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**Editorial**

# Enhancing Brain Functions and Memory with Foods

**Prof. Dr. Azhar Masud Bhatti**

Editor-in-Chief

The modern era of memory research can be said to have begun in 1957 when Brenda Milner described the profound effects on memory of bilateral medial temporal lobe resection, performed to relieve epilepsy in a patient who became known as H.M. (Scoville and Milner, 1957; Squire, 2009)<sup>1</sup>. H.M. exhibited profound forgetfulness against a background of largely intact intellectual and perceptual functions. The findings from H.M. established three fundamental principles that continue to guide experimental work. First, memory is a distinct cerebral function, separable from other cognitive abilities. Second, because H.M. did as well as others his age at retaining a number or a visual image for a short time, the medial temporal lobe is not needed for immediate memory. Third, the structures damaged in H.M. are not the ultimate repository of memory, because he retained his remote childhood memories.

Efforts to achieve an animal model of human memory impairment succeeded initially in the monkey (Mishkin, 1978)<sup>2</sup>. Cumulative behavioral work, together with neuroanatomical studies, eventually identified the anatomical components of the medial temporal lobe memory system that support declarative memory (Squire and Zola-Morgan, 1991)<sup>3</sup>: the hippocampus (including the CA fields, the dentate gyrus, and the subicular complex), together with the adjacent entorhinal, perirhinal, and parahippocampal cortices that make up much of the parahippocampal gyrus. The behavioral work in the monkey reproduced important features of human memory impairment, emphasizing the key idea that only tasks of declarative memory should be expected to reveal an impairment. The neuroanatomical studies identified the boundaries and the connectivity of the important areas, initially in the monkey and subsequently in the rat (Suzuki and Amaral, 1994; Burwell et al., 1995).

The hippocampus and related structures are essential for the formation of memory and its reorganization and consolidation during a lengthy period after learning. Alternative formulations, which emphasize the role of these structures in memory retrieval, have been considered over the years but have been largely abandoned (Squire, 2006)<sup>5</sup>. Two lines of work underlie the idea that medial temporal lobe structures have a temporary role in memory storage. First, damage to these structures typically spares remote memory and impairs more recent memory in a temporally graded manner (Squire and Bayley, 2007)<sup>6</sup>. Thus, in experimental animals, damage limited to the hippocampus, entorhinal cortex, or fornix typically impairs memory for material learned up to 30 d before

the damage is introduced. In humans, damage limited to the hippocampus impairs memory for material learned up to a few years before the damage occurred. Discussion continues about the possible special status of spatial memory and autobiographical memory (Moscovitch et al., 2006)<sup>7</sup>, though in each of these cases the temporally graded pattern has been described previously (Squire and Bayley, 2007)<sup>8</sup>.

For decades, the idea has been discussed that sleep might provide off-line periods favorable to memory consolidation, and experimental study of this idea has accelerated in recent years. Recordings of neural activity in rodents showed that firing sequences recorded in assemblies of hippocampal place cells during waking behavior are replayed during slow-wave sleep (SWS). The finding of similar, coordinated activity in neocortex suggests that a dialogue between hippocampus and neocortex (Ji and Wilson, 2007)<sup>9</sup>. This coordination could be part of the process by which recent memories become consolidated remote memories. To date, the replay phenomenon has been observed mainly in well trained animals running repeated paths along fixed tracks. The challenge remains to establish a clear link between these observations and memory consolidation and to determine how the replay that occurs during sleep relates to the replay that can occur during wakefulness (Karlsson and Frank, 2009)<sup>10</sup>.

In humans, SWS can modulate declarative memory. For example, the forgetting of declarative memory (in this case, word-pair memory) was attenuated by a night of sleep and attenuated further when the duration of SWS was increased by transcranial application of slow oscillations early in the night (at 0.75 Hz but not at 5 Hz) (Marshall et al., 2006)<sup>11</sup>. Questions remain whether such effects are related specifically to memory consolidation or to the nonspecific benefits of reduced interference during an early time after learning when memory is vulnerable (Wixted, 2004)<sup>12</sup>.

Research on brain function and memory explores how the hippocampus, neocortex, and amygdala handle explicit memories (facts/events), while basal ganglia handle implicit ones, involving processes like encoding, storing, and retrieving info, with studies often using frameworks like the "4 Cs" (Connection, Cognition, Compartmentalization, Consolidation) to understand memory's complex neural mechanisms. PDF resources often cover neuroscience of memory, cognitive psychology, and brain health tips like diet, sleep, and exercise.

The brain encodes, stores, and retrieves memories at a cellular level, often focusing on brain regions like the hippocampus (forming new explicit memories) and cerebellum (motor skills).

**Cognitive Frameworks:** Research uses models like the "4 Cs" (Connection, Cognition, Compartmentalization, Consolidation) to structure the vast field of memory research.

**Memory Types:** Studies differentiate between explicit (episodic/semantic) and implicit (procedural) memory systems, detailing which brain parts are involved.

**Brain Function & Health:** General brain functions (sleep, movement, emotions) and practical ways to improve memory, such as physical activity, healthy diet (berries, fish), good sleep, and managing stress.

Factors influencing memory span a wide range, including psychological states (attention, emotion, stress, motivation), lifestyle habits (sleep, diet, exercise, substance use), environmental cues (context, sounds, smells), physical health (age, brain health, genetics, chronic pain), and the memory process itself (encoding, storage, retrieval). Key elements are focusing well (attention), strong feelings (emotion), proper rest, and reducing distractions for better encoding, storage, and retrieval.

**Psychological Factors**

**Attention & Focus:** Strong concentration leads to better memory encoding; divided attention hinders it.

**Emotion:** Strong emotions (positive or negative) can enhance or distort memories.

**Stress & Anxiety:** High levels impair working memory and recall.

**Motivation:** Interest, need, or necessity improves memorization.

**Lifestyle & Health**

**Age:** Memory functions often decline with age, especially episodic memory.

**Sleep:** Crucial for memory consolidation (moving memories to long-term storage).

**Diet & Exercise:** General brain health impacts memory.

**Substance Use:** Alcohol, drugs, and even certain medications can interfere.

**Chronic Pain:** Can significantly impair memory.

**Environmental & Contextual Factors**

**Context-Dependent Cues:** Returning to the environment (sights, sounds, smells) where you learned something can trigger recall.

**Distractions:** Noisy or busy environments disrupt encoding.

**Memory Processes**

**Encoding:** How well you initially learn information.

**Storage:** Maintaining memories over time.

**Retrieval:** Accessing stored memories; can fail due to decay or interference.

**Information-Specific Factors**

**Meaning:** Material that is meaningful or relevant is easier to remember.

**Repetition:** Repeated exposure aids retention.

**Interference:** New or old information can block access to other memories

Some foods can play a vital role in maintaining a healthy brain and improving cognitive abilities like memory and concentration.

**Fatty Fish:** Fatty fish, such as salmon, trout, albacore tuna, herring, and sardines, are rich sources of omega-3 fatty acids. These omega-3s are crucial for building brain and nerve cells, supporting learning and memory, and potentially slowing down age-related cognitive decline.

**Coffee:** Coffee contains caffeine and antioxidants that can boost brain health. Caffeine enhances alertness, mood, and concentration by blocking the action of adenosine, a sleep-inducing chemical. Long-term coffee consumption has been associated with a reduced risk of neurological diseases like Parkinson's and Alzheimer's.

**Blueberries:** Blueberries are packed with anthocyanins, antioxidants known for their anti-inflammatory properties. These compounds help protect the brain from aging-related damage and improve communication between brain cells, potentially enhancing memory and cognitive functions.

**Turmeric:** The active compound in turmeric, curcumin, can cross the blood-brain barrier and offer various brain benefits. It may improve memory, alleviate depression symptoms, and promote the growth of new brain cells.

**Broccoli:** Broccoli is high in vitamin K, which plays a role in forming fats essential for brain cell structure. Studies suggest that higher vitamin K intake may lead to better memory and cognitive function in older adults.

**Pumpkin Seeds:** Pumpkin seeds are rich in antioxidants, magnesium, iron, zinc, and copper. These nutrients are crucial for nerve signaling, learning, memory, and brain function. Incorporating them into your diet can have a positive impact on brain health.

**Dark Chocolate:** Dark chocolate with high cocoa content contains flavonoids, caffeine, and antioxidants. Flavonoids may enhance memory and slow down age-related cognitive decline. Regular consumption of dark chocolate has been associated with improved mental tasks.

**Oranges:** Oranges are a rich source of vitamin C, an antioxidant that helps protect brain cells from oxidative damage. Adequate vitamin C intake supports focus, memory, and may reduce the risk of mental health conditions.

**Nuts:** Nuts, such as walnuts, are linked to better heart health, which in turn benefits the brain. Regular nut consumption is associated with a lower risk of cognitive decline. Nutrients like healthy fats, antioxidants, and vitamin E in nuts contribute to brain health.

**Eggs:** Eggs provide essential nutrients like vitamins B6, B12, folate, and choline. Choline is necessary for neurotransmitter regulation, mood, and memory. These nutrients can contribute to mental well-being and slow cognitive decline.

**Green Tea:** Green tea contains caffeine, which enhances brain function by improving alertness, performance, memory, and focus. It also includes L-theanine, an amino acid that promotes relaxation without inducing drowsiness. Green tea's polyphenols and antioxidants may protect the brain from mental decline and reduce the risk of neurodegenerative diseases.

Including these brain-boosting foods in your diet can contribute to better cognitive function, memory retention, and overall brain health.

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# Management and Clinical Assessment of Dermatitis in the presence of Barrier Dysfunction and Scaling: A Comparative Analysis of the Efficacy of SVR Topialyse Baume Protect+ in Improving the Skin Barrier Function

Tamarah Qays Al-Mohammed

## ABSTRACT

**Objective:** To evaluate the effectiveness of treatment in the presence of barrier dysfunction and scaling.

**Study Design:** A prospective randomized controlled trial study

**Place and Duration of Study:** This study was conducted took place in two dermatology centers in Baghdad, Iraq: Al-Zahraa Teaching Hospital and Tamara Skin and Laser Clinic from 1<sup>st</sup> October 2024 to 31<sup>st</sup> December 2024.

**Methods:** comparing 100 cases with moderate dermatitis to either SVR Topialyse Baume Protect+ (enriched with ceramide) or a standard moisturizer (10per cent glycerin + mineral oil) after four weeks. The results were SCORAD index, TEWL, patient-reported itch (VAS), and digital image analysis.

**Results:** Experimental group registered a 40 percent drop in SCORAD (60.0-36.0), 40 percent reduce in TEWL (25.0 15.0 g/m<sup>2</sup>/h) and 65 percent enhancement in itch (8.5-3.0 on VAS) which was significantly more than controls (  $p < 0.001$ ). Scaling, erythema and fissures showed significant improvement as evidenced by digital imaging.

**Conclusion:** SVR Topialyse Baume Protect+ is more effective based on active repair of the lipid barrier and provides a pathophysiology-based method of treating dermatitis.

**Key Words:** Skin barrier, Ceramides, Dermatitis, Transepidermal water loss, SCORAD, Emollient, Barrier repair.

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## INTRODUCTION

The skin is the largest organ of the body and the main point of interaction of homeostasis of the body with external environmental threats. It is highly essential as a protective barrier to withstand the entry of pathogens, reduce water loss and protection against chemical, physical, and immunological stress factors. This action is completely contingent upon the structural plumbing of the stratum corneum, the most outer epidermal layer which is structured into a bricks and mortar architecture: corneocytes (bricks) embedded with a lipid-rich intercellular matrix (mortar) containing a composition of ceramides, cholesterol, and free fatty acids (50 and 25 and 25 respectively).<sup>1,2</sup>

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Atopic dermatitis is marked by severe loss of ceramides, especially ceramide 1 (EOS), and the stratum corneum of the skin in atopic dermatitis is reported to be decreased by 30.50%.<sup>3,4</sup> This imbalance is caused by genetic (e.g., filaggrin mutations) and environmental factors (e.g., harsh cleansers, low humidity) that put a person in a vicious cycle of dryness, itch, scratching, and additional damage to the barriers.<sup>5,6</sup>

The waxy lipids ceramides are essential to close the intercellular spaces, decrease the loss of water to the environment, and prevent the penetration of allergens. Topical ceramide supplement is a rational, focused treatment method due to their depletion in dermatitis. Ceramide-enriched preparations in contrast to conventional emollients with either occlusives (e.g., petrolatum) or humectants (e.g., glycerin) in the past attempt to repair the lipid matrix itself rather than the hydration transiently, which attempts at repairing the pathophysiology of the epidermis.<sup>7</sup>

SVR Topialyse Baume Protect+ is a phytoceramide-enriched, medical-grade emollient which is designed to specifically redress the lipid deficiency of damaged skin using phytoceramides, niacinamide and licorice root extract. The paper compares its clinical and functional efficacy with a standard moisturizer in moderate cases of dermatitis in adult patients: multimodal assessment is

based on SCORAD, TEWL, patient-reported itch, and digital image analysis.

## METHODS

The study was a prospective, randomized, controlled trial study was took place in two dermatology centers in Baghdad, Iraq: Al-Zahraa Teaching Hospital and Tamara Skin and Laser Clinic from 1<sup>st</sup> October 2024 to 31<sup>st</sup> December 2024 vide IRB-2024-07 dated 24-7-2024. The research was in compliance with the declaration of Helsinki, 2013. A total of 100 adult patients with a moderate case of chronic dermatitis (SCORAD 20-60) and clinical evidence of barrier dysfunction (xerosis, scaling, erythema, fissures) were recruited were enrolled. The moderate dermatitis (SCORAD 20-60), visible barrier impairment, age 18-60, readiness to adhere to the protocol and none of the topical corticosteroids, calcineurin inhibitors, or systemic immunosuppressants in the last 2 weeks were included. The severe AD (SCORAD >60), active skin infection, psoriasis, ichthyosis, or genodermatoses, pregnancy or lactation and sensitivity to ingredients of study products were excluded.

Computer-generated block randomization (block size = 4) was used to randomly assign the participants (1:1) through Random Allocation Software (RAS v1.0). The allocation was hidden until consent and baseline tests.

**Experimental group (n=50):** SVR Laboratories, France Applied SVR Topialyse Baume Protect+ to the affected parts (hands, forearms, legs, feet) twice per day over 28 days.

**Control Group (n = 50):** Rubbed a generic moisturizer (10% glycerin + mineral oil) under the same conditions. Patients used one unit of fingertip (FTU) on each area and did not bathe the treated skin 30 minutes after the treatment. Adherence was also observed through daily diaries and weekly check-ins.

The measurements were done at the baseline (Day 0) and endpoint (Day 28).

**The Clinical Severity (SCORAD Index):** Judged by a dermatologist who is blind. SCORAD is an extent (6%), intensity (erythema, edema, excoriation, lichenification, dryness; 50%), and subjective symptom (pruritus, sleep loss; 44%). Score range: 0–103.

**Trans-Epidermal Water Loss (TEWL):** Tewameter TM300 (Courage and Khazaka, Germany) was used to measure it. Three readings: one per location (lesional/non-lesional); average value of that place (g/m<sup>2</sup>/h). Lower TEWL = improved barrier.

**Patient-Reported Outcome (Itch):** Measured using 10-point Visual Analog Scale (VAS): 0 = none, 10 = worst ever. The weekly average itch was measured on patients.

**Computerized clinical image analysis:** Canon EOS R5 (100mm macro lens) with a standardized lighting (5000K) at a distance of 30 cm with an angle of 90 degrees and a neutral white background. When the

images are analyzed through Antera 3D(R) (Miravex, Ireland) of:

- Erythema Index
- Melanin Index
- Skin Roughness (Ra)
- Pore Area

Two dermatologists rated scaling and fissure depth independently (0 = none, 3 = severe).

**Improvement Score in Composite Barrier:** Derived as an average of percent change in SCORAD, TEWL and Patient Global Assessment (PGA) all weighted equally to give a composite look at barrier recovery.

The statistical analysis was performed in SPSS-28.0. Normal test Shapiro Wilk was applied. Changes within groups: paired t-tests. Between-group comparisons: independent t-tests. p<0.05 was regarded as significant.

## RESULTS

It was found that there was a significant difference in the severity of clinical disease in the experimental group. The baseline of both groups had moderate and severe cases of dermatitis with mean SCORAD of 60.0±10.0 in the SVR group and 58.0±9.0 in the control group which showed similar cases of diseases at the beginning of the study. Four weeks post treatment the group that used SVR Topicalyse Baume Protect+ realized a significant decrease in SCORAD scores of 36.0±8.0, which had a 40% improvement in overall severity of the disease. This improvement included important effects of erythema, edema, excoriation, lichenification, and dryness. On the contrary, the control group with a traditional moisturizer reported less significant increase 20% reductions in SCORAD scores to 46.070 where the control group had a score of 70. The comparison of the two groups as far as the improvement is concerned showed that it was statistically significant (p<0.001), which indicates the improvement of the clinical efficacy of the ceramide-enriched formulation (Table 1).

The trans epidermal water loss (TEWL) was an important objective biomarker of skin barrier integrity. An increase in TEWL values means that the barrier is impaired and that water is lost more through the skin surface. The mean TEWL at baseline was 25.0 g/m<sup>2</sup>/h and 24.0 g/m<sup>2</sup>/h in experimental and control respectively. After the four-week intervention, experimental group showed a dramatic 40% decrease in TEWL with the mean value of 15.0±2.0 g/m<sup>2</sup>/h. This major decrease is a direct and quantitative indication that SVR Topialyse Baume Protect+ is a good agent in repairing the lipid matrix of the stratum corneum, thus restoring its capacity to hold moisture. The effect was less pronounced on the control group, as TEWL reduced to 20.0±3.0 g/m<sup>2</sup>/h, a 17% decline. This sharp difference in TEWL reduction also highlights the better barrier-repairing effect of the ceramide-based cream (Table 2).

Itching (pruritus) is another key factor leading to patient suffering and poor quality of life in dermatitis. The patient-reported outcome indicated that there was a deep difference between the two groups in terms of the relief of symptoms. Initially, the patients in the two groups had high-severe itch scoring (mean of 8.5 in the SVR group, and 8.0 in the control group which had a 10-point Visual Analog Scale or VAS). At the conclusion of the experiment, experimental group reported that there was a dramatic change, resulting in that average itch score dropped to 3.0 and that itch intensity had decreased by 65 percent. Such intense and quick relief probably helped in the breakage of the itch-scratch cycle, and the skin healed. The control group also felt somewhat relieved but it was much lower, and the scores dropped only to 5.5, which is a 31 per cent better result. This high patient-reported outcome in the SVR group highlights the efficacy of the formulation not only in skin repair, but patient comfort and well-being (Table 3).

A composite barrier improvement score was computed to give a holistic response to treatment efficacy and was based on the percentage change in SCORAD, TEWL and patient global assessment. This discussion showed that the experimental group had attained an overall 65 percent improvement of skin barrier function. This overall improvement demonstrates the synergy of the cream on clinical features, biophysical functioning, and perception of the patient. Comparatively, the control group experienced an improvement of 35% in the barrier functionality. SVR Topialyse Baume Protect+ provides a complete and effective solution to barrier repair in comparison to typical moisturizers (Table 4).

**Table No. 1: Comparative analysis of SCORAD scores before and after treatment in the experimental and control groups**

Group	Before Treatment (Mean SCORAD ± SD)	After Treatment (Mean SCORAD ± SD)	Change Rate
Experimental (SVR Topialyse Baume Protect+)	60±10	36±8	40%
Control (Traditional Moisturizer)	58±9	46±7	20%

The significant improvement in the hand dermatitis is shown in Figure 1. The skin had severe xerosis, deep fissure and large-scale before treatment. Four weeks of SVR Topialyse Baume Protect+ resulted in a definite and significant reduction in cracking, a significant decrease in scaling and generally an improved skin texture and increase in skin hydration. The skin was also smoother and firmer, and the fissures had a distinct healing process (Figs. 2-3). Moreover, these findings

were supported by the graphical representation of the information. The visual representation of reducing itchiness in the patient (Fig. 4) shows that the reduction in itchiness in the SVR group increased rapidly between the 8.5 and 3.0 values, whereas the reduction in the control group was more gradual. Fig. 5 gives a direct comparison of the overall barrier improvement as a bar chart that the overall bar in the experimental group was almost twice that of the control group (65 out of 35) which in itself presents a clear and immediate effective summary of the study overall conclusion.

**Table No. 2: Changes in transepidermal water loss (TEWL) as a measure of skin barrier function**

Group	Before Treatment (TEWL ± SD) (g/m <sup>2</sup> /h)	After Treatment (TEWL ± SD) (g/m <sup>2</sup> /h)	Change Rate
Experimental (SVR Topialyse Baume Protect+)	25±3	15±2	-40%
Control (Traditional Moisturizer)	24±4	20±3	-17%

**Table No. 3: Patient-reported itchiness reduction on a 10-point visual analog scale (VAS)**

Group	Before Treatment (Itchiness Scale 1–10)	After Treatment (Itchiness Scale 1–10)	Improvement Rate
Experimental (SVR Topialyse Baume Protect+)	8.5	3.0	65%
Control (Traditional Moisturizer)	8.0	5.5	31%

**Table No. 4: Composite barrier improvement percentage based on multimodal assessment**

Group	Barrier Improvement
Experimental (SVR Topialyse Baume Protect+)	65%
Control (Traditional Moisturizer)	35%



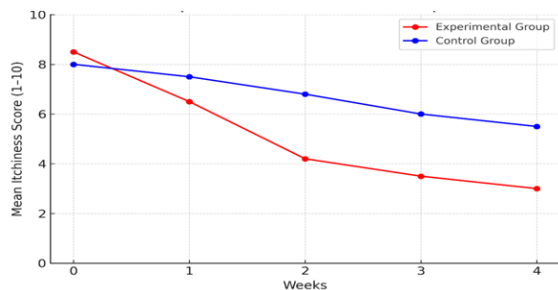
**Figure No. 1: Clinical improvement in hand dermatitis after four weeks of treatment with SVR topialyse baume protect+**



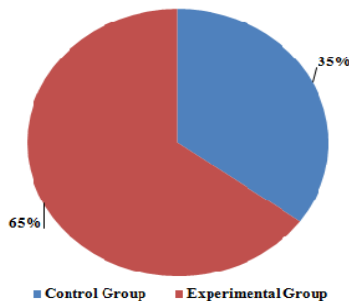
**Figure No. 2: Clinical improvement in foot dermatitis after four weeks of treatment with SVR topicalyse baume protect+**



**Figure No. 3: Clinical Improvement in Foot Dermatitis After Four Weeks of Treatment with SVR Topialyse Baume Protect+**



**Figure No. 4: Weekly reduction in patient-reported itchiness (VAS 1–10) in the experimental and control groups**



**Figure No. 5: Comparative barrier function improvement between treatment groups**

## DISCUSSION

SVR Topialyse Baume Protect+ is a better treatment choice when it comes to the management of dermatitis that is a result of the skin barrier dysfunction. Clinical severity (SCORAD), biophysical barrier functionality (TEWL), patient-reported symptoms (pruritus), and visual appearance of the skin all improved and are evidences that this ceramide-enriched emollient is more than a source of temporary hydration- it is an active agent in repairing the stratum corneum. Our findings are in agreement with the current studies on barrier repair therapy. The 40 percent decrease in TEWL when using the experimental group is also similar to the 38% improvement in 12 weeks of trial with a ceramide-dominant moisturizer when used by adult patients with atopic dermatitis.<sup>8</sup> Draelos et al<sup>9</sup> and Eichenfield et al<sup>10</sup> have revealed that ceramide-containing preparations are much superior to traditional moisturizers in terms of xerosis and skin hydration, our study has also indicated the same results with pruritus reduced by 65% and scaling and fissures significantly improved.

The 40 percent change in the SCORAD scores is comparable to the 42 percent decrease recorded by Del Rosso et al<sup>8</sup> in a comparable barrier-repair intervention. The reliability of the findings in various trials highlights the reliability and clinical applicability of ceramide-based therapy, which strengthens its place as a pillar of contemporary dermatological treatment.

The results specifically indicated the limitation of traditional moisturizers even though the control group made significant gains (20% in SCORAD, 17% in TEWL, and 31% in reduction of itchiness). Usually composed with occlusives (e.g. mineral oil, petrolatum) or humectants (e.g. glycerin ), they trap or draw in water but do not treat the underlying lipid deficiency of diseased skin. Fonacier et al<sup>11</sup> and Sidbury et al<sup>12</sup> aptly described more of band-aids, they only hydrate the surface but not the deeper structural damage. This is what our data prove: the use of standard moisturizers offered symptomatic relief, but did not improve the lamellar lipid architecture. Against this, SVR Topialyse Baume Protect+, fortified with phytoceramides actively replenishes the lipid matrix of intercellular system in favor of a real reconstruction of the barrier as opposed to a simple surface coating.<sup>13</sup>

One of the most clinical outcomes of it is the 65% patient-reported itch reduction. Pruritus is a significant cause of low quality of life, poor sleep, and lack of adherence to the treatment in dermatitis. SVR Topialyse Baume Protect+ can be used to interrupt the itch-scratch cycle and facilitate healing as well as increase patient compliance by reducing itch quickly. Niacinamide and glycyrrhetic acid could also help because they can inhibit inflammation and enhance skin strength.<sup>14</sup>

Objective biophysical evidence of barrier restoration is the 40% reduction in TEWL. The enhancement is probably due to the restoration of essential lipids, especially ceramide 1 (EOS) that is reportedly lacking in atopic dermatitis.<sup>15</sup> SVR Topialyse Baume Protect+

decreases skin permeability, prevents allergen penetration and stabilizes the cutaneous immune response by repairing the lipid matrix thus breaking the inflammatory cascade.<sup>16</sup>

According to these results, we suggest SVR Topicalyse Baume Protect+ as the initial choice in the use of barrier-repair in patients with dermatitis and possible or confirmed barrier dysfunction. It needs to be taken during flares, as well as the maintenance therapy to avoid the relapses. This method aligns with the existing recommendations of the American Academy of Dermatology<sup>6</sup> and the European Academy of Dermatology and Venereology<sup>5</sup>, which recommend the use of lipid-repair moisturizers regularly over the long-term management of atopic dermatitis.

