonstration had poor predictive accuracy. On the contrary, Endoscopic mucopurulence detection was substantially linked with positive CT CRS and absent in negative CT findings. In comparison to computed tomography, Endoscopic nasal examinations for mucopurulence in OMC had a sensitivity of 24% and a specificity of 100%. Their results suggest that endoscopy can prove a diagnosis of CRS, but it cannot definitively exclude it. CT scans should be performed when there is suspicion of chronic rhinosinusitis (CRS), particularly in the lack of mucopurulence during endoscopy (26-29), Another study conveyed a sensitivity of 95.6%, specificity of 80%, positive predictive value (PPV) of 97.7%, and negative predictive value (NPV) of 66.7%. The study showed that nasal endoscopy is as effective as CT in detecting chronic rhinosinusitis (CRS) (21).

Hussein and Jaf limited diagnostic nasal endoscopy to behave similarly to CT scanning regarding sensitivity and specificity. Moreover, it can lessen unneeded diagnostic CT scanning operations as an outpatient technique (30). In contrast, another research study showed that nasal endoscopy had a sensitivity of 46%, specificity of 86%, positive predictive value (PPV) of 74%, and negative predictive value (NPV) of 64%. The research revealed that there was a weak association between nasal endoscopy and sinus conditions (4, 24, 31, 32). Our study limitation included that a few patients scheduled to get CT scans did not have their scans conducted on the same equipment since they had already had CT scans before reaching the hospital.

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Conclusion

The existence of purulent (cream-purulent) discharge and polyps in the middle meatus during nasal endoscopy is adequate to diagnose CRS in patients with favorable clinical characteristics. Nasal endoscopy has matching diagnostic accuracy to a CT scan, and CT scan findings are extremely associated with sinus endoscopy outcomes, given its superior accuracy, cost-effectiveness, and lessened radiation exposure.

Recommendation

Our study findings indicate that in addition to clinical features. Nasal endoscopy is a precise and cost-effective diagnostic method with minimum radiation exposure, used for diagnosing CRS. Thus, we suggest utilizing it as a principal and feasible alternative diagnostic technique.

Abbreviations

AAO–HNSF: American Academy of Otolaryngology-Head and Neck Surgery Foundation

CRS: chronic rhinosinusitis

CT: Computed Tomography

ENT: ear, nose, throat

ESS: endoscopic sinus surgery

SPSS: Statistical Package for Social Sciences

PPV: positive predictive value

NPV: negative predictive value

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Conflict of interest

The author acknowledges no conflict of interest in this study.

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مقارنة التنظير الأنفي مع الأشعة المقطعية لتشخيص التهاب الجيوب الأنفية المزمن لدى المرضى البالغين في العراق

علي لفتة سلمان[1]

الملخص

الخلفية الدراسية: يتم تشخيص التهاب الجيوب الأنفية المزمن (CRS) غالبًا بناءً على الأعراض السريرية. يعتمد التأكيد في هذا السياق على اكتشاف علامات الالتهاب أثناء التنظير الأنفي والأشعة المقطعية للجيوب الأنفية. بينما تعتبر الأشعة المقطعية الطريقة الأكثر موثوقية، أظهرت الأبحاث أن التنظير الأنفي أيضًا ذو قيمة ويمكن أن يوفر معلومات إضافية لدعم الأشعة المقطعية في تشخيص CRS.

الهدف من الدراسة: كان الهدف من الدراسة هو توضيح موثوقية التنظير الأنفي مقارنةً بالأشعة المقطعية في تشخيص التهاب الجيوب الأنفية المزمن لدى المرضى البالغين المعالجين في مستشفى بعقوبة التعليمي.

المرضى وطرق العمل: تم جمع مئة عينه من المرضى البالغين والذين تم تشخيصهم سريريًا بإصابتهم بالتهاب الجيوب الأنفية المزمن في مستشفى بعقوبة التعليمي. جميع المرضى خضعوا لأشعة مقطعية للجيوب الأنفية وتنظير أنفي خلال ثلاثة أشهر موضوع هذه الدراسة، وتم ربط النتائج.

النتائج: أظهرت نتائج الدراسة أن الأعراض الأكثر شيوعًا التي لاحظت لدى المشاركين كانت إفرازات أنفية واحتقان أنفي، حيث أبلغ ٩٥٪ و٩٠٪ من المرضى، على التوالي. كانت الملاحظة الأكثر شيوعًا خلال التنظير الأنفي هي وجود إفرازات صديدية في المجرى الأوسط، حيث لوحظت في ٥٨٪ من المرضى. وكان الجيب الفكي الأكثر تأثرًا، حيث تم رؤيته في ٦٥٪ من المرضى في الأشعة المقطعية، وكان ٤٠٪ يعانون من انسداد في المركب العظمي الوصلي في صور الأشعة المقطعية. كانت حساسية التنظير الأنفي ٧٣,٣٪، وخصوصيته ٨٥,٣٪، وقيمة التنبؤ الإيجابي ٩٢,٧٪، وقيمة التنبؤ السلبي ٥٥,٨٪. كما لم تجد الدراسة اختلافات ذات دلالة إحصائية في قيمة التنبؤ الإيجابي بين التنظير الأنفي والأشعة المقطعية. بالمقابل، كانت حساسية التنظير الأنفي أكبر بشكل ملحوظ من الأشعة المقطعية.

الاستنتاجات: وجدت الدراسة أن نتائج التنظير الأنفي للمرضى الذين يعانون من سمات سريرية إيجابية كانت إفرازات صديدية (بلون الكريمة) ووجود زوائد في المجرى الأوسط، وهو ما يكفي لتشخيص التهاب الجيوب الأنفية المزمن؛ أظهرت الدراسة أن التنظير الأنفي دقيق تقريبًا مثل الأشعة المقطعية وأن نتائج الأشعة المقطعية تتوافق جيدًا مع التنظير الأنفي، نظرًا لدقته، وتكلفته المنخفضة، وجرعة الإشعاع.

الكلمات المفتاحية: التهاب الجيوب الأنفية المزمن، التنظير الأنفي، الأشعة المقطعية، مستشفى بعقوبة التعليمي.

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Histological and histopathological structural changes in the skin of the Basal Cells Carcinoma patients

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Abstract

Background: Basal Cell Carcinoma (BCC) is the most common type of skin carcinoma and is considered an epidemic disease due to its increasing frequency in many countries. The most important problem of BCC is local invasion It grows in a "silent" way into immediately adjacent tissue. It rarely metastasizes. The early tumors are commonly small, translucent or pearly, raised and rounded areas located on a few dilated, superficial vessels. There are six subtypes of BCC that include nodular, pigmented, superficial, morphea form, cystic. The most important risk factor for basal cell carcinoma is exposure to UV-radiation. Outdoor workers with a long history of work-related UV-exposure are at increased risk of developing BCC. Other risk factors include family history of skin carcinoma, light skin phototypes, advanced age.

Objective: The current study investigated pathological and histological changes in tissue sections to identify the factors contributing to the infection frequency.

Patients and Methods: Thirty-three BCC patients' samples have been collected from the main care center at al-Baquba Teaching Hospital of Diyala Province, Iraq. All patient groups were clinically diagnosed as BCC by dermatologists.

Results: The study showed macroscopic and microscopic histological changes. An ulcerated macroscopic appearance of the lesion was shown. The tumor lesions are located on the face. It was noted that the percentage of patients was higher in men than women and higher in light skin than dark skin. The study also showed that the age group 66-74 years had a higher infection percentage, while the lower percentage was of the age group > 83 years.

Conclusion: These findings pave the way for future research endeavors aimed at prevention, early detection, and targeted treatment strategies for this prevalent skin carcinoma.

Keywords: Basal Cell Carcinoma, skin tumor, non-melanoma skin cancer

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Introduction

Skin cancer is categorized into two main types: malignant melanoma (MM), which originates from melanocytes, and non-melanoma skin cancer (NMSC), where tumors derived from keratinocytes which are the most prevalent. Among NMSC, basal cell carcinoma (BCC) is the most common form. BCC accounts for approximately 77% of all skin cancer cases around world. It encompasses various subtypes, and classifying the tumor types is important for clinicians and pathologists to understand and predict their behavior (1). The primary histopathological types of basal cell carcinoma (BCC) consist of nodular BCC, which includes micronodular BCC; superficial BCC, appearing as multi-focal lesions; and infiltrative BCC, which encompasses the morphic type (2). The nodular type is the prevalent subtype, accounting for approximately 50% of basal cell carcinoma (BCC) cases worldwide. It is characterized by rounded tumor cell nests located in the dermis, exhibiting a distinct arrangement with nuclear palisading. On the other hand, the superficial type, comprising approximately 15% of BCC cases, manifests as small clusters of tumor cells that extend from the epidermis into the upper layers of the dermis (2).

The infiltrative type, comprising 10-20% of cases worldwide, is characterized by clusters of tumor cells with varying sizes, displaying an irregular shape and spiky projections. Unlike other types, peripheral palisading of nuclei is either absent or rare in this subtype. Typically, these lesions are observed on the face, ears, scalp, neck, or upper trunk. Basal cell carcinoma (BCC) often presents as a flat, firm, pale area that may be small, raised, pink or red, translucent, shiny, and waxy. Minor injuries to the affected area may result in bleeding. The size of the tumor can vary in diameter. BCC has a tendency to recur even after treatment, and the histopathological appearance and proliferative characteristics influence the recurrence rate. Furthermore, the likelihood of recurrence was observed to be highest in the morphic type of basal cell carcinoma, which is influenced by both the specific treatment approach and the tumor subtype (3, 4). Metatypical carcinomas encompass the clinical and histological features of basal cell carcinoma (BCC) (5, 6). While metastasis is rare in BCC, local destruction and disfigurement are more commonly observed outcomes (7). The etiology of BCC involves various factors such as genetic predisposition, immune deficiency, and chronic sun exposure (8-10). Many countries have reported an increasing frequency of BCC cases worldwide. In the United States, it is considered the most prevalent cancer type according to reports from The American Cancer Society. The rise in incidence rates could be attributed to improved detection methods and increased awareness of skin cancer within healthcare policies. Furthermore, Increasing the lifespan of individuals may contribute to the higher incidence of BCC. Recent data also suggest an increasing occurrence of BCC among younger populations. While BCC can affect individuals of all skin types, it is more commonly seen in fair-skinned individuals (type 1 or type 2 skin types), while dark-skinned individuals are rarely affected (11, 12). Among genders, men are affected twice as often as women, potentially due to occupational sun exposure. The frequency of BCC also rises with age (13, 14). Exposure to UV radiation remains the most significant risk factor for developing BCC (15). Considering the limited available data on BCC in Diyala province and the need to understand the underlying causes for its prevalence, a macroscopic and microscopic histological study was conducted. The study demonstrated a significant occurrence of BCC cases and aimed to identify the factors contributing to the infection frequency.

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Patients and Methods

Our study was conducted at the main care center at Baquba teaching hospital, spanning from March 2022 to December 2022. We enrolled a total of 33 patients diagnosed with basal cell carcinoma (BCC) through examination by a dermatologist. Following diagnosis and the assessment of macroscopic tumor findings, the affected area with BCC was sterilized using 70% alcohol and locally anesthetized. Dermatologists performed skin biopsies using the punch biopsy method, utilizing a punch tool to puncture the skin and collect 3-millimeter skin samples. The tumor samples were then preserved in a 10% neutral formalin solution for a minimum of three days. Subsequently, the samples underwent a series of alcohol solutions with increasing concentrations (50%, 70%, 80%, 95%, 100%). Afterward, they were immersed in a xylol solution in two stages before being embedded in paraffin wax. The embedded samples were cut into slices with a thickness of 5 mm using a microtome. Finally, the tissue slides were stained with the common hematoxylin and eosin stain and examined under a light microscope. diaphragmatic hernia, and lobar emphysema (16, 17). Transient tachypnea of newborn (TTN) has shorter and milder clinical course (neonate needs 24 hours oxygen supplementation). Symptoms usually improve after 24 hours. CXR shows perihilar streaking, representing perihilar interstitial edema, or it may be normal (18).

Results

Basal Cell Carcinoma BCC lesions were grossly examined and the results observed in Figure 1 showed that the location of the infection in a different area of the face: in the nose (A and B), the cheek (C and D), and forehead (F). The morphological examination showed in the current study's BCC samples which diagnosed in nose,

cheek, and forehead flat, red, scaly papules on the skin. Some of these papules were transparent,

ulcerated masses with irregular edges (rolled border), while other pearly surrounding a central papule. the examination also showed small red blood vessels telangiectasia present on the surface of the papule, especially in nodular BCC and there was melanin pigment in pigmented BCC. The result showed that the median age in the study group was 66 years, while the higher percentage was in patients aged 71 years (75%), the lowest percentage was in patients aged group 60 years (25%), as shown in Table 1. The result showed that the men percentage was higher than the women in the BCC groups (69.6% and 30%, respectively) Table 2. The result showed that the color of the skin had an effect on the appearance of BCC. IT increased in people with light skin (white and light skin) compared to people with dark skin as shown in Table 3. The results indicated that the infection increased with the increase in the age group. It showed that the highest percentage of the diseased patients' group was in the 66-74 years group (30.0%), while the lowest percentage of the aged group was in the>83 years group (3.0%) as shown in Table 4.

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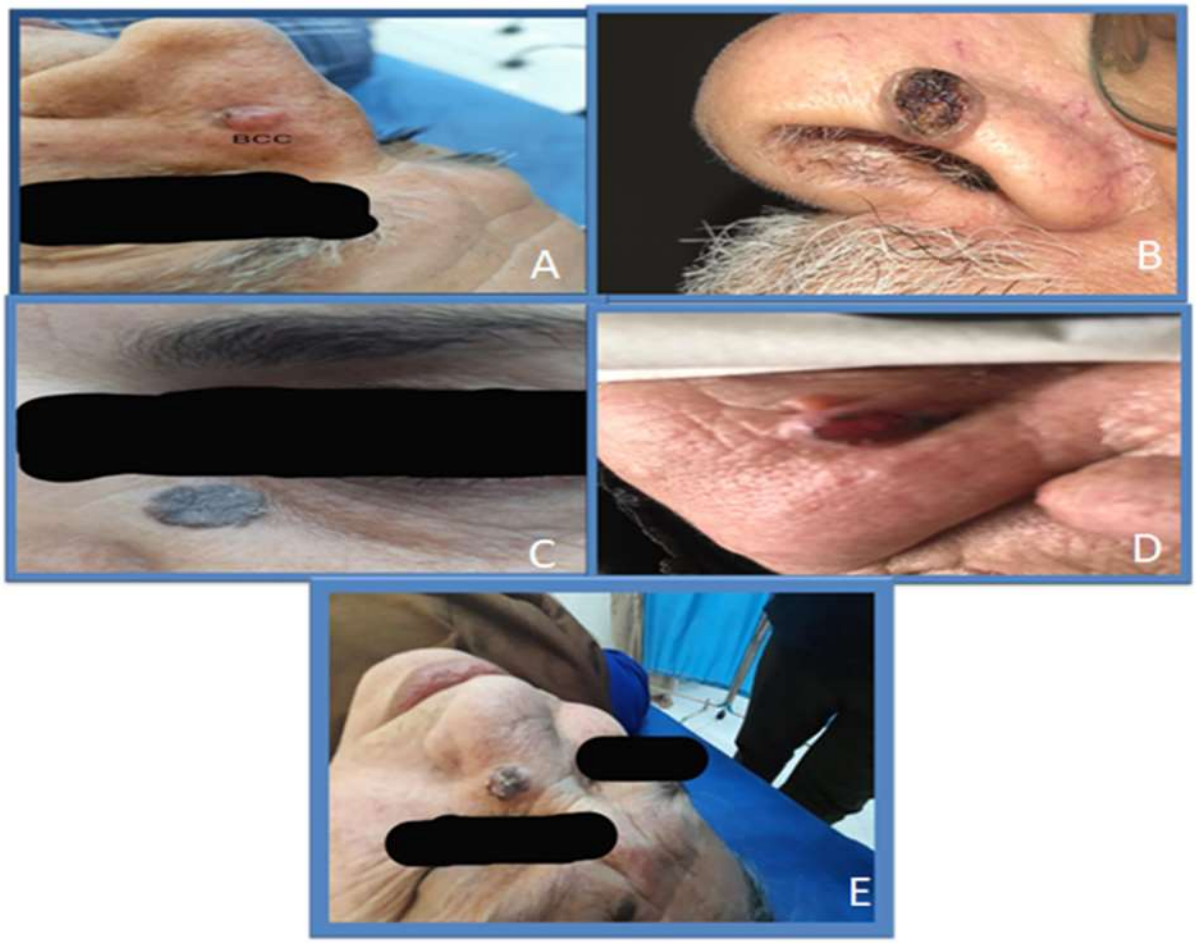

Figure (1): The location of BCC (A)in nose red, scaly papules on the skin. transparent, ulcerated masses with irregular edges (rolled border). (B)in nose there was melanin pigment. (C,D) in check irregular border and there was melanin pigment. (D) showed small red blood vessels telangiectasia present on the surface of the papule.

Table 1: The age of the study group

Age (Years) percentage	***Patients group***	***Control group***	***Probability***
Median	66.0	59	0.096 NS
Percentile 25%	60	35	
Percentile 75%	71	75	

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Table 2: The infection percentage in the patients' group

Gender	***Patient no.***	***Percentage***	***Control group***	***Percentage***	***Probability***
Male	23	69.6%	37	41.8	0.165 NS
Female	10	30%	30	58.2	
Total	33	100%	67	100%	

Table 3: The percentage of infection according to the skin color

Skin color	*Patient no.*	*Percentage*
Light skin	26	78.7%
Dark skin	7	21.3%
Total	33	100%

Table 4: The percentage of BCC according to age groups

Age groups	*Patients group No. (%)*	*Control group No. (%)*
21 – 29	0 (0.0)	14 (20.9)
30 – 38	0 (0.0)	4 (6.0)
39 – 47	4 (12.1)	5 (7.5)
48 – 56	4 (12.1)	8 (11.9)
57 – 65	8 (24.2)	9 (13.4)
66 – 74	10 (30.3)	9 (13.4)
75 - 83	6 (18.2)	15 (22.4)
> 83	1 (3.0)	3 (4.5)
Total	33 (100.0)	67 (100.0)

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Histological changes in BCC patients

The tissue samples that were stained with hematoxylin and eosin showed histological changes in the epidermal layer (Epidermis) of patients with basal cell carcinoma, as it was represented by the presence of cellular nests in varying sizes with pale cytoplasm, circular and oval nuclei with coarse chromatin known as hyperchromatic nuclei, and the cells of the border and peripheral layer were arranged in the palisading form. The melanin pigment was seen in separate areas of the tissue, pigmented Basal Cell Carcinoma type. While cancer cells are arranged in other cases, especially in the Nodular Basal Cell Carcinoma, in the form of cords. It was noted that the basal cells were found in the dermis layer in groups or masses and are not related to the epidermis layer, as shown in the figures (2, 3, 4, 5).