## CONCLUSION

Topicalyse Baume Protect+ is a proven product that restores the skin barrier in dermatitis, decreasing pruritus by 65% and TEWL by 40% and the standard moisturizers have only been shown to temporarily increase skin hydration. It is a pathophysiology-oriented, first-line, maintenance therapy of long-term skin condition and better adherence to treatment.

### Author’s Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Tamarah Qays Al-Mohammed
Drafting or Revising Critically:	Tamarah Qays Al-Mohammed
Final Approval of version:	The above author
Agreement to accountable for all aspects of work:	The above author

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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# Diagnostic Accuracy of Magnetic Resonance Imaging in Anterior Cruciate Ligament Injury

MRI in Anterior  
Cruciate  
Ligament Injury

Shahzad Saeed, Iram Amir, Sana Rehman, Ameenah Khan, Mouzma Marrium and Sheheryar Aamir

## ABSTRACT

**Objective:** This research set out to evaluate the diagnostic performance of magnetic resonance imaging (MRI) in identifying injuries of the anterior cruciate ligament (ACL), using arthroscopic assessment as the reference comparator.

**Study Design:** A cross-sectional analysis with a retrospective review

**Place and Duration of Study:** This study was conducted at the Department of Radiology, Services Institute of Medical Sciences/Services Hospital, Lahore covered a two-year period, extending from April 2024 to March 2025.

**Methods:** A cross-sectional analysis with a retrospective review of patient records was carried out. A total of 267 people were included, ages 16 to 60, who had a history of knee trauma and a clinical suspicion of an ACL injury. After undergoing an MRI, each patient had an arthroscopy done. A 1.5-Tesla MRI scanner was used for imaging, and standardized knee imaging sequences were used. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were then calculated by comparing the MRI observations with the arthroscopy findings. SPSS version 22 was used to process and analyze the data, and findings were considered statistically significant if the p-value was less than 0.05.

**Results:** MRI demonstrated a sensitivity of 97%, specificity of 95.12%, PPV of 98.5%, NPV of 90%, and overall diagnostic accuracy of 95% for ACL tears. Thickening or edema and discontinuity of ACL fibers were the most sensitive MRI findings, while posterior cruciate ligament angle and index showed the highest specificity. The diagnostic accuracy for both complete and partial tears was 93%.

**Conclusion:** MRI demonstrates strong diagnostic capability for identifying ACL injuries, assisting orthopedic surgeons in early management and reducing unnecessary arthroscopies.

**Key Words:** Arthroscopy, Anterior cruciate ligament (ACL); Magnetic resonance imaging (MRI); Knee trauma

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## INTRODUCTION

Anterior cruciate ligament (ACL) tears account for a significant segment of knee injuries, which are among the most common musculoskeletal issues in both orthopaedic and radiologic settings<sup>1</sup>. By preventing the tibia from moving forward relative to the femur and preserving rotational stability, the ACL is essential for knee joint stability.<sup>2</sup>

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Such injuries commonly result from rapid deceleration, sudden twisting, or direct impact — particularly in sports or road traffic accidents. If left undiagnosed or untreated, ACL injuries may progress to chronic knee instability and early degenerative joint changes, including osteoarthritis.<sup>3</sup>

Since arthroscopy allows for direct visualization of ligamentous structures and overall joint integrity, it has long been regarded as the gold standard for detecting intra-articular knee disorders.<sup>4</sup> Despite its diagnostic accuracy, arthroscopy is invasive, requires anesthesia, surgical expertise, and is associated with higher procedural risks and costs.<sup>5</sup> Magnetic resonance imaging (MRI), on the other hand, provides a noninvasive alternative capable of high-resolution multiplanar imaging that facilitates the assessment of ligament continuity, signal alterations, and associated soft-tissue lesions such as meniscal or chondral injuries.<sup>6</sup>

Prior studies carried out globally have reported MRI specificities between 92% and 96% and sensitivities between 95% and 97% for identifying ACL injuries.<sup>7-9</sup>

Despite these findings, there remains a lack of region-specific data evaluating MRI accuracy for ACL diagnosis in the Pakistani population relative to arthroscopic findings. Consequently, the current study was undertaken to evaluate how accurately MRI can identify ACL injuries, using arthroscopy as the reference benchmark. In addition, the study explored the utility of posterior cruciate ligament (PCL) angle and PCL index as supplementary indicators of ACL injury in the local clinical context.

**METHODS**

The Services Institute of Medical Sciences Department of Radiology at Services Hospital Lahore conducted this retrospective study, spanning the period from April 2024 to March 2025. Patients aged 16 to 60 years who presented with knee trauma and clinical suspicion of ACL injury and underwent both MRI and arthroscopy were included. Individuals with osteoarthritis, a history of previous knee surgery, developmental deformities, associated fractures or dislocations, or contraindications to MRI were excluded. Patient selection criteria is explained in figure 1.

MRI examinations were performed using a Canon Vantage-Titan 1.5 T scanner (Canon Medical Systems, Japan) fitted with a dedicated knee coil. Imaging included sagittal, coronal, and axial planes. Sequences acquired comprised T1-weighted, T2-weighted, STIR, and proton-density protocols, each with a 3 mm slice thickness. Sagittal sequences were obtained with the knee positioned in approximately 15° of flexion to improve visualization of the ACL. MRI assessments recorded the ligament’s integrity, classified tears as complete or partial, and documented both primary and secondary diagnostic features. Primary findings included discontinuity, thickening or edema, atrophy, and the empty notch sign. Secondary findings consisted of posterior cruciate ligament (PCL) angle, PCL index, bone contusion, and anterior tibial translocation.<sup>10</sup> The interval between MRI and arthroscopy did not exceed three months, and arthroscopic findings were used as the reference standard for comparison.

Mid-sagittal MRI evaluated secondary signs: PCL angle (abnormal <107°) and PCL index (abnormal ≤0.35). Measurements were performed via PACS by a radiologist with >5 years’ experience. Arthroscopy, conducted within three months by a similarly experienced surgeon, served as the comparative standard.

Data analysis used SPSS v22, presenting quantitative variables as mean±SD and categorical as frequencies. Chi-square tests assessed correlations (significance: p<0.05). Diagnostic accuracy, sensitivity, specificity, PPV, and NPV were calculated via 2x2 tables using arthroscopy as the reference. The study obtained IRB approval and ensured strict patient confidentiality.

**RESULTS**

A total of 267 participants fulfilled the eligibility requirements for the study. Among them, 201 individuals (75.3%) were male, while 66 (24.7%) were female, with an average age of 28 ± 4 years. More than half of the cohort (59%) was within the 21–40 years age group. Regarding the mechanism of injury, road traffic accidents were the predominant cause, accounting for 67% of cases, followed by sports-related injuries at 33%.

**Table No.1: Study Participants' Clinical and Demographic Details (n = 267)**

Variable	Categories	Frequency (n)	Percentage (%)
Gender	Male	201	75.3
	Female	66	24.7
Age (years)	Mean ± SD	28 ± 4	—
Age group	16–20	45	16.9
	21–40	158	59.2
	41–60	64	24.0
Mode of injury	Road traffic accident	179	67.0
	Sports injury	88	33.0
Side of injury	Left knee	164	61.4
	Right knee	103	38.6

**Table No. 2: Diagnostic Performance of MRI for ACL Tear (Arthroscopy as Gold Standard)**

Diagnostic Parameter	ACL Tear	Complete Tear	Partial Tear
Sensitivity (%)	97.0	91.5	92.0
Specificity (%)	95.12	93.5	92.5
Positive Predictive Value (%)	98.5	94.0	93.0
Negative Predictive Value (%)	90.0	89.0	88.0
Accuracy (%)	95.0	93.0	92.5

**Table No. 3 Comparison of Mean PCL Angle and PCL Index between Arthroscopy-Positive and Arthroscopy-Negative Groups**

Parameter	ACL Tear– Negative on Arthroscopy (n = 41)	ACL Tear– Positive on Arthroscopy (n = 226)	p-value
PCL Angle (°)	138.6 ± 6.4	104.7 ± 8.1	<0.001
PCL Index	0.44 ± 0.05	0.27 ± 0.04	<0.001

Note: The independent t-test was utilised to ascertain p-values, and numerical findings are displayed as mean ± standard deviation.

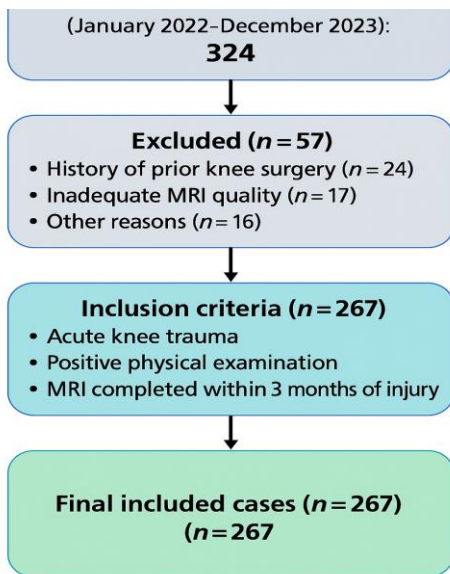


Figure No.1: Flow chart diagram of patient selection criteria



Figure 2 shows a complete ACL tear (white arrows) in both (A) sagittal proton-density fat-suppressed MRI and (B) sagittal T2-weighted fat-suppressed MRI. (C) A mid-substance fibre rupture is visible on the T2-weighted fat-suppressed sagittal MRI (white arrow).

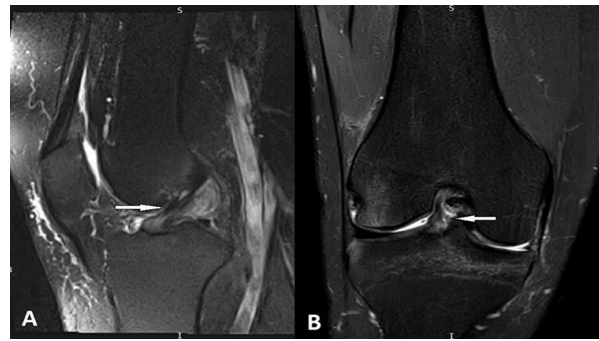


Figure No. 3: ACL partial thickness tear. (A) Thickened ACL fibers with a region of enhanced signal intensity (white arrow) are visible on sagittal fat-suppressed MRI. (B) A partial disruption of the anterior cruciate ligament fibers is shown by a coronal T2-weighted fat-suppressed MRI (white arrows).

MRI achieved 95% accuracy, 97% sensitivity, 95.12% specificity, 98.5% PPV, and 90% NPV compared to arthroscopy (Table 2). Thickening and edema were the most sensitive signs, while the PCL index and empty notch sign offered the highest specificity.

Among the 267 patients included in this study, 226 (84.6%) were ACL tear-positive on arthroscopy, while 41 (15.4%) were ACL tear-negative on arthroscopy and served as controls for comparison of MRI findings. The mean posterior cruciate ligament (PCL) angle and PCL index were significantly lower in arthroscopically confirmed ACL tear cases than in the control group ( $p < 0.001$ ). The mean PCL angle was  $104.7^\circ \pm 8.1^\circ$  in the ACL tear-positive group and  $138.6^\circ \pm 6.4^\circ$  in the ACL tear-negative group. The mean PCL index was  $0.27 \pm 0.04$  in ACL tear-positive cases and  $0.44 \pm 0.05$  in ACL tear-negative knees. These results shown in table 3 demonstrate that both reduced PCL angle and lower PCL index are statistically significant secondary MRI signs associated with ACL injury.

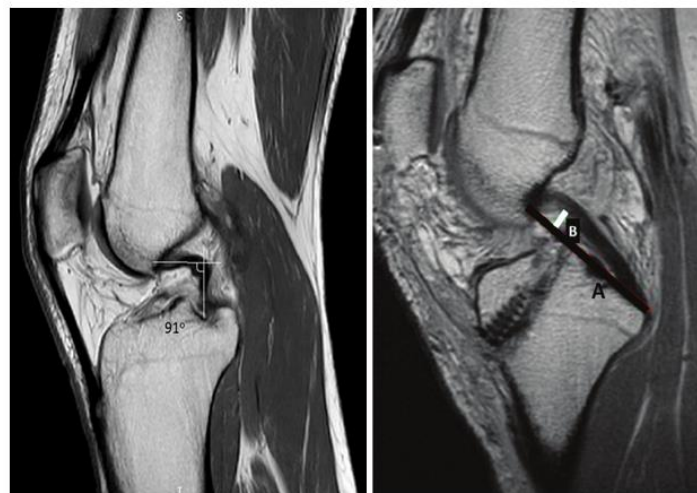


Figure No. 4: Proton-density-weighted sagittal MRI of the knee in (a) demonstrates posterior cruciate ligament (PCL) buckling with a reduced PCL angle, a finding suggestive of a total ACL rupture. (b) A schematic illustration of how to measure the PCL index A/B on an oblique sagittal image.

**DISCUSSION**

With sensitivity, specificity, and overall accuracy that compare favorably to international standards, MRI is identified in this study as a very sensitive diagnostic technique for the diagnosis of ACL rupture. When compared to the gold standard of arthroscopy, MRI in this series showed a sensitivity of 97%, a specificity of 95.12%, a PPV of 98.5%, and an overall diagnostic accuracy of 95%.

These findings support the various published reports regarding the diagnostic reliability of MRI for ACL injuries.<sup>11,12</sup> International studies have recorded sensitivities as high as 94-98% and specificities from 92% to 96%, thus coming quite close to our results. Regional data also show similar diagnostic performances, supporting that MRI is a highly reliable modality.<sup>13,14</sup>

The high diagnostic performance observed in this study may be attributed to multiple factors, including the use of a high-field 1.5-Tesla MRI scanner, optimized knee protocols, and interpretation by experienced musculoskeletal radiologist. Thin-slice sagittal and coronal images obtained with proton-density and T2-weighted sequences were particularly useful for delineating ACL fiber integrity. Previous studies have pointed out that proper imaging orientation and inclusion of oblique sagittal sequences increase the sensitivity in detecting ACL disruption.<sup>15,16</sup>

The present study also demonstrated the importance of secondary MRI signs like the PCL angle and the PCL index in the diagnosis of ACL deficiency. In the ACL-deficient knee, the PCL angle was decreased and the PCL index was found to be lesser compared with studies conducted earlier. These parameters indicate indirect injury to the ACL and are especially useful in cases where the primary signs are subtle, such as in discontinuity or signal abnormality. Dar et al. further emphasized the clinical utility of MRI-based grading for ACL tears, enhancing the role of MRI in both diagnosis and treatment planning.<sup>17</sup>

In contrast to all other imaging modalities, MRI remains unparalleled for assessing soft tissue knee injuries, including meniscal tears and collateral ligament involvement, which very often accompany ACL injuries. Ultrasonography is relatively inexpensive and widely available; however, it lacks the spatial resolution for deep intra-articular structures. Similarly, CT arthrography is useful for delineation of bony details but is not reliable for visualization of ligamentous tissue or edema.<sup>18</sup>

Some variation in diagnostic performance across the published literature may arise from differences in sample size, magnetic field strength, sequence parameters, and the inclusion of partial tears. For example, lower-field MRI systems (0.3–1.0 Tesla) have resulted in reduced sensitivity, especially for partial

ACL tears, because of poor spatial and contrast resolution. These, along with variations in patient positioning and knee flexion during scanning, may affect ligament visualization.<sup>19</sup>

The small number of discordant cases (two false positives, three false negatives) likely reflects acute haemorrhage and technique-dependent limitations.

Matching meta-analyses, MRI confirms >90% accuracy for ACL and meniscal/cartilage injuries. Although mucoid degeneration or scarring can mimic tears, MRI prevents unnecessary arthroscopies when correlated clinically<sup>20</sup>. It enables early surgery to prevent osteoarthritis and chronic instability, serving as a cost-effective triage tool in resource-limited settings<sup>22</sup>

**CONCLUSION**

Magnetic resonance imaging is a highly sensitive and specific modality for diagnosing anterior cruciate ligament injuries, demonstrating excellent agreement with arthroscopic findings. Its noninvasive nature, multiplanar capability, and ability to identify both primary and secondary signs of ligament disruption make it an indispensable tool in the diagnostic workflow of knee trauma.

Future multicenter studies with larger and more diverse populations, standardized imaging protocols, and multi-observer validation are recommended to refine diagnostic criteria, reduce interobserver variability, and further improve accuracy in differentiating partial from complete ACL tears. Incorporating advanced imaging techniques, including 3D isotropic sequences and quantitative MRI biomarkers, may provide additional insights into ligament integrity and postoperative healing assessment.

**Ethical Considerations:** Approval for this study was obtained from the Institutional Review Board of the Services Institute of Medical Sciences, Lahore (IRB/2024/1286/SIMS). Because the study relied on retrospective data, the requirement for individual informed consent was waived. All patient information was anonymized, and strict confidentiality protocols were followed during data handling and analysis.

**Author’s Contribution:**

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# Neck Node Metastasis in Oral Squamous Cell Carcinoma: A Clinicopathological Analysis

Neck Node  
Metastasis in  
Oral Squamous  
Cell Carcinoma

Rubab Mannan Shaikh<sup>1</sup>, Muhammad Rahil Khan<sup>2</sup> and Kashif Ali Channar<sup>1</sup>

## ABSTRACT

**Objective:** To identify the incidence of metastases from lymph nodes and its association with several clinicopathological variables.

**Study Design:** Retrospective cohort study

**Place and Duration of Study:** This study was conducted at the oral and maxillofacial surgery department of Liaquat University of Medical and Health Science in Jamshoro carried out this study in October 2024 and August 2025.

**Methods:** The study incorporated 117 cases of OSCC that were reported to our institute in total. All OSCC cases with biopsy evidence were included in the research. Data analysis was done using IBM SPSS Statistics v27.

**Results:** Of the 117 patients in the current study, 71.8% were men and 28.2% were women. The mean age was  $45.52 \pm 12.31$  years, and the majority (45.3%) were between the ages of 36 and 50. The tumor's average size was  $1.17 \pm 0.97$  cm, and its average depth of invasion was  $3.31 \pm 1.71$  cm. 51 out of 117 patients (43.6%) in our study had nodal metastatic disease. There was significant association of nodal metastasis with tumor size ( $p=0.018$ ), depth of invasion ( $p=0.002$ ), and stage ( $p=0.000$ ).

**Conclusion:** We discovered significant association between nodal metastasis with tumor size, depth of invasion, stage, peri-neural invasion, and extra-nodal extension. Nodal metastasis was more common in patients who were male, older than 35, had moderately differentiated tumors, and had peri-neural invasion.

**Key Words:** Oral Squamous Cell Carcinoma, Neck Node Metastasis, Prognostic Factors

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## INTRODUCTION

Oral squamous cell carcinoma (OSCC) stands as one of the most prevalent forms of head and neck malignancies, accounting for significant morbidity and mortality worldwide. Among the myriad factors influencing the prognosis of OSCC, neck node metastasis emerges as a critical determinant, profoundly affecting survival rates and treatment outcomes<sup>1</sup>. According to the most recent data available, it is anticipated that there were around 177,757 deaths from lip and oral cavity cancer and 377,713 new instances of the disease worldwide in 2020.

These tumours rank as the 18th most common type of cancer overall, out of all the neoplasm instances that have been reported. Squamous cell carcinomas make up more than 90% of these malignancies<sup>2</sup>. In addition to making clinical therapy more difficult, the existence of metastatic cervical lymph nodes calls for a thorough comprehension of the clinicopathological foundations of the condition. Oral squamous cell carcinoma, which arises from the oral epithelial lining, is the most prevalent type of cancer in the head and neck region<sup>3</sup>. Nearly 50% of newly diagnosed patients with OSCC have cervical node metastases, and it shows strong biological activity of growth and invasion together with regional lymph node metastases. One of the important predictors is the involvement of neck lymph nodes, and even if there is only one node, the overall survival rate decreases by 50% if the neck lymph node is positive. The methods of managing neck in oral SCC are contentious and whenever employed, they should be done effectively<sup>4</sup>. Nodal involvement, specifically cervical nodes in OSCC, is one of the critical predictors of prognosis and treatment plan in the clinical setting. The following processes are necessary for the development of this cancer: local progression and tumour cell invasion. The specialised epithelial cells of the oral cavity give birth to OSCC, which is mostly caused by genetic changes and secondarily by the

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effects of alcohol and tobacco use, which modify the levels of tumour suppressor genes and oncogenes<sup>5</sup>. Lymph Node Metastasis also known as the nodal involvement is the most unfavorable predictor of OSCC and has been estimated to affect forty percent of patients. Patients are diagnosed without lymph node metastases (LNM), according to the eighth American Joint Committee on Cancer (AJCC) staging criteria, they exhibit 5 year rates of survival overall above 80%; in contrast, patients who are comprising of stage N3 have a comparably low 5-year survival of about 20%. Surprisingly, the process of LNM in OSCC is still not well understood, although the management of cervical lymph nodes in OSCC remains a topic of debate even today<sup>6</sup>. The question of whether a contralateral lymph node dissection is required in intraoral SCCs has been the subject of a few investigations. Not all tumours crossing the midline have a high-risk, containing stage I and II tumours that do not involve the floor of the mouth, and not all tumours that do not affect the midline have a low-risk, containing stage III and IV tumours that involve the floor of the mouth, in relation to one study that explained a mathematical modelling approach to the evaluation of contralateral neck dissections in oral SCC<sup>7</sup>. Furthermore, there is a need to identify the clinical factors linked to nodal metastasis because radical neck dissection is associated with a high rate of morbidity. Our research may be useful in the patient stratification process for those who can benefit from selective neck dissection rather than radical neck dissection the prevalence of lymph node metastasis and its association with several clinicopathological variables.

**METHODS**

The department of oral and maxillofacial surgery at Liaquat University of Medical and Health Science in Jamshoro conducted this retrospective study in October 2024 and August 2025. The study included 117 cases of OSCC that were reported to our institute in total. All OSCC cases with biopsy evidence were included in the research. Institutional archives provided the clinicopathological information for the cases included in the study that were reported during the study period. Clinical referral forms provided the age, gender, and tumor site of the patient, among other clinical data.

**RESULTS**

This study included 117 patients with OSCC, of whom 71.8% were male and 28.2% were female. The mean age was 45.52 ± 12.31 years, with most patients (45.3%) between 36 and 50 years. The average tumor size was 1.17 ± 0.97 cm, and the mean depth of invasion (DOI) was 3.31 ± 1.71 cm. Tumor staging showed that 7.7% were stage I, 19.7% stage II, 25.6% stage III, 35.9% stage IV-A, and 11.1% stage IV-B; T2 was the most frequent T-stage (33.3%).

**Table No.I: Demographic and clinicopathological parameters**

	n (%)
<b>Gender: Male</b>	84(71.8)
Female	33(28.2)
<b>Age (years); Mean± Std. Dev</b>	45.52±12.31
<b>Age Group: ≤35 years</b>	29(24.8)
36-50 years	53(45.3)
>50 years	35(29.9)
<b>Tumor Size (cm); Mean± Std. Dev</b>	3.31±1.71
<b>Tumor Size Group : ≤2 cm</b>	21(17.9)
2.1-4.0 cm	73(62.4)
>4 cm	23(19.7)
<b>Depth of Invasion (cm); Mean± Std. Dev</b>	1.17±0.97
<b>Depth of Invasion Group</b>	
<0.5 cm	16(13.7)
0.5-1.00 cm	49(41.9)
>1 cm	52(44.4)
<b>Tumor Stage : Stage-I</b>	9(7.7)
Stage-II	23(19.7)
Stage-III	30(25.6)
Stage IV-A	42(35.9)
Stage IV-B	13(11.1)
<b>T Stage: T1</b>	12(10.3)
T2	39(33.3)
T3	31(26.5)
T4	16(13.7)
T4a	19(16.2)
<b>N Stage: N0</b>	66(56.4)
N1	16(13.7)
N2a	2(1.7)
N2b	6(5.1)
N3b	5(4.3)
N2	1(0.9)
N2b	14(12)
N3b	7(6)
<b>Tumor Site: Buccal mucosa</b>	71(60.7)
Tongue	25(21.4)
Lower Lip	15(12.8)
Maxilla	3(2.6)
Lower alveolus	1(0.9)
Retromolar trigone	2(1.7)
<b>Histological Type</b>	
Moderately differentiated	114(97.4)
Well differentiated	3(2.6)
Lympho-vascular Invasion	3(2.6)
Peri-neural Invasion	13(11.1)
Extra nodal Extension	15(12.8)
Submandibular gland Invasion	2(1.7)
<b>Nodal Metastasis</b>	
Positive	51(43.6)
Negative	66(56.4)

The buccal mucosa was the predominant tumor site (60.7%), followed by the tongue (21.4%) and lower lip

(12.8%). Perineural invasion occurred in 11.1% of cases, extranodal extension in 12.8%, lymphovascular invasion in 2.6%, and submandibular gland invasion in 1.7%. Nodal metastasis was identified in 51 patients (43.6%), with Level-IB being the most common site of involvement (37.3%). Among node-positive patients, 62.7% had buccal mucosa tumors and 25.5% had

tongue tumors. Nodal metastasis demonstrated significant associations with tumor size (p = 0.018), DOI (p = 0.002), and overall stage (p < 0.001). Smaller tumors (≤2 cm) and shallower DOI (<0.5 cm) had significantly lower odds of metastasis. N-stage was significantly associated with extranodal extension (p < 0.001) and submandibular gland invasion (p = 0.032).

**Table No.2: Association and odds for nodal metastasis with demographic and clinicopathological parameters**

	Nodal Metastasis		p-value	Odds Ratio (95% CI)	p-value
	Positive	Negative			
<b>Gender</b>					
Male	39(76.5)	45(68.2)	0.323	1.517(0.662-3.474)	0.325
Female	12(23.5)	21(31.8)		Ref	
<b>Age Groups</b>					
≤35 years	16(31.4)	13(19.7)	0.349	1.846(0.682-5.001)	0.228
36-50 years	21(41.2)	32(48.5)		0.984(0.412-2.354)	
>50 years	14(27.5)	21(31.8)		Ref	
<b>Tumor Size</b>					
≤2 cm	4(7.8)	17(25.8)	0.018*	0.151(0.038-0.598)	0.007*
2.1-4.0 cm	33(64.7)	40(60.6)		0.530(0.204-1.379)	
>4 cm	14(27.5)	9(13.6)		Ref	
<b>Depth of Invasion</b>					
<0.5 cm	2(3.9)	14(21.2)	0.002*	0.097(0.020-0.471)	0.004*
0.5-1.00 cm	18(35.3)	31(47)		0.393(0.176-0.878)	
>1 cm	31(60.8)	21(31.8)		Ref	
<b>Tumor Stage</b>					
Stage-I	0(0)	9(13.6)	0.000*	NA	0.999
Stage-II	0(0)	23(34.8)		NA	
Stage-III	12(23.5)	18(27.3)		0.056(0.006-0.485)	
Stage IV-A	27(52.9)	15(22.7)		0.150(0.018-1.269)	
Stage IV-B	12(23.5)	1(1.5)		Ref	
<b>T Stage</b>					
T1	3(5.9)	9(13.6)	0.282	0.300(0.061-1.467)	0.137
T2	16(31.4)	23(34.8)		0.626(0.208-1.888)	
T3	12(23.5)	19(28.8)		0.568(0.179-1.804)	
T4	10(19.6)	6(9.1)		1.500(0.387-5.814)	
T4a	10(19.6)	9(13.6)		Ref	
<b>Histological Type</b>					
Moderately differentiated	50(98)	64(97)	1.000	1.562(0.138-17.727)	0.719
Well differentiated	1(2)	2(3)		Ref	

Chi-square/fisher exact test was applied.

Binary logistic regression was applied.

\*Significant at 0.05 levels.

**Table No.3: Association of N stage with demographic and clinicopathological parameters (n=51)**

	N Stage							p-value
	N1	N2a	N2b	N3b	N2	N2b	N3b	
<b>Gender</b>								
Male	12(75)	2(100)	6(100)	3(60)	1(100)	10(71.4)	5(71.4)	0.773
Female	4(25)	0(0)	0(0)	2(40)	0(0)	4(28.6)	2(28.6)	
<b>Age Groups</b>								
≤35 years	4(25)	0(0)	1(16.7)	2(40)	0(0)	6(42.9)	3(42.9)	0.878
36-50 years	6(37.5)	2(100)	4(66.7)	2(40)	1(100)	4(28.6)	2(28.6)	
>50 years	6(37.5)	0(0)	1(16.7)	1(20)	0(0)	4(28.6)	2(28.6)	

<b>Tumor Size</b>								
≤2 cm	2(12.5)	0(0)	0(0)	0(0)	0(0)	1(7.1)	1(14.3)	0.206
2.1-4.0 cm	12(75)	2(100)	3(50)	2(40)	1(100)	11(78.6)	2(28.6)	
>4 cm	2(12.5)	0(0)	3(50)	3(60)	0(0)	2(14.3)	4(57.1)	
<b>Depth of Invasion</b>								
<0.5 cm	1(6.3)	0(0)	0(0)	0(0)	0(0)	0(0)	1(14.3)	0.113
0.5-1.00 cm	9(56.3)	0(0)	1(16.7)	0(0)	1(100)	6(42.9)	1(14.3)	
>1 cm	6(37.5)	2(100)	5(83.3)	5(100)	0(0)	8(57.1)	5(71.4)	
<b>Tumor Stage</b>								
Stage-III	12(75)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0.000*
Stage IV-A	4(25)	2(100)	6(100)	0(0)	1(100)	14(100)	0(0)	
Stage IV-B	0(0)	0(0)	0(0)	5(100)	0(0)	0(0)	7(100)	
<b>T Stage</b>								
T1	1(6.3)	0(0)	0(0)	0(0)	0(0)	1(7.1)	1(14.3)	0.258
T2	9(56.3)	0(0)	0(0)	0(0)	1(100)	5(35.7)	1(14.3)	
T3	2(12.5)	1(50)	2(33.3)	2(40)	0(0)	4(28.6)	1(14.3)	
T4	1(6.3)	0(0)	2(33.3)	1(20)	0(0)	3(21.4)	3(42.9)	
T4a	3(18.8)	1(50)	2(33.3)	2(40)	0(0)	1(7.1)	1(14.3)	
<b>Histological Type</b>								
Moderately differentiated	15(93.8)	2(100)	6(100)	5(100)	1(100)	14(100)	7(100)	1.000
Well differentiated	1(6.3)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	
<b>Lymph vascular Invasion</b>								
Present	2(12.5)	0(0)	0(0)	0(0)	0(0)	1(7.1)	0(0)	1.000
Absent	14(87.5)	2(100)	6(100)	5(100)	1(100)	13(92.9)	7(100)	
<b>Peri neural Invasion</b>								
Present	4(25)	0(0)	2(33.3)	1(20)	0(0)	3(21.4)	19(14.3)	0.976
Absent	12(75)	2(100)	4(66.7)	4(80)	1(100)	11(78.6)	6(85.7)	
<b>Extra nodal Extension</b>								
Positive	0(0)	2(100)	1(16.7)	5(100)	0(0)	1(7.1)	6(85.7)	0.000*
Negative	16(100)	0(0)	5(83.3)	0(0)	1(100)	13(92.9)	1(14.3)	
<b>Submandibular gland Invasion</b>								
Positive	0(0)	0(0)	0(0)	2(40)	0(0)	0(0)	0(0)	0.032*
Negative	16(100)	2(100)	6(100)	3(60)	1(100)	14(100)	7(100)	

Chi-square/fisher exact test was applied.

\*Significant at 0.05 levels.

## DISCUSSION

This study provides a comprehensive evaluation of demographic, clinicopathological, and invasion characteristics among 117 patients with oral squamous cell carcinoma (OSCC), with a primary focus on nodal metastasis. Consistent with global trends, a greater proportion of OSCC cases occurred in men, reflecting established associations between male gender and lifestyle risk factors such as tobacco use, betel-quid chewing, and alcohol consumption<sup>12</sup>. Although the mean surface tumor diameter appeared small (1.17 cm), the average depth of invasion (DOI) was 3.31 cm, indicating biologically aggressive behavior despite

modest surface dimensions. Most patients presented with advanced disease (stage IV-a and stage IV-b), underscoring persistent delays in diagnosis and the need to strengthen early detection pathways. The buccal mucosa was the most common tumor site, followed by the tongue and lower lip—anatomical regions frequently exposed to carcinogens in high-risk populations<sup>13</sup>. Invasion characteristics demonstrated notable incidences of perineural invasion (PNI) and extranodal extension (ENE), both regarded as adverse prognostic features in OSCC<sup>14</sup>. Submandibular gland invasion was relatively uncommon. Nodal metastasis remains one of the strongest predictors of survival in OSCC, and previous literature suggests that nodal

involvement can increase mortality risk by up to 50%<sup>15</sup>. In the present study, nodal metastasis was detected in 43.6% of patients. Level IB emerged as the most commonly involved nodal basin, reinforcing the need for meticulous clinical and radiologic assessment of this level. Buccal mucosa tumors exhibited the highest nodal involvement, consistent with earlier findings reporting their aggressive biological behavior and early lymphatic spread<sup>13</sup>. Our results corroborate evidence that DOI is a critical predictor of nodal metastasis. Tumors  $\leq 2$  cm with DOI  $< 0.5$  cm demonstrated markedly lower nodal involvement. Jangir et al. reported similar findings, identifying a DOI  $> 5$  mm as significantly associated with increased nodal metastasis<sup>16</sup>. Kane et al. similarly emphasized DOI  $> 5$  mm as a reliable predictor for cervical nodal spread<sup>17</sup>. Although gender did not show a statistically significant association with nodal metastasis in the present study, male patients exhibited higher odds of nodal positivity, aligning with the findings of Heft Neal et al<sup>18</sup>. The study also demonstrated that tumor size and PNI were significantly associated with nodal disease, consistent with prior reports linking PNI and larger tumor dimensions with more extensive lymphatic dissemination<sup>14,19</sup>. This study has several limitations. As a retrospective, single-center analysis, generalizability is limited. Follow-up data were not available to assess overall survival or disease-free survival. Treatment-related variables and biomarker correlations were not evaluated. Additionally, the absence of molecular markers limits insight into biological pathways underlying nodal spread. Future prospective, multicenter studies integrating clinicopathological and molecular parameters are warranted. Overall, these findings highlight the importance of early OSCC detection, careful assessment of DOI and PNI, and vigilant evaluation of Level IB lymph nodes. Strengthening early diagnostic strategies and risk-stratified management may improve outcomes in high-risk OSCC patients.

**CONCLUSION**

We discovered significant association between nodal metastasis with tumor size, depth of invasion, stage, peri-neural invasion, and extra-nodal extension. Nodal metastasis was more common in patients who were male, older than 35, had moderately differentiated tumors, and had peri-neural invasion. Furthermore, as the tumor's invasion depth and size increases, so does the risk of nodal metastasis. This study may aid in the patient stratification that would help prevent neck dissection by highlighting the major pathological predictors of nodal metastasis in OSCC.

**Author's Contribution:**

Concept & Design or acquisition of analysis or	Rubab Mannan Shaikh, Muhammad Rahil Khan
------------------------------------------------	------------------------------------------

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# Diabetes Mellitus: A Risk Factor for the Development of Lumbar Disc Herniation

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## ABSTRACT

**Objective:** To investigate the relationship between diabetes and lumbar disc herniation and also the potential of long-term complications that may develop in these patients.

**Study Design:** A retrospective observational study

**Place and Duration of Study:** This study was conducted at the Al-Kindi Teaching Hospital Baghdad, Iraq from 1<sup>st</sup> November 2024 to 30<sup>th</sup> April 2025.

**Methods:** A total 150 patients with lumbar disc patients who also had diabetes were enrolled.

**Results:** Statistically significant relationship between type 2 diabetes mellitus and the presence of multilevel disc herniation, as well as increased rates of neurological complications such as foot drops and saddle numbness. Patients with poorly controlled diabetes and receiving insulin therapy were particularly prone to multilevel spinal injury and higher rates of surgical intervention. Most lumbar disc herniation cases occurred in weight-bearing lumbar areas, especially L3-L5, and were associated with higher pain scores and increased dependence on daily life in diabetics.

**Conclusion:** The Iraqi patients with lumbar disc herniation had high levels of glucose in their blood, and this is a clear indication of the impact of glucose on LDH, especially type 2 diabetes, where they were found to be the most affected or exposed to multilevel disc disease with more severe neurological consequences such as foot drop and saddle numbness.

**Key Words:** Lumbar disc herniation (LDH), Diabetes mellitus, Obesity, Lumbar disc

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## INTRODUCTION

Lumbar disc herniation is a common disease, especially in the elderly, and is a common cause of low back pain in addition to other neurological diseases.<sup>1</sup> 70% of people have a lifetime related to this type of disease that they will develop at some point in their lives.<sup>2</sup> Most important symptom of intervertebral disc degeneration is low back pain and may lead to a herniated disc.<sup>3</sup> It is possible to know that the disc is a very complex structure and the reasons that lead to the acceleration of disc degeneration include several factors, including age,

genetic factors, mechanical stress, as well as other lifestyles such as smoking and weight gain.<sup>2</sup>

People with chronic type 2 diabetes are more likely to develop lumbar disc herniation due to its potential role as a systemic factor in intervertebral disc degeneration through several factors, as high sugar can make the metabolism of collagen less effective, which is an essential substance in the structure of the disc, and therefore this structure will weaken by increasing the level of sugar, and it can also cause inflammation in the disc tissues, and as a result, triple will occur in the tiny blood vessels that supply the disc with nutrients.<sup>4</sup> It is important to understand how diabetes, which is one of the most common diseases worldwide, can affect the pathophysiology of lumbar disc herniation and this will help us develop prevention and treatment plans. It is also possible that the genetic factor plays an important role as one of the causes of disc degeneration and this topic should receive great attention through several studies and thus their accumulation leads to a theory of adding the genetic factor as one of the causes of this disease and based on previous studies.<sup>5</sup>

People with a genetic causative factor may be more likely than the general population to develop disc degeneration.<sup>6</sup> It also looked at how physical stress at work affects disc degeneration, as there is also research that has found a link between manual labor and an increased risk of disc degeneration, and therefore unstable lifestyles may lead to disc herniation due to

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static axis overload, and conversely, other studies have shown that there is a weak or non-existent relationship between physical stress and disc degeneration.<sup>7</sup> For obesity, overweight, and metabolic syndrome, these conditions were found to be systemic conditions that promote arch degeneration by intensifying inflammation and altering disc metabolism.<sup>8</sup> Other changes related to age and environmental factors as well as excessive exercise may be a factor that negatively affects disc balance.<sup>9</sup> Inflammation is associated with degenerative disc disease; however, its role in disc pain and hernia regression is still controversial.<sup>10</sup>

## METHODS

This study was conducted in Baghdad, Iraq, Al-Kindi Teaching Hospital from 1<sup>st</sup> November 2024 to 30<sup>th</sup> April 2025 vide letter No. 4545/QM/Approval/SJKDH379 dated 9<sup>th</sup> March 2024. This retrospective observational study to elucidate the concept of the effect of hyperglycemia on patients with lumbar disc herniation as well as to elucidate DM effect mechanism on LDH and its prevalence among individuals with Lumbar disc herniation and to help identify possible clinical associations. The study focused on the validity of diagnoses using clinical and radiological evaluations of 150 patients who attended the rheumatology outpatient clinic. Where the inclusion criteria ensure that the study focused on adult patients with LDH confirmed disease and complete medical records. The age of patients diagnosed with LDH patients aged from 18 to 100 years through clinical assessment. The data was entered and analyzed through SPSS-25.

## RESULTS

The most frequent anatomical levels were 20.67% L3-L5 followed by 16.67% L2-L5 and 16% L3-L4 other recurrent anatomical levels were L4-L5 with 11.33% and L1-L3 4%, it was observed that there was high prevalence of L4-S1 17.33% levels but that L5-S1 5.33% with low levels. 2% for L3-S1 and 6.67% L2-L4, 23 patients (15.33%) had foot drop, 17 patients (11.33%) developed incontinence, and 16 patients (10.67%) developed saddle anaesthesia as a result of LDH problems. Thirty-three patients (22%), who have a history of Disc surgery, there must be a subgroup of patients living with recurrent or severe spinal diseases. the level of L3-L5 was determined as the most frequent area (20.67%) and this may be mainly due to its poor biomechanics and ability to bear weight in addition to the ability to increase mobility, L2-L5 and L4-S1 hernia was also remained in 16.67%, 17.33 respectively of the participating patients, which confirms the high prevalence of hernia in the lumbar disc while 16% L3-L4 and L4-L5 saw 11.33%. These levels occur in classical disc degeneration syndromes and nerve compression and are often associated with radiculopathy where the most rarely affected levels were found to be

L1-L3 (4%) and L5-S1 (5.33%), 6.67% agreed with L2-L4 and the lowest observed level (2%) L3-S1 (Table 1). A slight inverse association was suggested by the slightly lower chance of single-level herniation presentation in T2DM patients ( $\phi=-0.25$ ). Through the results of a moderate positive association between patients with type 2 diabetes and multilevel disc herniation, these patients are more likely to have a multi-level Disc injury so that there is a strong association in the three-level group ( $\phi=0.36$ ) and also the results showed that the two-level discs herniation is slightly positive, indicating a weak but positive relationship between type 2 diabetes and bi level disc disease ( $\phi=0.18$ ). T2dM patients show weak positive impact of high glucose levels on LDH complications represented as Foot drop, a common consequence of nerve involvement ( $\phi=0.19$ ). Thus, T2DM patients with multi-level disease may be at a slightly higher risk of foot drop compared to those without diabetes. Additionally, patients with uncontrolled high glucose levels exhibited a modest correlation with an elevated necessity for surgical intervention ( $\phi=0.21$ ), indicating that patients with diabetes and greater disc involvement may necessitate more surgical procedures (Tables 2-3, Fig. 1).

Patients with multi-level disease had a higher prevalence of type 2 diabetes mellitus (T2DM) (47 in three-level, 40 in single-level, and 26 in two-level). Diabetes and LDH were statistically significantly correlated ( $p=0.026$ ), and more severe herniation was strongly correlated with type 2 diabetes. In terms of pharmacological management, most diabetic patients across all groups used oral hypoglycemic agents (OHAs); however, patients with multi-level herniation were significantly more likely to use insulin ( $p=0.002$ ). The two-level group consisted primarily of insulin-dependent patients (29 patients), indicating that patients with more severe spinal involvement may also be those with more advanced disease or poorly managed diabetes (Table 4).

Most common symptoms in patients with disc herniation are root pain or irradiation in 67 cases (44.67%) and SLR-positive in 92 patients (61.33%) We also find that 77 patients (51.33%) suffer from paraesthesia and 74 patients (49.33%) have FST positive while 52 patients (34.67%) have fall symptoms and 45 patients (30%) have a feeling of weakness For most people, we find the emergence of clinical results that support the high frequency of nerve wall irritation or compression of the vertebrae that causes paraesthesia or abnormal sensation such as tingling or numbness Table five shows that more than 50% of the population has involvement in sensory fibers. Other symptoms were segmental focal tenderness (FST), radiation (sharp, radiant pain along the skin), muscle weakness, walking and falling, associated with both gait instability and neuropathy and motor disorders (Table 5, Fig. 2).

**Table No. 1: Lumbar disc herniation (LDH) characteristics**

LDH	No.	%
L3-L4 L4-L5	31	20.67
L4-L5 L5-S1	26	17.33
L2-L3 L3-L4 L4-L5	25	16.67
L3-L4	24	16
L4-L5	17	11.33
L2-L3 L3-L4	10	6.67
L5-S1	8	5.33
L1-L2 L2-L3	6	4.0
L3-L4 L4-L5 L5-S1	3	2.0

**Table 2: Frequency of complications**

Variable	No.	%
LDH Complications		
Foot drop	23	15.33
Incontinence	17	11.33
Saddle anaesthesia	16	10.67
History of spinal surgery	33	22.0

**Table 3: Correlations of LDH levels according to DM disease**

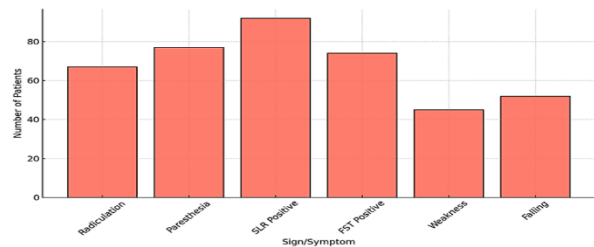
LDH Level	Correlation	Strength	Interpretation
Single-Level (L4-L5, L5-S1, etc.)	$\phi = -0.25$	Weak (-)	T2DM patients are slightly less likely to have single-level LDH.
Two-Level (e.g., L3-L4 & L4-L5)	$\phi = 0.18$	Weak (+)	Mild association with two-level involvement.
Three-Level (e.g., L2-L3, L3-L4, L4-L5)	$\phi = 0.36$	Moderate (+)	T2DM patients are more likely to have multi-level spinal involvement.
Foot Drop (Yes/No)	$\phi = 0.19$	Weak (+)	Slightly higher risk of foot drops in T2DM with multi-level LDH.
Surgical Intervention (Yes/No)	$\phi = 0.21$	Weak (+)	T2DM with multi-level LDH may require more surgical treatment.

**Table 4: Distribution of lumbar disc herniation (LDH) by diabetes mellitus type and treatment**

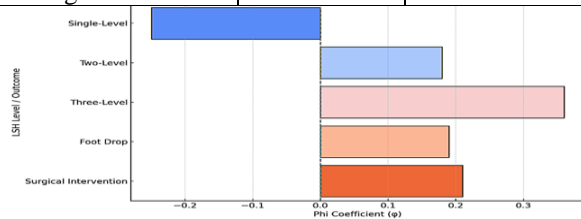
LDH in DM patients	Single Level	Three Levels	Two Levels	Chi <sup>2</sup>	df	p
DM type						
Non-DM	7	2	23	11.03	4	0.026
T1DM	2	0	3			
T2DM	40	26	47			
Drug						
No	7	2	23	16.48	4	0.002
OHA	24	19	21			
Insulin	18	7	29			

**Table No. 5: Signs and symptoms of LDH patients of the studied groups**

Signs & symptoms	No.	%
Radiculation	67	44.67
Paraesthesia	77	51.33
Straight leg raise	92	61.33
Femoral nerve stretch test	74	49.33
Weakness	45	30
Falling	52	34.67



**Figure No.. 2: Histogram of signs and symptoms in LDH patients**



**Figure No. 1: Correlations of LDH according to DM**

## DISCUSSION

Anatomically, the lumbar disc herniation in this Iraqi population predominantly involved multi-level segments, with L3-L4, L4-L5 (20.67%), L2-L3, L3-L4, L4-L5 (16.67%), and L4-L5, L5-S1 (17.33%) being the most frequent sites, while upper lumbar involvement L1-L2, L2-L3 was rare (4%). This multi-segmental involvement correlates with biomechanical principles describing the lumbar Disc's segmental load distribution; the middle to lower lumbar levels bears the greatest axial loads and demonstrate increased mobility

that predisposes these segments to disc degeneration and herniation. These findings are consistent with global imaging and pathological studies showing the L4-L5 and L5-S1 levels as the most common sites for lumbar disc herniation.<sup>11</sup> Although in our cohort L3-L5 had highest prevalence, possibly reflecting regional lifestyle or occupational factors. Regionally, similarly high rates of multi-level lumbar disc lesions have been reported. A study by Hmood<sup>12</sup>, assessing lumbar disc herniation in young and middle-aged patients in Erbil (Northern Iraq), documented that multi-level lumbar disc disease was commonly seen with predominant involvement of lower lumbar segments (L4-L5 and L5-S1), corroborating our anatomical distribution findings. In terms of clinical repercussions, 22% of patients in this study reported previous spinal surgery, indicating the chronic and recurrent nature of lumbar herniation in this cohort. This aligns with the clinical reality globally where lumbar disc herniation is a leading indication for disc surgery, especially when conservative treatments fail or neurological deficits progress.

In Iraqi tertiary care centres report similar rates of surgical intervention among lumbar disc patients, emphasizing surgical need in advanced cases.<sup>13</sup> The results substantiate a strong association between T2DM and more severe multi-level herniation in specific (L2-L3), (L3-L4) and (L4-L5), in concordance with large-scale epidemiological studies.<sup>14,15</sup> T2DM patients were significantly more likely to have multi-level herniation and related neurological complications such as foot drop and saddle anaesthesia. This is consistent with nationwide cohort studies demonstrating that individuals with DM have a more than twofold increased risk of developing lumbar disc disease.<sup>16</sup>

The mechanisms linking diabetes to lumbar Disc degeneration include chronic hyperglycemia-induced oxidative stress, systemic inflammation, impaired microcirculation, and disruption of extracellular matrix metabolism within the intervertebral disc.<sup>17,18</sup> Through previous studies, it has been shown that the deterioration of the disc matrix and the resulting programmed cell death in individuals with diabetes is consistent with the positive relationship shown in the results of this study between the duration and severity of diabetes and lumbar disc disease, thus these results confirm the importance of controlling blood sugar for the health of the disc.<sup>19</sup> The results also show that diabetic patients who use insulin are the most likely to develop multiple hernias.<sup>20</sup>

## CONCLUSION

The Iraqi patients with lumbar disc herniation had high levels of glucose in their blood, and this is a clear indication of the impact of glucose on LDH, especially

type 2 diabetes, where they were found to be the most affected or exposed to multilevel disc disease with more severe neurological consequences such as foot drop and saddle numbness. Most of the injuries occur in the weight-bearing parts of the lower back, especially L3-L5, and this is shown in the anatomical distribution of the lumbar that closely follows biomechanical principles. Diabetic patients with lumbar disc herniation showed suboptimal functional outcomes of higher pain scores, increased ADL dependence, and a higher incidence of surgical interventions that necessitated severe symptoms and heat resistance.

### Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Ali Falah Zbala, Mohammed A. Ameer Muhieldeen,
Drafting or Revising Critically:	Haider Omran Hayat Ali
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# Enhancing Critical Care Nurses' Awareness, Problem-Solving Skills, and Attitudes Through AI-Integrated Learning Designs

Ejaz Khan, Sarfraz Masih and Madiha Mukhtar

## ABSTRACT

**Objective:** To assess the effects of an AI-integrated learning designs on enhancing awareness, problem-solving skills and attitude of critical care nurses.

**Study Design:** A quasi-experimental, two-group pretest–posttest study

**Place and Duration of Study:** This study was conducted at the critical care units of Doctors Hospital and Medical Center, Lahore from June 2025 to August 2025.

**Methods:** About 84 nurses were selected through convenient sampling technique and equally assigned to experimental (n=42) and control (n=42) groups. Data were collected using an artificial intelligence knowledge questionnaire, problem solving inventory, and attitude questionnaire. Data were analyzed using SPSS version 25. Wilcoxon sign rank test and Mann Whitney U test were employed, with  $p \leq 0.05$  considered significant.

**Results:** Results demonstrated that most of participants were aged 20–40 years, with equal gender distribution and no significant differences in age, gender, marital status, experience, or department across groups. The AI-integrated educational intervention significantly improved nurses' awareness, problem-solving skills, and attitudes. In the experimental group, poor awareness good awareness rose to 45.2%. Problem-solving skills improved markedly, with 78.6% achieving good skills post-intervention compared to none at baseline. Attitudes also shifted substantially, as 90.5% of nurses developed good attitudes post-intervention compared to 100% poor attitudes at baseline.

**Conclusion:** The AI-integrated educational intervention significantly enhanced the experimental group nurses' awareness, problem-solving skills, and attitudes compared to the control group. These findings highlight the effectiveness of structured training in preparing nurses for technology-driven healthcare.