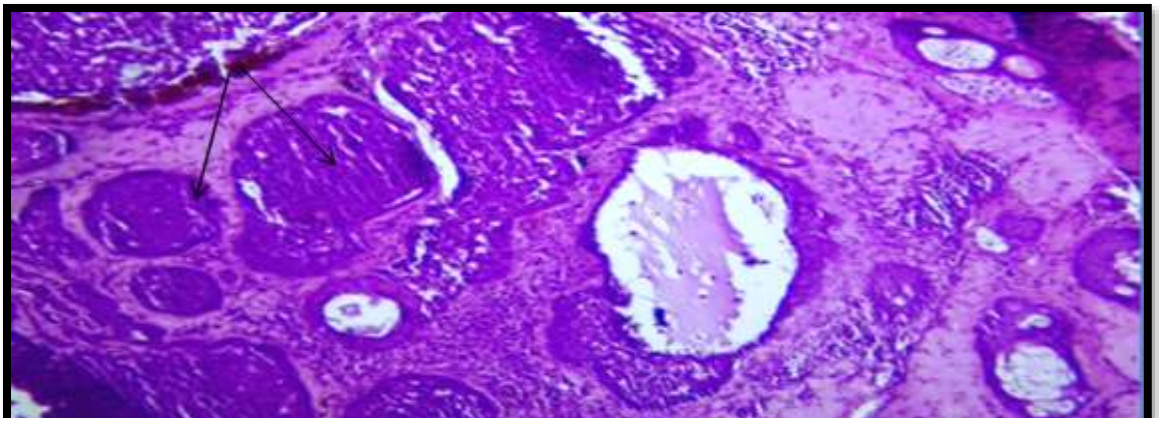

Figure 2: The histological changes of BCC showed masses or nodules aggregated of BCC in the dermis that pointed arrow and melanin pigment seen in the section which seen in the pigmented BCC (H&E stain, 40x).

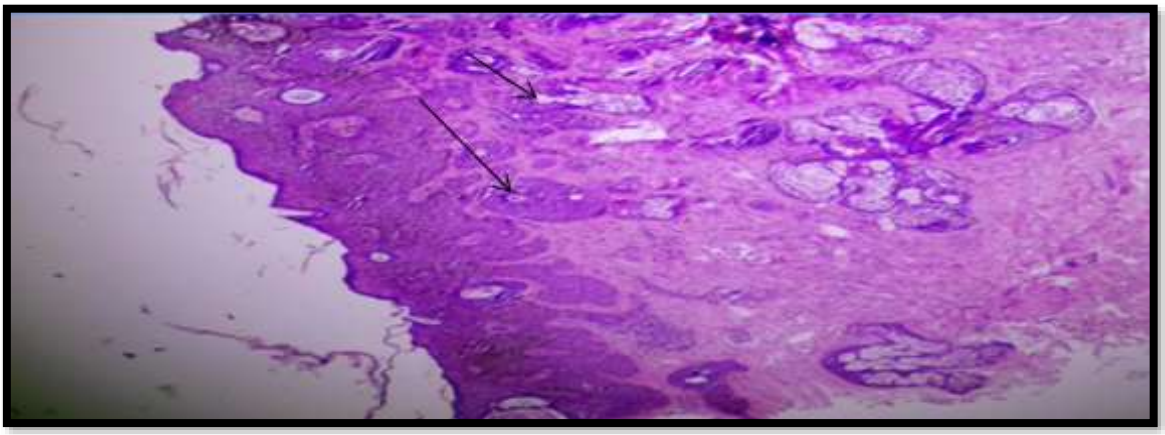

Figure 3: The histological changes of BCC showed epidermis and dermis, Masses or nodule of BCC seen in the dermis that pointed arrow (H & E stain,10x).

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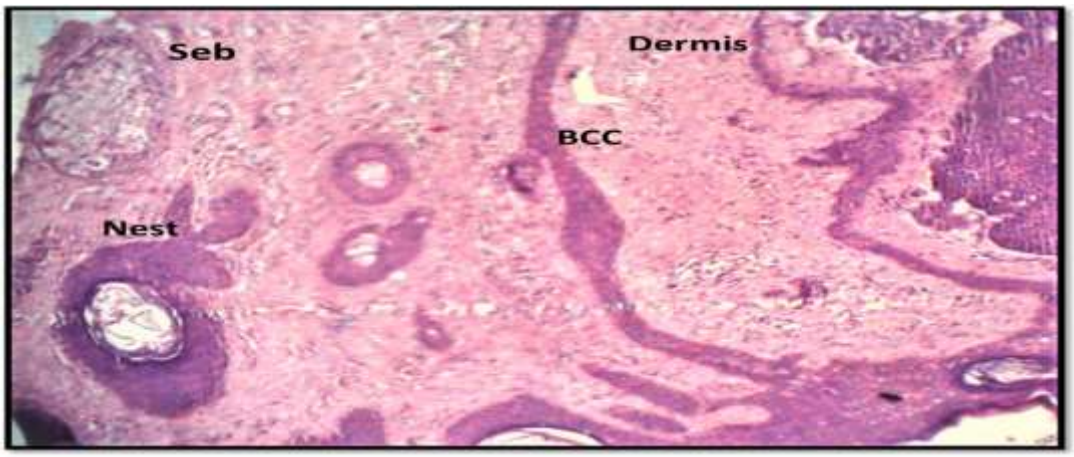

Figure 4: The histological changes of BCC showed nest and cords or strands and masses of BCC in vary sizes in Dermis, (H & E stain, 40x).

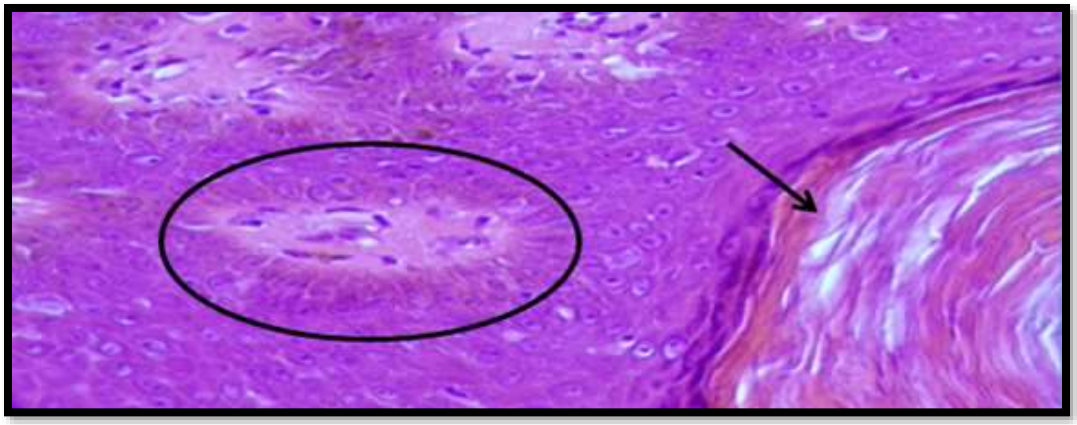

Figure 5: The histological changes of BCC showed keratotic pearl formation that pointed arrow and the cells of the border and peripheral layer were arranged in the palisade form which seen in circle.

Discussion

Human skin cancers are a disease that affects people at a high rate, and the pathological rate and public health are greatly affected by the pathological investigation of these tumors (16-19). Studies from various nations that demonstrated increased frequency in BCC globally were compared to local studies to find similarities in the rates of occurrence of skin malignancies. According to the American Cancer Society, it is the most prevalent cancer in the country. Almost 10,000 deaths (2% of all cancer deaths) and 1 million new cases are diagnosed each year. Several factors, including awareness of skin cancer in health policy, could be to blame for this rise. Enhanced longevity could also effect the rising prevalence of BCC, and recent data also indicate that incidence is rising among the young population perhaps the increasing in temperature and the nature of peoples work due to their exposure to high temperatures for long time (20, 21). According to this study, males had a larger percentage of infection (69.6%) than females (30%). The increased occurrence among men may be related to their work-related exposure to the sun, and numerous

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studies have demonstrated that ozone layer depletion increases the amount of UV radiation that reaches the earth (20). Since fair-skinned people are more likely to develop BCC than dark-skinned people, this result was consistent with many studies. The high percentage of infection in light skin (78.7%) and low result in dark skin (21.3%) explained that BCC is seen in all skin types, but dark-skinned people are rarely affected (22, 23). This color characteristic gives dark skin protection from damage to the skin due to sunlight. Table (3) demonstrated that the age group (66-74 years) had a greater percentage of infection at 36.3%, which was consistent with the numerous references that highlighted that BCC frequency rises with age (16). A macroscopic and microscopic inspection revealed that the tissue had changed (skin tissue affected by the disease). Patients with basal cell carcinoma frequently present with an ulcer that is sluggish to heal and has a variable duration. The lesions are frequently found on the face (Figure 1) in the nose (A, B), in the check (C, D) and in the forehead (E), and they revealed changes in tissue that resulted in ulceration, which was supported by other investigations (23, 24). Ulcer formation could indicate that the patient has been affected for a while before arriving. As a result, the majority of affected tissues turned into ulcerations over time.

The environmental pollution that our country was subjected to in the final decade of the 20th century as a result of the wars in which weapons were employed is one of the many causes of this malignancy that many researchers refer to as a primary reason for skin cancer. In addition to other elements like poor immunity and malnutrition. However, all research, including the rise in the occurrence of these cancer tumors, has shown that basal cells are the most susceptible to damage and that exposure to low amounts of sunlight is associated with an increased risk of BCC cancer (10, 25- 27).

Conclusion

Macroscopic and microscopic histological changes in the skin was observed in this study. An ulcerated macroscopic appearance of the lesion was shown. The tumor lesions are located on the face. Microscopic changes represented by the presence of cellular nests in varying sizes with pale cytoplasm, circular and oval nuclei, and the cells of the border and peripheral layer were arranged in the palisading form. It was noted that the percentage of patients was higher in men than women and higher in light skin than dark skin. The study also showed that the age group 66-74 years had a higher infection percentage, while the lower percentage was of the age group > 83 years.

Source of funding

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Ethical clearance

Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024HYK820).

Conflict of interest

The author acknowledges no conflict of interest in this study.

Recommendation

These findings contributed to a better understanding of the pathological and histological features of BCC and highlighted the demographic and phenotypic characteristics associated with this epidemic disease. Further research is warranted to explore preventive measures, early detection strategies, and targeted treatments for BCC.

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التغيرات النسجية والكيمونسجية المرضية في جلد مرضى سرطان الخلايا القاعدية في محافظة ديالى

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الملخص

الخلفية الدراسية: سرطان الخلايا القاعدية (BCC) هو النوع الأكثر شيوعًا من بين انواع سرطانات الجلد، ويعتبر مرضاً وبائياً نظراً لتزايد انتشاره في العديد من البلدان. المشكلة الأكثر أهمية في سرطان الخلايا القاعدية هي الغزو الموضعي. فهو ينمو بطريقة "صامتة" في الأنسجة ونادرا ما ينتشر لباقي الانسجة. عادة ما تكون الأورام المبكرة صغيرة وشفافة أو لؤلؤية ومرتفعة ومستديرة. وهناك ستة أنواع فرعية من سرطان الخلايا القاعدية (BCC) تشمل العقدية، والمصبغة، والسطحية، والمتشكلة، والكيسية المسبب الرئيسي لسرطان الخلايا القاعدية هو التعرض للأشعة فوق البنفسجية. العاملون لساعات طويلة في الهواء الطلق هم الاكثر عرضة للإصابة بسرطان الخلايا القاعدية . وهناك عوامل أخرى منها التاريخ العائلي لسرطان الجلد، وكذلك لون البشرة، والتقدم بالعمر.

الهدف من الدراسة: أجريت الدراسة الحالية لدراسة التغيرات المرضية والنسجية في مختلف الأنسجة الجلد للتعرف على العوامل المساهمة في تكرار الإصابة.

المرضى وطرق العمل: تم جمع ثلاثة وثلاثين عينة من مرضى سرطان الخلايا القاعدية من المركز الاستشاري لمستشفى بعقوبة التعليمي في محافظة ديالى، العراق. تم تشخيص جميع المرضى سريرياً على أنهم مصابين بسرطان الخلايا القاعدية من قبل أطباء الأمراض الجلدية.

النتائج: أظهرت الدراسة التغيرات النسجية العيانية والمجهرية في انسجة المرضى. وقد ظهر مظهر مجهري متقرح للآفة. اوضحت الدراسة اماكن الاصابة حيث تمركزت آفات الورم على الوجه. ولوحظ أن نسبة المرضى من الرجال كانت أعلى من النساء، وارتفاع نسبة الإصابة في البشرة الفاتحة مقارنة بالبشرة الداكنة. كما أظهرت الدراسة أن الفئة العمرية ٦٦-٧٤ سنة كانت أعلى نسبة إصابة بينما النسبة الأقل كانت للفئة العمرية > ٨٣ سنة.

الاستنتاجات: ساهمت هذه النتائج في فهم أفضل التغيرات المرضية والنسيجية لـ BCC وسلطت الضوء على الخصائص الديموغرافية والمظهرية المرتبطة بهذا المرض الوبائي. لذلك يحب ان تكون هناك المزيد من البحوث لاستكشاف التدابير الوقائية، واستراتيجيات الكشف المبكر، والعلاجات المستهدفة لسرطان الخلايا القاعدية .

الكلمات المفتاحية: سرطان الخلايا القاعدية ,سرطان الجلد ,سرطان الجلد غير الميلانيني

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Incidence of head and neck cancer among Baquba Teaching Hospital Patients

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Abstract

Background: Squamous cells lining the tissues of the head and neck region, such as the nasal cavity, paranasal sinuses, oral cavity, lip, salivary glands, and hypopharynx, give growth to a group of malignancies together recognized as squamous cell carcinoma of the head and neck, which is the seventh utmost communal cancer diagnosis around the world.

Objective: Determine the prevalence of head and neck cancer in Diyala province during 2022-2023 and their distribution according to age and gender of patients. In addition, this study aimed to identify the numbers of each type of head and neck cancer.

Patients and Methods: A retrospective study achieved on the prevalence of head and neck cancer in the region accomplished in oncology center of Baquba teaching hospital in Diyala province, Iraq. Head and neck cancer patients recorded from 2022 to 2023. During this dated, a total of 172 patients were recorded. A search was accomplished on numerous databases, moreover, the information evaluated by age, gender and cancer type.

Results: Regarding patients during 2022 (first group) which is contained of (94) patients with different head and neck cancer, 38(40.4%) were males and 56(59.6%) were females with statistically significant relationship. The patients during 2023 (second group) comprises of (78) patients with different head and neck cancer, 43(50.1%) were men and 35(44.9%) were women with statistically no significant correlation.

Conclusion: Oral and pharyngeal cancer is more common in men than in women. The most common age group is 4th and 5th decade for head and neck cancer.

Keywords: Head and neck cancer, Lymphoma, gender, and age.

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Introduction

Head and neck cancers (HNCs) reason for over 325,000 deaths and 660,000 new cases yearly, creation them the seventh most prevalent cancer diagnosed universally (1-3). Cancers of the pharynx, larynx, nose, oral cavity, lips, and salivary glands are identified as HNCs. In the Gulf Cooperation Council countries, HNCs abundant as the 18th utmost common cancer to be diagnosed and as the ≥11th furthermost common reason of cancer deaths (1). Squamous cell carcinoma, which initiates from the epithelial lining of the pharynx, oral cavity, and larynx, comprise for about ninety percent of HNCs (1). In comparison to entirely body malignancies, the prevalence of head and neck cancer varieties from 9.8 to forty percent. Certain environmental and lifestyle risk factors, counting alcohol, tobacco, poor nutrition, smoking, and UV light, are thoroughly related to HNCs (4). Changes in factors of lifestyle, such as rising alcohol and tobacco usage in developing countries, and the cumulative incidence of oropharyngeal cancer accompanying to the human papillomavirus (HPV) are partially accountable for head and neck squamous cell carcinoma (HNSCC). Oropharyngeal HNSCC will become more public than oral cancer (which is frequently accompanying to use of tobacco) as HPV is predicted to pass tobacco as the primary reason of HNSCC cancer worldwide (1,2,5-7). While alcohol and tobacco usage were earlier thought to be the recognized danger factors, (2,8). There is no doubt that socioeconomic rank plays a role in the hazard; HNCs are documented among non-drinking, non-smoking individuals. Furthermore, it seems that oropharyngeal cancer is most possibly caused by the human papillomavirus (8,9). A massive quantity of economic straining, considerable psychological distress, and distinguished functional impairments are being located on people, communities, and healthcare systems due to the growing incidence of cancer (counting HNCs) (10,11). Inadequate oral hygiene, insufficient diet, exposure to environmental or occupational carcinogens (such as wood dust or asbestos), and genetic vulnerability are further risk factors for carcinoma (squamous cell) in head and neck. Chronic oral inflammation and infections, like chronic periodontitis, have also been associated to a higher danger of HNC (12-15). Radiation therapy in the past, for whichever benign or malignant diseases, has been accompanying to an increased risk of sarcomas, salivary gland tumors, squamous cell carcinomas, and thyroid cancer. However, there is a relationship, it should be remembered that there is a long period of time before any probable negative consequences appear, and the hazard is still rather low overall (16). Malignant tumors of the lymphocyte cell lines are recognized as lymphomas. The spleen, lymph nodes, and other non-hemopoietic tissues are mostly affected. They are mainly categorized as either non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (NHL), and as initiating from B or T lymphocytes. After the gastrointestinal system, the head and neck are the second most prevalent location for extra-nodal lymphomas. The oral and paroral areas are the place of around 2.5% of malignant lymphomas, which primarily evident as Waldeyer's ring (i.e., tonsils, base of the tongue and nasopharynx) (17). Amongst primary oral and paroral NHL, diffuse large B-cell lymphoma (DLBCL) looks to be the most dominant kind (17,18). Lymphatic tissue is rich in the head and neck region, mainly in the salivary glands, oral cavity, Waldeyer's ring, and thyroid. Due to the 200–300 lymph nodes that surround the head and neck, these areas are perfect anatomical places for the appearance of lymphoproliferative disorders (19). Malignant lymphomas make for 5% of all malignancies in the head and neck (20). Therefore, the present study was designated to determine the prevalence of head and neck cancer in Diyala province during 2022-2023 and distribution according to age, gender and cancer type.

Patients and Methods

A retrospective study achieved on the prevalence of head and neck cancer in the region accomplished in oncology center of Baquba teaching hospital in Diyala. Head and neck cancer patients recorded from January/ 2022 to December/ 2023. During this dated, a total of 172 patients were recorded. A search was accomplished on numerous databases, moreover, the information evaluated by age, gender and cancer type. This study comprised collecting all types of cancer in the head and neck area, including lymphomas that have symptoms in the head and neck area. The Scientific and Ethical

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Committee of the College of Medicine at the University of Diyala approved this study. Code No. (2024HMI867).

Statistical Analysis

Two programs were used to find the influence of different elements in research parameters: Statistical Analysis System- SAS (2018) program and the Graphpad Prism program (Graphpad, California, United States). In this study Chi-square test was employed to significant comparison between percentage (0.05 and 0.01 possibility).