**Key Words:** Critical Care Nursing, Artificial Intelligence, Problem Solving, Attitude of Health Personnel, Education

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## INTRODUCTION

The rapid evolution of healthcare, driven by technological innovations, has positioned Artificial Intelligence (AI) as a transformative force in improving the quality of care<sup>1,2</sup>. AI's growing role in healthcare extends to nursing education, where it is redefining traditional learning by fostering critical thinking, clinical reasoning, and decision-making skills among students<sup>3</sup>. By simulating human intelligence, AI performs complex tasks such as data analysis, pattern recognition, and predictive modelling, enabling healthcare professionals to make informed decisions<sup>4</sup>.

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The integration of AI into nursing education introduces tools like machine learning, deep learning, and natural language processing, enhancing both teaching and clinical training<sup>5</sup>.

In nursing education, the development of professional identity is deeply influenced by factors such as clinical experience, ethical standards, and educational environments<sup>6</sup>. The integration of AI into curricula offers opportunities to strengthen this identity through innovative learning strategies and exposure to technology-driven clinical scenarios<sup>7</sup>. Successful implementation of AI in nursing education depends on thoughtful curriculum design, faculty training, and ethical considerations<sup>8</sup>. Preparing nurses who are technologically competent and ethically grounded ensures that they are capable of combining traditional nursing skills with AI-driven insights to deliver patient-centered care in an increasingly digital healthcare landscape (Abuzaid et al., 2022).

As AI technologies become integral to healthcare systems, their capacity to analyze vast datasets and support decision-making has gained significant attention<sup>9</sup>. AI health technologies (AIHTs) facilitate efficient organization of clinical data, enhancing

diagnostic accuracy and personalized care<sup>10</sup>. However, concerns persist regarding job displacement, ethical dilemmas, and data bias. Nurses play a pivotal role in shaping AI’s responsible use, making their active engagement essential. Embracing AI not only enhances nursing practice but also strengthens the collaboration between human expertise and machine intelligence, paving the way for innovation and improved patient outcomes in modern healthcare<sup>11</sup>.

**METHODS**

A quasi-experimental two-group pre and post-test design was used to conduct the study at Doctors Hospital and Medical Center, Lahore. The study, conducted from June 2025 to August 2025 after ethical approval from the University of Lahore (REC-UOL-/448 Dated 28.08.2024), included 84 nurses equally divided into experimental and control groups, selected through convenient sampling. The independent variable was the AI-integrated learning design, while dependent variables were nurses’ awareness, problem-solving skills, and attitudes, measured using validated and reliable tools (CVI: 0.81–0.86; Cronbach’s  $\alpha$ : 0.79–0.86). Data were collected in three phases—pre-intervention, intervention, and post-intervention. Data were analyzed with SPSS version 25 using non-

parametric tests (Wilcoxon signed-rank and Mann–Whitney U), with  $p \leq 0.05$  considered significant. Ethical principles of consent, confidentiality, anonymity, and voluntary participation were strictly maintained.

**RESULTS**

Among the participants, most were aged 20–40 years, with similar age distribution across groups ( $p = 0.537$ ). Gender distribution was equal, and marital status also showed no significant difference ( $p = 0.633$ ,  $p = 0.182$ ). Educationally, 29.8% held a Diploma in General Nursing, 36.9% had Post RN BSN, and 33.3% had BSN, showing a significant difference between groups ( $p = 0.001$ ). Most nurses (65.5%) had up to 5 years of experience, and the rest had more than 5 years ( $p > 0.999$ ). Departmental distribution was 40.5% in Medical ICU, 40.5% in Surgical ICU, and 19% in Pediatric ICU, with no significant difference ( $p = 0.337$ ).

Table 2 shows that the experimental group had significantly higher awareness scores than the control group both before (6.00 vs. 4.00,  $p < 0.001$ ) and after the intervention (7.00 vs. 5.00,  $p = 0.042$ ), indicating the intervention effectively improved nurses’ awareness.

**Table No. 1: Comparison of demographic characteristics of control and experimental group of nurses(n=84)**

Demographic Variables	Category	Group	
		Experimental f (%)	Control f (%)
Age in Years	20-30 Year	15(35.70%)	14(33.30%)
	31-40 Year	13(31.00%)	18(42.90%)
	41- 50 Year	6(14.30%)	6(14.30%)
	> 50 Year	8(19.00%)	4(9.50%)
Gender	Male	22(52.40%)	20(47.60%)
	Female	20(47.60%)	22(52.40%)
Marital Status	Single	28(66.70%)	22(52.40%)
	Married	14 (33.30%)	20(47.60%)
Education Qualification	Diploma in General Nursing	6(14.30%)	19(45.20%)
	Post RN BSN	15(35.70%)	16(38.10%)
	BSN	21(50.00%)	7(16.70%)
	MSN	0(0%)	0(0%)
Experience	1-5 years	28(66.70%)	27(64.30%)
	> 5 years	14(33.30%)	15(35.70%)
Department	Medical ICU	14(33.30%)	20(47.60%)
	Surgical ICU	18(42.90%)	16(38.10%)
	Paeds ICU	10(23.80%)	6(14.30%)

**Table No. 2: Comparison of awareness before and after intervention of experimental group and control group nurses (n=84)**

Variable	Control Group Median (IQR)	Experimental Group Median (IQR)	p-value
Pre-Intervention Awareness	4.00(3.00-5.00)	6.00(5.00-7.00)	<0.001
Post- Intervention Awareness	5.00 (3.75-6.00)	7.00(6.00-8.00)	0.042

**Table No. 3: Comparison of problem-solving skills of experimental group and control group of nurses before and after intervention (n=84)**

Variable	Control Group Median (IQR)	Experimental Group Median (IQR)	p-value
Pre-Intervention Problem Solving Skills	112.00(104.00-118.00)	118.50(111.25-125.25)	<0.001
Post- Intervention Problem Solving Skills	112.00(104.00-118.00)	165.50(156.00-177.50)	<0.001

**Table No. 4: Comparison of attitude of experimental group and control group of nurses before and after intervention (n=84)**

Variable	Control Group Median (IQR)	Experimental Group Median (IQR)	p-value
Pre-Intervention Attitude	47.00(43.00-50.00)	44.00(41.00-48.00)	0.006
Post- Intervention Attitude	46.00(43.00-51.00)	87.00(84.00-91.00)	<0.001

Table 3 shows a significant improvement in problem-solving skills among the experimental group, with scores increasing from 118.50 to 165.50 after the intervention, while the control group remained unchanged at 112.00. The difference was highly significant ( $p < 0.001$ ), indicating the intervention effectively enhanced nurses' problem-solving abilities. Table 4 shows a significant improvement in nurses' attitudes in the experimental group, with scores rising from 44.00 to 87.00 after the intervention, while the control group remained nearly the same (47.00 to 46.00). The difference was highly significant ( $p < 0.001$ ), indicating the intervention greatly enhanced nurses' attitudes.

## DISCUSSION

The demographic results of this study align with recent literature (2021–2025), showing that most nurses were young (20–40 years), single, and had less than five years of ICU experience, reflecting a growing early-career nursing workforce. Gender distribution was balanced, and educational qualifications indicated a gradual shift from diploma to degree programs, consistent with regional trends. These findings mirror studies by Glauberma et al. (2023)<sup>12</sup> and De Gagne (2023)<sup>13</sup>, confirming that critical care units are primarily staffed by younger, transitioning professionals. The study found that the AI-integrated learning intervention significantly improved nurses' awareness. In the experimental group, poor awareness declined sharply, while fair and good awareness increased considerably, showing the intervention's effectiveness. These results are supported by Schneidereith & Thibault (2023)<sup>14</sup> and Taskiran (2023)<sup>15</sup>, who noted that AI-based learning enhances engagement and knowledge. The findings also reflect Abuzaid et al. (2024)<sup>16</sup>, emphasizing that AI promotes active learning and greater understanding of complex healthcare concepts. Problem-solving skills also improved substantially among nurses in the experimental group, while the control group showed no change. This outcome supports prior studies (El Arab et al., 2025; Cucci et al., 2025) (El Arab et al., 2025),

(Cucci et al., 2025) that demonstrated AI's ability to strengthen analytical and decision-making skills through adaptive simulations and problem-based learning. The intervention enabled nurses to practice reasoning in realistic scenarios, improving their confidence and readiness for critical situations<sup>17</sup>. Nurses' attitudes toward AI showed the most notable change, with 90.5% of participants in the experimental group developing positive attitudes post-intervention. This aligns with findings by Lifshits & Rosenberg (2024)<sup>18</sup>, who reported that structured AI education fosters openness and confidence in technology use. Overall, the study highlights that AI-integrated learning effectively enhances nurses' awareness, problem-solving abilities, and attitudes, preparing them for evolving, technology-driven healthcare environments<sup>19</sup>.

## CONCLUSION

The study concluded that both groups were demographically comparable, except for a difference in educational qualifications. The AI-integrated learning intervention had a significant positive impact, greatly improving nurses' awareness, problem-solving skills, and attitudes. The experimental group showed marked gains in all areas, while the control group showed little or no change. Overall, AI-integrated education proved highly effective in enhancing knowledge, critical thinking, and positive attitudes among critical care nurses, equipping them for the evolving demands of modern healthcare.

### Author's Contribution:

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Drafting or Revising Critically:	Ejaz Khan, Madiha Mukhtar
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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# Medicolegal Examination and Interpretation of Firearm Injuries

Ahmad Raza Khan, Riasat Ali and Aatiqa Abass

## ABSTRACT

**Objective:** This objective of this study is to gather detailed information regarding firearm injuries and their repercussions on the victims and this is to be monitored by scrutiny of the medicolegal protocol implemented by the initial medicolegal examiner, regarding history taking, injuries documentation and clothes examination with the sole purpose of fabrication assessment.

**Study Design:** Prospective cohort study

**Place and Duration of Study:** This study was conducted at the Medicolegal Clinic of Mayo Hospital Lahore of the year 2024 from 1<sup>st</sup> January 2024 to 31<sup>st</sup> December 2024.

**Methods:** The sample size was based on the number of victims reporting in the emergency department for firearm injury examination for the year 2024. The victims were questioned and examined after obtaining a valid informed consent and assent at every step of examination with absolute anonymity and confidentiality. Inclusion criteria was that all these participants were volunteers, male, female, adults, minors coming to medicolegal office for with history of firearm injury. All the other physical assault cases including injuries by blunt means, sharp edge weapons poisoning and sexual assault cases reporting to medicolegal office of Mayo Hospital Lahore were excluded from this study.

**Results:** Male victims were dominantly more in number as compared to female counterpart and dacoity was highlighted as a main cause followed by fight with either neighbors or family.

**Conclusion:** Firearm injuries are a horrific trauma to begin with followed by consequential sequelae in form of health along with financial issues, causing undesirable consequences at individual and community level both.

**Key Words:** firearm crimes, assailants, terminal ballistics, medicolegal examination

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## INTRODUCTION

Humans have an inbuilt vehemence trait which expresses itself either in ferocity or as a defense strategy. This human nature exhibits itself as either one on one combat or use of any weapon of assault including firearms. Targeting the main objective of the study firearm weapons usage is to be elaborately discussed in this study as to what leads to such heinous crime activity as either part of aggression, self-defense or totally fabricated scenario with sole purpose of incriminating someone for either blackmail intent or money extortion and when they are actual real injuries, what long lasting health, financial and legal complications arise due to this assault.<sup>1</sup>

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This study shall address the interactive association of firearm injuries with their medicolegal outcome ranging from clinical disabilities to death.<sup>2</sup> Homicidal, suicidal and accidental modes shall be examined in detail to differentiate the intent assessing the nature of injury specially to rule out the possibility of a manipulated friendly hand injury or an absolute lack of use of any ballistics weaponry. This medicolegal differentiation of whether it is a genuine firearm injury, manipulated or fabricated is entirely dependent upon the forensic expertise of the initial medicolegal examiner.<sup>3</sup>

Furthermore, the investigative procedures comprising of crime scene circumstantial and corroborative evidence collection by the police is yet another clue for the medicolegal examiner to proceed into the matter with cross examining the history narrated by the victim with the evidentiary proof provided and examining the injured along with clothes scrutiny for any gunshot residue. All this hectic exercise is for eventual declaration of the medicolegal case.<sup>4</sup> All the legal proceedings in the court of law are dependent upon the medicolegal case report provided by initial medical examiner narrating the intricate details of the weapon used, resultant injuries suggesting the distance, direction and extent of damages for punishment of the assailant and monetary compensation to the victim.<sup>5</sup> By highlighting the multifaceted nature of this issue, we hope to stimulate further discussion and inspire

preventive measures to reduce the prevalence of firearm-related violence.

The medicolegal clinic entertains all categories of violent crimes including physical assault, sexual offences, accidental along with poisoning cases. In this paper we shall individualize the firearm cases especially in accordance with establishing the use of friendly hand or fabricated injuries mimicking the terminal ballistics of a firearm inflicted damage. How victims at times depict a specified history of being assaulted by a rifled or a smooth bore weapon but somehow on meticulous examination by a forensic expert can scrutinize the possibility of concoction and forgery.<sup>3</sup>

Medicolegal examiner has to face various firearm resultant injuries inflicted from different weapons like rifled and smooth bore firearm weapons, ranging from individual lacerated wounds of entry and exit to multiple penetrating injuries respectively. The most important factor under consideration for a medicolegal examiner is to decide the possibility of a friendly hand or even fabrication simulating a firearm injury which has its eventual effect on legal proceedings in court of law. Hence objectivity of this research is targeted towards the final decision of declaration of injury as genuine or fake.<sup>6</sup>

**METHODS**

It is an Observational study with analytical longitudinal design in prospective cohort design with consecutive sampling technique. The study was conducted in the medicolegal clinic of emergency department of Mayo Hospital Lahore. The sample size was based on the number of victims reporting in the emergency department for firearm injury examination for the year 2024. The victims were questioned and examined after obtaining a valid informed consent and assent at every step of examination with absolute anonymity and confidentiality. Inclusion criteria was that all these participants were volunteers, male, female, adults, minors coming to medicolegal office for with history of firearm injury. All the other physical assault cases including injuries by blunt means, sharp edge weapons poisoning and sexual assault cases reporting to medicolegal office of Mayo Hospital Lahore were excluded from this study.

Retrospective data was collected regarding all the information including biodata, time of incidence, time of reporting the incidence to the medicolegal clinic, clothes examination and dispatch to PFSA for gunshot residue and ultimately declaring final opinion of the case. Collected data was analyzed using IBM SPSS Statistics version 26.0. This retrospective study design cannot establish causation due to potential confounding factors not accounted for in the analysis.

**Ethical Declaration:** Ethical review board proceedings were conducted in Mayo Hospital Lahore under the

Chairmanship of Prof. Muhammad Imran, Secretary Institutional Review Board, Chairman Department of Medicine, King Edward Medical University/Mayo Hospital, Lahore and project was approved vide letter no. 96/RC/KEMU dated 04<sup>th</sup> December 2023.

**RESULTS**

Male victims were dominantly more in number as compared to female counterpart and dacoity was highlighted as a main cause followed by fight with either neighbors or family.

**Table No. 1: Showing 86% male versus 14% female victim**

GENDER	FREQUENCY	PERCENT
Male	8	14.3
Female	48	85.7
Total	56	100

**Table No. 2: In 84% of the cases there was a single assailant**

ASSAILANTS	FREQUENCY	PERCENT
One	47	83.9
Two	7	12.5
Three	2	3.6

Table 3. In 64% of the cases the victim was fired upon from a distance of more than 3 feet with only 23% being attacked from within a distance of 1 foot

**Table No.3: Distance frequency percentage in patients**

DISANCE	FREQUENCY	PERCENT
Within six inches	1	1.8 %
Within one foot	13	23.2 %
Within two feet	3	5.4 %
Within three feet	3	5.4 %
More than three feet	36	64.2 %
Total	56	100 %

**Table No.4: Mostly used weapon was a handgun (pistol/revolver)**

WEAPON	FREQUENCY	PERCENT
Pistol	49	87.5 %
Revolver	3	5.4 %
Rifle	3	5.4 %
Smooth bore	1	1.8 %

**Table No. 5: Victims were fired upon from predominantly from front/ right or left side**

DIRECTION	FREQUENCY	PERCENT
Front	16	28.6 %
Right side	18	32.1 %
Left side	17	30.4 %
Front and right	1	1.8 %
Front and left	1	1.8 %
Back	3	5.4 %

Table No. 6: Lower limb injuries including fracture and muscle damage were 41% followed by 23% resultant damage to upper limbs with abdominal injuries were reportedly 18%

**Table No.6: Injuries, frequency percentage**

INJURIES	FREQUENCY	PERCENT
Muscle deep upper limb	6	10.7 %
Muscle deep lower limb	12	21.4 %
Fracture upper limb	7	12.5 %
Fracture lower limb	11	19.6 %
Head injury	3	5.4 %
Chest cavity deep	7	12.5 %
Abdominal cavity deep	10	17.9 %

## DISCUSSION

In Lahore alone eight teaching institutes along with five rural health centers cater the medicolegal cases.<sup>7</sup> In this study the target population was the firearm injured personnel reporting in Emergency Department of Mayo Hospital, Lahore. Total number of firearm cases reported were 56 in number in the year 2024, with the presented data sheds light on the concerning prevalence and patterns of firearm injuries. The overwhelming majority of victims were male 48 out of 56, highlighting a significant gender disparity in firearm-related violence. This trend may be linked to societal factors, cultural norms, and potential involvement in criminal activities, which substantially portrays the accessibility of the male gender to firearm weapon and a dominant predilection of the males to fall prey to a dispute leading to drastic outcome like firearm involved fights.<sup>8</sup> Preponderance of single-assailant incidents i.e. 84 % of the reported cases suggested a high degree of targeted attacks, possibly driven by personal vendettas, disputes, or criminal intent which were a leading trait of the study showing a lack of arbitrary communication and tolerance among the individuals.<sup>9</sup> These individuals being short-tempered and having an access to a firearm weapon whether legal licensed or any random illegal piece which makes it even more difficult for the police personnel to follow through with the investigation. Mostly the licensed weapons are for either personal protection carried by one's own self or by the recruited bodyguards.<sup>10</sup> Other than this shot guns are usually for the prophylaxis of the sown crops from the wild animals like bores and hyenas. The widespread use of illegal handguns like pistols and revolvers, highlights the accessibility of firearms and their potential for lethal harm, the easy availability of hand guns from black market is cardinal reason for rifled arms brutality.<sup>11</sup> Besides these one on one targeted attacks multifaceted diverse motivational intents were also observed. The varied motivations behind these attacks, including dacoity, neighbor disputes, and domestic violence, underscore the complex nature of firearm-related

violence.<sup>12</sup> This diversity necessitates an ambidextrous approach to prevention and intervention strategies.

Coming on to the next facet of the inquisitory intent was to establish a link between distance and angle of attack: The majority of attacks i.e. 64% occurred from a reasonable distance of more than three feet with a single assailant targeting a single victim, indicated a deliberate intent to inflict harm. However, a significant proportion of 23% involved close-range confrontations, suggested impulsive or reactive violence.<sup>13</sup>

The most notorious aspect of the legality outcome is the injury infliction pattern motivated by the accountability and penalty denouement. The amercement for first degree murder meaning intentional killing of someone is either death penalty or life imprisonment for 25 years however this considerably reduced in case when the intent is only to warn or harm the individual rather than to actually kill him. The sentence is mitigated down to around 15 years being further abridged down to 7-10 years with good behavior. Hence the high incidence 36 out of 56 i.e. 64% of lower and upper limb injuries suggest that many attacks were focused on incapacitating victims rather than causing immediate fatalities. However, the significant number of injuries underscored the potential for severe internal damage and life-threatening consequences i.e. 13% chest, 18% abdominal and 5% attacks directed towards the head were suggestive of deliberate premeditated murders.<sup>14</sup>

Lastly coming on to the objective of the study which is to elucidate the pattern of injuries and their configuration, dimensions correlation with the narrated history to establish a reasonable conclusion that either the injury is either genuine or by a friendly hand and finally it is not a firearm injury to begin with and it has it been a manipulated or maneuvered wound either created by an icepick or a screw driver or any other point sharp edge weapon.<sup>6</sup> But unluckily this segment of the medicolegal examination has been a neglected chunk with no detailed meticulous history and no well-expressed injury description stating the collar of abrasion, inverted and everted margins of entry and exit wound respectively.

This discussion can now be concluded by stressing on the implications and recommendations for public health, law enforcement, and policymakers. The very first step is to improve the quality of the medicolegal work and train the medical officers as to how to follow the protocol of medicolegal examination as it is a specific mindset of a forensic medical expert that can appreciate the intricate details than an untrained personnel.<sup>15</sup> Further rationale of the study is to prevent easy provision and accessibility of the illegal, unlicensed firearm weapons to public specially the minors who possess such ballistics.<sup>16</sup> Strict implementation of the existent law needs to be enforced regarding as to whom the firearm weapon is to be sold under proper licensed authority to prevent easy accessibility and misuse. Besides a legal crack down should be executed against the illegal sale and purchase of the guns and finally those who get incriminated shall

face the punitive reforms for preventing recidivism.<sup>17</sup> Finally provision of prompt medicolegal care and rehabilitative services to the victims shall ensure survivability and productive society.<sup>18</sup>

## CONCLUSION

Educating the masses about violence and ramifications of firearm injuries is the first step towards reduction of this heinous crime. Secondly a strict disciplinary law enforcement for prevention of easy availability of the weapons to public especially the minors is yet another reformatory maneuver, and finally an effective medicolegal proceedings leading to quick, successful, authoritative court proceedings shall impose a productive effect in the society.

### Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Ahmad Raza Khan, Riasat Ali
Drafting or Revising Critically:	Ahmad Raza Khan, Aatiqa Abass
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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# A Phenomenological Study of Resident Physicians' Experiences of Bedside Teaching

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## ABSTRACT

**Objective:** This study explores the perceptions, challenges, and impact of BST on the clinical skills of resident physicians.

**Study Design:** A descriptive phenomenological study

**Place and Duration of Study:** This study was conducted at the medical ward of Khyber Teaching Hospital, Peshawar from December 2024 to June 2025.

**Methods:** A descriptive phenomenological approach was employed to investigate the lived experiences of nine resident physicians. Semi-structured, in-depth interviews were conducted using purposive sampling. Data collection continued until saturation was reached. Ethical approval was obtained, and confidentiality was ensured through anonymized, audio-recorded interviews. The transcribed data were analyzed using Colaizzi's thematic analysis method.

**Results:** Four key themes emerged: (1) perceived value of BST, (2) challenges faced, (3) impact on clinical skills, and (4) recommendations for improvement. Most residents found BST valuable for real-time learning, clinical reasoning, and patient communication. However, barriers such as time constraints, inconsistent teaching styles, and patient privacy concerns hindered its effectiveness. Residents acknowledged BST's role in enhancing diagnostic accuracy, recognition of clinical signs, and efficiency in physical examination. Suggestions for improvement included structured sessions, interactive discussions, detailed feedback, and small-group bedside discussions.

**Conclusion:** Despite its recognized value in clinical training, BST remains underutilized due to systemic challenges. Addressing time limitations and improving teaching consistency could enhance its effectiveness. Implementing structured, interactive, and feedback-oriented BST sessions may optimize resident learning and improve patient care.

**Key Words:** Bedside teaching, medical education, resident physicians, phenomenology, clinical skills

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## INTRODUCTION

Bedside teaching (BST) has long been regarded as a fundamental method of clinical education, allowing learners to develop essential skills in history-taking, physical examination, diagnostic reasoning, and patient communication. Sir William Osler famously stated, "Medicine is learned by the bedside and not in the classroom," emphasizing the irreplaceable value of direct patient interactions in medical training<sup>1,2</sup>.

However, despite its effectiveness, BST has seen a significant decline in recent decades due to various systemic challenges, including increased reliance on diagnostic technology, time constraints, concerns about patient privacy, and evolving educational models that prioritize simulation over direct patient contact<sup>3,4</sup>.

Historically, BST constituted a major part of medical education, with up to 75% of clinical training occurring at the bedside in the early 20th century. However, this figure has now dropped to less than 20% in many institutions<sup>3</sup>. A major factor contributing to this decline is the increasing dependence on imaging and laboratory diagnostics, which, while beneficial, have inadvertently reduced the emphasis on clinical skills such as physical examination and patient-centered communication<sup>3,4</sup>. Moreover, administrative pressures to shorten hospital stays, as well as concerns regarding patient comfort and confidentiality, have led to a reduction in bedside interactions between trainees and patients<sup>2,3</sup>. For resident physicians, BST plays a crucial role in bridging the gap between theoretical knowledge and practical application. Studies have shown that bedside learning enhances diagnostic accuracy, improves clinical decision-making, and fosters a more patient-centered

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approach<sup>1,5</sup>. Furthermore, BST provides an opportunity for role modeling, where senior clinicians demonstrate best practices in clinical reasoning, professionalism, and patient engagement<sup>5,6</sup>. However, despite its benefits, BST is often hindered by inconsistent teaching approaches, lack of structured frameworks, and competing clinical demands<sup>7</sup>. Given the importance of BST in medical education, this study aims to explore the lived experiences of resident physicians regarding bedside teaching. By identifying the perceived benefits, challenges, and impact of BST on clinical competency, this study seeks to provide insights into optimizing bedside learning for future medical training programs.

**METHODS**

A descriptive phenomenological approach was used to obtain data from Resident Physicians in order to obtain in-depth understanding of residents' perception, challenges and influencing clinical skills of bedside teaching. This study was conducted in department of medicine, Khyber Teaching Hospital from December 2024 to June 2025. Ethical approval was obtained from Khyber Medical College Research Ethics Committee. All medical B Ward resident Physicians was considered in this study.

An information sheet indicating the purpose of the research has been provided before taking written informed consent to assure confidentiality. In-depth semi-structured one-on-one interviews with the resident physicians was carried out in a comfortable atmosphere using an interview guide with open-ended questioning using purposive sampling technique. Face validity was chosen to ensure that the interview questionnaires are appropriate for the purpose of the research. The sample size was calculated by data saturation, when no new theme is obtained from Resident Physicians. Confidential interviews were audio-recorded to facilitate subsequent transcription and analysis of results. Data will be analyzed using the phenomenological method of Colaizzi.

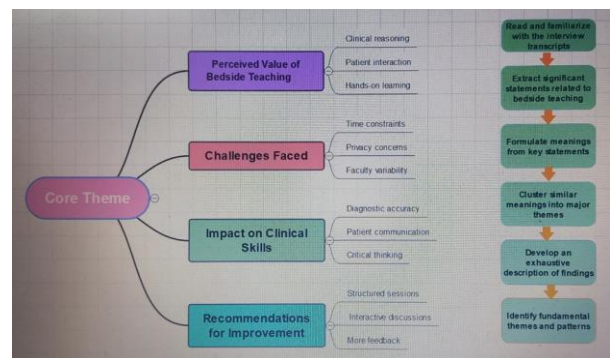
**RESULTS**

The study included nine resident physicians. Out of nine resident five were female and four were male. Five were general medicine trainees, while four were specialty trainees. Regarding residency year, 5 were first-year, 2 were second-year, and 1 each from third and fourth year.

**Core Theme:** The study employed thematic analysis using Colaizzi's method to explore residents' experiences with bedside teaching. Data from semi-structured interviews of the nine resident physicians were transcribed, coded, and categorized into four key themes, 1. Perceived Value of Bedside Teaching, 2. Challenges Faced, 3. Impact on Clinical Skills and 4. Recommendations for Improvement.

**Table No.1: Characteristics of the participants**

Gender	Residency year	Specialty	Frequency of participation in rounds
Female	First	Specialty	Few times a week
Female	First	Specialty	Few times a week
Female	First	Specialty	Daily
Male	First	General	Daily
Male	Third	General	Few times a week
Male	Second	Specialty	Daily
Female	First	General	Daily
Female	Second	General	Daily
Male	Fourth	General	Daily



**Figure No.1: Thematic Analysis Framework**

**General Experience with Bedside Teaching**

Most residents found bedside teaching valuable, with 3 rating it as excellent, 4 as good, and 2 as average. "Bedside teaching allows real-time learning, making complex cases easier to understand," one resident stated. However, time constraints and workload limited participation, with only 2 residents attending daily, 4 a few times a week, 2 once a week, and 1 rarely.

**Perceptions of Bedside Teaching:** Residents appreciated bedside teaching for enhancing clinical reasoning, patient communication, and hands-on skills. "Unlike lectures, bedside teaching helps me connect theory with actual patient cases," one participant noted. However, 3 residents preferred case-based discussions over bedside teaching.

**Challenges Faced During Bedside Teaching:** The biggest challenges were time constraints, patient privacy concern, and inconsistent teaching styles "Each consultant teaches differently, making it difficult to follow a structured approach". "Sometimes, we rush through bedside rounds due to workload, reducing learning opportunities," one resident mentioned.

**Impact on Clinical Skills:** Most residents felt bedside teaching significantly improved their diagnostic and examination skills. Common impact on clinical skills

are “better recognition of clinical signs”, “improved diagnostic decision-making”, and “efficiency in physical examinations”. " I learned how to diagnose a case after clinical exposure, and ward rounds helped me recognize conditions that I would have missed in a classroom setting" one resident shared.

**DISCUSSION**

The findings of this study reinforce the crucial role of bedside teaching (BST) in medical education while highlighting the challenges that limit its effectiveness. The thematic analysis revealed key insights into residents' perceptions, the barriers they encounter, and the potential strategies to enhance BST. These findings align with existing literature and contribute to the growing discourse on optimizing bedside learning. Residents in this study acknowledged BST as an essential component of their training, particularly in enhancing clinical reasoning, diagnostic accuracy, and patient communication. These findings are consistent with prior studies that have highlighted the superiority of BST over classroom-based learning in fostering hands-on clinical skills<sup>8,9</sup>. BST has also been described as a unique learning experience that strengthens professionalism and teamwork<sup>10,11,12</sup>. Despite its declining use, literature suggests that BST remains a powerful tool for bridging theoretical knowledge and real-world clinical practice<sup>2,13</sup>.

While residents valued BST, they faced several challenges that restricted its implementation. Time constraints due to increasing patient loads and administrative duties were the most significant barriers, similar to findings from previous studies<sup>10,14</sup>. Additionally, inconsistent teaching styles among faculty members led to variations in BST quality. This lack of a structured approach has been widely documented as a limitation in medical education<sup>7,15-17</sup>. Patient privacy concerns also emerged as a key challenge. Residents expressed discomfort discussing cases openly at the bedside, fearing potential breaches of confidentiality. Prior research confirms that patients often feel uneasy when multiple learners are present, yet many are willing to participate in BST if adequately informed and reassured<sup>8,18,19</sup>. Addressing these concerns through proper patient consent and communication may help mitigate these barriers<sup>20</sup>.

Most residents agreed that BST significantly improved their ability to recognize clinical signs, perform efficient physical examinations, and make sound clinical decisions. These findings align with studies suggesting that bedside learning enhances diagnostic reasoning and practical competence more effectively than didactic lectures<sup>10</sup>. Furthermore, BST fosters a sense of responsibility and engagement in patient care, reinforcing its role in shaping well-rounded clinicians<sup>7</sup>. However, the effectiveness of BST varies depending on faculty involvement and teaching quality. Some

residents reported that BST sessions were often rushed due to workload pressures, limiting their ability to fully engage with patients and ask questions. This aligns with previous research indicating that faculty members often prioritize efficiency over teaching during rounds<sup>21</sup>. Structured BST sessions with dedicated teaching time may improve learning outcomes<sup>7</sup>. Residents provided several recommendations to improve BST, many of which are supported by existing literature. Structured BST sessions with a defined curriculum can ensure consistency across faculty members<sup>21</sup>. Additionally, incorporating interactive discussions, detailed feedback, and small-group bedside teaching could enhance learning experiences<sup>8</sup>. Another promising approach is the integration of video recordings for later review, which was suggested by several residents in this study. This aligns with research advocating for blended learning models that combine traditional BST with digital resources to reinforce key concepts [7]. Moreover, faculty development programs focused on effective bedside teaching strategies could help address inconsistencies in teaching styles and improve overall BST quality<sup>21</sup>.

**CONCLUSION**

This study highlights BST’s importance in clinical education while acknowledging barriers that limit its effectiveness. Despite challenges such as time constraints and inconsistent teaching methods, BST remains a vital learning tool when structured and properly implemented. To optimize BST, institutions should adopt standardized teaching frameworks, provide faculty development programs, and incorporate technology-assisted learning. Future research should assess the impact of these interventions on BST effectiveness and resident learning outcomes.

**Author’s Contribution:**

Concept & Design or acquisition of analysis or interpretation of data:	Shah Umam, Essa Hassan
Drafting or Revising Critically:	Shah Umam, Mohammad Haroon
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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# Comparative Evaluation of Renal Tissue Changes Associated with Anti-Obesity Therapies: Hoodia Gordonii Extract, Liraglutide (Saxenda), and Their Combination

Evaluation of Renal Tissue Changes with Anti-Obesity Therapies

Zeinab Hameed Abbas<sup>1</sup> and Dalal Abdel-Hussein Kadhim AL-Essawi<sup>2</sup>

## ABSTRACT

**Objective:** To assess the histopathological effects of Hoodia gordonii extract and Saxenda as well as the effect of the combination on renal tissue under experimental conditions that simulated the effect of metabolic stress associated with obesity.

**Study Design:** Experimental study

**Place and Duration of Study:** This study was conducted at the University of Kufa, Iraq from 11<sup>th</sup> September 2024 to 28<sup>th</sup> February 2025.

**Methods:** This study was conducted to examine the effects Hoodia gordonii extract (150 mg/kg/day), Saxenda (0.1 mL/day, subcutaneous) and a combination of both on renal effects were investigated using experimental models over 30 and 45 days. Kidney specimens were fixed in 10% neutral buffered formalin and then sectioned and stained with Hematoxylin and Eosin (H&E) and observed under the microscope to determine glomerular and tubular changes.

**Results:** Samples exposed to Hoodia gordonii exhibited intact renal architecture that was not affected by glomerular or tubular injury. Saxenda exposure on the other hand caused histological alterations which included interstitial inflammation, tubular necrosis and glomerular enlargement. The joint regimen showed better morphology of the kidneys, almost normal histological characteristics and less damage.

**Conclusion:** Hoodia gordonii seems a safe natural adjunct in obesity control, and it shows a protective effect against the nephrotoxicity of the drug.

**Key Words:** Hoodia gordonii, Saxenda; obesity, Nephrotoxicity, Renal protection, Histopathology, Oxidative stress

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## INTRODUCTION

Obesity has emerged as one of the most enduring nutritional and societal challenges of the contemporary age, especially in industrialized countries. It is defined by a pathological increase of adipose tissue because of an excessive number of fat cells, which is usually expressed by the body mass index (BMI), with a BMI of 30 kg/m<sup>2</sup> or more indicating obesity.

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The rising cases of obesity are much linked to the upsurge in chronic health-related diseases, including cardiovascular diseases, type 2 diabetes, some cancers and early deaths.<sup>1,2</sup>

Pathogenesis of obesity has a multifactorial nature, consisting of a complex of inherited predisposition, environmental factors, behavioral, and hormonal dysregulation, in addition to which recent studies have also introduced the significance of adipose tissue as a significant endocrine gland contributing to the overall chronic low-grade inflammation and metabolic complications associated with insulin resistance and lipid abnormalities.<sup>3-5</sup> The COVID-19 pandemic has also increased the rates of obesity, particularly in the most industrialized nations, including the United States, which has also.<sup>6</sup>

The existing anti-obesity interventions include lifestyle, surgical, pharmacologic and dietary supplements. The pharmacological agents are used to reduce appetite, prevent nutrient absorption or increase energy consumption. Although many drug candidates have been developed, it is unclear whether many of them will be safe and effective in the long term and few of them are approved by the regulatory authorities.<sup>7,8</sup>

A glucagon-like peptide-1 (GLP-1) receptor agonist has become the drug of interest, namely liraglutide (Saxenda), as it induces satiety and gastric emptying, as well as improves the metabolic parameters. Even though it shows encouraging weight loss effects, there are side effects like gastrointestinal discomfort and possible risks to other vital bodily organs such as kidneys and pancreas and hence the need to do some research on it.<sup>9,10</sup>

In line with the development of pharmacology, herbal remedies to control obesity have shown an increasing trend all over the world. *Hoodia gordonii* is a succulent plant that is indigenous to Southern Africa and has been used naturally as an appetite suppressant by indigenous people. The plant is a source of bioactive compounds including pregnane glycosides, including well-known P57 molecule which has been linked to appetite suppressive activity and metabolic control in preclinical models.<sup>11-13</sup>

Nonetheless, there are the ongoing worries as to the systemic safety of the synthetic and natural anti-obesity agents specifically, the absence of adequately-conducted clinical trials of *Hoodia gordonii* and the emerging cases of organ-specific toxicity when using liraglutide are subject to serious safety concerns. The histopathological examination is a useful model to measure tissue-level modifications caused by such interventions, especially in those organs vulnerable to drug toxicity, e.g. the liver, kidney, pancreas and heart.<sup>14</sup>

## METHODS

The current experimental study was carried out in University of Kufa, Iraq between 11th September 2024 and 28th February 2025 under letter No. 37967 dated 5-10-2024. Thirty-two healthy adults, who were experiment subjects, were used and taken through a two-week acclimatization period prior to the start of an experiment. The experimental groups were randomly assigned eight samples ( $n = 8$  per group) to test the histological effects of various doses of *Hoodia gordonii* extract, Saxenda (liraglutide) and the combination of the two at two time intervals, 30 and 45 days. These samples were randomly split into eight experimental groups ( $n = 8$  each group) which were aimed at testing the histological effects of varying doses of *Hoodia gordonii* extract and Saxenda (liraglutide) and *Hoodia gordonii* extract combined with Saxenda (liraglutide): at two time points; 30 and 45 days. All the subjects were kept to the standard laboratory conditions at controlled temperatures of 22ff 1oC, relative humidity was kept at 5560 and 12-hour light dark cycle. Standard diet and water were given ad libitum, with exceptions made when the samplers were on a fast. All the procedures carried out in the laboratory were done in line with experimental ethical standards as well as the National institute of health (NIH) guidelines on the treatment and

utilization of the laboratory models. The procedure of dosing was done through oral gavage (extract) and subcutaneous injection (Saxenda), with the specific dilutions being made every day in fresh solutions.

Authenticated *Hoodia gordonii* powder was supplied by Farm Vredelus PTY LTD, Douglas, Namibia, accompanied by a Certificate of Analysis and LC-MS chemical profiling. For extract preparation, 20 g of dry powder was soaked overnight in 100 ml of a dichloromethane–methanol solution (1:1), following the method by Corley and Miller. (2009). The extract was separated via centrifugation ( $3000 \times g$  for 15 minutes), pooled, and evaporated at 40°C. The final yield was 8% w/w of the original dry mass.

All the subjects were seeded and starved overnight before the treatment period of the 30 and 45 days were complete. Kidney samples were immediately washed in cold saline after which the samples were immobilized in 10 percent neutral buffered formalin (NBF) with a ratio of tissue to fixative of 1:10 and left to incubate with freshly prepared fixative.

After fixation, the tissues were dehydrated using ethanol graded (70, 80, 90, 95 and 100 percent) cleared in xylene and embedded in molten paraffin wax. Embedding The treatment involved using stainless steel moulds to orient the correct tissue then cooled in order to create paraffin blocks.

Paraffin blocks were sectioned into thin slices of 4-5 m thick with the help of a rotary microtome. The sections were then floated in a water bath at 40 to 45 degrees Celsius and put on adhesive covered glass slides and left there to dry overnight at 37 degrees Celsius.

Standard Hematoxylin and Eosin (H&E) staining was performed using the following sequence:

- Deparaffinization: Xylene (2 changes, 5 minutes each)
- Rehydration: Descending ethanol series (100% to 70%) → distilled water
- Staining: Hematoxylin (3–5 minutes) → tap water rinse → differentiation (acid alcohol) → bluing (alkaline water)
- Counterstaining: Eosin (1–2 minutes)
- Dehydration and clearing: Ascending ethanol → xylene
- Mounting: DPX mounting medium with coverslip

A light microscope was used to examine prepared slides at different magnifications. (40×, 100×, 400×) to assess:

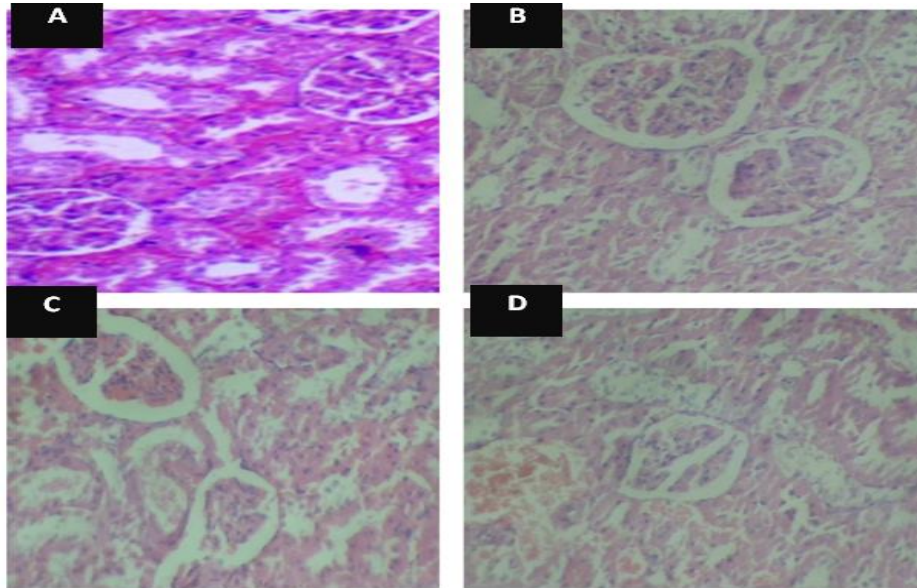
- Cell morphology
- Tissue architecture
- Signs of degeneration, necrosis, inflammation, congestion, or fibrosis
- Comparative histological damage scores

## RESULTS

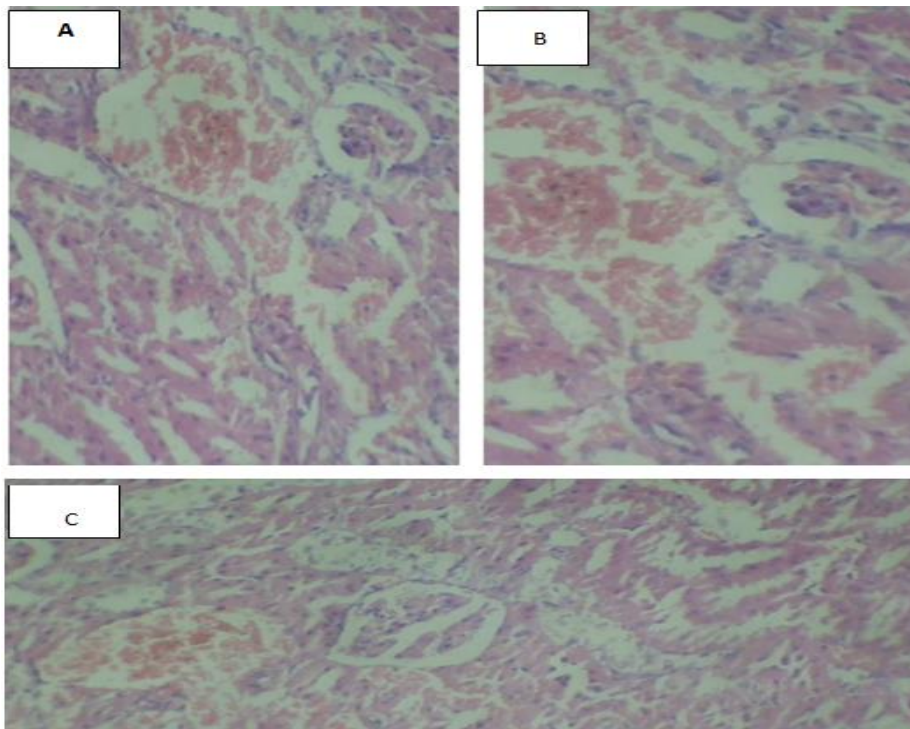
The histological examination of the kidney tissue of the control group revealed that the tissue had normal renal

structure, intact nephrons and tubules. Similarly, the exposure of 30 and 45 days of the samples to the hot aqueous extract of the Hoodia gordonii seeds at 100mg/kg showed no histopathological variation hence the preservation of the renal structure use. On the other hand, kidney samples of subjects treated with Saxenda 0.1mg/kg, 30 and 45 days revealed varied changes of

pathology, including tubular degeneration and glomeruli atrophy. However, preventive groups which were co-administered with Hoodia gordonii extract and the Saxenda also exhibited a normal or nearly normal kidney structure, suggesting that the plant extract was preventive (Figs. 1-2).



**Figure No. 1: A normal kidney tissue control group. B: group treated with the aqueous extract of Hoodia at 150 mg/kg .C: group treated with the drug (0.1) mg/kg for 30 days. D: group that received treatment for 30 days with 150 mg/kg of Hoodia aqueous extract plus 0.1 mg/kg of the medication**



**Figure No. 2: A: section of kidney of a sample of the group that was tested with Hoodia at concentration of 150mg, B: group treated with the drug (0.1)mg/kg over 45 days. C: A kidney belonging to a male rat of the group that was treated with an aqueous extract of hoodia at a concentration of 150 mg/kg + the drug at a concentration of (1.0)mg/kg in 45 days**

## DISCUSSION

The current research compared the results of renal histology of chronic administration of Hoodia gordonii extract (150 mg/kg), Saxenda (liraglutide, 0.1mg/kg), and combination of the two in an obesity model. We have found a disturbing difference in the tissue reaction of kidneys between the plant-based extract and the pharmacological agent with the combination group providing potentially valuable nephroprotective information. The Hoodia gordonii extract administered to the animals at a 30 and 45 days did not cause any histopathological deviation of the renal tissues. The fact that glomerular and tubular structures are not affected, and these findings can be seen in the light microscopy, means that there is no nephrotoxicity, even at the highest dose used (150 mg/kg). This is in line with previous reports that Hoodia is safe in traditional medicine use<sup>15</sup>, and this hypothesis supports the hypothesis that bioactive phytochemicals of Hoodia have renoprotective effects.<sup>16</sup>

The lack of tubular necrosis, interstitial fibrosis, and glomerular enlargement in the Hoodia-treated sample proves the activity of plant-derived antioxidant in preserving renal tissue integrity. The pregnane glycosides and other bioactive compounds of Hoodia can have stabilizing properties on cell membranes and mitochondrial activity, which might be through free radical scavenging or through manipulation of inflammatory cascades.<sup>17</sup>

In contrast, sample treated with Saxenda (0.1 mg/kg) displayed clear signs of renal damage, consistent with early-stage drug-induced nephropathy. Histological abnormalities included glomerular hypertrophy, evidence of tubular epithelial cell necrosis, and interstitial infiltration by inflammatory cells. These observations echo findings in prior studies on glucagon-like peptide-1 (GLP-1) receptor agonists, where nephrotoxic manifestations have been linked to oxidative stress, impaired renal hemodynamics, and off-target metabolic effects.<sup>18,19</sup>

The low dose of this study (0.1 mg/kg) was chosen to represent the lower part of the therapeutic window in preclinical research, but even this relatively lower level of exposure caused tissue-level renal damage. This highlights the need to carry out additional safety assessment of chronic use of GLP-1 receptor agonists in groups with preexisting renal susceptibility.

Interestingly, the co-treated group (with Hoodia extract 150 mg/kg) before and during the administration of Saxenda portrayed an almost normal renal histology. The glomerular and tubular injury mitigation effect in this group indicates that the natural extract and the synthetic drug have a nephroprotective interaction.

The mechanisms by which this protective effect might be explained are likely to be several synergistic mechanisms:

1. Increasing of antioxidants defense: Hoodia extract can increase endogenous antioxidant enzyme activities, including superoxide dismutases (SOD), catalase, and glutathione peroxidases, and eliminate reactive oxygen species (ROS) generated by Saxenda.
2. Anti-inflammatory modulation: Bioactive phytoconstituents in Hoodia especially pregnane glycosides can inhibit pro-inflammatory cytokines including TNF- alpha and IL-6, which are involved in glomerular and tubular inflammation.<sup>20</sup>
3. Mitochondrial Preservation: Hoodia contains natural compounds that might stabilize mitochondrial membranes, inhibit cytochrome c release, and block the apoptotic cascade of events in renal tubular epithelial cells, which is often mediated by pharmacological nephrotoxins.<sup>21</sup>
4. Vascular stabilization and hemodynamic stability: Hoodia has the potential to induce renal perfusion and capillary stability indirectly and counteract the effect of Saxenda on disruptions in renal blood flow caused by changes in nitric oxide or endothelin.

## CONCLUSION

Hoodia gordonii appears a harmless natural adjunct in the management of obesity, and it displays a protective effect on the nephrotoxicity of the medication as well as stimulates further preclinical and clinical studies in integrating plant-based therapy with pharmacological treatment to minimize the negative impacts of organ in association with drugs.

### Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Zeinab Hameed Abbas, Dalal Abdel-Hussein Kadhim AL-Essawi
Drafting or Revising Critically:	Zeinab Hameed Abbas, Dalal Abdel-Hussein Kadhim AL-Essawi
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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# Evaluating the Efficiency of Potential Risk Program in Enhancing Nurses' Knowledge and Practices at Hemodialysis Units

Shady Shafeek Anees Dowarah and Sahar Adham Ali

## ABSTRACT

**Objective:** To assess the efficacy of a potential risks training program on the skills and knowledge of nurses in hemodialysis units.

**Study Design:** A quantitative quasi-experimental study

**Place and Duration of Study:** This study was conducted at the hemodialysis centers at Karbala City namely Imam Al-Hussein Medical City (Dr. Adel Al-Sabbah Hemodialysis Center and Habib Ibn Mazaher Al-Asadi center) and Imam Al-Hassan Al-Mujtaba Teaching Hospital Iraq from 1<sup>st</sup> January 2025 to 30<sup>th</sup> June 2025.

A quantitative quasi-experimental study design comprising of 100 purposively selected nurses in two hemodialysis units in Karbala randomly assigned to different groups; control and interventional. The knowledge questionnaire and the practices observational checklist were used to collect data, and their validity was based on expert advice and their reliability was ensured by statistics.

**Results:** The majority of the study population was between the ages of 22 and 26 and 27 and 31. Both groups were equally distributed in terms of sex (66% male, 34% female). The findings showed that both group members' pre-test knowledge and practice levels were inadequate. On both post-tests, however, the interventional group demonstrates a notable improvement in context of knowledge and practices.

**Conclusion:** The educational program demonstrated its efficiency in enhancing nurses' knowledge and practices regarding possible risks in hemodialysis units. Continuous in-service training, and conducting further studies with expanded sample sizes and governorates were recommended.

**Key Words:** Patient Injuries, Hemodialysis, Hand hygiene, Medication errors

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## INTRODUCTION

Nurses are essential for the safe management of HD patients in healthcare environments. They play a crucial role in interrupting the transmission of infection by adhering to prevention and control of infections protocols.<sup>1</sup>

The most efficient method of preventing healthcare-associated infection, particularly in hemodialysis units, is hand hygiene, which necessitates the appropriate technique, appropriate use of sanitizers, and frequent checking of adherence.<sup>2,3</sup>

Hands that are visibly dirty need to be washed using soap and water, otherwise they should be sanitized using alcohol.