Results

It was collected 94 patients with different head and neck cancer during 2022 (first group) which is contained of 38 (40.4%) males and 56 (59.6%) females with statistically significant relationship as shown in table (1). The patients during 2023 (second group) comprises of 78 patients with different head and neck cancer types, including 43 (50.1%) men and 35 (44.9%) women with statistically no significant correlation as shown in table (1). It was shown that the total of head and neck cancer patients was 172 in Diyala province during these two years.

Table 1: Distribution of sample study according to difference gender in difference groups.

Factors		Male No. (%)	Female No. (%)	Total No.	P-value
Groups	2022	38(40.4%)	56 (59.6%)	94	0.0457 *
	2023	43 (55.1%)	35(44.9%)	78	0.365 NS
	Total No. (%)	81(47.1%)	91(52.9%)	172	0.445 NS
P-value		0.578 NS	0.0272 *		---
* (P≤0.05), NS: Non-Significant.					

In this study, it was demonstrated that head and neck cancer patients increased in the ages from 41 to 60 years old, which contain 62 cases (36.04%) followed by the patients in ages from 20 to 40, and more than 60 years old with 47 (27.33%). It was shown that the numbers of head and neck cancer patients decreased in the ages less than 20 years old with 16 cases (9.3%) with statistically highly significant correlation.

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Table 2: Distribution of sample study according to age group distributed by gender.

Age (Years)	Male No (%)	Female No (%)	P-value	Total No (%)
< 20	6 (3.49%)	10 (5.81%)	0.384 NS	16 (9.3%)
20-40	25 (14.53%)	22 (12.8%)	0.697 NS	47 (27.33%)
41-60	25 (14.53%)	37 (21.51%)	0.0498 *	62 (36.04%)
> 60	25 (14.53%)	22 (12.8%)	0.697 NS	47 (27.33%)
Total	81 (47.10%)	91 (52.9%)	0.445 NS	172 (100%)
P-value	0.0074 **	0.0069 **	---	0.0001 **
** ($P \leq 0.01$).				

The study found that tongue cancer, pharyngeal cancer, throat cancer, lip cancer and jaw cancer in male more than female as shown in table (3). Furthermore, it was determining the most prevalent type of cancer was lymphoma 61(35.47%) followed by brain tumor 39 (22.67%). However, it was found that the less common type was lip cancer, jaw cancer and cheek cancer with 1 case for each of these type (0.58%) as shown in table (3).

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Table 3: Distribution of sample study according to age group distributed by gender with difference parameters.

Parameters	Age group distributed by gender									
	<20		20-40		41-60		>60			
	M	F	M	F	M	F	M	F	C.S. P-value	
	N	N	N	N	N	N	N	N		Total N %
Brain tumor	1	4	9	4	6	11	2	2	0.0084 **	39 (22.67%)
Lymphoma	3	5	11	9	3	11	6	13	0.0051 **	61(35.47%)
Tongue cancer	0	0	0	0	0	0	2	0	0.287 NS	2(1.16%)
Pharyngeal cancer	0	0	1	1	4	1	4	1	0.0497 *	12(6.98%)
Eye cancer	0	1	0	0	0	0	1	0	0.877 NS	2(1.16%)
Throat cancer	1	0	1	1	4	4	3	1	0.0497 *	15(8.72%)
Nose cancer	1	0	1	2	3	2	2	1	0.096 NS	12(6.98%)
Thyroid cancer	0	0	2	5	3	6	2	2	0.0317 *	20(11.63%)
Salivary gland cancer	0	0	0	0	2	2	1	1	0.766 NS	6(3.49%)
Lip cancer	0	0	0	0	0	0	1	0	0.902 NS	1(0.58%)
Jaw cancer	0	0	0	0	0	0	1	0	0.902 NS	1(0.58%)
Cheek cancer	0	0	0	0	0	1	0	0	0.902 NS	1(0.58%)
Total	6	10	25	22	25	38	25	21	0.0001 **	172

* (P≤0.05), ** (P≤0.01), NS: Non-Significant.

In the current study, it was determining the number of cancer patients according to the cancer types in Diyala province. It was found that the most common type was lymphoma with 61 cases during 2022 and 2023, and the less common type was lip cancer, jaw cancer and cheek cancer with one case for each of these types (Figure 1).

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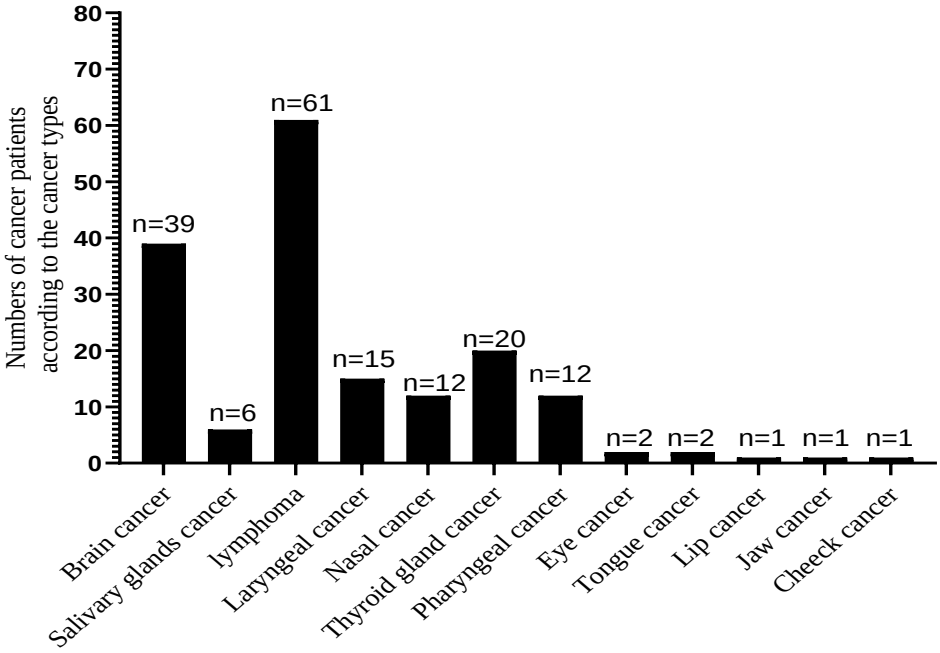

Figure (1): Numbers of head and neck cancer patients according to the cancer types.

It was identifying the numbers of males and females of head and neck cancer patients for each type of this cancer, and it was shown that the cancer cases in female more than in male especially in lymphoma and thyroid gland cancer that occur in 38 and 14 females, respectively compare with 23 and 6 males, respectively. However, the pharyngeal cancer found in males more than in females with numbers 9 and 3, respectively (Figure 2).

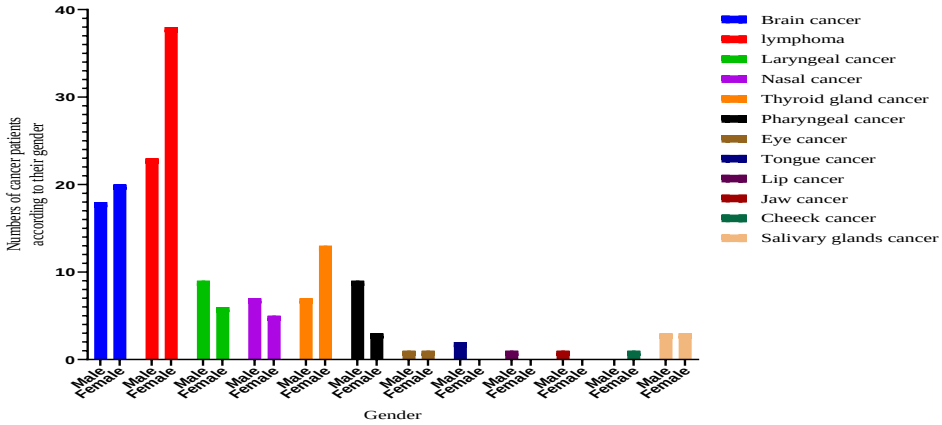

Figure (2): Numbers of each type of head and neck cancer patients according to their gender.

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To determine the ages of each type of head and neck cancer patients, it was divided the cancer patients according to their ages to specify the risk ages for occurring each cancer type. It was shown that all the types of head and neck cancer in Diyala province, which were 12 types occurred in the age more than 60 years old. In addition, it was shown that the ages less than 20 years old and from 20 to 30 years old were the less common ages for head and neck cancer occurring. Interestingly, it was demonstrated that the lymphoma, laryngeal cancer, and laryngeal cancer occurred in high numbers in the patients in ages more than 60 years old. On the other hands, thyroid cancer occurred more in patients in the ages from 40-50 years old (Figure 3).

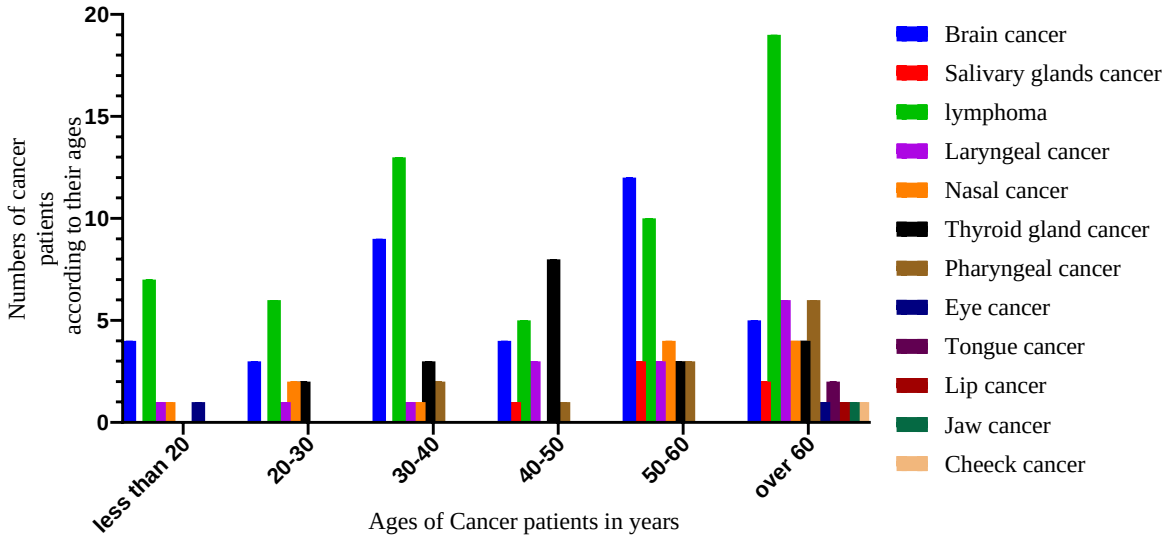

Figure (3): Distribution of head and neck cancer patients according to their ages in each cancer types.

Discussion

In this study found that tongue cancer, pharyngeal cancer, throat cancer, lip cancer and jaw cancer in male more than female. This agree with many studies, in India, both men and women are at markedly high risk of receiving HNC. On the other hand, the incidence of HNC is three times higher in male than in female (21). Around the world, the incidence of head and neck squamous cell carcinoma is higher in males than in women, with a male: female ratio of nearly 2:1, and in individuals over 50 (1).

The present study showed patients increase in (41-60) age group with 62 (36.04%), this agrees with study in India, in relations of age, those 40 years of age and older had a higher incidence of HNC (21). It is anticipated that by 2030, there will be a 30% annual rise in the incidence of head and neck squamous cell carcinoma around the world. This growth has been detected in many nations, particularly in younger populations (1). Shunyu and Syiemlieh supposed that the fourth decade is the greatest common age group, mainly for male patients with oropharyngeal, oral, and hypopharyngeal cancer (4). The variances in

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rates of the incidence may be partially clarified by that variance in exposure to a variety of risk factors, such as use of tobacco (22) and consumption of alcohol, (23) human papillomavirus (HPV) incidence increased, (24) and familial and diet risk. (25) Additional factors of risk that have a positive connection with cancers (oral and oropharyngeal), such as bacterial infection, poor oral hygiene, and genetics predispositions. (26). The fourth and fifth decade is the most common age group in our study. The significant incidence of HNC in the young population permits careful consideration. The probably explanation for this could be that a someone who subsequently customs alcohol and tobacco in their lifetime may get an early habit that causes cancer. Males are more likely than females to consume alcohol and tobacco, which may be one cause why HNC is more common in young people, mainly in men (4). Many carcinogenic constituents, including aldehydes, aromatic amines, nitrosamines, and polycyclic aromatic hydrocarbons, are found in tobacco. These elements are generated through high temperature burning and are recognized to damage DNA in oropharyngeal cells, which can consequence in cancer. Compared to smokeless individuals, heavy smokers have a (5–25) fold higher risk of HNSCC (27). Since alcohol is a solvent, it makes mucosal tissue more susceptible to toxins like smoking and food nitrites. It has also been established that alcohol dehydrogenase, which alters ethanol to acetaldehyde, is mutagenic. Many of the symptoms of extreme alcohol use, like headaches and flushing, are triggered by acetaldehyde, whose conversion is repressed by disulfiram and other medications that have similar effects, like abacavir or metronidazole, which reasons reactions when drinking (28). When compared to males, female see a distinguished rise in the number of new HNC cases or death rates. These results may be explained by its distinct demographic composition, which includes a large variety of ethnic backgrounds accompanying to various health-related behaviors (29). Additionally, there has been a rise in female HPV infections (24), and these results disagree with the current study. The enhanced prognosis and better response to radiation and immunotherapy may be clarified by the fact that HPV-positive HNSCCs display less genetic mutations, additional B-cell infiltration into the tumor microenvironment, and an intact apoptotic response (30).

Conclusions

Oral and pharyngeal cancer is more common in men than in women. The most common age group is 4th and 5th decade for head and neck cancer.

Recommendations

It is important to raise public awareness of tobacco use and to facilitate better access to medical facilities, early cancer detection, treatment, and palliative care. In addition, more genetic studies are required about the factors that play a role to increase the cancer cases in Diyala province, Iraq.

Source of funding

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Ethical clearance

Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024HMI882).

Conflict of interest

The author acknowledges no conflict of interest in this study.

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نسبة الإصابة بسرطان الرأس والرقبة بين مرضى مستشفى بعقوبة التعليمي

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الملخص

الخلفية الدراسية: الخلايا الحرشفية المبطنة لأنسجة منطقة الرأس والرقبة، مثل تجويف الأنف والجيوب الأنفية وتجويف الفم والشفة والغدد اللعابية والبلعوم السفلي، تعطي نموًا لمجموعة من الأورام الخبيثة المعروفة معًا بسرطان الخلايا الحرشفية في الرأس والرقبة، وهو سابع أعلى تشخيص للسرطان الشائع في جميع أنحاء العالم.

الهدف من الدراسة: تحديد مدى انتشار سرطان الرأس والرقبة في محافظة ديالى خلال الأعوام ٢٠٢٢-٢٠٢٣ وتوزيعهم حسب العمر والجنس. بالإضافة إلى ذلك، هدفت هذه الدراسة إلى التعرف على أعداد كل نوع من سرطان الرأس والرقبة.

المرضى وطرق العمل: دراسة استرجاعية أجريت على مدى انتشار سرطان الرأس والرقبة في المنطقة في مركز الأورام في مستشفى بعقوبة التعليمي في محافظة ديالى، العراق. تم تسجيل سرطان الرأس والرقبة في الفترة من ٢٠٢٢ إلى ٢٠٢٣. خلال هذا التاريخ تم تسجيل ١٧٢ مريضا. تم إجراء البحث على العديد من قواعد البيانات، علاوة على ذلك، تم تقييم المعلومات حسب العمر والجنس ونوع السرطان.

النتائج: فيما يتعلق بالمرضى خلال عام ٢٠٢٢ (المجموعة الأولى) والتي تتكون من (٩٤) مريضاً يعانون من سرطانات الرأس والرقبة المختلفة، ٣٨ (٤٠,٤٪) ذكور و٥٦ (٥٩,٦٪) إناث مع وجود علاقة ذات دلالة إحصائية. يتكون المرضى خلال عام ٢٠٢٣ (المجموعة الثانية) من (٧٨) مريضًا يعانون من سرطانات الرأس والرقبة المختلفة، ٤٣ (٥٥,١٪) كانوا رجالًا و٣٥ (٤٤,٩٪) نساء مع عدم وجود علاقة ذات دلالة احصائية.

الاستنتاجات: سرطان الفم والبلعوم أكثر شيوعاً عند الرجال منه عند النساء. الفئة العمرية الأكثر شيوعاً هي العقد الرابع والخامس للإصابة بسرطان الرأس والرقبة.

الكلمات المفتاحية: سرطان الرأس والرقبة، سرطان الغدد الليمفاوية، الجنس، والعمر.

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Antimicrobial activity of blue mold (Penicillium italicum) Filtrates against some species of pathogenic bacteria

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Abstract

Background: Penicillium saprophytic species, which primarily consume organic biodegradable materials, is a common example of a fungal species. The preparation filtrates of Penicillium italicum, a saprophyte on citrus fruits frequently linked to post-harvest diseases in this crop, were included in the current investigation.

Objective: This investigation aimed determine the most efficient culture medium for the production of antibacterial secondary metabolites.

Patients and Methods: included identifying the growth medium for P. italicum and produce its metabolites through the use of gas chromatography-mass spectrometry (GC MS) for both solid-state fermentation filtrate (SSFF) and liquid fermentation filtrate (LFF). Additionally, the antimicrobial activity of the mold filtrate against certain pathogenic bacteria was assessed using the agar well diffusion method.

Results: indicated that the biomass used for mold growth was heavier in SSFF than LFF, and according to the findings, the selective active isolate's crude filtrate from two duplicates of the P. italicum Yeast Extract Sucrose YES culture medium was 0.063 mg, while the crude extract from rotten orange (as a solid medium) containing P. italicum was 0.11 mg. Tetracosane and other substances with a track record of therapeutic activity were found in the two mold extracts, according to GC MS data. Overall, both SSFF and LFF demonstrated antibacterial activity against Klebsiella pneumonia, Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa and Staphylococcus aureus, with the inhibition zones± standard deviation (IZ± SD) being 24.7± 0.57, 18.2± 0.28, 26.3± 0.59, 21.6± 0.51, and 32.8± 0.21 (for SSFF) mm and 0.0, 12.3±0.57, 28.16±0.20, 19.3±1.15, and 28±0.2 (for LFF) mm, respectively.

Conclusion: the filtrate of P. italicum from a natural medium (rotted orange) as a solid state fermentation was more weighted and gave many effective metabolites compared to what was produced by liquid fermentation on a synthetic medium, and both liquid and solid fermentation filtrates demonstrated efficacy against harmful bacteria.

Keywords: Penicillium italicum, SSFF, LFF, GC MS, antibacterial activity.