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The five-moment of Hand Hygiene guide by WHO assist in minimizing healthcare-associated infections.<sup>4</sup>

Proper hand hygiene and infection control policies are required to be maintained by having sufficient hand washing and sanitizing stations, continuous training, and monitoring of the healthcare personnel.<sup>5</sup>

Simple Hand Sanitization (SHS) is used to eliminate temporary microbes, sweat, oil, and dead cell of the hands. Liquid soap and 40-60 seconds of rubbing hands, followed by rinsing and using disposable tissue should be used by healthcare workers.<sup>6</sup>

Personal protective equipment including fluid-proof gown, face mask, gloves, and face shield or eyewear in hemodialysis should be used when the staff might be exposed to blood during a procedure, e.g., when starting or ending dialysis sessions, inserting catheters, and disinfecting the area. Selection and use of PPE must be based on risk assessment and adherence to CDC guidelines. Nurses must be trained in donning and doffing PPE correctly to minimize contamination.<sup>7</sup>

The polypharmacy in HD patients is sometimes viewed as a burden resulting in poor patient adherence. The consequence of poor adherence is the inability to get the desired outcome of the treatment, prescribing medications that are unnecessary and, therefore, wasting money and time.<sup>8</sup>

Polypharmacy can cause drug-related problems, including wrong drug choice, incorrect dose or route, side effects, interactions, missed doses, unaddressed indications, and unnecessary medications.<sup>9</sup>

As far as hemodialysis units' types of errors are concerned, slightly over 11% of medication errors were related to intravenous heparin (both omitted and dose). Other faults included such as vitamin D, erythropoietin, and antibiotics.<sup>10</sup>

Dialysis patients are more likely to experience falls because most of them are older than 65. Risk factors for falls include age, diabetes, motor strength, pharmaceutical use, prior fall incidents, and visual impairment.<sup>11</sup> The lack of education about fall prevention in nurses and nephrologists indicates the necessity to learn about the occurrence of falls, as well as about risk factors in this group of patients.<sup>12</sup>

A report was made for each fall, and episodes of orthostatic hypotension (drop in systolic > 20 mmHg) following dialysis were monitored. Fall risk can be decreased by monitoring blood pressure, educating staff, and assisting high-risk patients.<sup>13</sup>

## METHODS

This quantitative quasi-experimental study was conducted at hemodialysis centers at Karbala City namely Imam Al-Hussein Medical City (Dr. Adel Al-Sabbah Hemodialysis Center and Habib Ibn Mazaher Al-Asadi center) and Imam Al-Hassan Al-Mujtaba Teaching Hospital Iraq from 1<sup>st</sup> January 2025 to 30<sup>th</sup> June 2025 vide letter No. 57 Dated 17<sup>th</sup> December 2024. A purposive non-probability sample of 100 nurses with at least one year of experience in hemodialysis units at Imam Al-Hussein and Imam Al-Hassan Al-Mujtaba hospitals in Karbala was recruited. Participants were allocated equally and randomly into control and interventional groups. The study used a questionnaire adapted from Wadi14 and an observational checklist, adopted from the CDC.<sup>15</sup> was applied and observed three times during pre-test, post-test 1, and post-test 2 phases. The questionnaire used yes/no questions with a 2/1 scale to rate and score, with knowledge scales of unsatisfied (>1.5), fair (=1.5), and good (<1.5). Performance was also noted in three audits with a score of always (3), sometimes (2), never (1), and poor (1.0-1.6), fair (1.7-2.39), and good (2.4-3.0).

An expert panel of nine faculty members with at least 15 years of experience assessed the validity of the instruments and program, incorporating their feedback. Factor analysis results showed a KMO value of 0.780 and a significant Bartlett's Test, indicating acceptable validity. At Dr. Adel Al-Sabbah Hemodialysis Center, a pilot test was done among ten hemodialysis nurses. Two-week test-retest reliability of the questionnaire indicated a high correlation coefficient of 0.81, a coefficient of 0.827 was obtained by inter-rater reliability of the checklist, both are acceptable.

The needs assessment revealed unsatisfactory knowledge and practices. Both groups underwent a pretest. The control group was not subject to any intervention, and the post-tests were two weeks apart. The interventional group, which is subdivided into small groups of 4-6 nurses, had to attend 30-45 minutes educational sessions in the morning and evening shifts and do post-tests right after the sessions and in 2 weeks. The SPSS-26 was used to analyze the data. Baseline homogeneous was evaluated using T-tests as the two experimental and control groups. The level of significance was divided into highly significant ( $P < 0.01$ ), significant ( $0.01 > P < 0.05$ ), and non-significant ( $P > 0.05$ ).

## RESULTS

The subjects of both groups did not differ according to marriage status, age, or sex ( $p = 0.05$ ), except in educational qualification ( $p = 0.036$ ). A higher percentage of the participants were diploma holders in the interventional group (44%), in comparison to high proportion of bachelors (68%) and analytic completion of bachelor-level courses (2%) in the control group (Table 1).

The knowledge of hand hygiene of the interventional group improved greatly following the educational program. As an illustration, there was an increase in the level of understanding that improved adherence by 1.50 to 1.82 and knowledge about alcohol-based hand rub use by 1.58 to 1.98. The exposure to germs and handwashing technique also improved, whereas the control group experienced minor improvements, which also indicates the effectiveness of the intervention (Table 2).

The interventional group improved their knowledge about PPE steadily through all tests, with higher mean scores and lower variability. As an example, the knowledge about hand hygiene was increased, such as the comprehension of using gloves, disposing, reusing, and removing PPE improved to 1.88. However, control group did not change significantly, which is an indication of the effectiveness of the intervention (Table 3).

The interventional group was steadily increasing their learning about medication errors in the hemodialysis units, and such areas as prevention of drug errors, and prompt administration of enalapril increased. Despite the lack of statistical significance ( $p > 0.05$ ), the effect was positive, whereas the control group was not subject to substantial change (Table 4).

No statistically significant difference was found between interventional and control groups ( $p > 0.05$ ), but the knowledge regarding the prevention of injuries, such as the use of side rails (1.78) and the use of fall interventions (1.90) improved consistently in the former, whereas the latter experienced slight changes, which is a hint that the educational intervention made a positive impact (Table 5).

**Table No.1: Demographical Characteristics (n=50)**

Characteristics		Control group		Interventional group		P value
		No.	%	No.	%	
Age (years)	22-26	26	52.0	14	28.0	0.162
	27-31	8	16.0	21	42.0	
	32-36	7	14.0	7	14.0	
	37-41	5	10.0	6	12.0	
	42-46	4	8.0	3	6.0	
Gender	Female	17	34.0	17	34.0	0.134
	Male	33	66.0	33	66.0	
Marital status	Single	20	40.0	31	62.0	0.160
	Married	30	60.0	19	38.0	
Educational Qualifications	Secondary Nursing School	4	8.0	2	4.0	0.036
	Diploma	11	22.0	22	44.0	
	Bachelor	34	68.0	26	52.0	
	Postgraduate	1	2.0		100.0	
Residence	Rural	12	24.0	13	26.0	0.69
	Urban	38	76.0	37	74.0	

**Table No. 2: Interventional and control group nurses' knowledge toward hand hygiene at hemodialysis units**

Control Group				Interventional Group			
Pre-test	Post-test 1	Post-test 2	P value	Pre-test	Post-test 1	Post-test 2	P value
1.10±0.30	1.10±0.30	1.10±0.30	0.263	1.50±0.50	1.80±0.40	1.82±0.38	0.082
1.38±0.49	1.66±0.49	1.52±0.50		1.58±0.49	1.86±0.35	1.98±0.14	
1.44±0.50	1.30±0.46	1.32±.047		1.52±0.50	1.74±0.44	1.90±0.30	
1.38±0.49	1.48±0.50	1.46±.050		1.46±0.50	1.66±0.47	1.76±0.43	
1.42±0.49	1.52±0.50	1.38±.049		1.52±0.50	1.76±0.43	1.74±0.44	
1.44±0.50	1.60±0.49	1.34±.047		1.52±0.50	1.92±0.27	1.88±0.32	

**Table No.3: Interventional and control group nurses' knowledge toward personal protective equipment at hemodialysis units**

Control Group				Interventional Group			
Pre-test	Post-test 1	Post-test 2	P value	Pre-test	Post-test 1	Post-test 2	P value
1.04±0.19	1.02±0.14	1.04±0.19	0.263	1.42±0.49	1.88±0.32	1.68±0.47	0.082
1.50±0.50	1.80±0.40	1.48±0.50		1.46±0.50	1.82±0.38	1.92±0.27	
1.12±0.32	1.10±0.630	1.02±0.14		1.52±0.50	1.70±0.46	1.80±0.40	
1.40±0.49	1.30±0.46	1.32±0.47		1.52±0.50	1.68±0.47	1.82±0.38	

**Table 4: Interventional and control group nurses' knowledge toward medication errorsat hemodialysis units**

Control Group				Interventional Group			
Pre-test	Post-test 1	Post-test 2	P value	Pre-test	Post-test 1	Post-test 2	P value
1.54±0.50	1.54±0.50	1.24±0.43	0.069	1.54±0.50	1.90±0.30	1.86±0.35	0.301
1.36±0.48	1.66±0.47	1.26±0.44		1.46±0.50	1.80±0.40	1.68±0.47	
1.30±0.46	1.28±0.45	1.20±0.40		1.54±0.50	1.76±0.43	1.70±0.46	
1.32±0.47	1.28±0.45	1.16±0.37		1.46±0.50	1.62±0.49	1.86±0.35	
1.30±0.46	1.28±0.45	1.20±0.40		1.52±0.50	1.68±0.47	1.86±0.35	

**Table No. 5: Nurses' knowledge toward patient injuries at hemodialysis units**

Control Group				Interventional Group			
Pre-test	Post-test 1	Post-test 2	P value	Pre-test	Post-test 1	Post-test 2	P value
1.52±0.50	1.78±0.41	1.46±0.50	0.213	1.56±0.50	1.86±0.35	1.78±0.41	0.218
1.08±0.27	1.46±2.83	1.06±0.24		1.54±0.50	1.50±0.50	1.90±0.30	
1.48±0.50	1.64±0.48	1.36±0.48		1.48±0.50	1.86±0.35	1.84±0.37	
1.44±0.50	1.44±0.50	1.24±0.43		1.50±0.50	1.76±0.43	1.84±0.37	

Practice scores differed in the interventional group as compared to the control group in all tests. The control group initially had a higher score (1.5024±0.16) but following the intervention, interventional group scored higher at the post-test 1 (2.37±0.53) and retained the higher score at posttest 2 (1.75±0.13), which proves the intervention lasts impact on the nursing practice performance.

## DISCUSSION

The demographic characteristics of both groups aligned with findings from previous studies. In the control group, most participants (52%) were aged 22-26 years, while in the interventional group, the largest proportion (42%) were aged 27-31 years. These results are consistent with Mahmood and Khudur.<sup>16</sup> Age is an important factor in evaluating the educational program, as younger nurses tend to be more receptive to newly introduced knowledge and methods.

A total of 66% males and 34% females participated in both of them, but research articles such as Osman et al<sup>17</sup> indicate that females constitute a larger fraction of the nursing population in some Arab countries.

The level of education was also significantly different ( $p = .036$ ): 68% of bachelor's degree graduates belonged to the control group and 52% of interventional graduates, which is in line with regional and international studies.<sup>17,18</sup>

The interventional group had substantial knowledge of hand hygiene relative to the control group after the educational program. These results can be supported by the recent literature, including Abdelrahman et al<sup>19</sup> who have shown the effectiveness of structured training interventions in enhancing hand hygiene compliance.

The interventional group showed significant improvement in knowledge of personal protective equipment across all testing phases compared to the control group. These results are consistent with previous studies which reported that targeted training interventions and workshops improve nurses' compliance with PPE use, and hand hygiene<sup>20</sup>, and overall infection prevention practices.<sup>21</sup>

Nurses in the interventional group showed steady improvement in their knowledge of medication errors in hemodialysis units across all pretest, posttest 1+2, demonstrating the positive effect of the educational program. These results are in line with previous research, such as Abu Hussein et al.<sup>22</sup>

The educational intervention enhanced the knowledge of nurses in prevention of patient injury in hemodialysis units, and there were consistent increases in the fall prevention and side rail in the interventional group. These outcomes are consistent with Ojo and Thiamwong<sup>23</sup> who discovered that patient outcomes and nurse behavior are improved with specialized fall prevention programs.

The educational intervention greatly benefited the interventional group with respect to the practices of hemodialysis nurses and evidence-based argument that specific training leads to better compliance with safety measures.<sup>24</sup> The sustained improvement at Post-test 2 further indicates the lasting effect of the educational program, corroborating similar findings by Heleno et al.<sup>25</sup>

## CONCLUSION

The knowledge and practices of hand hygiene, PPE, medication safety, and preventing patient injury demonstrated progressive changes in the interventional group, which prove that a systematic educational program is an effective intervention in improving nurse competence in hemodialysis units.

### Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Shady Shafeek Anees Dowarah, Sahar Adham Ali
Drafting or Revising Critically:	Shady Shafeek Anees Dowarah, Sahar Adham Ali
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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# Cytotoxic and Immunologic Effects of Measles Oncolytic Virus on Colon Cancer Cells

Effects of Measles  
Oncolytic Virus on  
Colon Cancer  
Cells

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Kaiser N. Madlum<sup>3</sup>

## ABSTRACT

**Objective:** To evaluate the effects of the measles virus (MV) in combination with standard therapeutic agents cetuximab and chemotherapy on colon tumor cells.

**Study Design:** Descriptive study

**Place and Duration of Study:** This study was conducted at the College of Medicine, University of Babylon, Iraq from 1<sup>st</sup> December 2024 to 30<sup>th</sup> May 2025.

**Methods:** Cells were exposed to various doses of attenuated MV, cetuximab, 5-fluorouracil, and cisplatin. Viability, apoptosis (caspase-3 levels), and immune markers (IFN- $\gamma$ , TGF- $\beta$ , IL-10, TNF- $\alpha$ ) were assessed using biochemical assays to identify optimal therapeutic ratios.

**Results:** Cetuximab alone increased caspase-3 levels, while combination therapies induced greater cell death through alternative mechanisms. MV markedly elevated IFN- $\gamma$  ( $55.50 \pm 12.10$  vs.  $24.15 \pm 3.73$ ,  $P < 0.001$ ). Combination treatments suppressed immunosuppressive cytokines; TGF- $\beta$  was significantly reduced in the measles virus cisplatin group ( $0.161 \pm 0.001$  vs.  $0.182 \pm 0.002$ ,  $P = 0.005$ ), and IL-10 and TNF- $\alpha$  levels were lowered dose-dependently, with triple combinations achieving near-complete suppression ( $5.00 \pm 0.80$  vs.  $203.63 \pm 22.19$ ,  $P < 0.001$ ).

**Conclusion:** Measles virus based combination therapy produces potent immunomodulatory effects, enhancing anti-tumor action beyond apoptosis by reducing immunosuppressive cytokines and controlling inflammation. Optimizing dose ratios and ensuring clinical safety remain crucial for future applications.

**Key Words:** Oncolytic virus, Measles virus, Cetuximab, Combination therapy, Colon cancer, Immunomodulation

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## INTRODUCTION

Currently, colorectal cancer is one of the most common causes of cancer death globally, with around 1.9 million new cases of colorectal cancer diagnosed each year.<sup>1</sup> Despite significant advances in surgical techniques, as well as chemotherapy treatments and targeted therapies, the five-year survival rate for metastatic colorectal cancer has not improved and continues to be under 15%. This highlights the need for new, innovative therapies.<sup>2</sup>

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Oncolytic viruses are classified as cancer-targeted viruses that can occur naturally or be engineered.<sup>3</sup>

Oncolytic viruses selectively replicate in and kill cancer cells while leaving normal tissues unharmed. There are several benefits of using oncolytic virus therapies over conventional treatment, including the possibility of tumor selectivity, the systematic recruitment of the immune system, and the chance to circumvent drug resistance mechanisms.<sup>4</sup> Measles virus (MV) is one of the several natural or engineered oncolytic viruses constructed, tested, and studied for oncolytic virotherapy in a variety of cancers and is the most promising oncolytic virus for use due to its excellent safety profile, characterized biology, and potent oncolytic activity.<sup>5</sup>

The vaccine strain of the measles virus (MV) preferentially targets cancer cells through several mechanisms. Cancer cells frequently over express CD46, which is the cellular receptor for measles virus and also serves as a regulatory protein in the complement system.<sup>6</sup> Moreover, many cancer cell lines exhibit aberrant interferon responses and defective DNA repair pathways, which promote viral replication and hinder the clearance of viral infections.<sup>3</sup> When considering direct oncolytic effects, measles virus (MV) infection can induce strong anti-tumor immune

responses by activating both innate and adaptive immune responses.<sup>7</sup>

The basis of combination therapy in oncological settings is that multiple therapeutic modalities can act synergistically to produce superior outcomes than single-modality therapies.<sup>8</sup> The use of oncolytic viruses in combination with chemotherapy and targeted agents offers several benefits, including complementary mechanisms of action, a decreased likelihood of resistance, and the potential to reduce the dose of individual agents while maintaining or increasing efficacy.<sup>9</sup>

Cetuximab is a chimeric monoclonal antibody that targets the epidermal growth factor receptor (EGFR) and is efficacious in managing colorectal cancer, particularly in tumors harboring wild-type KRAS.<sup>2</sup> There is overexpression of EGFR in approximately 60-80% of colorectal cancers, and EGFR encourages tumor proliferation, survival, and metastasis.<sup>10</sup> Combination chemotherapy with cetuximab has shown improved outcomes in metastatic colorectal cancer, suggesting that additional combination strategies can be explored.

Conventional chemotherapeutic agents, such as 5-fluorouracil (5FU) and cisplatin, remain the primary agents in colorectal cancer management. 5-FU is a fluoropyrimidine analogue that interferes with DNA synthesis and repair, while cisplatin forms DNA cross-links to induce apoptosis.<sup>11</sup> The immunomodulatory effects, particularly the induction of immunogenic cell death, make cytotoxic agents attractive collaborators with oncolytic virus therapy.<sup>12</sup>

Despite the potential advantages of combination approaches, the ideal combination and use of an oncolytic viral therapy with conventional therapies have not been elucidated. The interplay between viral replication, immunogenicity, immune activation, and drug-induced cytotoxicity should be further explored to identify synergistic combinations and to reduce (or avoid) those that appear antagonistic.<sup>13</sup>

This study evaluated measles virus with cetuximab and chemotherapy in SW480 cells to assess cytotoxicity, apoptosis, immune modulation, and optimal dosing.

## METHODS

This study was conducted at College of Medicine, University of Babylon, Iraq from 1<sup>st</sup> December 2024 to 30<sup>th</sup> May 2025 vide letter No. 314 dated 25<sup>th</sup> November 2024. Human SW480 colon cancer cells were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and maintained in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 100 U/ml penicillin, and 100 µg/ml streptomycin. Cells were cultured at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>. Cell viability was assessed using the trypan blue exclusion method, and only cultures with viability greater than 95% were used for experiments.

**Measles Virus:** Live attenuated measles virus vaccine strain (Edmonston-Zagreb) was obtained from the Iraqi Ministry of Health vaccine repository. Working concentrations of 10 µg/ml were used based on preliminary dose-response studies.

**Cetuximab:** Cetuximab (Erbitux®) was obtained as a clinical-grade formulation and used at a concentration of 100 µg/ml based on published literature and preliminary optimization studies.

**Chemotherapeutic Agents:** 5-fluorouracil (Sigma-Aldrich) and cisplatin (Sigma-Aldrich) were prepared as stock solutions in dimethyl sulfoxide (DMSO) and phosphate-buffered saline (PBS), respectively. Working concentrations ranged from 15-500 µg/mL, as determined by dose-response characterization.

**Experimental Design:** SW480 cells were seeded in 96-well plates at a density of 5×10<sup>3</sup> cells per well and allowed to adhere for 24 hours. Cells were then treated with various combinations of therapeutic agents according to the following experimental groups:

**1. Single Agent Studies:** Control (untreated), measles virus alone, cetuximab alone, 5FU alone, cisplatin alone

**2. Dual Combination Studies:** MV + cisplatin, MV + 5FU, cetuximab + cisplatin, cetuximab + 5FU

**3. Triple Combination Studies:** MV + cetuximab + cisplatin, MV + cetuximab + 5FU

Each treatment condition was evaluated at multiple time points (24, 48, and 72 hours) with at least six replicates per condition. Dose-response relationships were established for chemotherapeutic agents using concentrations of 15, 31, 62, 125, 250 and 500 µg/ml.

Cell viability was assessed using the crystal violet (CV) assay. Following treatment, cells were fixed with 4% paraformaldehyde for 15 minutes, washed with PBS, and stained with 0.1% crystal violet solution for 30 minutes. After washing and drying, bound dye was solubilized with 10% acetic acid, and absorbance was measured at 590 nm using a microplate reader (BioTek Instruments, Winooski, VT, USA).

Caspase-3 levels were determined using a commercial ELISA kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instruction. Briefly, cells were lysed using the provided lysis buffer, and protein concentrations were normalized using the Bradford assay. Cell lysates were then incubated in ELISA plates coated with anti-caspase-3 antibodies, followed by detection using horseradish peroxidase-conjugated secondary antibodies and the development of a colorimetric substrate.

**Cytokine Analysis:** Culture supernatants were collected at specified time points and stored at -80°C until analysis. Cytokine levels (IFN-γ, TGF-β, IL-10, and TNF-α) were measured using commercially available ELISA kits (R&D Systems) according to the manufacturer's protocols. All samples were analyzed in

duplicate, and cytokine concentrations were calculated based on standard curves generated using recombinant proteins.

**IFN- $\gamma$  Measurement:** IFN- $\gamma$  levels were determined using a human IFN- $\gamma$  quantikine ELISA kit with a detection limit of 8 pg/ml and an inter-assay coefficient of variation <10%.

**TGF- $\beta$  Analysis:** TGF- $\beta$ 1 levels were measured using a human TGF- $\beta$ 1 quantikine ELISA kit following acid activation to convert latent TGF- $\beta$  to its active form. The detection limit was seven pg/mL.

**IL-10 Quantification:** IL-10 concentrations were determined using a human IL-10 quantikine ELISA kit with a sensitivity of 3.9 pg/ml and intra-assay precision <5%.

**TNF- $\alpha$  Assessment:** TNF- $\alpha$  levels were measured using a human TNF- $\alpha$  quantikine ELISA kit with a minimum detectable dose of 0.18 pg/ml.

The data was entered and analyzed through SPSS-25. Statistical significance was assessed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. Differences were considered statistically significant at  $P < 0.05$ .

## RESULTS

The cell viability was significantly reduced after the treatment with Cisplatin and 5-FU at all concentrations (500-31.25  $\mu\text{g/ml}$ ) compared to the control group. Cisplatin exhibited greater cytotoxicity than 5-FU, which demonstrated a dose-dependent effect (Fig. 1).

Cancer cells treated with cetuximab (100  $\mu\text{g/ml}$ ) and varying doses of 5-FU or cisplatin (500–31.25  $\mu\text{g/ml}$ ) showed reduced viability versus controls. Only 5-FU + cetuximab at 62.5  $\mu\text{g/ml}$  differed significantly; cisplatin + cetuximab showed no significant change across concentrations (Fig. 2).

Treatment with anticancer drugs combined with Cetuximab and Measles virus significantly reduced the cell population. Cisplatin treatment was more cytotoxic than 5-Fu at all concentrations tested (Fig. 3).

Combination treatments markedly reduced caspase-3 levels compared to cetuximab alone. In 5-FU–cetuximab and cisplatin-cetuximab groups, caspase-3 decreased dose-dependently ( $P < 0.001$ ). The triple combination with measles virus caused the greatest reduction across all concentrations, indicating alternative, non-apoptotic cell death mechanisms enhancing cytotoxic efficacy (Fig. 4).

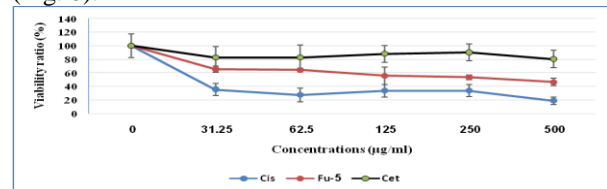
Measles virus markedly increased IFN- $\gamma$  production (55.503 $\pm$ 12.109 vs. 24.147 $\pm$ 3.730;  $P < 0.001$ ), confirming strong immune activation. Adding 5-FU or cisplatin caused dose-dependent attenuation of IFN- $\gamma$ , while triple combinations with cetuximab and chemotherapy yielded intermediate but still elevated IFN- $\gamma$  levels, indicating balanced immunomodulatory effects (Fig. 5).

The cisplatin–measles virus combination significantly suppressed TGF- $\beta$  levels ( $P = 0.002$ , power = 0.939),

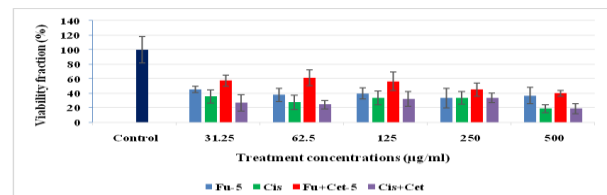
while other treatments showed no notable effects. Several cisplatin concentrations (31–500  $\mu\text{g/ml}$ ) markedly reduced TGF- $\beta$  compared with controls, suggesting a unique synergistic immune-modulating interaction between cisplatin and the measles virus (Fig. 6).

Combination treatments significantly reduced IL-10 levels compared with controls across all protocols. Cetuximab and 5-FU combinations showed gradual dose-dependent decreases, while cisplatin–measles virus combinations achieved the strongest IL-10 suppression. Triple therapy with cisplatin, cetuximab, and MV also markedly lowered IL-10, confirming enhanced immunomodulatory synergy across treatment regimens (Fig. 7).

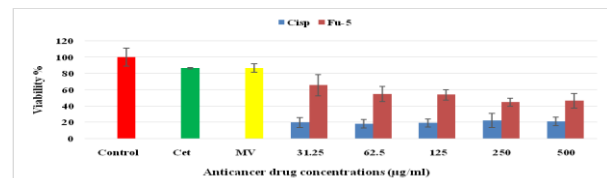
Combination treatments caused strong, dose-dependent reductions in TNF- $\alpha$  levels. In the 5-FU–cetuximab study, TNF- $\alpha$  significantly decreased from 200.4 $\pm$ 10.3 in controls to 60.6  $\pm$  5.3 at 500  $\mu\text{g/ml}$  ( $P < 0.001$ ). Cisplatin-based combinations produced even greater suppression, while the triple therapy (cisplatin-cetuximab -MV) achieved near-complete inhibition, reducing TNF- $\alpha$  to 5.0 $\pm$ 0.8 at 500  $\mu\text{g/ml}$  ( $P < 0.001$ ). These results demonstrate a potent, concentration-dependent anti-inflammatory effect across regimens, with the triple combination exhibiting the most profound cytokine suppression, suggesting a strong therapeutic synergy in modulating tumor-promoting inflammation and enhancing anticancer efficacy (Fig. 8).



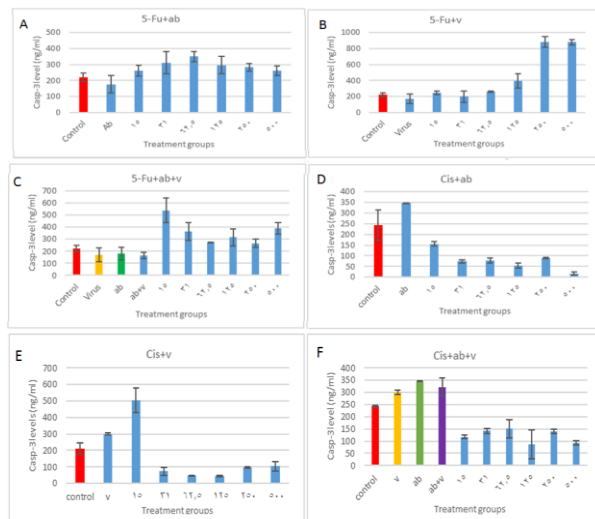
**Figure No. 1: Cytotoxicity of cisplatin, 5-fluorouracil, and cetuximab on SW480 colon cancer cells**



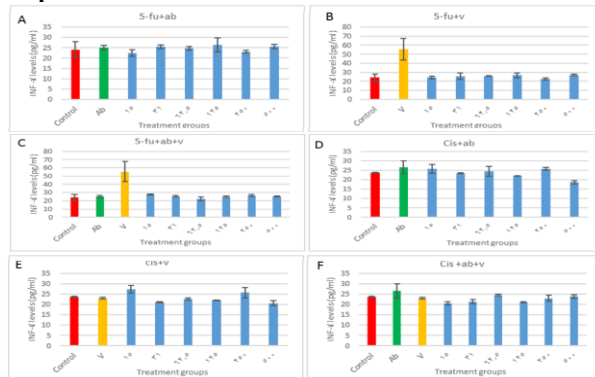
**Figure No. 2: Effect of cetuximab in combination with cisplatin and 5-fluorouracil on SW480 colon cancer cells**



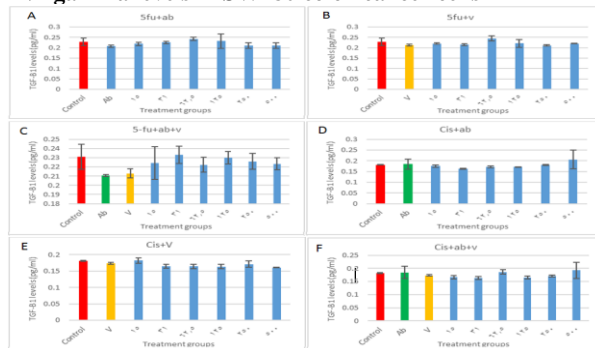
**Figure No. 3: Effect of oncolytic measles virus treatment combined with anticancer drugs Cisplatin (Cisp) and 5-Fluorouracil (5-Fu) in the presence of Cetuximab monoclonal antibody (Cet) on the viability of SW480 colon cancer**



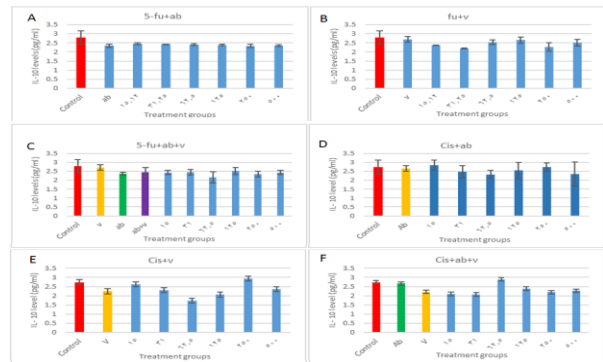
**Figure No. 4:** Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C), Cisplatin-Cetuximab(D), Cisplatin-MV (E), and Cisplatin-Cetuximab-MV (F) on caspase-3 levels in SW480 colon cancer cells



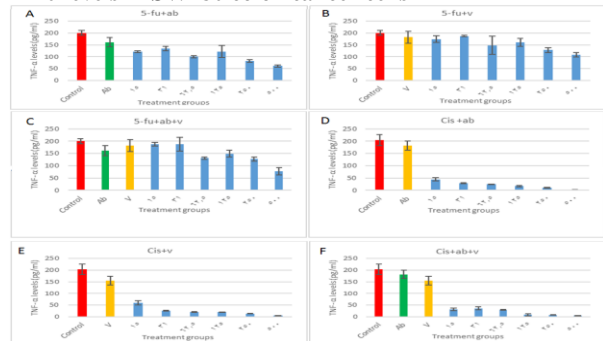
**Figure No. 5:** Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C) Cisplatin-Cetuximab(D), Cisplatin-MV (E) and Cisplatin-Cetuximab-MV (F) on the INF gamma levels in SW480 colon cancer cells



**Figure No. 6:** Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C) Cisplatin-Cetuximab (D), Cisplatin-MV (E) and Cisplatin-Cetuximab-MV (F) on the TGF-b levels in SW480 colon cancer cells



**Figure No. 7:** Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C) Cisplatin-Cetuximab(D), Cisplatin-MV (E) and Cisplatin-Cetuximab-MV (F) on the IL10 levels in SW480 colon cancer cells



**Fig. 8:** Effect of 5-Fu -Cetuximab (A), 5-Fu -MV (B), 5-Fu -Cetuximab-MV (C) Cisplatin-Cetuximab(D), Cisplatin-MV (E) and Cisplatin-Cetuximab-MV (F) on TNF levels in SW480 colon cancer cells

## DISCUSSION

This study compared the cytotoxic and immunomodulatory effects of cisplatin, 5-fluorouracil (5-FU), cetuximab, and measles virus (MV) combinations on colon cancer cells. Cisplatin exhibited superior cytotoxicity to 5-FU, aligning with previous studies showing that platinum agents cause more severe and irreparable DNA damage than the metabolic interference caused by 5-FU.<sup>14</sup> The dose-dependent cytotoxicity observed for both agents matched earlier pharmacodynamic data, confirming their reproducibility across colorectal cancer models. While both drugs were effective individually, cisplatin demonstrated higher potency across all concentrations tested (500-31.25 μg/ml).

The mechanism of 5-FU involves inhibition of thymidylate synthase and disruption of RNA/DNA synthesis, leading to apoptosis.<sup>15</sup> However, its cytotoxicity is also time-dependent.<sup>16</sup> Interestingly, cisplatin-5-FU combinations sometimes show reduced efficacy compared to monotherapy due to complex interactions affecting the cell cycle.<sup>17</sup> The addition of cetuximab (100 μg/ml) modestly enhanced 5-FU effects but did not significantly improve cisplatin activity, possibly because cetuximab efficacy depends on KRAS

wild-type status.<sup>18</sup> The limited response in this study may therefore reflect intrinsic resistance due to KRAS mutations or other downstream alterations.<sup>19</sup>

The most promising outcome emerged from the triple combination of MV, cetuximab, and chemotherapy especially MV + cetuximab + cisplatin which resulted in the most pronounced tumor cell reduction. The measles virus preferentially targets tumor cells expressing high CD46 receptor levels, leading to oncolysis and immune activation.<sup>20</sup> MV can also induce immunogenic cell death (ICD), stimulating long-term anti-tumor immunity.<sup>21</sup>

Interestingly, although cetuximab alone increased caspase-3 (apoptosis marker), combination therapies reduced caspase-3 levels despite higher overall cytotoxicity. This suggests that alternative regulated cell death pathways such as necroptosis, pyroptosis, or ferroptosis may predominate, offering advantages in overcoming apoptosis resistance and promoting immunogenicity.<sup>22</sup> The reduced caspase-3 may thus indicate a shift toward ICD, wherein tumor cells release danger signals (DAMPs) that activate adaptive immunity.

MV treatment significantly elevated IFN- $\gamma$  levels, activating both innate and adaptive immune responses.<sup>23</sup> IFN- $\gamma$  promotes MHC class I expression, cytotoxic T-cell activation, and macrophage polarization. Combination therapies also reduced TGF- $\beta$  levels especially with cisplatin-MV suggesting a shift from an immunosuppressive to an immunostimulatory tumor microenvironment.<sup>24</sup> This reprogramming could transform “cold” immune-resistant tumors into “hot” responsive ones.<sup>25</sup>

Furthermore, IL-10 suppression across treatment groups reduced anti-inflammatory signaling, enhancing anti-tumor activity.<sup>26</sup> The most striking immunologic outcome was near-complete TNF- $\alpha$  suppression in high-dose triple therapy. Although TNF- $\alpha$  contributes to anti-tumor immunity, chronic elevation supports tumor progression and angiogenesis.<sup>19</sup> Its down-regulation may therefore disrupt inflammatory circuits that sustain colorectal tumor growth.<sup>27</sup>

## CONCLUSION

Combining oncolytic virotherapy with chemotherapy and cetuximab provides superior anti-tumor activity through complex immune modulation beyond classical chemotherapy effects. The treatment shifted cancer cell death from apoptosis to alternative, more effective mechanisms while enhancing immune activation via IFN- $\gamma$  production. It also suppressed key immunosuppressive mediators (TGF- $\beta$ , IL-10) and inflammatory cytokines (TNF- $\alpha$ ), reprogramming the tumor microenvironment. These dose-dependent effects highlight the need for rational, immune-targeted combination design.

### Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Reyam Abdul Khuder Mohammed, Kaiser N. Madlum
Drafting or Revising Critically:	Reyam Abdul Khuder Mohammed, Zaytoon Abdulrida Al-Khafaji
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

**Source of Funding:** None

**Ethical Approval:** No. 314 Dated 25.11.2024

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# Early Predictors of Preterm Labor: Single Center Retrospective Study

Rana Hatem Matrood Alkhazraji

## ABSTRACT

**Objective:** To identify possible risk factors of preterm birth.

**Study Design:** A retrospective cohort study

**Place and Duration of Study:** This study was conducted at the Diwaniyah Maternity Hospital, Diwaniyah province, Iraq from 1<sup>st</sup> January 2025 to 30<sup>th</sup> June 2025.

**Methods:** During this study, records of women with single gestation for the last five years (January 2020 to January 2025) were retrieved and analyzed. After reviewing all reports of pregnant women admitted to Maternity Teaching Hospital, twin pregnancies and cases with abortion were excluded from study. The first case for each year of the five years of the study was selected based on a random number generated by the Microsoft Excel software and then Systematic random sample was applied by selecting every other 10 cases. Only women with singleton pregnancy who gave birth after 28 weeks gestation and their age was in the range of 18 to 45 years were enrolled. At the end of the study, 428 cases of women with singleton pregnancy were enrolled.

**Results:** Logistic regression analysis confirmed the findings of univariate analysis in that age, body mass index, history of abortion and history of preterm are the significant predictors of preterm labor ( $p<0.05$ ). An increase of one year of age is associated with 1.14 increased risk of preterm labor ( $p<0.001$ ). An increase of one kg/m<sup>2</sup> of body mass index is associated with 1.57 increased risk of preterm labor ( $p<0.001$ ). History of abortion is associated with 10.53 increased risk of preterm ( $p=0.003$ ) and history of preterm labor is associated with 28.82 increased risk of preterm ( $p=0.003$ ).

**Conclusion:** Advanced maternal age >40 years, high body mass index >25 kg/m<sup>2</sup>, previous abortion and previous preterm labor are associated with increased likelihood of preterm labor.

**Key Words:** Preterm labor, Maternal age, Body mass index

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## INTRODUCTION

According to the World Health Organization, preterm birth is considered when delivery of live baby happens before complete 37 weeks of gestation and it can be further categorized as extremely preterm (before 28 weeks), very moderately (between 28 and 32 weeks), moderate preterm (between 32 and 34 weeks), and late preterm (between 34 and 37 weeks).<sup>1</sup> The condition can be spontaneous<sup>2</sup> or can be associated with early rupture of membrane.<sup>3</sup> The estimated global incidence rate of preterm labor was 9.9 % at 2020.<sup>4</sup> In Iraq, the annual incidence rate of preterm labor is approximately 6.5%.<sup>5</sup> This condition is associated with increased rates of neonatal morbidity and mortality.<sup>6</sup>

In general the complications, in association with prematurity, show inverse correlation to gestational age.<sup>7</sup> Therefore, preventing these long term complications via early recognition of women at risk of preterm labor with successful medical intervention to delay birth as near as possible to term onset is the best way to reduce the burden of such long term complications. Actually, there is strong evidence that even late preterm neonates are at higher risk of long - and short -term complications in comparison to their term counterparts including metabolic syndrome, neurodevelopmental delay, infection, jaundice, hypoglycemia, hypothermia and respiratory distress syndrome.<sup>1</sup>

Premature cervical ripening, decidual activation and myometrial contractions have been linked to a variety of risk factors including uterine overdistension, cervical disease, uteroplacental disorders, infection and all has been linked to spontaneous preterm birth.<sup>8-13</sup> The difficulty in creating globally applicable guidelines to prevent, diagnose, and treat the clinical issue is explained by the variability of etiology in preterm birth. However, screening high-risk women who are asymptomatic is highly advised, and the most thoroughly studied methods include fetal fibronectin and cervical length measurements.<sup>1</sup> The current study set out to determine potential risk factors for preterm birth.

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**METHODS**

This retrospective cohort study which is single center and hospital based was Diwaniyah Maternity Hospital, Diwaniyah province, Iraq from 1<sup>st</sup> January 2020 to 30<sup>th</sup> June 2025 during which records of women with single gestation for the last five years (January 2020 to January 2025) were retrieved and analyzed vide letter No. 92 dated 25-12-2024. After reviewing all reports of pregnant women admitted to Maternity Teaching Hospital, twin pregnancies and cases with abortion were excluded from study. The first case for each year of the five years of the study was selected based on a random number generated by the Microsoft Excel software and then Systematic random sample was applied by selecting every other 10 cases. Only women with singleton pregnancy who gave birth after 28 weeks gestation and their age was in the range of 18 to 45 years were enrolled. At the end of the study, 428 cases of women with singleton pregnancy were enrolled.

The following information were retrieved from patient’s records and were included in the study: about age, body mass index (BMI), level of education, residence, anemia, history of comorbidity, smoking, gravidity, history of abortion, history of preterm labor, history of contraception, history of antenatal care, presence of urinary tract infection, and level of vitamin D during pregnancy. The primary outcome was preterm birth which was considered when birth happens before completing 37 weeks of pregnancy.

The data was entered and analysed through SPSS-26. Student test was used to compare mean age and mean BMI between preterm and term groups. Chi-square and Fischer exact tests were used to compare proportions between preterm and term groups. Logistic regression analysis was used to adjust for confounders included in univariate analysis. Significance level was set at p value of  $\leq 0.05$ .

**RESULTS**

Preterm delivery was reported in 44 (10.3%) is shown in figure 1. The range of age of participating women was between 18 and 45 years with the mean  $27.15 \pm 7.02$  years (Table 1).

The univariate analysis after dividing the sample of pregnant women into 2 groups, term group (number of cases = 44) and preterm group (number of cases = 384). The following variables showed significant differences between preterm group and term group: age, body mass index (BMI), history of PTL and history of abortion ( $p < 0.001$ ). With respect to age, mean age of preterm group was higher significantly in comparison to mean age of term group, 26.49 years versus 32.86 years. We performed further analysis of age by categorizing women into 3 groups, <20 years, 20-40 years and >40 years (Table 2). Women less than 20 years of age experienced higher rate of preterm labor when compared to women between 20 and 40 years of age, 11.4% versus 4.6%, respectively. Regarding BMI, it was higher significantly in preterm group in comparison to term group,  $27.64 \text{ kg/m}^2$  versus  $23.20 \text{ kg/m}^2$  ( $p < 0.001$ ) and women with BMI  $> 25 \text{ kg/m}^2$  (overweight or obese) experienced significantly higher rate of PTL in comparison to women with BMI  $< 25 \text{ kg/m}^2$  (normal weight), 19% versus 5.9%, respectively ( $p < 0.001$ ). History of abortion was reported in 20.5% of preterm group compared to 0.5% of term group ( $p < 0.001$ ). In addition, history of PTL was reported in 27.3% of preterm group compared to 2.1 % of term group ( $p < 0.001$ ). Other variables showed no significant association with preterm labor ( $p > 0.05$ ) [Table 3].

Logistic regression analysis confirmed the findings of univariate analysis in that age, BMI, history of preterm and history of miscarriage are the significant predictors of PTL ( $p < 0.05$ ). A rise in age of one year is correlated to 1.14 higher risk of PTL ( $p < 0.001$ ). An increase of one  $\text{kg/m}^2$  of BMI is correlated to 1.57 higher risk of PTL ( $p < 0.001$ ). History of abortion is correlated to 10.53 higher likelihood of preterm ( $p = 0.003$ ) and history of PTL is correlated to 28.82 higher risk of preterm ( $p = 0.003$ ) [Table 4].

**Table No. 1: Results of univariate analysis**

Characteristic		Preterm Group (n=44)	Term Group (n=384)	P value
Age (years)		32.86±10.45	26.49±6.21	<0.001***
Body mass index (kg/m <sup>2</sup> )		27.64±5.03	23.20±2.43	<0.001***
Residence	Urban	34 (77.3%)	287 (74.7%)	0.713 N
	Rural	10 (22.7%)	97 (25.3%)	
Education	Illiterate	3 (6.8%)	24 (6.3%)	0.336 N
	Primary	15 (34.1%)	150 (39.1%)	
	Secondary	19 (43.2%)	180 (46.9%)	
	Tertiary	7 (15.9%)	30 (7.8%)	
Anemia	Yes	21 (47.7%)	191 (49.7%)	0.800 N
	No	23 (52.3%)	193 (50.3%)	

Comorbidity	Yes	3 (6.8%)	12 (3.1%)	0.192 N
	No	41 (93.2%)	372 (96.9%)	
Smoking	Yes	1 (2.3%)	10 (2.6%)	1.000 N
	No	43 (97.7%)	374 (97.4%)	
Gravidity	Nulliparous	9 (20.5%)	108 (28.1%)	0.280 N
	Multiparous	35 (79.5%)	276 (71.9%)	
History of abortion	Yes	12 (27.3%)	8 (2.1%)	<0.001***
	No	32 (72.7%)	376 (97.9%)	
History of PTL	Yes	9 (20.5%)	2 (0.5%)	<0.001***
	No	35 (79.5%)	382 (99.5%)	
History of contraception	Yes	2 (4.5%)	52 (13.5%)	0.089 N
	No	42 (95.5%)	332 (86.5%)	
ANC	Yes	43 (97.7%)	360 (93.8%)	0.496 N
	No	1 (2.3%)	24 (6.3%)	
UTI	Yes	22 (50%)	191 (49.7%)	0.974 N
	No	22 (50%)	193 (50.3%)	
Vitamin D deficiency	Yes	33 (75%)	304 (79.2%)	0.522 N
	No	11 (25%)	80 (20.8%)	

BMI: Body mass index; PTL: Preterm labor; ANC: Antenatal care; UTI: Urinary tract infection; N: not significant; \*\*\*Significant at p< 0.001

**Table No. 2: The association between preterm labor and age of pregnant women**

Age (years)	Preterm group (n=44)	Term group (n=384)	P value
<20	8 (11.4%)	62 (88.6%)	<0.001 (Significant)
20-40	15 (4.6%)	313 (95.4%)	
>40	21 (70%)	9 (30%)	

**Table No. 3: The association between preterm labor and body mass index (BMI) of pregnant women**

Body mass index (kg/m <sup>2</sup> )	Preterm group (n=44)	Term group (n=384)	P value
Overweight and obese	27 (19.0 %)	115 (81.1 %)	<0.001 (Significant)
Normal weight	17 (5.9 %)	269 (94.1 %)	

**Table No. 4: The logistic regression analysis which was carried out to find significant predictors of preterm labor**

Variable	P value	OR	95 % (CI)
Age (years)	<0.001*	1.14	1.07 -1.21
BMI (kg/m <sup>2</sup> )	<0.001*	1.56	1.34 -1.82
Residence	0.463	0.66	0.22 -1.99
Education	0.742	0.90	0.50 -1.65
Anemia	0.625	0.80	0.33 -1.96
Comorbidity	0.844	0.82	0.12 -5.74

Smoking	0.918	0.88	0.08 -9.73
Gravidity	0.484	1.51	0.48 -4.78
History of Abortion	0.003*	10.53	2.27-48.84
History of PTL	0.001*	28.82	4.00 -207.88
History of Contraception	0.07	0.08	0.01 -1.23
ANC	0.345	4.19	0.21 -81.89
UTI	0.147	2.00	0.79 -5.07
Vitamin D deficiency	0.469	0.69	0.25 -1.89

BMI: body mass index; PTL: preterm labor; ANC: antenatal care; UTI: urinary tract infection; \*Significant p<0.05

## DISCUSSION

In this study, we identify 4 main risk factors in association with PTL, namely age, BMI, previous abortion and previous PTL. Regarding age, majority of cases of PTL were seen when the age of women was >40 years. In addition, young females <20 years of age were also at higher likelihood of having PTL in comparison to women within 20-40 years of age. Fuchs et al<sup>14</sup> found that increased women age (greater than 40 years) was significantly correlated to higher risk of PTL and that women between 30 and 34 years of age were less likely to have PTL.

Our findings are consistent with two published cohort studies. In a group of Danish women, Lawlor et al<sup>15</sup> discovered a U-shaped correlation between risk of preterm birth and female age, with the lowest risk age

being between 24 and 30 years old. The threshold age for preterm birth in Finland, according to a more recent countrywide register-based cohort research, was 28 years old (OR 1.10, 1.02–1.19).<sup>16</sup> It is often believed that early labor induction for medical reasons accounts for a major portion of the increased risk of preterm birth among older moms.<sup>14</sup> However, in our study, all women with PTL experienced spontaneous PTL. Given our findings, we cannot rule out the possibility that, as McIntyre et al<sup>17</sup> and Fuchs et al<sup>14</sup> found in a population-based cohort research, advanced maternal age is independently linked to spontaneous preterm.

With respect to BMI, our findings suggest that overweight and obesity are associated with increased risk of PTL. Several previous studies have shown that BMI greater than 25 kg/m<sup>2</sup> is associated with higher risk of PTL in comparison with normal BMI (<25 kg/m<sup>2</sup>).<sup>18,19</sup> Obesity and overweight are linked to a higher risk of gestational diabetes and hypertension<sup>20,21</sup>, which are linked to a higher risk of planned caesarean section and/or induction of labor.

Regarding previous abortion, most previous articles deals with increased risk of PTL following induced abortion (not spontaneous abortion).<sup>22</sup> After one spontaneous abortion, the chance of preterm delivery rose, and after multiple spontaneous abortions, the risk increases even more.

Moreover, Agrawal et al<sup>23</sup> have shown in their study that spontaneous abortion is associated with increased risk of future PTTL. Regarding previous PTL, we have shown that patients with previous PTL are at higher risk of PTL in the future pregnancies. This finding is consistent with Iams and Berghella<sup>24</sup> who stated that preterm delivery is more likely to occur in subsequent pregnancies for women who gave birth to a child between 16 and 36 weeks of gestation and that the risk is inversely related to the gestational age of the prior preterm birth and rises with each further preterm birth.

It is recommended that women should complete their families before 40 years of age, and that women in their reproductive life should follow certain dietary measure and routine exercise to keep normal weight. In addition, women with previous repeated abortions and/ or PTL should be informed about the future risk of PTL and that avoiding pregnancy is encouraged if they have satisfactory family number, or at least to get treated in special PTL obstetric center during future pregnancy.

**CONCLUSION**

Advanced maternal age >40 years, high body mass index >25 kg/m<sup>2</sup>, previous abortion and previous preterm labor are associated with increased likelihood of preterm labor.

**Author’s Contribution:**

Concept & Design or acquisition of analysis or interpretation of data:	Rana Hatem Matrood Alkhazraji
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Drafting or Revising Critically:	Rana Hatem Matrood Alkhazraji
Final Approval of version:	The above author
Agreement to accountable for all aspects of work:	The above author

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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# Incidence and Risk Factors of Prolonged Air Leak After Pulmonary Lobectomy: A Prospective Observational Study

Osamah Obaid Ibrahim

## ABSTRACT

**Objective:** To determine the incidence of prolonged air leak after pulmonary lobectomy and identify independent risk factors in an Iraqi tertiary care center.

**Study Design:** prospective observational study

**Place and Duration of Study:** This study was conducted at the Nasiriyah Teaching Hospital Iraq from 1<sup>st</sup> February 2023 to 31<sup>st</sup> January 2025.

**Methods:** Prolonged air leak was defined as persistent asthmatic gas leak for  $\geq 7$  days postoperatively. Perioperative data were extracted including demographics, comorbidities, surgical approach, intraoperative factors and postoperative outcomes. Independent risk factors for prolonged air leak were identified using multivariable logistic regression analysis.