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Introduction

P. italicum is the primary citrus post-harvest phytopathogen that causes the blue mold infection. Citrus is one of the most significant fruit genera in the world. Due to unfavorable weather patterns and an increase in mold infections, orange production has significantly decreased recently (1,2). Because oranges are an acidic fruit (pH of 4-5 in healthy varieties), fungi are more likely than bacteria to cause rot in most oranges (3,4). However, mycotoxins a low molecular mass secondary metabolites generated by filamentous fungi that are poisonous to the host and other microorganisms sharing the same environment-can be created and multiplied by phytopathogenic (plant-pathogenic) fungi (5). One of the most common types of fungi is penicillium, which grows on a variety of decomposing materials. Because Penicillium conidia are always present in the air, cultures frequently become contaminated by Penicillium colonies. Penicillin was discovered by coincidence; P. italicum and P. digitatum cause citrus fruits to rot, whereas P. expansum causes brown rot in apples (6,7). Among the most well-known examples of fungi are penicillium saprophytic species, which primarily feed on organic biodegradable materials. These species can grow on foods and other stored seeds because they prefer to flourish in low-humidity environments and to spread quickly through aerial dispersal when the seeds are appropriately moist (8). P. italicum is commonly associated with Citrus fruits and in the agricultural sector, It is an acute wound pathogen that affects all species and varieties of Citrus and can infect fruit in the field, packing house and even during distribution and marketing (9). Traditional fungal fermentation is being used today to produce foods and beverages all over the world. Penicillium species are utilized in Europe to help cheeses and meats mature (10). However, solid state fermentation has benefits over submerged (liquid) fermentation, including: greater volumetric productivity, typically simpler and requiring less energy; potential ease of meeting aeration requirements; resemblance to certain fungi's and bacteria's natural habitat; simpler downstream processing; fungal hyphae are submerged in a liquid medium, preventing desiccation; Temperature control is usually not too difficult, allowing the organism to be exposed to a consistent temperature throughout its growth cycle; O2 availability to the biomass can be reasonably well controlled at a specific level of medium saturation; nutrient availability to the organism can be controlled within relatively narrow limits if desired through the feeding of nutrient solutions; although shear forces do occur in mechanically stirred bioreactors, the nature and magnitude of these forces are well understood, and low-shear environments, like bubble columns or air lift bioreactors, can be used if the organism is highly susceptible to shear damage Lastly, it is not too difficult to give pH control (11, 12). The current study aims to identify the active medium for P. italicum metabolite growth and production using GC MS technology and to identify the mold filtrate's antibacterial activity against a few harmful bacteria. According to Webster and Weber classification (6). Penicillium italicum belongs to Kingdom fungi, phylum Ascomycota, class Eurotiomycetes, order Eurotiales and family Trichocomaceae.

Patients and Methods

The laboratory methods were performed in the Lab. of Fungi and Natural products at the department of Biotechnology/college of Sciences / University of Diyala.

Sampling and Identification of Penicillium italicum

From naturally rotting citrus fruits, fifty mold isolates were isolated. Citrus sinensis L.) In Baqubah city, Diyala province, Iraq), all isolates were cultured on Sabouraud Dextrose

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Agar SDA for primary isolation, then sub-cultured on Czapic Dox Agar CZA for identification. Lactophenol Alanine Blue stain was used in the laboratory to identify the fungi based on the following criteria: Colony morphology, which includes color and consistency, reverse color, which changes with age, and microscopic features, such as conidial size, arrangement, form, and ontogeny. The selected isolate of P. italicumm was subcultured and preserved in Potato Dextrose Agar slants and then placed as stock cultures at 4°C (13).

Growth conditions for Penicillium italicum and metabolite identification

➢ Preparation spore suspension of P. italicum

After growing the mold for seven days at 28 ± 0.5 ºC, the spores were harvested by stirring the culture with a sterile 0.85% NaCl, the conidia suspension was gently probed with a pipette tip and filtered to separate conidia from hyphal fragments.

➢ Preparation of P. italicum filtrate by solid state fermentation

A method was followed by Richard and Mary (14) according to the following steps with slight modifications:

• Twenty-five grams of each orange fruit Citrus sinensis L. (which were collected from a local market of Baqubah city and exposed to the ambient air for contamination 25 °C, 56 % relative humidity) in 250 ml cotton-stoppered Erlenmeyer flask which was sterilized by sodium hypochlorite and used for Penicillium filtrate production as solid substrate. The moisturizing ratio is 5:1 (w/v) by D.W.

• The selected isolate spores were fermented by growing on un-infected samples of chopped C. sinensis L. fruit (which was inoculated with 1 ml of spore suspension and put in an Erlenmeyer flask then incubated in state cooling incubator at 28±2º C for two months (January and February).

• Fruit that had fermented with homogenizing using an electric magnetic stirrer for 10 minutes was given 75 milliliters of chloroform to complete the extraction process from rotten oranges (solid fermentation). Next, the extracted solution was filtered using a Whatman filter paper No. 1 and 50 ml of chloroform through a separating funnel. Following that, the filtrate fractions were combined and dried at 45°C by evaporation. The dried filtrate was kept in storage at 4°C (15).

➢ Preparation of P. italicum filtrate by liquid fermentation

• The selected isolate spore was secondly fermented by growing on the liquid culture of YES (prepared by dissolving 40 g of Sucrose and 20 g of yeast extract in 1000 ml of distilled water and sterilized by autoclave). The mixture was then allowed to incubate for ten days at 28±2º C in a state cooling incubator. One milliliter of spore suspension was added to the medium to create two replicates for culture.

• 100 milliliters of liquid culture and 50 milliliters of chloroform were added to an Erlenmeyer flask, which was then electro-homogenized for ten minutes with the use of a magnetic stirrer. A Whatman filter paper No. 1 was then used to filter the extracted solution, and a separating funnel was used to filter 50 ml of chloroform. The separated components were combined and dried at 45°C using evaporation. Dried filtrate was stored at 4°C (8,15).

Evaluation of Penicillium italicum filtrates quantitatively

A sensitive electric balance was used to weigh the filtrates after they had been collected and dried to compare the different types.

Determination of the qualitative assessment of Penicillium italicum filtrates by Gas chromatography – Mass Spectrum analysis

Equal volumes of the two dried filtrates of the mold prepared in the previous paragraphs were

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weighed to compare the types of filtrates. Then, to make the fungal filtrate stock solution for chemical analysis, each dried mold filtrate was dissolved in chloroform. GC–MS analysis of penicillium italicum filtrates was performed on a GC system (Agilent 7890A series, USA). Helium (He), the carrier gas, was allowed to flow at a rate of 1 mL min−1, with a split ratio of 1:50. While the detector temperature was fixed at 280◦C, the injector temperature was altered to 250◦C. The National Institute of Standards and Technology (NIST, USA) database was used to interpret the mass spectrum.

Determination of the antibacterial activity of Penicillium italicum filtrates

➢ Preparation of bacterial isolates

Pathogenic bacterial isolates of Klebsiella pneumonia, Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa and Staphylococcus aureus of multidrug-resistant to antibiotics were obtained from Teaching Laboratories at Baqubah Teaching Hospital in Diyala province.

➢ Measurement of antibacterial activity

The agar well diffusion method was used according to Obeidat et al (16) with slight modifications as follows:

• Bacterial suspension for each species was prepared by transporting several bacterial colonies with a loop and put in a test tube containing brain heart infusion broth for activating the bacteria, the tube was then incubated at 37°C 18-24 hrs (17).

• The bacterial suspension was compared to the standard McFarland solution which is equal to 1.5 x 108 CFU ml-1. After that, the suspension of bacteria was spread by sterile swab on the plates containing Muller Hinton Agar and the plate was then left to be dried.

• Three 5mm diameter holes were made in the culture medium using a sterilized cork borer.

• A concentration of 50 mg ml-1 of each fungal filtrate was made using DMSO 10% by dissolving 250 mg of dry filtrate in 5 ml of DMSO 10%, to obtain a concentration of 50 mg ml-1.

• 100 µl of the concentration of the test filtrates were added to the holes individually by micropipette. The third pit (control) was represented by adding DMSO 10%, and three replicates worked each dish. After that, incubate the dishes at 35±2 °C for 18-24 hrs.

• The effectiveness of each filtrate was determined by measuring the inhibition zone (IZ) diameter around each hole and then compared with the control.

Statistical analysis

Analysis of variance (ANOVA) using statistical software. $P < 0.001$, 0.02, 0.05 and 0.06 values were used for the statistical tests as a significance level.

Results

Twenty-two of the fifty mold isolates that obtained through culturing on SDA were recognized as Penicillium italicum and twenty-eight as P. digitatum from naturally rotting citrus fruits. Microscopic examination showed that the conidial apparatus is made up of asymmetric penicilli that bear tangled chains of conidia; conidiophores, which are more or less cylindrical, smooth-walled, terverticillate metulae that bear three to six phialides each, originate from the substratum or occasionally from superficial hyphae. The phialides have cylindrical, short necks that are easily distinguished. Conidia are 4.0–5.0 × 2.5–3.5 µm in size, smooth, greenish, and have smooth walls. Phialides are generated single, in groups, or from branched metulae, giving them a brush-like look (a penicillus). Figure 1 shows the microscopic and macroscopic characteristics of this mold.

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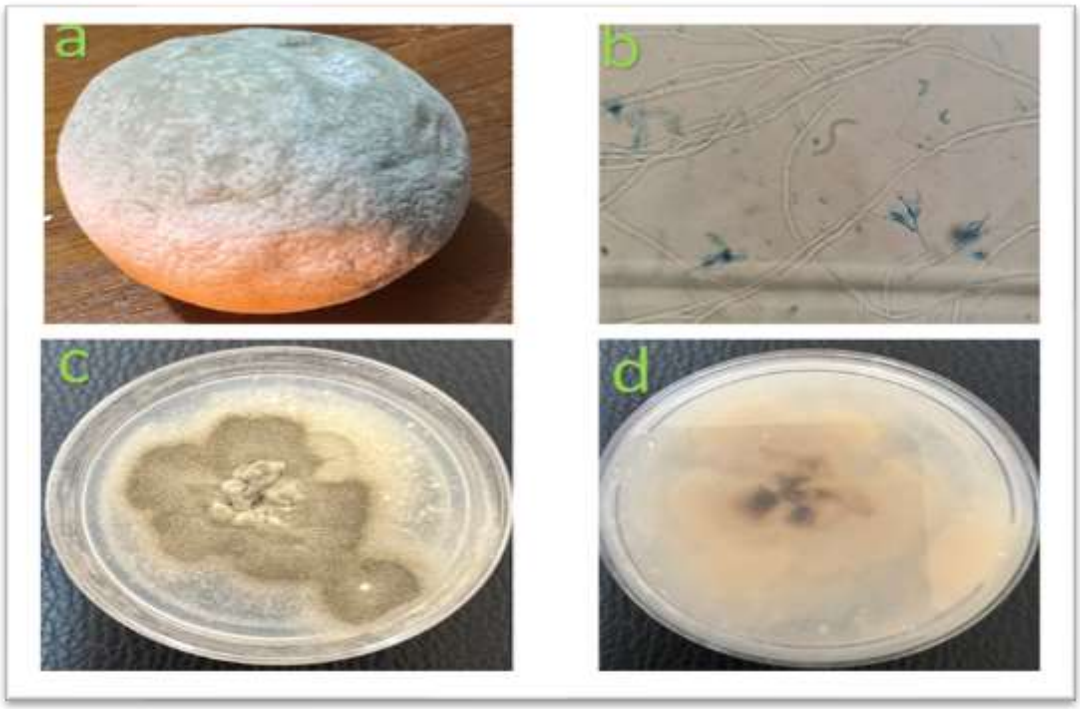

Figure 1:
Penicillium italicum a Rotted orange Citrus sinensis L. with the mold. b, microscopic view of the mold stained with Lactophenol cotton blue 40X. c, macroscopic top appearance grew on CZA at 28±2°C and pH 5.6 for 7 days of incubation, d-reversed view.

For quantitative estimation of growing Penicillium italicum filtrates metabolites, 0.11 mg of P. italicum was present in the rotten orange crude extract (filtrate). On the other hand, the chosen isolate of this mold contained 0.063 mg of crude extract from two replicates of P. italicum YES growth media. Figures 2 and 3 depict the process of fermentation and filtrate extraction.

Figure 2: a, homogenizing Penicillium italicum on the solid-state fermented orange by magnetic stirrer b, extraction of P. italicum filtrate by separating funnel using Chloroform

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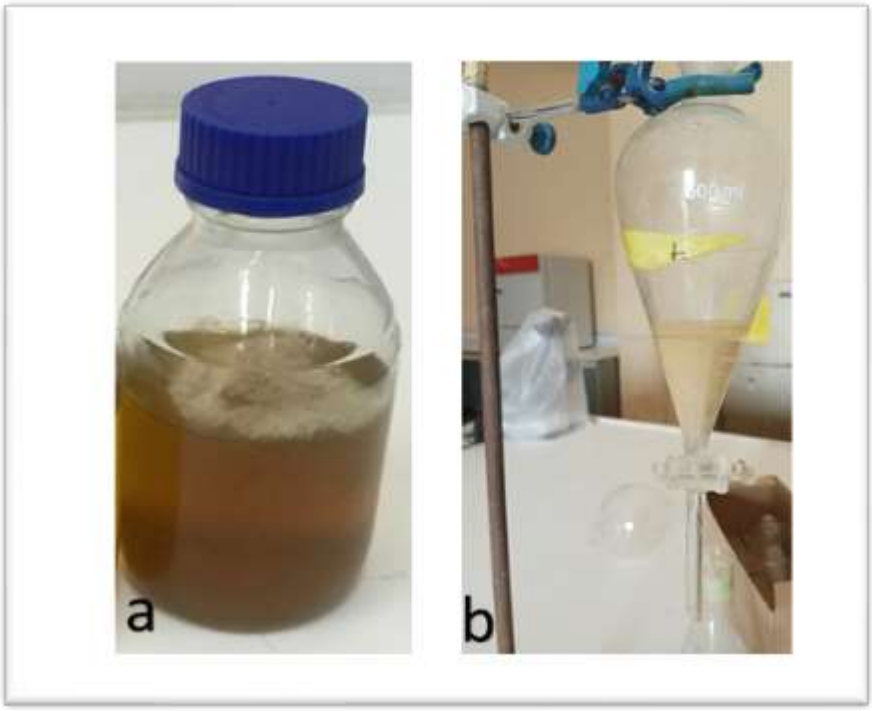

Figure 3: Liquid fermented Penicillium italicum YES medium b, extraction of P. italicum filtrate by separating funnel using Chloroform

Through quantitation chemical analysis of P. italicum chloroformic extract; results showed that sixteen compounds were identified in the liquid fermentation filtrate LFF and thirty-one compounds were detected in the solid-state fermentation filtrate SSFF (tables 1 and 2). The identification of chemical compounds was based on the peak area, retention time, molecular weight and chemical structure.

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Table 1: GC MS analysis of Penicillium italicum liquid fermentation filtrate for chemical compounds detection

No	RT (min)	Area%	Name	Quality	CAS Number	M.W
1	23.933	3.67	2-HYDROXY-3,5,5-TRIMETHYL-2-CYCLOHEXENONE	50	004883-60-7	154.21
2	25.147	9.27	2-(n-Butyl-N-(2-methylpropanoyl))amino-4-methyl-oxazole	37	000000-00-0	1422.7
3	25.428	30.28	2-Hydroxy-3,5,5-trimethyl-cyclohex-2-enone	59	004883-60-7	154.21
4	27.923	7.15	methyl dihydromalvalate	46	000000-00-0	294.5
5	30.741	2.67	Iron, tricarbonyl[N-(phenyl-2-pyridinylmethylene)benzenamine-N,N']-	90	074764-11-7	398.2
6	32.1	4.28	Tetracosane	98	000646-31-1	338.65
7	32.764	4.23	Benzonitrile, m-phenethyl-	37	034176-91-5	207.27
8	33.008	2.61	2-Nonadecanone, O-methyloxime	60	036379-39-2	311.5
9	33.408	4.13	Nonadecane	95	000629-92-5	268.52
10	33.579	1.96	4'-Benzyl-2'-hydroxy-6'-methyl-3'-phenylacetophenone	49	064648-09-5	438.5
11	33.813	5.07	3.beta.-Acetoxy-17-methyl-5.alpha.-18(13-17)abeoandrost-13-ene	83	072166-08-6	332.5
12	33.968	3.62	1a,9b-dihydro-4-methyl-1H-phenanthro[9,10-b]azirine	83	111005-47-1	362.3
13	34.145	8.31	1,1-DICYANO-2-METHYL-4-(P-CYANOPHENYL)PROPENE	83	000000-00-0	207.23
14	34.383	3.36	1H-Indole, 2-methyl-3-phenyl-	80	004757-69-1	207.27
15	34.669	3.42	Nonadecane, 9-methyl-	95	013287-24-6	282.5
16	35.888	2.83	Eicosane	96	000112-95-8	282.55

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Table 2: GC MS analysis of Penicillium italicum solid state fermentation filtrate for chemical compounds detection

No	RT (min)	Area%	Name	Quality	CAS Number	M.W
1	10.749	0.35	.BETA. FENCHYL ALCOHOL	90	000470-08-6	154.25
2	13.81	0.27	.beta.-Myrcene	42	000123-35-3	136.23
3	17.333	0.43	Valencene	99	004630-07-3	204.35
4	17.686	0.66	4-Methyl-2,6-di-tert-butylphenol	98	000128-37-0	250.38
5	25.148	0.76	Methyl palmitate	97	000112-39-0	270.45
6	25.926	0.30	E-11-Hexadecenoic acid, ethyl ester	53	000000-00-0	282.5
7	26.227	2.19	Hexadecanoic acid, ethyl ester	99	000628-97-7	284.47
8	27.778	0.69	8,11-Octadecadienoic acid, methyl ester	99	056599-58-7	294.5
9	27.877	0.76	Methyl trans-8-octadecenoate	99	026528-50-7	296.5
10	28.281	0.28	Methyl stearate	98	000112-61-8	298.5
11	28.78	2.40	Ethyl linoleate	99	000544-35-4	308.5
12	28.873	1.43	Ethyl Oleate	98	000111-62-6	310.51
13	29.314	0.28	Docosane	62	000629-97-0	310.602
14	30.736	0.46	Tricosane	96	000638-67-5	324.63
15	32.095	0.30	Tetracosane	98	000646-31-1	338.65
16	32.759	0.50	Azetidine, 1-benzyl-3,3-dimethyl-2-phenyl-	37	022606-97-9	251.4
17	33.408	0.48	Nonadecane, 9-methyl-	93	013287-24-6	282.5
18	33.813	0.79	3.beta.-Acetoxy-17-methyl-5.alpha.-18(13-17)abeoandrost-13-ene	90	072166-08-6	332.5
19	34.103	70.34	Diisooctyl phthalate	91	027554-26-3	390.6
20	37.419	0.30	Squalene	93	007683-64-9	410.7
21	40.392	0.29	Octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl-	43	019095-24-0	577.2
22	41.736	0.68	24-methylcholesta-5,7,24(28)-trien-3.beta.-ol	38	023582-83-4	396.6
23	41.959	1.16	ERGOST-5-EN-3.BETA.-OL	52	004651-51-8	400.7
24	42.395	0.45	Octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl-	49	019095-24-0	577.2
25	43.199	6.63	Stigmasterol, 22,23-dihydro-	99	000000-00-0	412.7
26	43.489	0.25	1,1,1,3,5,5,5-Heptamethyltrisiloxane	42	001873-88-7	221.5
27	43.77	1.85	Bis(methyloxmine), monotrimethylsilyl-6.alpha.-Hydroxyandrostenedione	86	000000-00-0	302.4
28	44.019	3.27	3',4',5,6,7,8-Hexamethoxyflavone	91	000478-01-3	418.4
29	44.413	0.29	Demecolceine	43	000518-11-6	371.4
30	45.404	0.56	Testosterone Cypionate	47	000058-20-8	412.61
31	48.865	0.31	N-Methyl-1-adamantaneacetamide	42	000000-00-0	207.31

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The results of the current study shown in figure 4 appeared the chloroformic extracts activity of P. italicum SSFF and LFF against pathogenic bacteria. Table 3 explains the significant differences between them at $p < 0.001$, 0.02, 0.05 and 0.06, with IZ: 24.7± 0.57, 18.2 ± 0.28, 26.3 ± 0.59, 21.6 ± 0.51 and 32.8 ± 0.21 (for SSFF) mm respectively and 0.0, 12.3±0.57, 28.16±0.20, 19.3±1.15 and 28±0.2 (for LFF) mm respectively.

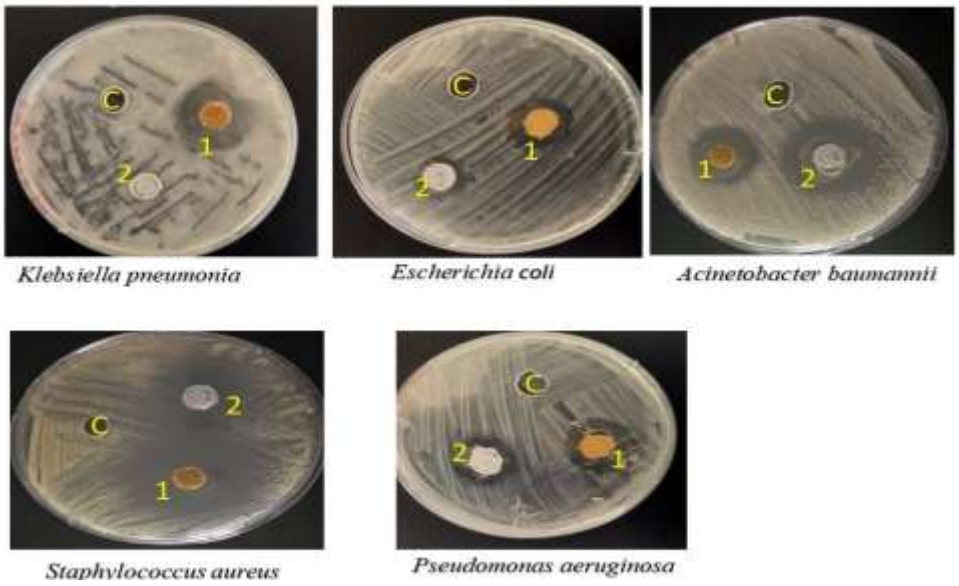

Figure 4:
Effect of 50 mg mL -1 of Penicillium italicum filtrates on pathogenic bacteria measured by the diameter of the inhibition zone (mm): 1, Solid state fermentation filtrate 2, Liquid fermentation filtrate C, Control (DMSO 10%).

Table 3: Effect of 50 mg mL -1 of SSFF and LFF on pathogenic bacteria measured by the mean diameter of the inhibition zone ± Standard deviation (mm)

Name of bacteria	SSF Filtrate (mean ± SD)	LF Filtrate (mean ± SD)	P value	Control			P value
Klebsiella pneumonia	24.7 ± 0.57	0.00	**p< 0.001**	0.00	0.00	0.00	**p< 0.001**
Escherichia coli	18.2 ± 0.28	12.3±0.57	**p< 0.05**	0.00	0.00	0.00	**p< 0.001**
Acinetobacter baumannii	26.3 ± 0.59	28.16±0.20	**p< 0.06**	0.00	0.00	0.00	**p< 0.001**
Pseudomonas aeruginosa	21.6 ± 0.51	19.3±1.15	**p< 0.01**	0.00	0.00	0.00	**p< 0.001**
Staphylococcus aureus	32.8 ± 0.21	28±0.2	**p< 0.02**	0.00	0.00	0.00	**p< 0.001**

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SSFF: Solid State Fermentation Filtrate

LFF: Liquid Fermentation Filtrate

SD: standard deviation

P: Probability of significant difference

Discussion

Upon culturing on SDA, colonies of mold appear fast growing; the colony size of P. italicum can reach 5cm within a week when grown on CZA at 28±2 °C, but quickly assumes a greenish-blue pigmentation due to abundant conidium formation; the pigmentation of mature conidia is at least partly due to melanin (6). Microscopic examination showed the conidiophores, which are terverticillate, hyaline metulae that are more or less cylindrical, smooth-walled, and bear three to six phialides each, originate from the substratum or occasionally from superficial hyphae. The asymmetric penicilli bearing tangled chains of conidia make up the conidial apparatus. The phialides have short, distinct necks and are cylindrical and narrow. Conidia are 4.0–5.0 × 2.5–3.5 µm in size, smooth, greenish, and have smooth walls. Phialides can be generated single, in groups, or from branched metulae, giving the appearance of a brush (a penicillus) (18,19). Figure 1 shows the macroscopic and microscopic characteristics of this mold. The amount of the extract depends on the nature of the culture medium for mold growth, where the orange is a nutrient-rich material (20), Moreover, the secondary metabolites that this mold produces are known as virulence factors, and it is well established that these substances both promote the development of disease and impede or inhibit the fruit's defense mechanism in various pathogen-host interactions (2) and this explains the increased amount of mold filtrate growing on the infected fruit as solid-state fermentation. While YES medium is a medium that contains only two components, yeast extract and sucrose(15).

Through chemical analysis of P. italicum filtrates under consideration, it was found that they contain many compounds that are biologically effective, especially against microorganisms, sixteen bioactive compounds were identified in the chloroformic extract of P. italicum in liquid fermentation filtrate LFF and thirty-one compounds were detected in the extract of solid-state fermentation filtrate SSFF (tables 1 and 2). The identification of bioactive chemical compounds is based on the peak area, retention time, molecular weight and chemical structure. Several previous studies were conducted on the chemical content of secondary metabolites for this mold filtrate (21). In a study performed by Mohammed et al (8) of liquid fermentations, they found that twenty-eight bioactive chemical constituents were identified by (GC-MS) from methanolic extract of the P. italicum in liquid fermentation by potato dextrose broth (PDB) medium and the main composite was decanoic acid and its derivatives. A chemical study with The FTIR analysis of P. italicum performed by Al Mousawi and Razaq, (22) showed the presence of functional group assignment Alkenes, Alkyl halides, Amide, and Alkane. However, there is no prior study on the solid-state fermentation of this mold in terms of the chemical content of the filtrate. The results of the current study shown in Table 3 appeared that the chloroformic extracts of SSFF and LFF of P. italicum against pathogenic bacteria were highly effective in suppressing the growth of gram-positive and gram-negative bacterial species with significant differences between them at $p < 0.001$, 0.02, 0.05 and 0.06, with IZ: 24.7± 0.57, 18.2 ± 0.28, 26.3 ± 0.59, 21.6 ± 0.51 and 32.8 ± 0.21 (for SSFF)mm respectively and 0.0, 12.3±0.57, 28.16±0.20, 19.3±1.15 and 28±0.2 (for LFF)mm respectively. As shown in Figure 4, Klebsiella pneumonia was resistant to LFF and the reason may be due to that this bacterium contains a capsule, which is considered a virulence factor that makes it resistant to antibacterial agents, while both filtrates showed the highest efficacy against Staphylococcus aureus with significant difference at $p< 0.02$; the reason for

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the high efficacy can be attributed to the fact that this bacterium is gram-positive; so the most important causes of resistance in bacteria is the genetic and the environmental factors, and the fact that the patient does not take antibiotics frequently, so the bacteria become sensitive to antibacterial agents (23). In a previous study conducted by Faid and Tantaoui-Elaraki (24) for sterile filtrates toxigenesis test of twenty-four isolates of P. italicum against Bacillus megaterium, the filtrates showed toxicity at about 96%. Mohammed et al. (8) demonstrated the antibacterial activity of P. italicum volatile chemicals by showing how well they inhibited Proteus mirabilis growth at 6.08±0.21 mm. According to Al Mousawi and Razaq (22), this mold was extremely aggressive against Escherichia coli (6.02±0.18) mm. The identification of P. italicum bioactive chemical products using in vitro antimicrobial determination serves as a foundation for additional phytochemical and pharmacological research aimed at developing novel compounds with potential antibacterial and antifungal properties (8). Investigations into the toxicity of sterile culture filtrates of Penicillium aurantiogriseum and P. viridicatum against Bacillus subtilis were conducted. The effect on B. subtilis varied according to the amount of filtrate utilized, and the same study's chemical analysis of the filtrate revealed that it included numerous mycotoxins with cytotoxic activity, including aurantiamine, terrestric acid, and penicillic acid (25). Conclusions: the filtrate of Penicillium italicum from a natural medium (rotted orange) as a solid state fermentation was more weighted and gave many effective metabolites compared to what was produced by liquid fermentation on a synthetic medium, and both liquid and solid fermentation filtrates demonstrated efficacy against harmful bacteria.

Recommendations

Study of the effectiveness of blue mold filtrates as antifungal, ant parasite, and anticancer activities.

Acknowledgments

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Source of funding

No source of funding

Ethical clearance

Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2024AFH885).

Competing interests

The author declares that they have no conflict of interest.

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النشاط الضد ميكروبي لراشح العفن الأزرق ضد بعض انواع البكتريا المرضية

انعام فؤاد حسين [1]

الملخص

الخلفية الدراسية: تعد الأنواع الرمية من البنسليوم من بين أشهر الفطريات والتي تعيش بشكل أساسي على المواد العضوية القابلة للتحلل. تضمنت الدراسة الحالية تحضير راشح العفن الأزرق وهو عفن نباتي رمي شائع في يهاجم النبات ما بعد الحصاد يرتبط عادةً بالحمضيات.

الهدف من الدراسة: استهدفت الدراسة تحديد الوسط الأكفأ لنمو العفن وإنتاج نواتج الأيض الثانوي المضادة للبكتريا.

طرق العمل: شملت الدراسة تحديد وسط النمو للعفن الازرق وانتاج مواد الايض الثانوي له من حلال استخدام تقنية كروماتوغرافيا الغازية مطياف الكتلة وتخمر الحالة السائلة لكل من راشح تخمر الحالة الصلبة وتخمر الحالة السائلة بالإضافة الى ذلك ،تم تقييم النشاط الضد ميكروبيي لراشحي العفن ضد البكتريا المرضية باستخدام طريقة الانتشار من الحفر.

النتائج: أوضحت النتائج أن الكتلة الحيوية لراشح العفن كانت أكبر كمية في حالة تخمر الحالة الصلبة مقارنة بتخمر الحالة السائلة. كان وزن المستخلص الخام من مكررين من الوسط السائل ٠,٠٦ ملغم ٠,١١ ملغم والمستخلص الخام من البرتقال المتعفن كان ملغم
أظهرت نتائج الكروماتوغرافيا الغازية أن راشحي العفن يحتويان على عدة مركبات معروفة بفعاليتها الطبية مثل التيتراكوزان . عموما" أظهر كلا الراشحين فعالية تثبيتيه ضد البكتريا المرضية وبأقطار تثبيتيه تمثلت بـ:
٢٤,٧ ±٠,٥٧ , ١٨,٢ ± ٠,٢٨, ٢٦,٣ ± ٠,٥٩, ٢١,٦ ± ٠,٥١ , ٣٢,٨ ± ٠,٢١
لراشح تحمر الحالة الصلبة مقاسا" بالملم على التوالي.
وبأقطار تثبيتيه تمثلت بـ :
١٢,٣ ±٠,٥٧, ٢٨,١٦ ±٠,٢٠, ١٩,٣ ±١,١٥ and 28±0.2
لراشح تخمر الحالة السائلة مقاسا" بالملم على التوالي

الاستنتاجات: كان لراشح العفن الأزرق المستخلص من البرتقال المتعفن وزن أكبر وكمية مواد ايض ثانوي أكثر مقارنة براشح العفن المستخلص من تخمر الحالة السائلة فيما اظهر كلا النوعين من الراشح الفعالية المضادة للبكتريا المرضية

الكلمات المفتاحية: العفن الأزرق، راشح تخمرات الحالة الصلبة، راشح تخمرات الحالة السائلة الكروماتوغرافيا الغازية، النشاط المضاد للبكتيريا

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Histological Determination of Cinnamon and Olive Oil Extract on Traumatic Oral Ulcer in Laboratory Rabbit

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Abstract

Background: The mucosa of oral cavity is the mucous membrane which covers the tissues of the mouth cavity. In order to repair damage from a local aggressor, many cell strains and their byproducts work together throughout the vital physiological process of wound healing. This process culminates in tissue repair and starts relatively early in the inflammatory phase. . The supplements of cinnamon and olive oil can dramatically raise blood levels of antioxidants while lowering those of inflammatory indicators like C-reactive protein.

Objective: The aim of the study was to determine the local histological effect of topical application of cinnamon and olive oil extract on the rabbit oral mucosa

Patients and Methods: 20 adult male rabbits that weight about 700-900 Kg and age about (6-8) months where used in this experimental study. Ulcer induction: Prior to the creation of the ulcers, rats were fixed on their backs and all animals were anaesthetized and induction the ulcer with round filter papers 5.5 mm in diameter were soaked in 15 ml of 50% acetic acid. In order to create round ulcer, an acid-soaked filter paper was pressed onto the right buccal mucosa for 60 seconds. Then divided the groups according to the healing time with 10 rabbits as a control group left healed normally and 10 rabbits as an experimental group that daily used mixture of cinnamon extract and olive oil ready extract topically applied on the traumatic ulcer. The animals were sacrificed along three- and seven-days healing periods and then prepared H&E stain for analyzed the results.

Results: In comparison to the control group, the histological results of oral ulcers that were created and treated with a daily application of a herbal mixture consisting of cinnamon extract and olive oil extract showed greater epithelization, reduced inflammation, and increased angiogenesis, all of which sped up the healing process. Furthermore, there was a noteworthy distinction in the formation of extracellular matrix and collagen fiber synthesis between the experimental and control groups.

Conclusion: Topical treatment using ready herbal extracts of olive oil and cinnamon was more successful in facilitating the recovery of traumatic ulcers.

Keywords: herbal extract, traumatic ulcers, cinnamon extract olive oil extract.

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Introduction

Mucosa of oral cavity is the term for the mucous membrane that covers the structures inside the mouth cavity. Three layers make up the oral mucosa histologically. The first layer is the epithelium of oral cavity, which is a surface squamous stratified epithelium (1). The submucosa, which is located at the lowest level, is a dense, irregular connective tissue that lies beneath the lamina propria, all is connective tissue (2). The production of necessary nutrients, defense of the underlying tissues against mechanical, chemical, and biological stimuli, and the development of a sensory function that permits the experience of temperature, touch, pain, and taste are just a few of the many functions of the oral mucosa plays (3-4). The keratinized or para-keratinized stratified squamous epithelium that lines these surfaces awards the masticatory mucosa its capability to withstand the stress that it experiences at mastication time. Lastly, a particular mucosa on the back of the tongue has a squamous stratified epithelium which may or may not be keratinized (2). Furthermore, the non-keratinized epithelium, found on the lining mucosa, losses the granular layer, and the spinous layer is recognized to be in general thinner (5). Desmosomes hold the epithelium's cells together as they progressively flatten from the stratum basale to the stratum corneum, where they take on a scaly or squamous look. Beneath the epithelium lies a layer of connective tissue called the lamina propria, which is composed from blood vessels, neurons, mast cells, fibroblasts, macrophages, and inflammatory cells (6). Oral ulcers are a common presenting indication of a variety of disorders affecting the mouth that have multiple causative causes. Because various types of ulcerated lesions share similar clinical and histologic characteristics, these lesions may present a special diagnostic difficulty for medical professionals. (7,8). A biopsy may be necessary to rule out neoplasia or other disorders in chronic ulcerations, which may not always show a clear and obvious trauma source. Acute trauma ulcers typically heal on their own without complications after 14 days (9).

Cinnamomum spp., as the plant is known scientifically, is a versatile herb used in herbal therapy. Mucilage, tannin, sugar, resin, limonene, safrole, and essential oil with antimicrobial, antiseptic, antiviral, and antifungal qualities are among its constituents (10). With strong antioxidants on par with synthetic antioxidants, cinnamon bark has the potential to enhance the oxidative stability of food (11). Studies have indicated that olive oil consists a major part in the health benefits of the Mediterranean diet (MED) (12). The chemicals found in olive oil have demonstrated potential as antibacterial, anti-inflammatory, and antioxidant agents (13). The aim of the study was to determine the local histological effect of topical application of cinnamon and olive oil extract on the rabbit oral mucosa.

Patients and Methods

Study protocol

The experiment done at Diyala province-Baqubah and from 1st November 2023.

Study population and Study design

The 20 male rabbits were randomly assigned and used in the work into two groups consisting of 10 animals each, the experimental group and the control group. Each group was divided into two group according to healing periods to 3 days and 7-days healing intervals (5 rabbits to each interval). The combination of xylazine 2% (0.08 ml/kg B.W.) and ketamine 10% (3 mg/kg B.W.) was administered intramuscularly (IM). Prior to the procedure, all surgical supplies and towels were autoclaved for 30 minutes at 121°C and 15 bar/cm2 of pressure to sterilize them.

Ethical considerations

This study was approved by the Ethics Committee of College of Medicine,

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University of Diyala and according to the ethical approval (2024MAH823).

Ulcer Induction

Circular filter sheets soaking in 15 milliliters of 50% acetic acid, with a diameter of 5.5 mm. An acid-soaked filter paper was applied to the right buccal mucosa for 60 seconds in order to induce a circular ulcer [figure 1]. Ten milliliters of sterile distilled water were used topically once a day to treat the ulcer (Control Group). A single daily micropipette dose of 10 mL of ready extract mixture (buying from herbal company) that diluted to 1 g/ml was used to treat the ulcer (14). Animals were euthanized with an excess of general anesthesia at the conclusion of the three and seven-day healing periods after ulceration in order to obtain ulcer samples for histological and histochemical analysis. In order to create slides, the specimens were embedded in paraffin, fixed in 10% formalin solution, and sectioned into thin 5 m slices. Hematoxylin and eosin (H&E) staining was carried out for histological assessment under a light microscope (15, 16).

Figure 1: induce ulcer

Statistical analysis

The detailed explanation of all variable was analyzed by used the Statistical Package for the Social Sciences (SPSS) version 25. The data were expressed using the mean, standard deviation, standard error, 95% confidence interval, minimum, and maximum values. Mann-Whitney The test was employed to examine the relationship between the variables that were being studied. If the confidence level was 95% and the P-value was 0.05 or below, it was deemed to have statistical significance.

Results

Ulcer size analysis

The average ulcer size for each groups on days 3, and 7 is showed decreasing induced ulcer sizes with time, with the mixture of herbal material group showing a greater mean value on day seven of the healing periods. The percentage of rabbits who reported a recovery in ulcer size at day 3 and day 7 for the groups that were examined showed an increase over the duration of the study. The mixture of two extract group had the highest mean percentage value at day seven, as indicated in (Table 1).

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Inflammatory cells

According to the quantity of inflammatory cells that were scored the mean number of inflammatory cells to be at its maximum level after just 7 day in the extract mixture group, while it was at its lowest level after seven days in the oil group Table (2). Mann-Whitney U test was used in order to test the correlation between variables of two groups that were researched and presented in Table 3. Highly significant difference was between the mixture of two herbal material group and the control group (P = 0.013) at 3 days healing periods, and there was also a highly significant difference between the mixture of two herbal material group and the control group (P = 0.013).

Epithelial cells

The mean epithelial thickness of each of the groups that there was not a significant difference between any of the groups that were evaluated during any of the healing periods. Whereas this is evident on day 3 (P=0.631) and day 7 (P=0.109), respectively Table 4.

Mann-Whitney U test was used in order to test the correlation between variables of two groups showed Non-significant difference was between the mixture of two herbal material group and the control group (P = 0.631) at 3 days healing periods, and there was also a non-significant difference between the mixture of two herbal material group and the control group (P = 0.109) at 7 days (Table 5).

Blood vessels and cells

The average number of blood vessels in the examined groups during all healing phases there was high average number of blood at 3 & 7 days in compare to control group and there was high important distinction between the researched groups through any of the recovery intervals. Where on day 3 the (P=0.004) and on day 7 the (P=0.002) between the studied groups (Tables 6,7).

Table (1): Descriptive statistics of mean of ultimate ulcer size in researched groups in all recovery intervals

Day	Group	N	Mean	SD	SE	95% Confidence interval for mean	Min.	Max.
Day 3	Extract mixture	6	6.1	0.43	0.11	5.7-6.5	5.72	6.3
	Control	6	7.3	0.31	0.12	6.7-7.3	6.74	7.4
Day 7	Extract mixture	6	1.7	0.92	0.45	0.7-2.5	2.1	2.9
	Control	6	2.9	0.71	0.32	2.2-3.7	2.4	3

Table 2: Descriptive statistics of the mean of inflammatory cells at day 3 and 7

Day	Group	N	Mean	SD	SE	95% Confidence interval for mean	Min.	Max.
Day 3	Extract mixture	5	25.9	25.9	3.21	1.31	19.5-26.3	19.2
	Control	5	20.8	27.8	1.42	0.62	23.3-26.2	23.42
Day 7	Extract mixture	5	20.4	20.4	3.41	1.45	15.8-23.0	15.21
	Control	5	22.6	22.6	2.14	0.91	24.4-28.8	24.43

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Table 3: Comparison of the studied groups by Mann-Whitney test, according to the mean of inflammatory cells

Day	Group	Mean rank	P value
Day 3	Extract mixture	5.58	0.010*
	Control	7.42	
Day 7	Oil	3.92	0.013*
	Control	9.08	

Table 4: Descriptive statistics of the mean of epithelial cells at day 3 and 7

Day	Group	N	Mean	SD	SE	95% Confidence interval for mean	Min.	Max.
Day 3	Extract mixture	5	224.2	19.4	7.9	193.9-234.6	187.36	233.27
	Control	5	202.7	22.5	9.2	195.0-242.3	187.23	247.08
Day 7	Extract mixture	5	341.6	46.3	18.9	253.0-350.2	235.27	360.05
	Control	5	259.6	46.7	19.1	203.5-301.6	197.06	312.23

Table 5: Comparison of the studied groups by Mann-Whitney U test, according to the mean rank of epithelial cells

Day	Group	Mean rank	P value
Day 3	Extract mixture	6	0.631
	Control	4	
Day 7	Extract mixture	8.17	0.109
	Control	6.83	

Table 6: Descriptive statistics of mean of blood vessels in studied groups in all healing periods

Day	Group	N	Mean	SD	SE	95% Confidence interval for mean	Min.	Max.
Day 3	Extract mixture	5	13.7	2.4	1	9.2-14.2	9	15.3
	Control	5	10.5	3.9	1.6	5.4-13.6	6	17
Day 7	Extract mixture	5	15.7	2.1	0.9	10.5-14.8	10	15.6
	Control	5	12.3	3.1	1.2	8.1-14.5	7	16

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Table 7: Comparison of the studied groups according to blood vessels

Day	Group	Mean rank	P value
Day 3	Extract mixture	8.08	0.004
	Control	4.92	
Day 7	Extract mixture	7.33	0.002
	Control	5.67	

Histological results

The histological finding at 3 days, the oral ulcer that created in control group revealed presence of granulation tissue and inflammatory cell less than that at experimental group figure 2-3, while at 7 days with complete healing the ulcer in experimental group and presence rate ridges and papillary portion with normal lamina propria while the ulcer in control group that revealed newly formed thin epithelium in ulcer area The lamina propria showed granulation tissue formation with moderate to severe number of inflammatory cells, with scanty collagen fibers and few blood vessels figure 4-5. Histological finding (Hematoxylin and Eosin staining).

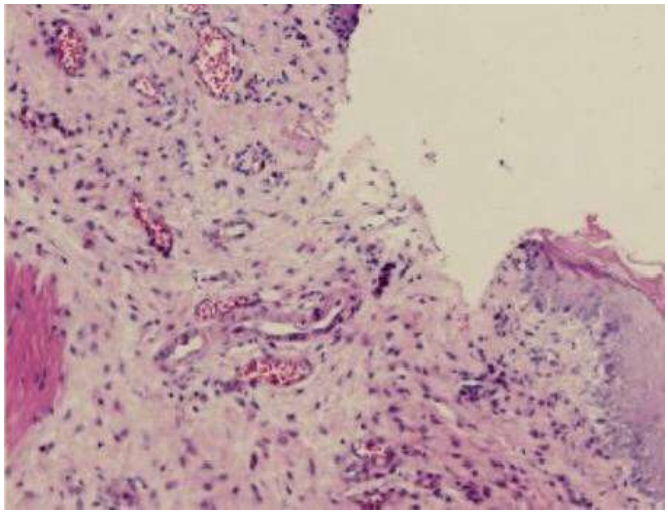

Figure 2: At the 3rd day in control group shows limited epithelium migration from the margin toward the center area with less number of the inflammatory cells H& E stained slide (x10).

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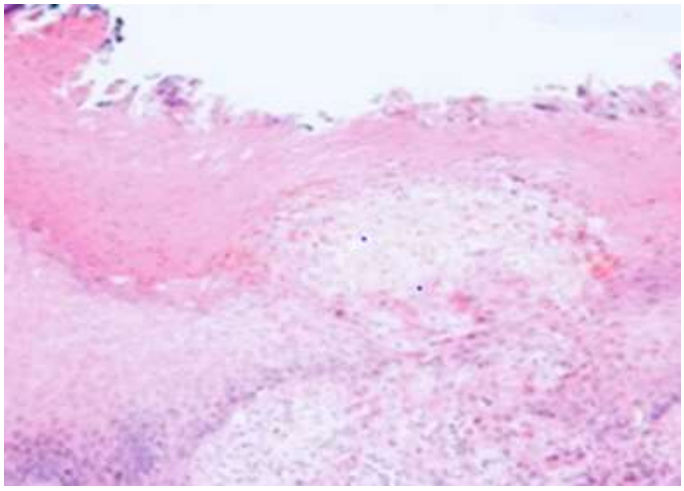

Figure 3: View of the study group at 3 day reveals an ulcer with epithelial and connective tissue migration and large number of the inflammatory cells H& E stained slid (x10).

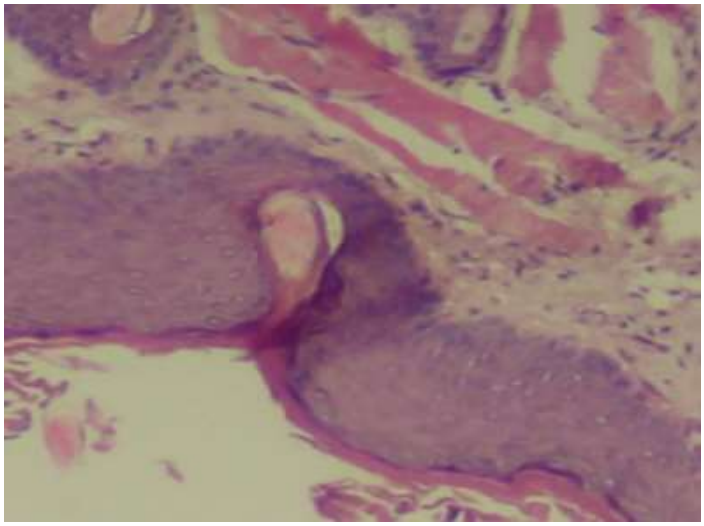

Figure 4: View of the control group at ٧ day reveals control group, showed newly formed thin epithelium in ulcer area cells with early mature rete ridges H& E stained slid (x10).

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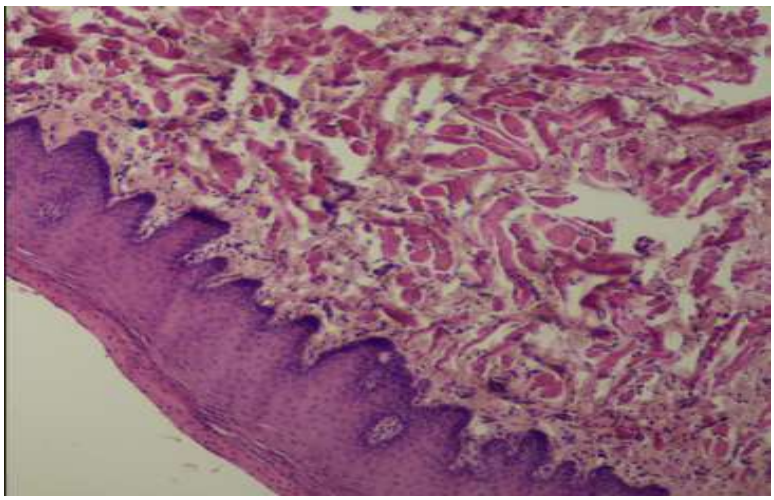

Figure 5: View of the study group shows at 7 day reveals mature keratinized stratified squamous epithelium with mature rete ridges H& E stained slid (x10)

Discussion

Trauma induced ulcers are damages to the mucosa of oral cavity performed by physical or mechanical trauma, or chemical burning for example acetic acid, unexpected chewing through mastication, chewing while talking, piercing by sharp objects, clefted, distorted, or Caries teeth or sharp edge (17). Olive oil and cinnamon extract has the ability to accelerate incision recovery because its influence on incision contraction, re-epithelization, early neovascularization, and enhanced collagen intensity (18). In every group, the average percentage of healing ulcer size increased over time, with the monitoring group owning the lowest mean value compared to the mixture extract group. This result of olive oil's & cinnamon effect due to antibacterial characteristics, which reduce the period wanted for incision contraction and cancel bleeding after surgery this finding agree with (19). In the present study, histological finding of inflammatory cells revealed varying degrees of variability across all healing intervals. The experimental groups' inflammatory response decreased over time, whereas the monitoring group's elevated. This perhaps because the mixed oil contains anti-bacterial and anti-inflammatory actions (18) that are absent in the control group. This is agreed with (20), that employed myrrh powder in their work and diluted with sodium chloride to treat intraoral mucosal ulcers and showed that this enhanced the anti-inflammatory impact of myrrh in comparison to the control group this similar to the action of cinnamon and olive oil extract. It's also agree with (21) who utilized myrrh oil in the therapy of skin wound healing and improved the anti-inflammatory effect of myrrh in comparison to the control group. In the current research, the new blood vessels in both the monitoring and experimental groups was examined with a clear

difference between the groups. The mixture extract group had the highest mean value of blood vessels on the first and seventh day compared to the control group. In agreement with (21) the present study revealed that experimental groups had more angiogenesis than control groups. Re-epithelization is the

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process by which basal and suprabasal cells proliferate and migrate through the recovery stage in an attempt to mend a wound. The current study showed that re-epithelialization increased over time for both the experimental and control groups. The mixture extract oil group recorded a high mean value on days 3 and 7, which was marginally higher than the monitoring group. This was attributed to exceed neovascularization, fibroblast cells, and collagen fiber, as well as increased epithelial cell proliferation and progression. This is consistent with earlier researches (20,21). The keratin layer, subepithelial infiltration of mononuclear cells, and an obvious grade of re-epithelialization with the recuperation of rete ridges were all visible with the use of H&E stain. A significant rise in the combination extract groups in the basement membrane, especially on days 3 and 7 of the recovery periods; the histochemical results corroborate this (22).

Conclusion

According to the findings of this study, the topical application of essential olive oil extract when mixed with cinnamon extract is significantly more beneficial than the control group in promoting the healing of oral traumatic ulcers.

Source of funding

No source of funding

Conflict of interest

The author acknowledges no conflict of interest in this study

Recommendations

Herbal elements are among the most important lines of treatment that are recommended due to their many uses in healing oral and skin wounds. It is necessary to take into consideration additional matters such as the type, size, and location of the wound, in addition to the blood supply, infection, and other matters that may hinder the healing process and hinder the action of the materials used in treatment.

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التقييم النسيجي والنسيجي لشفاء جروح تجويف الفم لدى الأرانب عن طريق تغذية الأحماض الأمينية القابلة للامتصاص

منار عبد الرزاق حسن[1]

الملخص

الخلفية: قرحة الفم المؤلمة هي آفة منخفضة ومحدودة بشكل جيد مع خلل ظهاري مغطى بجلطة الفيبرين، مما يؤدي إلى مظهر أصفر-أبيض، يحدث بسبب إصابة كيميائية أو ميكانيكية أو حرارية للغشاء المخاطي للفم مع تآكل مؤلم. الأحماض الأمينية ضرورية لشفاء الجروح لأنها تعزز نمو النسيج الضام وكذلك تنشيط وتكاثر الخلايا الليفية.

الهدف من الدراسة: تقييم تأثير التطبيق المنهجي لجمع الأحماض الأمينية (تناول الفم) في علاج تقرح الفم المؤلم خلال فترة زمنية محددة عن طريق التقييم النسيجي والنسيجي لشفاء الأنسجة الرخوة.

المواد والطرق: تم استخدام ٢٠ ذكر أرنب بالغ بوزن حوالي ٧٠٠-٩٠٠ كغم وأعمار حوالي (٦-٨) أشهر حيث تم استخدامها في هذه الدراسة التجريبية. تم إنشاء القرحة المؤلمة بقطر (٨ مم)، و(١ مم) بواسطة مثقاب ماسي دائري جراحي في الغشاء المخاطي للخد الأيمن، ثم تم تقسيم المجموعات إلى مجموعتين، ١٠ أرانب للمجموعة الضابطة التي تركت تلتئم بشكل طبيعي، و١٠ أرانب للمجموعة التجريبية التي يستخدم يومياً خليط من الأحماض الأمينية نظامياً من خلال خلطه مع الماء لمدة شهر. تمت التضحية بالحيوانات خلال فترات شفاء مدتها ٣ و٧ أيام وتم فحص الأنواع تشريحيا بعد التحضير النسيجي للقرحة المؤلمة.

النتائج: أظهرت النتائج النسيجية والنسيجية انخفاض الالتهاب، وتسريع إعادة تنسج سطح القرحة، وتولد الأوعية الدموية بشكل أفضل، وتعزيز إعادة تشكيل المصفوفة خارج الخلية مما يؤدي إلى تعزيز نضج الأنسجة والشفاء الكامل في جميع الحالات مجموعات الدراسة منها في المجموعة الضابطة.

الاستنتاج: الدواء الكيميائي الذي يمثله التطبيق الجهازي للأحماض الأمينية فعال في تسريع شفاء القرحة المصابة في المجموعة التجريبية مقارنة بالمجموعة الضابطة عن طريق تكاثر الخلايا المتسارع وإعادة تنسج الغشاء المخاطي.

الكلمات المفتاحية: القرحة المؤلمة، الأحماض الأمينية، إعادة التظاهر

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Role of surfactant therapy in reducing oxygen requirement and mortality among neonates suffering from respiratory distress syndrome: A Prospective study at Al – Batool teaching hospital in Diyala province

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Abstract

Background: Respiratory distress syndrome (RDS) is a major cause of neonatal morbidity and mortality. It is a breathing disorder characterized by a deficiency or inactivity of surfactant in the lungs of preterm and term babies and if not treated, it leads to serious complications like pneumothorax, emphysema, bronchopulmonary dysplasia and death.

Objective: To estimate the effect of surfactant therapy on oxygen requirement and neonatal mortality as well as the incidence of RDS in the special care neonatal unit (SCNU) in the AL Batool Teaching Hospital in Diyala Governorate.

Patients and Methods: A sample of 2000 patients with signs and symptoms of RDS at the time of presentation was prospectively collected from the 1st of July 2022 until the 1st of March 2023 in SCNU at Al-Batool Teaching Hospital. Gestational age, body weight, the use of oxygen, surfactant therapy, and continuous positive airway pressure (CPAP) were taken into consideration in assessing the outcome of RDS neonates.

Results: There was a significant relationship between surfactant administrations, the period of staying on CPAP, and oxygen demand as the p-value was < 0.001 for both. Neonates who received surfactant had a lower mortality rate, with an incidence of 2.5%; the p-value was < 0.001. Incidence of neonatal RDS was 694 (34.7%).

Conclusion: Since the incidence of RDS was 34.7%, surfactant therapy should be routine in neonatal special and intensive care units. Proper use of surfactant (proper timing and mode of administration) reduces oxygen demand, the need for CPAP, hospitalization, and mortality among those neonates.

Keywords: Neonates, respiratory distress syndrome, Incidence, continuous positive airway pressure.

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Introduction

Respiratory distress syndrome (RDS) is observed in premature babies due to a deficiency of surfactant and in term neonates who have meconium aspiration; pneumonia; sepsis; and pulmonary hemorrhage due to surfactant inactivity. RDS, if untreated, might end with respiratory failure (1). Early surfactant therapy decreases mortality and morbidity in neonates with respiratory distress. The incidence of RDS is higher at small gestational ages. About 60 – 80% with gestational age < 28 weeks will develop RDS, 30% of neonates with gestational age between 28 – 34 weeks develop RDS and those with gestational age > 36 weeks develop RDS in 5% of cases (2, 3). Surfactant is a mixture of dipalmitoyl phosphatidylcholine (lecithin), Phosphatidylglycerol, Apo proteins, and cholesterol (4). Surfactant reduces the surface tension of alveoli and keeps the alveoli open. Because of immaturity, the amount produced is not enough. Surfactant is synthesized in the fetal lung by 20 weeks of gestation and appears in amniotic fluid between 28 and 32 weeks of gestation. RDS is manifested by dyspnea, tachypnea, grunting, nasal flaring, intercostal and subcostal retraction and cyanosis (5). Deficiency of surfactant leads to atelectasis and perfused but not ventilated alveoli, resulting in hypoxia and hypercapnia. This causes pulmonary arterial vasoconstriction, which ends with ischemic injury, together with oxygen toxicity results in the effusion of proteinaceous material into the alveolar spaces causing apnea, irregular respiration, and cyanosis. If the cases are untreated, there will be more apnea and cyanosis, resulting in mixed respiratory-metabolic acidosis. This will cause more complications represented by edema, paralytic ileus, oliguria, emphysema, pneumothorax, pulmonary hemorrhage, and sometimes intraventricular hemorrhage (IVH). Respiratory failure may occur in RDS infants with rapid progression (6). RDS can be diagnosed by clinical features, chest x-ray (CXR) findings, and blood gas analysis. CXR shows ground glass opacity of lung parenchyma with the characteristic air bronchogram appearance or white lung (Figure 1) (7). In spite of that, CXR might be normal during the first few hours. Laboratory investigation might reveal hypoxemia, hypercapnia, which might be associated with metabolic acidosis. RDS must be differentiated from early onset sepsis, congenital pneumonia, cyanotic heart disease, persistent pulmonary hypertension, meconium aspiration, spontaneous pneumothorax, pleural effusions, congenital lung anomalies, diaphragmatic hernia, and lobar emphysema (8, 9). Transient tachypnea of newborn (TTN) has shorter and milder clinical course (neonate needs 24 hours oxygen supplementation). Symptoms usually improve after 24 hours. CXR shows perihilar streaking, representing perihilar interstitial edema, or it may be normal (10).

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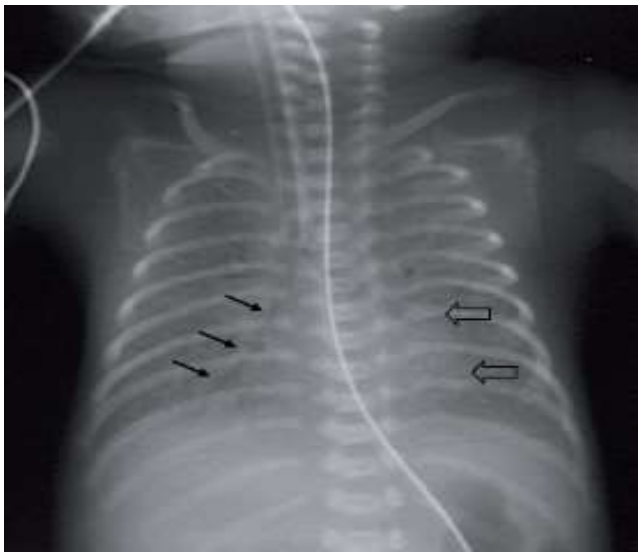

Figure 1: CXR of 4 hours old neonate with respiratory distress syndrome showing bilateral ground-glass opacification of the lung fields, air-bronchogram (small arrows) and loss of cardiac borders (black arrows)

Surfactant is the treatment of choice, and it is given by endotracheal tube in two ways: prophylactic method for premature neonates with very low birth weight (≤ 1500 g) and those with gestational age ≤ 32 weeks immediately after birth, or the rescue method for those with RDS above these limits, as the surfactant should be given during the first 24 hours of life. When oxygen saturation cannot be kept at about 91-95% with nasal oxygen between 50 and 70 mmHg, the neonates should be connected to CPAP at pressure of 5-10 cm H2O via nasal prongs after administration of surfactant. CPAP reduces the collapse of surfactant deficient alveoli and improves ventilation perfusion matching (11 – 13). Effects of surfactant replacement therapy can be noticed by improvement of Alveolar oxygenation, reduced ventilator support and improvement of chest radiographic appearance (14 – 16).

Aim of the study

To estimate the effect of surfactant on decreasing mortality, and the duration of oxygen requirements as well as the incidence of RDS in a special care neonatal unit in Al-Batool Teaching Hospital in Diyala Governorate.

Patients and Methods

A sample of 2000 patients was prospectively collected over a period of 7 months extending from the 1st of July 2022 until the 1st of March 2023 in the SCNU at Al-Batool Teaching Hospital. All cases with clinical signs and symptoms of respiratory distress at the time of presentation were included in this study and classified into RDS and TTN on the bases of clinical examination, CXR, and laboratory findings. Approximately 2mL of venous blood was aspirated into a heparinized syringe and sent to the laboratory for blood gas analysis. RDS neonates were followed for their response to natural surfactant (Survanta 4 ml vial 25 mg / ml, AbbVie Inc, United states), which was administered in a dose of 100mg/kg during the first 24 hours of life, in four positions with separate doses (15 seconds apart) by using an ambu bag with the INSUR technique (intubation, administration of surfactant, and extubating) (17, 18). Then we put the patient on CPAP. Bubble CPAP at 5 cm H2O is used to maintain Spa O2 within the range of 89-95%. Weaning from CPAP commences after improvement and the

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neonates change to nasal oxygen (19, 20). RDS neonates were assessed according to gestational age, body weight, surfactant administration, period of stay on CPAP, oxygen demand, and outcome. The cut point for giving surfactant was the birth weight and gestational age. Those with very low birth weight (≤ 1500 g) and those with gestational age ≤ 32 weeks received surfactant as prophylactic, while those above this level were given surfactant according to the rescue method. Birth asphyxia and congenital anomalies were excluded.

Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22 software. The variables are expressed as frequencies and percentages. The relationship between neonatal RDS and gestational age, body weight, surfactant administration, oxygen demand, CPAP stay, and the outcome were tested by the Chi - square test. A P-value of less than 0.05 was regarded as statistically significant.

Ethical considerations

The research will not expose patients to further risk. Only the main investigator has the right to access the patient's information. The research was conducted after the approval of the research proposal by the ethical committee at Al-Batool Teaching Hospital. (Document no. 2023SQM804).

Results

The collected data were analyzed to find the effect of surfactant therapy on the number of hours spent on CPAP, oxygen demand, and their outcome as well as the incidence of neonatal RDS and its relation to various risk factors. Descriptive statistics revealed that among the studied sample, there were 1037 (51.9%) male and 963 (48.2%) female neonates. RDS accounts for 694 (34.7%) of cases, while the remaining 1306 (65.3%) suffered from TTN. Neonates who received surfactant were 297 (14.9%) and those who did not receive it represented 1703 (85.2%). The gestational ages of the newborns at the time of delivery were: 22 (1.1%) found to be less than or equal to 27 weeks; 65 (3.3%) had gestational age from 28 – 31 weeks; 396 (19.8%) were from 32 – 36 weeks (i.e., preterm neonates account for 24.2 % of all cases); and those with gestational age above or equal to 36 weeks were 1517 (75.9%). In addition to that, neonates who had been born with a body weight less than 1kg were 7 (0.4%), those who weighed between 1 and 1.499 kg were 88 (4.4%), those weighing from 1.5 – 2.499 kg were 325 (16.3%) i.e., low birth weight neonates account for 21.1%, while those with a body weight above 2.5 kg account for 1580 (79%). CPAP usage was 34.4%. 1314 (65.7%) neonates did not necessitate the use of CPAP, 65 (3.3%) of neonates needed the CPAP for less than 4 h, 187 (9.4%) of neonates needed the CPAP for 5 – 12 h, 246 (12.3%) of neonates needed the CPAP from 13 – 24 h, 166 (8.3%) neonates needed the CPAP from 24 – 48 h, and 22 (1.1%) of neonates require the use of CPAP for more than 48 h. Neonates who required oxygen for less than 24 h were 1476 (73.8%), those who needed oxygen from 24 – 48 h were 215 (10.8%) and those who needed oxygen for more than 48 h were 309 (15.5%). The outcome of neonates in the studied sample was 1861(93.1%) alive neonates while, the remaining 139 (6.9%) died as shown in Table 1.

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Table 1: Frequencies and percentages of neonatal RDS, possible risk factors & the need for surfactant therapy

Variables		Frequency n=2000	Percentage 100.0%
Cases	RDS	694	34.7%
	TTN	1306	65.3%
Surfactant	Yes	297	14.9%
	No	1703	85.2%
Gestational age	≤27W	22	1.1%
	28-31W	65	3.3%
	32-36W	396	19.8%
	≥36 W	1517	75.9%
Weight	<1kg	7	0.4%
	1-1.499kg	88	4.4%
	1.5-2.499kg	325	16.3%
	>2.5	1580	79%
Sex	Male	1037	51.9%
	Female	963	48.2%
CPAP	No CPAP	1314	65.7%
	<4h	65	3.3%
	5-12h	187	9.4%
	13-24h	246	12.3%
	25-48h	166	8.3%
	>48h	22	1.1%
Oxygen	<24h	1476	73.8%
	24-48h	215	10.8%
	>48h	309	15.5%
Outcome	Alive	1861	93.1%
	Dead	139	6.9%

Analytic statistics showed a significant relationship between the development of RDS and the gender of the neonates, since RDS appeared to be more common in male infants, as the p –value was < 0.001, as shown in Table 2.

Table 2: The relationship between RDS and neonatal gander

Respiratory distress	Gender		Total	P-Value
	Male	Female		
RDS	398 (57.3 %)	296 (42.7)	694	< 0.001
TTN	639	667	1306	
Total	1037	963	2000	

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On the other hand, the relationships between parenteral administrations of surfactant and various relevant parameters were tested by using the Chi – square test as shown in Table 3 which revealed the presence of significant relationships between surfactant administration and neonatal distress, neonatal outcome, oxygen demand, neonatal boy weight, gestational age at time of delivery, and the period of staying on CPAP, as the p – values were < 0.001 for each relation. It was clear that RDS neonates necessitate the use of surfactant, while those with TTN do not need surfactant therapy. Neonates with RDS showed a significant improvement in neonatal outcome with the use of surfactant therapy. Oxygen demand was significantly reduced in RDS neonates after using parenteral surfactant. It was evident that the lower the birth weight and gestational age at the time of delivery, the more risk for RDS development and the more the need for parenteral surfactant therapy. With the administration of surfactant, RDS neonates needed less hours on CPAP.

Table 3: The relationship between administration of surfactant and various relevant parameters

		Administration of surfactant		Total	P-values
		Yes	No		
Neonatal distress	RDS	297	397	694	< 0.001
	TTN	0	1306	1306	
	Total	297	1703	2000	
Outcome	Alive	246	1615	1861	< 0.001
	Dead	51	88	139	
	Total	297	1703	2000	
O2 demand	< 24 h	112	1364	1476	< 0.001
	24 – 48 h	92	123	215	
	> 48 h	93	216	309	
	Total	297	1703	2000	
Body weight	< 1 kg	7	0	7	< 0.001
	1 – 1.499 kg	53	35	88	
	1.5 – 2.499 kg	158	167	325	
	> 2.5 kg	79	1501	1580	
	Total	297	1703	2000	
Gestational age	< 27 w	15	7	22	< 0.001
	28 – 31 w	42	23	65	
	32 – 36 w	171	225	396	
	> 36 w	69	1448	1517	
	Total	297	1703	2000	
Staying on CPAP	0 h	0	1314	1314	< 0.001
	< 4 h	48	17	65	
	5 – 12 h	103	84	187	
	13 – 24 h	100	146	246	
	24 – 48 h	42	124	166	
	> 48 h	4	18	22	
	Total	297	1703	2000	

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Discussion

RDS is one of the main causes of morbidity and mortality among preterm neonates in the SCNU and NICU. Therefore, understanding pathophysiology and risk factors and the proper use of therapeutic methods, including antenatal steroids, monitoring oxygenation and ventilation, exogenous surfactant, and supportive care can reduce the mortality rate among those neonates (21). In this study, we found that 34.7% were RDS cases and among them 57.3 % were male neonates. Preterm neonates account for 24.2 % of all cases, while low birth weight neonates account for 21.1%. Neonates with RDS who received surfactant and required oxygen for less than 24 h were 16.1% versus 8% who did not take surfactant; those who needed oxygen from 24 – 48h were 9.5% versus 17.7% and those who needed oxygen for more than 48h were 13.4% versus 31.1%. In RDS neonates who received surfactant, CPAP usage less than 4 hours was 6.9% versus 2.4% in the untreated neonates while those who needed CPAP from 13-24 hour were 14.4% versus 21%, those who needed CPAP from 24-48 hour were 6% versus 17.8% those who needed CPAP more than 48 hours among the treated neonates were 0.57% versus 2.59 %. Neonates that died from RDS were 6.9% those who took surfactant were 2.5% versus 4.4% in the untreated neonates. It was obvious that parenteral administration of surfactant therapy decreased with increasing gestational age and neonatal body weight at the time of delivery. The use of rescue method and early administration of surfactant in premature and low birth weight neonates (less than 2.5 kg) have decreased the hours of demand for oxygen and CPAP usage since the p-value was < 0.001 and this coincides with a study conducted by Rojas-Reyes et al (2012) in which they stated that all infants delivered at a gestational age less than 32 weeks should be treated with surfactant as soon as they are intubated since the need for mechanical ventilation was lower in the treated group, which was 26% compared with the control group, which was 39% (22). In addition to that Kattwinkel et al (1993) reported that prophylaxis use of surfactant associated with less neonatal RDS, less mechanical ventilation or supplemental oxygen during the first four days, and fewer neonatal deaths (23). Plavka et al (2002) mentioned that early use of surfactant has decreased oxygen consumption and the death rate among premature neonates suffering from RDS (29% early treated versus 64% delayed treated) since the p – value was 0.02 (24). Previous studies stated that the early use of surfactant therapy can improve the duration on mechanical ventilation and oxygen therapy in premature infants with insignificant relationship with mortality rate (25 – 27). On the other hand, the Osiris Collaborative Group (1992) (28) reported a 16% reduction in mortality rate among neonates who received surfactant in early and late groups, which was (early 7% versus delayed 25%) which appeared to be similar to our result. Similarly, Sankar et al (2016) found that giving surfactant to distressed neonate decreases the rate of mortality (29), while others reported a insignificant reduction in the mortality rate among neonates receiving surfactant with NIPPV/CPAP, and those who connected to NIPPV/CPAP and did not receive surfactant (30, 31). Preterm neonates were more likely to develop RDS, but in spite of that, full – term infants could also develop RDS due to the inactivity of surfactant as in congenital pneumonia, sepsis (32) and meconium aspiration. This runs in parallel with a study performed by et al who showed that using surfactant wash in neonates suffering from meconium aspiration leads to an improvement in arterial oxygen saturation, which reach up to 80% within 12 minutes in most cases (33). In this study, the mortality rate among neonates who received

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surfactant was 2.5% while for untreated neonates, due to the unavailability of surfactant in the hospital at that time and the inability of their families to bring it due to its high cost, it was 4.4%. Untreated neonates were connected to CPAP and ventilators. These results coincide with a study done by Hamvas et al (1993) in which he reported that 20% of premature babies with RDS have little or no response to surfactant. due to: structural lung immaturity; they may have other diseases such as pneumonia or pulmonary hypoplasia; pulmonary edema from lung damage results in inactivation of surfactant; or it occurs from left-to-right shunting through the patent ductus arteriosus, and maldistribution of surfactant in the lungs (34).

Conclusion

The mortality rate has decreased after administration of surfactant from 4.4% to 2.5%, and the period of staying on CPAP has also decreased, which allowed for the rapid turnover of neonates on CPAP, also needed less time on oxygen and thus decreased the period of staying in hospital.

Source of funding

No source of funding

Conflict of interest

The author acknowledges no conflict of interest in this study.

Recommendation

1. Encourage the use of the prophylactic method in the administration of surfactant to any neonate less than or equal to 1500 g or less than 32 weeks gestation.
2. Encourage the use of the rescue method for any neonate above 32 weeks gestation or 1500 g with severe RDS.
3. Give surfactant to any intubated neonate with RDS.
4. Proper monitoring of heart rate, respiratory rate, SP O2, blood gas analysis and repeat CXR after 8 – 12 hours if the baby is still on CPAP in order to give another dose of surfactant.

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دور الفاعل بالسطح في تقليل متطلبات الأكسجين ومعدل الوفيات عند الولدان المصابين بعسر التنفس الولادي. دراسة استطلاعية في مستشفى البتول التعليمي في ديالى

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الملخص

الخلفية الدراسية: تعتبر متلازمة عسر التنفس السبب الرئيسي لوفيات الأطفال حديثي الولادة. هو اضطراب في التنفس يتميز بنقص أو عدم نشاط الفاعل بالسطح في رئتي الأطفال الخدج والأطفال الناضجين وإذا لم يتم علاجه؛ فهو يؤدي إلى مضاعفات خطيرة مثل استرواح الصدر وانتفاخ الرئة وخلل التنسج القصبي الرئوي والوفاة.

الهدف من الدراسة: معرفة معدل حدوث متلازمة عسر التنفس الولادي في وحدة الرعاية الخاصة لحديثي الولادة (SCNU) في مستشفى البتول التعليمي في محافظة ديالى وتأثير العلاج بالسطح على متطلبات الأكسجين ووفيات الأطفال حديثي الولادة.

المرضى وطرق العمل: تم جمع عينة من ٢٠٠٠ مريض يعانون من علامات وأعراض عسر التنفس الولادي بأثر تقدمي في الفترة من ١ تموز ٢٠٢٢ حتى ١ اذار ٢٠٢٣ في وحدة العناية الخاصة لحديثي الولادة بمستشفى البتول التعليمي. تم أخذ عمر الحمل ووزن الجسم واستخدام الأكسجين والعلاج بالسطح وضغط بالاعتبار عند تقييم نتائج حديثي الولادة (CPAP) مجرى الهواء الإيجابي المستمر

النتائج: كشفت هذه الدراسة أن معدل حدوث الضائقة التنفسية عند الأطفال حديثي الولادة كان ٦٩٤ (٣٤,٧٪). وهناك علاقات هامة بين إعطاء الفاعل بالسطح وانخفاض فترة البقاء على الأكسجين وجهاز الضغط العالي للاوكسجين حيث كانت القيمة الاحتمالية ٠,٠٠١ لكليهما. كان لدى حديثي الولادة الذين تلقوا الفاعل بالسطح معدل وفيات أقل بنسبة ٢,٥٪، وكانت القيمة الاحتمالية ٠,٠٠١.

الاستنتاجات: بما أن نسبة حدوث متلازمة عسر التنفس كانت ٣٤,٧٪ ، يجب أن يكون العلاج بالفاعل بالسطح روتينيًا في وحدات العناية المركزة والخاصة لحديثي الولادة ، فالاستخدام السليم للفاعل بالسطح (التوقيت المناسب وطريقة الإعطاء) يقلل من الطلب على الأكسجين، والحاجة الى جهاز الضغط العالي للاوكسجين والاستشفاء والوفيات بين حديثي الولادة.

الكلمات المفتاحية: RDS حديثي الولادة، الإصابة، ضغط مجرى الهواء الإيجابي المستمر.

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Cholera outbreak in diyala province

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Abstract

Background: Vibrio cholerae is a primary cause of severe dehydrating diarrhea and remains a serious public health problem in low- and middle-income countries (LMICs) with insufficient water, sanitation, and hygiene. Cholera remains a public health threat the worldwide, mainly in countries with poor access to safe water and sanitation facilities. According to estimates, there are 21,000–143,000 deaths and 1.3–4 million cases of cholera annual.

Objective: This study aims to carry out an analysis of the available information on cholera outbreaks in Diyala province, 2022.

Patients and Methods: A descriptive study conducted in the department of public health using the data of cases reported from eight sectors in province. The data was collected from the surveillance unit, communicable control division of the public health department in Diyala province, IRAQ in 2022.

Results: The total number of confirmed cases of cholera was (n = 139), female (72) 52 % and male (67) 48%, death reported for two of these cases. According to the date of onset, the registration of cases began from July 19 to October 25, 2022. However, the case fatality ratio (CFR) was 1.4%, while the attack rate in the governorate is 7.6 per 100,000 populations during 2022, the highest attack rate in Khanaqin district was (77 cases) 46, while the lowest attack rate in Baldruze, Al-Mansuria, and Al-Khalis districts was (1 case) 0.3,0.6, and 0.8 respectively. The age mean of patients was (38.7 ± 17.14 years) and the occurrence of the disease is more incidence in the age group 30-44 and females more than males.

Conclusion: Occurrence Cholera outbreak during year 2022 without confirmed cases recorded since 2015 and the occurrence of cholera cases in governorate is greater during the months of August and September and most of the cases were from Khanaqin district.

Keywords: Outbreak, Cholera, Iraq, Diyala, CFR.

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Introduction

Vibrio cholerae is a primary cause of severe dehydrating diarrhea and remains a serious public health problem in low- and middle-income countries (LMICs) with insufficient water, sanitation, and hygiene (1). V. cholerae is disseminated by two different fecal-oral mechanisms: the first is direct transmission from person to person through the consumption of food or water infected with bacteria, and the second is drinking water from ponds, lakes, or rivers that has been contaminated on an environmental level (2).

Cholera remains a public health threat the worldwide, mainly in countries with poor access to safe water and sanitation facilities. (3). According to estimates, there are 21,000–143,000 deaths and 1.3–4 million cases of cholera annual (4). In 2020, 80 countries reported statistics on cholera to world health organization (WHO). Of them, 27 countries reported a total of 323,320 cholera cases and 857 deaths, 0.27% case fatality rate (CFR) (5). The goal of the Ending Cholera: A Global Roadmap to 2030 cholera control plan is to reduce cholera mortality by 90% (6). Globally the WHO reported around 2.9 million new cases of cholera in 69 endemic countries (7). Nine out of 22 countries in the Eastern Mediterranean Region (EMR) experienced cholera outbreaks and occasionally epidemics in the past ten years. In many parts of Iraq, cholera has been regarded an endemic disease since 1966, when the first epidemic of cholera occurred, with a case fatality rate of 8.8%. Iraq remained cholera endemic, with recorded outbreaks in 1998, 2007, 2008, 2012, and 2015 (8). According to the Iraqi Ministry of Health, new cholera epidemics occur in Iraq on June 20, 2022, mostly in the Kurdistan regions Sulaymaniyah province (9). Some challenges facing Iraq its location along the Tigris and Euphrates rivers, whose polluted waters provide the majority of the country's water supply, in addition to its contact with neighboring countries with periodic disease outbreaks, which make it more vulnerable to waterborne and infectious diseases (10). Open defecation, improper sewage disposal, and poorly maintained water and sewage systems have put the community in danger of catching water-borne illnesses like cholera (9). Despite Diyala governorate being free of cholera since the year 2015; it has faced an epidemic of cholera starting on 19/June till 12/11/2022, the total number of laboratories confirmed cases of cholera was 141 cases and two deaths only. This study aims to carry out an analysis of the available information on cholera outbreaks in Diyala province, 2022

Patients and Methods

Study protocol:

A descriptive study was conducted in the department of public health.

Study Period

The period of the study was from 1st January 2023 to 5th January 2023.

Setting of Study

This study was conducted in Diyala province, Diyala health directorate, public health department. It is about 57 kilometers northeast of Baghdad city the capital of Iraq and has an area of 17,685 square kilometers, and accounts for 4.1% of the total area of Iraq. According to the Central Statistical Organization (CSO), Ministry of Planning, Republic of Iraq, the total population of Diyala province in 2022 was 1,814,368.

Study population

All sectors that were included in the surveillance system in this study were 8. The data was collected from the surveillance unit, communicable control division of the public health department in Diyala, 2022.

Exclusion Criteria

Cases reported from districts outside the governorate were excluded from the study.

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Study Sample

Cases reported from eight health sectors in province.

Sampling Technique

All surveillance data of cholera from eight health sectors were included.

Official approval:

Official approval was granted from Diyala Directorate Health.

Statistical analysis:

Analysis of data was carried out using excel software (version 19). The data has been analyzed statistically for cholera reported cases that were recorded according to person, place, and time. Data were presented by frequency, percentage, attack rate, and case fatality ratio (CFR).

Results

The total number of confirmed cases of cholera was 139, death reported for two of these cases. According to the date of onset, the registration of cases began from July 19 to October 25, 2022 with a clear increase in the number of cases, especially in September, where the highest recorded ten cases in one day figure (1).

The total number of cholera cases was (n = 139), female (72) 52 % and male (67) 48%. However, the case fatality ratio (CFR) was 1.4%. While the attack rate in the governorate is 7.6 per 100,000 populations during 2022 shown in table (1) and the age mean of patients was (38.7 ± 17.14 years) and the occurrence of the disease is more incidence in the age group 30-44 and females more than males as shown in figure (2). Notifications and data surveillance indicate that the first and highest recorded cases were recorded in the Khanaqin district in (77 case) 55%, while the lowest cases were in Baldruze, Al-Khalis, and Al-Mansuria districts, with (1 case)1% figure (3).

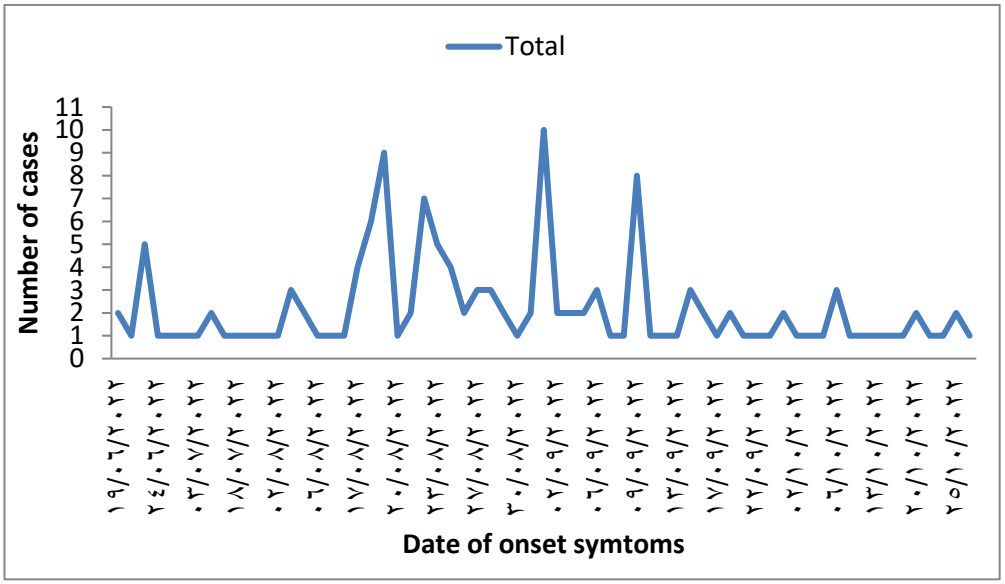

Figure (1): Number of cholera cases by date of onset in Diyala governorate, 2022.

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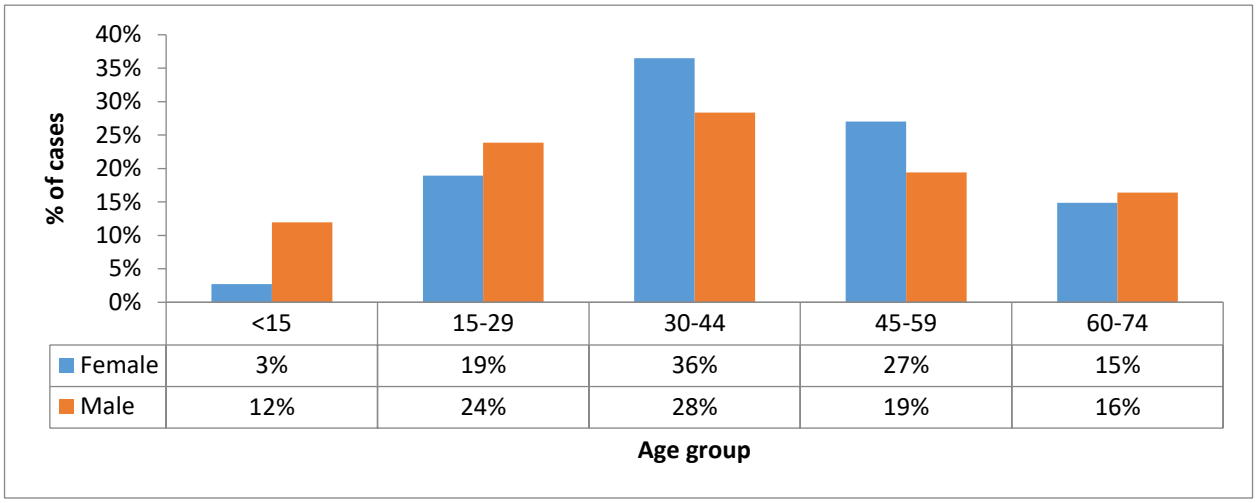

Figure (2): Cholera cases according to age group in Diyala governorate, 2022

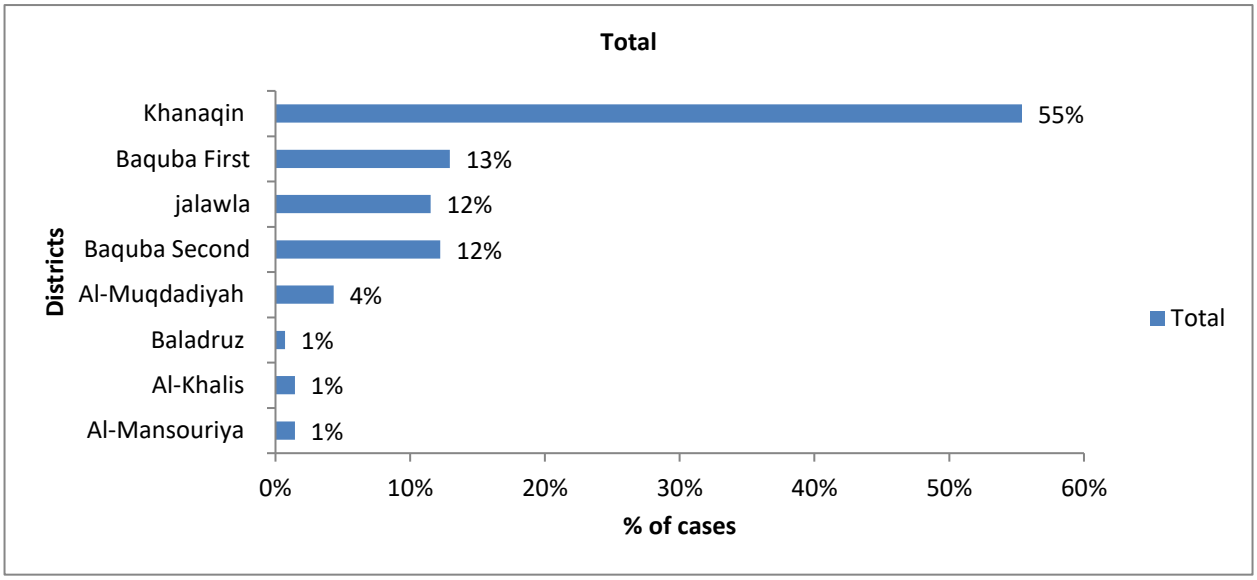

Figure (3): Distribution of cholera cases according to Districts in Diyala governorate during 2022

The attack rate of cholera cases in Diyala governorate, 2022

Table (1): Showed the attack rate of Cholera cases in the governorate was 7.6 per 100,000 populations, the highest attack rate in Khanaqin district was (77 cases) 46, while the lowest attack rate in Baldruze, Al-Mansuria, and Al-Khalis districts was (1 case) 0.3,0.6, and 0.8 respectively. It is known that infection rates are influenced by the population of the community at risk, meaning that the rates differ depending on the population in the sectors.

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Districts	Count cases	Total pop	Attack rate per 100,000
Baladruz	1	295328	0.3
Al-Mansouriya	1	161050	0.6
Al-khalis	1	127610	0.8
Al-Muqdadiyah	6	175011	3.4
Baquba 2	17	401953	4.2
Baquba 1	18	281582	6.3
Jalawla	16	83461	19.2
Khanaqin	77	168736	46
Total	139	1,814,368	7.6

Discussion

According to the World Health Organization, cholera is an acute diarrheal infection caused by the ingestion of the bacterium Vibrio cholera via contaminated food and water (11). Ninety-five percent of deaths and 2.86 million cases are caused by the disease, which is still endemic in nearly 69 countries (12). In this study, the total number of cholera cases was (n = 139), but the case fatality ratio (CFR) was 1.4%. This percentage is lower than a study done in Iraq during the 2022 outbreak that attacked many governorates (13) and also agree with the study done in Alborz Province, Iran (14). Globally this CFR is higher than a study done in India, 2011–2020 (15), and lower than study conducted in Syria linked deaths at a 0.08% case fatality rate (12). According to the date of onset, the registration of cases began from July 19 to October 25, 2022 with a clear increase in the number of cases, especially in September, where the highest recorded ten cases in one day this result agree with another study done in waist governorate, Iraq 2017(21). The age mean of patients in the current study was (38.7 ± 17.14 years), these results agree with the study done in Iraq (16, 13). The occurrence of the disease is more prevalent in the age group 30-44 and females more than males, this result agrees with a study done in Iraq in 2017 (17),study done in Iraq at national level showed a comparable distribution of ages (16) and disagrees with another study done in Iraq which found the male more than female (18) and study done in Iran a five-year study on the epidemiological approaches to cholera (19), this result disagrees with a study done in West Africa which found the sex ratio of females / males was equal (20). Regarding the distribution of cholera cases by districts in the governorate, the study showed that all the districts that were reported and most of the cases were from Khanaqin district. There are several issues related to this sector, sewage system, and insufficient supply of potable water in the governorate due to the acute shortage of river water, which affected the water supply and its provision to populations. On the other hand, people rely on groundwater from wells to fill the need for water for daily use, and this is considered not subject to examination periodicity by health oversight. It is possible that this interpretation could be similar to another interpretation from another study conducted in the Wasit governorate during 2017 interpreted

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the annual distribution of the disease may show little or no control over the risk factors that lead to cholera, like inactive sewage disposal and using disinfectant water in daily life activities like cooking or drinking (21) and a study done in Iraq at the national level found people rely on rivers, streams, and estuaries for domestic purposes, such as drinking water or supplying vehicle water or maybe a shortage in water provision and use of electrical pumps to draw unsafe water from the old pipes that may be contaminated with sewage disposal net due to the damage of both systems (16). The attack rate in the governorate is 7.6 per 100,000 populations during 2022 this rate is higher than a study conducted in the Wasit governorate, Iraq in 2017 and nationally in the same year (21) and higher than a study included Iraq during 2017 (16), this study at the governorate level has a high attack rate when compared with a study done in Syria at the national level with an attack rate of 0.1% (22) also higher than a study done in Yemen attack rates were below 1% (23). Travelers visiting cholera-endemic nations run the risk of contracting the disease, and individuals living in cholera-free nations may bring the infection with them from endemic or epidemic areas, imported cholera cases may be far higher than officially reported cases, as the World Health Organization (WHO) estimated that officially reported cases represent only 5%–10% of the true number of cases (24).

Recommendations

Awareness of the importance of the cholera disease, emphasizing the ways of transmission of the disease and how to prevent it and ensuring safe drinking water and uncontaminated food and dispose of waste and sanitation.

Source of funding

No source of funding

Ethical clearance

Official approval has been obtained to use data and data were analyzed without the names to protect privacy. This study was conducted according to the approval of College of Medicine/ University of Diyala and in accordance with the ethical guidelines of the Declaration of ethical committee of the College (Document no. 2023AHI808).

Conflict of interest

The author acknowledges no conflict of interest in this study

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تفشي الكوليرا في محافظة ديالى

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الملخص

الخلفية الدراسية: لا تزال الكوليرا تشكل تهديدا للصحة العامة في جميع أنحاء العالم، وخاصة في البلدان التي تعاني من ضعف الوصول إلى المياه المأمونة ومرافق الصرف الصحي. وفقا للتقديرات، هناك ٢١٠٠٠-١٤٣٠٠٠ حالة وفاة و١,٣-٤ مليون حالة إصابة بالكوليرا سنويا.

الهدف من الدراسة: تهدف هذه الدراسة إلى إجراء تحليل للمعلومات المتاحة عن تفشي الكوليرا في محافظة ديالى، ٢٠٢٢.

النتائج: بلغ العدد الإجمالي لحالات الكوليرا المؤكدة (ن = ١٣٩)، والإناث (٧٢) ٥٢ ٪ والذكور (٦٧) ٤٨ ٪، تم الإبلاغ عن وفاة اثنين من هذه الحالات. وفقا لتاريخ البدء، بدأ تسجيل الحالات من ١٩ يوليو إلى ٢٥ أكتوبر ٢٠٢٢. ومع ذلك، بلغت نسبة الوفيات ١,٤ ٪، في حين بلغ معدل الاصابة في المحافظة ٧,٦ لكل ١٠٠,٠٠٠ نسمة خلال عام ٢٠٢٢، وكان أعلى معدل اصابة في قضاء خانقين (٧٧ حالة) ٤٦، في حين كان أدنى معدل اصابة في مناطق بالدروز والمنصورية والخالص (١ حالة) ٠,٣ و٠,٦ و٠,٨ على التوالي. كان متوسط عمر المرضى (٣٨,٧ ± ١٧,١٤ سنة) وحدوث المرض أكثر في الفئة العمرية ٣٠-٤٤ والإناث أكثر من الذكور

الاستنتاجات: حدوث تفشي الكوليرا خلال عام ٢٠٢٢ دون تسجيل حالات مؤكدة منذ عام ٢٠١٥ وحدوث حالات الكوليرا في المحافظة أكثر خلال شهري أغسطس وسبتمبر ومعظم الحالات كانت من قضاء خانقين.

الكلمات المفتاحية: تفشي المرض، الكوليرا، العراق، ديالى، معدل وفيات الحالات.

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