**Results:** Overall prolonged air leak incidence in 54 (18.1%) patients. Mean age was  $58.7 \pm 12.4$  years, comprising 62.4% males. Right upper lobectomy was performed most often (34.2%). Independent risk factors for prolonged air leak were: older age (OR 1.04, 95% CI 1.01-1.07,  $p=0.008$ ), chronic obstructive pulmonary disease (OR 2.89, 95% CI 1.45-5.76,  $p=0.003$ ), need for adhesiolysis (OR 3.21, 95% CI 1.68-5.76,  $p<0.001$ ), incomplete fissure (OR 2.45, 95% CI 1.15-5.28,  $p=0.021$ ), and prolonged air leak patients had significantly longer hospital stay (12.8 vs 6.2 days,  $p<0.001$ ) and readmission rates (22.2% vs 4.9%,  $p<0.001$ ).

**Conclusion:** Prolonged air leak incidence after lobectomy in our Iraqi population aligns with international rates. Identified risk factors enable enhanced preoperative counselling and targeted preventive strategies, potentially improving patient outcomes and reducing healthcare burden in resource-limited settings.

**Key Words:** Prolonged air leak, Lobectomy, Thoracic surgery, Complications

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## INTRODUCTION

Pulmonary lobectomy is the gold standard of care for early stage non-small cell lung cancer and many benign pulmonary conditions with more than 50,000 operations performed each year worldwide.<sup>1</sup> Despite remarkable improvement in surgical techniques and perioperative care, postoperative complications remain to affect patient outcome, with prolonged air leak (PAL) being one of the most common and clinically important.<sup>2,3</sup> Pulmonary air leak, which classically is defined as a respiratory leak that persists beyond postoperative day 7, is reported to occur in 8-25% of patients after pulmonary resection, with high heterogeneity between populations and health care systems.<sup>4,5</sup>

This complication greatly lengthens hospital stay, increases health care costs and morbidity, with economic burden in excess of \$10,000 per case in developed health care systems.<sup>6</sup>

The pathophysiology of PAL is thought to be due to disruption of visceral pleural integrity with incomplete lung expansion or the failure of air leak sites to seal well.<sup>7</sup> PAL development has been associated with multiple patient-specific variables such as advanced age, chronic obstructive pulmonary disease (COPD), smoking history, and surgical factors including extent of resection, surgical approach and intraoperative complications.<sup>8,9</sup> However, the relative importance of these factors differs substantially across populations and settings of care.

However, little information is available about the incidence and risk factors for PAL in Middle Eastern populations, especially in Iraq's health care setting, despite the clinical importance of PAL. In addition, the unique demographic profile of the study population, the environmental factors and the healthcare infrastructure in Iraq may result in different PAL incidence and risk factors than in western populations.<sup>10</sup> An understanding of these factors is key to improving surgical outcomes,

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and to optimizing the allocation of resources in developing healthcare systems.

The purpose of this study is to estimate the prevalence of PAL after pulmonary lobectomy and to identify independent risk factors in an Iraqi tertiary care center.

**METHODS**

This prospective observational study was performed at Nasiriyah Teaching Hospital, a tertiary referral center that's affiliated with the University of Thi-Qar, Iraq between January 2023 and January 2025 vide letter No. 9352/QM/Approval/KJD863 dated 5-1-2023. All consecutive patients aged  $\geq 18$  years undergoing elective pulmonary lobectomy for malignant or benign indications were included. The patients of emergency surgery, concurrent chest wall resection, prior ipsilateral thoracic surgery, patients requiring mechanical ventilation  $>48$  hours postoperatively, incomplete follow-up data, and withdrawal of consent by patient were excluded.

All lobectomies were performed by experienced thoracic surgeons using standardised techniques. Surgical approach: VATS or open thoracotomy depending on tumor properties, patient anatomy and surgeon preference. Mediastinal lymph node sampling or dissection was performed systematically in cases of malignancy according to oncological principles. Intraoperative air leak test was done by saline immersion technique at positive pressure of 25-30 cmH2O. Fissure completion was scored and reported. Pleural space drainage was performed by means of 28-32 Fr chest tubes connected to digital drainage devices (Medela Thopaz+, Switzerland) with constant suction level at -20 cmH2O. Comprehensive perioperative data were prospectively collected using standardized case report forms. Variables included:

**Patient demographics and comorbidities:** Age, gender, body mass index (BMI), smoking history, chronic obstructive pulmonary disease (COPD), diabetes mellitus, cardiovascular disease, previous chemotherapy or radiotherapy, and preoperative pulmonary function tests.

**Surgical variables:** Indication for surgery, surgical approach (VATS vs. open), lobe resected, operative time, intraoperative complications, blood loss, fissure completeness, requirement for adhesiolysis, and intraoperative air leak presence.

**Postoperative variables:** Chest tube duration, air leak pattern, complications, hospital length of stay, readmissions within 30 days, and mortality.

**PAL definition:** Leakage of air persisting  $\geq 7$  days after surgery, which is established through the measurements of the digital drainage system and clinical evaluation. Air leak was measured on standard scales and recorded on a daily basis.

The data was entered and analyzed through SPSS-25. The distribution of normality was determined by

Shapiro-Wilk test. Student t -test or Mann-Whitney U test were used to analyze continuous variables and chi-square or Fisher exact test was used to analyze non-parametric variables in univariate analysis and variables associated with  $p < 0.20$  were entered into multivariate logistic regression model to determine independent PAL risk factors. The performance of the models was evaluated in terms of area under the receiver operating characteristic curve (AUC-ROC), Hosmer- Lemeshow goodness-of-fit test and calibration plots.

**RESULTS**

Sixty-two percent of the participants were male, and the average age varied between 58.7 and 12.4 years. The benign conditions, which include bronchiectasis and inflammatory illnesses, accounted for 21.5% of the indications for lobectomy, while non-small cell lung cancer accounted for 78.5% of the indications (Table 1). The right upper lobectomy, which was conducted the most frequently (34.2% of all surgeries), the left upper lobectomy was performed the second most frequently (28.9% of all treatments). A total of seventy-eight percent of the cases involved the utilization of the VATS method, with eight percent of the VATS operations resulting in the conversion to open thoracotomy (Table 2).

**Table No. 1: Baseline patient characteristics and comparison between PAL and non-PAL groups (n=298)**

Variable	No PAL (n=244)	PAL (n=54)	p-value
Age (years)	57.8±12.1	62.4±12.9	0.008*
Male gender	149 (61.1%)	37 (68.5%)	0.297
BMI (kg/m <sup>2</sup> )	25.1±4.1	23.7±4.5	0.032*
Smoking history	154 (63.1%)	44 (81.5%)	0.009*
Pack-years >20	108 (44.3%)	34 (63%)	0.012*
COPD	65 (26.6%)	24 (44.4%)	0.008*
Diabetes mellitus	52 (21.3%)	15 (27.8%)	0.295
Cardiovascular disease	78 (32%)	20 (37%)	0.462
FEV1 (% predicted),	80.1±18.2	71.8±19.8	0.003*
Previous chemotherapy	35 (14.3%)	10 (18.5%)	0.423

Pulmonary embolism was identified to occur at a prevalence of 54 (18.1%) patients affected. The mean air leakage of affected patients was 9.8 above 3.2 days. The table on the left-hand side shows that at the postoperative stage, there exist significant differences in the postoperative outcomes between PAL and non-PAL groups (Table 3, Fig. 1).

A multivariate logistic regression model found five independent risk factors associated with the development of PAL (Table 4). The last model exhibited

a sufficient model (AUC-ROC = 0.78, 95% CI 0.72-0.84) and sufficient calibration (Hosmer-Lemeshow p=0.543).

**Table No. 2: Surgical characteristics and intraoperative factors**

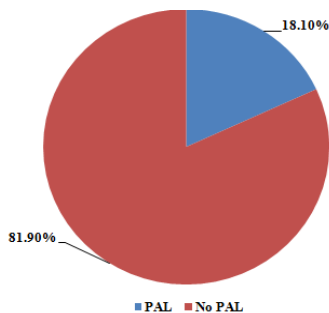
Variable	No PAL (n=244)	PAL (n=54)	p-value
<b>Surgical Approach</b>			
VATS	172 (70.5%)	30 (55.6%)	0.033*
Open thoracotomy	72 (29.5%)	24 (44.4%)	
<b>Lobe Resected</b>			
Right upper	81 (33.2%)	21 (38.9%)	0.187
Right middle	30 (12.3%)	4 (7.4%)	
Right lower	57 (23.4%)	10 (18.5%)	
Left upper	69 (28.35)	17 (31.5%)	
Left lower	7 (2.9%)	2 (3.75)	
Operative time (minutes)	179.2±50.8	206.8±57.9	
Estimated blood loss (mL), median (IQR)	200 (150-300)	300 (200-450)	0.002*
Adhesiolysis required	52 (21.3%)	24 (44.4%)	<0.001*
Incomplete fissure	68 (27.9%)	26 (48.1%)	0.003*
Intraoperative air leak	65 (26.6%)	22 (40.7%)	0.038*
Lymph node dissection	194 (79.5%)	40 (74.1%)	0.377

**Table No. 3: Postoperative outcomes and complications**

Variable	No PAL (n=244)	PAL (n=54)	p-value
Chest tube duration (days), median (IQR)	4 (3-5)	10 (8-13)	<0.001*
Hospital length of stay (days)	6.2±3.1	12.8±7.9	<0.001*
<b>Postoperative complications</b>			
Pneumonia	15 (6.1%)	8 (14.8%)	0.034*
Atrial fibrillation	12 (4.9%)	6 (11.1%)	0.093
Empyema	2 (0.8%)	3 (5.6%)	0.027*
Respiratory failure	4 (1.6%)	4 (7.4%)	0.032*
<b>30-day outcomes</b>			
Readmission	12 (4.9%)	12 (22.2%)	<0.001*
Mortality	2 (0.8%)	1 (1.9%)	0.477
<b>90-day outcomes</b>			
Mortality	5 (2%)	2 (3.7%)	0.454

**Table No. 4: Multivariable logistic regression analysis of independent PAL risk factors**

Variable	Odds Ratio	95% Confidence Interval	p-value
Age (per year increase)	1.04	1.01-1.07	0.008*
COPD	2.89	1.45-5.76	0.003*
Smoking history >20 pack-years	2.67	1.34-5.32	0.005*
Adhesiolysis requirement	3.21	1.68-6.13	<0.001*
Incomplete fissure	2.45	1.28-4.68	0.007*



**Figure No. 1: Incidence of prolonged air leak (PAL) among patients undergoing pulmonary lobectomy (n = 298)**

## DISCUSSION

This study showed an 18.1% incidence replying to the international literature ranges of 8-25%.<sup>11</sup> 19.2% PAL incidence in a German multicenter study of 1,247 patients<sup>12</sup>, and found 16.8% in a Chinese cohort of 892 patients.<sup>13</sup> The results of our work are important information on the risk factors of PAL in a population in the Middle East, which is underrepresented in the evidence base of developing healthcare systems. This resemblance implies that even though healthcare systems and populations of patients differ, the

underlying biological and surgical conditions that determine PAL are similar regardless of the environment.

Advanced age was an independent risk factor of PAL (OR 1.04 per year,  $p=0.008$ ), which is similar to numerous other studies.<sup>14,15</sup> The biologic changes in lung compliance, pleural curing ability, and physiological reserve increase with age and lead to a progressive increase in air leaks are similar. Aprile et al<sup>16</sup> demonstrated in a cohort of 1,156 patients, in which age over 65 years related to a considerable higher risk of PAL (OR 1.8, 95% CI 1.2-2.7).

COPD was the most significant patient-related PAL risk factor (OR 2.89,  $p=0.003$ ), which is consistent with a substantial body of literature supporting the impaired air leakage and elastic recoil in patients with emphysema and the compromised response of the pleural healing process.<sup>17, 18</sup> Our result is also consistent with the analysis of the Society of Thoracic Surgeons database by Heiden et al<sup>19</sup>, which found that COPD is an important PAL predictor (OR 2.4, 95% CI 1.8-3.2) on a group of 15,259 lobectomy patients. History of smoking (20 pack-years) was a predictor of PAL (OR 2.67,  $p=0.005$ ) on its own, as previous smoking history has been shown to predict smoking-associated wound healing impairment and heightened risk of infection.<sup>20</sup> Surprisingly, we had a lower PAL rate among the heavy smokers 24.3% as compared to the reported 31.2%, which could be due to differences in the smoking habit or type of tobacco (common in the Middle East).<sup>21</sup>

Adhesiolysis emerged as the most significant surgical risk factor (OR 3.21,  $p<0.001$ ) positive indicator of more pleural trauma and abnormality of normal healing processes. The clinical implications include observation who noted 3.1-fold risk of PAL after extensive adhesiolysis<sup>22</sup>, and it is important to note that in our population there is larger prevalence of pleural adhesions, which could be due to the endemic respiratory infections and occupational exposures. Incomplete fissure also was a strong predictor of PAL (OR 2.45,  $p=0.007$ ), which is rather expected since the literature underlines the significance of fissure anatomy in the formation of air leaks post-surgery.<sup>23,24</sup> Unclosed fissures mean that a lot of dissection and parenchymal division need to be done, leaving several possible sites of air leaks. Preoperative computed tomography fissure assessment is found to be useful in risk stratification and surgery planning<sup>25</sup> as supported by our findings. Surgical approach (VATS vs. open), unlike some reports, was not significantly predictive of PAL on multivariate analysis, although higher rates of PAL in open operations (25.0% vs. 14.9%  $p=0.033$ ) appeared on univariate analysis. This implies that the observed relationship between surgical style and PAL could be confounded by factors of case complexity and patient selection as opposed to reflecting a causal relationship.<sup>26</sup> In our cohort, the clinical effect of PAL was large:

affected individuals had longer rates of hospitalization (12.8 vs. 6.2 days,  $p<0.001$ ) and readmission (22.2 vs. 4.9,  $p<0.001$ ). These findings are consistent with other findings in the world that prove that there is a high healthcare burden in relation to PAL.<sup>27</sup> In resource-constrained health systems such as the case of Iraq, the increased burden of long stays on the already constrained bed capacity and health resources.

The results of the present study have a multifold clinical implication. Risk factors identified make it possible to conduct better preoperative counseling and informed consent procedures, setting realistic expectations about the course of postoperative experience and possible complications. Perioperative management choices such as the choice of chest tube, postoperative care protocols, and discharge planning might be informed by the risk stratification models that include these factors. Moreover, high-risk patients may receive a better preventive plan, such as preoperative pulmonary rehabilitation, smoking cessation programs, or alternative surgery.

## CONCLUSION

The number of risk factors including old age, chronic obstructive pulmonary disease (COPD), having a history of heavy smoking, abnormal requirement of adhesiolysis and inadequate fissure anatomy. The evidence-based risk classification and enhance the preoperative counseling, and create more specific preventive measures. The extreme clinical and economic effects of PAL that encompass doubling duration of stay in the hospital and raising the likelihood of readmission underscores the importance of identifying patients at high risk and implementing the right care procedures.

### Author's Contribution:

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# Prevalence of Renal Artery Stenosis in Hypertensive patients on Treatment Undergoing Coronary Angiography; In Multi Cardiac Centers

Renal Artery Stenosis in Hypertensive patients on Treatment

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## ABSTRACT

**Objective:** To determine the prevalence of renal artery stenosis.

**Study Design:** The cross-sectional study

**Place and Duration of Study:** This study was conducted at the Iraqi Center of Heart Diseases and Baghdad Cardiac Center Iraq from 1<sup>st</sup> August 2023 to 30<sup>th</sup> June 2024.

**Methods:** Sixty hypertensive patients who experience elective coronary angiography were enrolled. They were divided into two groups, controlled and uncontrolled hypertension.

**Results:** The mean age was 61.4 years and 53.3% males. The majority of them had uncontrolled hypertension (70%), diabetes (60%), and dyslipidemia (65%). Abnormalities were observed in 41.7 percent of patients on coronary angiography and the severe coronary disease was present in 25 percent. RAS was identified in 15 per cent and had a strong correlation with the abnormal angiography coronary findings ( $P = 0.002$ ) and ineffective control of hypertension ( $P = 0.033$ ). There was no significant correlation with diabetes, dyslipidemia, smoking, and echocardiographic outcomes.

**Conclusion:** Renal artery stenosis is one of the frequent observations in hypertensive patients with coronary artery disease, which requires effective blood pressure management and multidisciplinary approach to minimize cardiovascular and kidney problems.

**Key Words:** Hypertension, Renal artery stenosis, Coronary artery disease, Atherosclerotic.

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## INTRODUCTION

Renal artery stenosis (RAS) is a vascular disease that has a massive impact on cardiovascular health of patients with hypertension and coronary artery disease (CAD).<sup>1</sup> It is a constriction of the renal artery(s) or arteries, causing less blood access to the kidneys and resulting in permanent high blood pressure, and eventual kidney failure.<sup>2</sup>

Uncontrolled hypertension is considered to be one of the predisposing factors and outcomes of RAS.<sup>3</sup> The World Health Organization says that uncontrolled hypertension occurs when the blood pressure is 140/90mmHg or higher regardless of treatment or no treatment. Hypertension is a significant cause of stroke, heart attack and kidney disease and affects over 21 percent of the world adult population.<sup>4</sup>

Dysfunction in renal perfusion initiates the renin-angiotensin-aldosterone system (RAAS) leading to the release of angiotensin II and aldosterone which elevates blood pressure by causing vasoconstriction and sodium reabsorption. This produces a vicious cycle whereby hypertension worsens the RAS and CAD.<sup>5</sup> Renal artery stenosis makes CAD more difficult by enhancing myocardial ischemia because decreased renal blood flow imposes additional hemodynamic load on the heart, and it may trigger cardiac events.<sup>6</sup> Furthermore, the treatment of hypertension among CAD patients with RAS is complicated due to the fact that the usual antihypertensive medications may deteriorate the renal hypoperfusion. Thus, the maintenance of renal perfusion and blood pressure should be carefully combined with the efforts of interventional radiologists, cardiologists, and nephrologists.<sup>7,8</sup>

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Imaging methods that are commonly used in diagnosing RAS include Doppler ultrasound, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or conventional angiography, which are able to determine the extent and location of stenosis.<sup>9</sup> Renal artery stenosis-based interventions are necessary in hypertensive CAD patients to restore the renal perfusion, blood pressure, and cardiovascular risk of hypertensive patients.<sup>10</sup> It can be treated with pharmacological therapy with RAAS inhibitors, calcium channel blockers, and diuretics and revascularization, like percutaneous transluminal angioplasty (PTA) with or without a stent or surgery in selected cases.<sup>11</sup>

Renal artery stenosis may be categorized according to its cause. The most widespread form is called atherosclerotic RAS, which is caused by the accumulation of the plaque reducing the lumen of the renal artery and reducing the perfusion of the kidneys.<sup>12</sup> Fibromuscular Dysplasia (FMD) is a non-atherosclerotic, non-inflammatory disease that is associated with unusual growth of cells of the arterial walls and results in localized or generalized stenosis, and may be common among women younger than 50.<sup>13</sup> The congenital RAS is the result of inherited structural defects in the form of fibrous bands or inappropriate patterns of branching.<sup>14</sup> Traumatic RAS is caused by renal or abdominal trauma of a blunt trauma, or surgery.<sup>15</sup> Inflammatory RAS can be a by-product of autoimmune or infectious vasculitis.<sup>5</sup> Iatrogenic RAS is acquired after medical interventions that lead to the scarring of arteries i.e. catheterization<sup>16</sup>, whereas Radiation-Induced RAS develops after abdominal or pelvic radiotherapy of cancers.<sup>17</sup>

There are a number of risk factors that are linked to RAS. The biggest determinant is age and the disease is more common among people above 50 years.<sup>18</sup> Hypertension, diabetes, smoking, and dyslipidemia favor atherosclerosis and lead to the narrowing of the arteries.<sup>19</sup> Familial history of cardiovascular disease, chronic kidney disease (CKD) and obesity also make one more susceptible.<sup>20</sup> Besides, ethnicity and gender also play a role in prevalence African Americans are at more risk, and RAS associated with FMD is more prevalent in women younger than 50.<sup>21</sup>

## METHODS

The study was carried out in the Iraqi Center of Heart Diseases and Baghdad Cardiac Center, Iraq from 1<sup>st</sup> August 2023 to 30<sup>th</sup> June 2024 vide letter No. 4545/QM/Approval/4JKJD8 dated January 9, 2023 and 60 hypertensive patients who attended elective coronary angiography based on a referral following the detection of the presence of chest pain or ischemic signs with the help of non-invasive tests were enrolled. The patients were divided into controlled and uncontrolled hypertension (blood pressure below 140/90 mmHg and above 140/90 mmHg, respectively). The inclusion

criteria were a history of treated hypertension and a referral to coronary angiography with exclusion criteria being serum creatinine greater than 1.5 mg/dl and excessive use of contrast. The complete data were gathered that included demographics, medical and family history, laboratory tests (CBC, RBS, HbA1c, blood urea, serum creatinine, uric acid, lipid profile), ECG, echocardiography, and findings of coronary and renal angiography. All angiogram optimally assessed by a qualified interventional cardiologist and RAS was determined under the basis of significant stenosis. The statistical analysis was conducted and calculated using SPSS-26.0. The categorical data were tested with 2-tailed 125,  $p = -0.05$  as the statistically significant  $p$ -value.

## RESULTS

The mean age was  $12.18 \pm 6.8$  years. Most of the patients, 73.04% had poor control of hypertension, 36 (60%) patients had history of DM with an average of  $11.53 \pm 6.04$  years and 21 (35%) patients had history of IHD. None of the patients was chronic kidney disease (CKD). Another 39 (65%) patients and 27 (45%) patients were on statin therapy. Smoking was a common characteristic among the respondents with 33 (55%) patients being identified as smokers. Also, when analyzing premature coronary artery disease (CAD) 18 (30%) patients, a sedentary lifestyle was observed, 39 (65%) patients had a positive family history (Tables 1-2).

A strong and statistically significant association between renal and coronary angiography findings ( $P = 0.002$ ). Among patients with abnormal renal angiography, 88.9% also had abnormal coronary results, while only 11.1% showed normal coronary findings. However, no significant relationship was found between the site of renal lesions (ostial or proximal) and coronary outcomes ( $P=0.134$ ), nor between the severity of renal lesions (critical or intermediate) and coronary results ( $P=0.134$ ) [Table 3].

The duration of hypertension showed no significant difference between patients with abnormal and normal renal findings ( $P = 0.780$ ). However, hypertension control was the only factor significantly associated with renal results - patients with well-controlled blood pressure all had normal renal findings, while 21.4% of those with poorly controlled hypertension showed abnormalities ( $P = 0.033$ ). Diabetes, dyslipidemia, and smoking showed no significant associations with renal angiography outcomes ( $P = 0.238, 0.103, \text{ and } 0.445$ , respectively), though abnormal findings were slightly more frequent among diabetics, dyslipidemic patients, and smokers. Overall, poor hypertension control emerged as the main clinical factor linked to abnormal renal angiography results, emphasizing the importance of effective blood pressure management in preventing renal vascular complications (Table 4).

**Table No. 1: Descriptive statistics of the patients**

Variable	Mean±SD
Duration of hypertension	12.18±6.8
Systolic blood pressur	154.3±23.5
Diastolic blood pressure	90.9±16.3
Duration of diabetes mellitus	11.53±6.04

**Table No. 2: Demographic features of the patients**

Variable	Category	No.	%
Control of hypertension	Good	18	30.0
	Poor	42	70.0
Diabetes mellitus	No	24	40.0
	Yes	36	60.0
Control of diabetes mellitus	Good	11	18.3
	Poor	25	41.7
Ischemic heart disease	No	39	65.0
	Yes	21	35.0
Chronic kidney disease	No	60	100
	Yes	0	0.0
Dyslipidemia	Negative	21	35.0
	Positive	39	65.0
Use of statins	Negative	33	55.0
	Positive	27	45.0
Smoking status	Negative	27	45.0
	Positive	33	55.0
Sedantary life style	Negative	42	70.0
	Positive	18	30.0
Family history of premature Coronary artery disease	Negative	21	35.0
	Positive	39	65.0

**Table No. 3: Distribution of renal artery stenosis, side and severity with coronary angiography findings**

Variable for renal angiography		Coronary angiography				P value
		Abnormal		Normal		
		No.	%	No.	%	
Renal angiography	Abnormal	8	88.9	1	11.1	0.002
	Normal	17	33.3	34	66.7	
Site	Ostiallesion	2	66.7	1	33.3	0.134
	Proximal lesion	6	100.0	-	-	
Severity	Critical	6	100.0	-	-	0.134
	Intermediate	2	66.7	1	33.3	

Table 5 shows no significant association between echocardiographic findings and renal angiography results (P=0.327). Among patients with normal echocardiograms, 10.5% had abnormal renal findings, while 9.5% of those with hypertensive heart disease and 27.8% with ischemic heart disease showed abnormal renal results. All patients with severe mitral regurgitation had normal renal findings. The mean ejection fraction was slightly lower in patients with abnormal renal findings (55.78±7.65%) compared to those with normal findings (59.94±7.60%), but the difference was not statistically significant (P=0.135). Overall, echocardiographic abnormalities did not significantly correlate with renal angiography outcomes.

**Table No. 4: Analysis of variables associated with renal angiography findings**

Variable		Coronary angiography				P value
		Abnormal		Normal		
		No.	%	No.	%	
Height duration		12.78±6.379		12.08±6.962		0.780
Control of hypertension	Good	-	-	18	100.0	0.033
	Poor	9	21.4	33	78.6	
Diabetes mellitus	No	2	8.3	22	91.7	0.238
	Yes	14	29.7	33	70.3	
Dyslipidemia	Negative	1	4.8%	20	95.2%	0.103
	Positive	16	24.3	50	75.7	
Smoking Status	Negative	3	11.1%	24	88.9%	0.445
	Positive	10	19.6	41	80.4	

**Table No. 5: ECG and echocardiographic findings associated with renal angiography results**

Variable		Coronary angiography				P value
		Abnormal		Normal		
		No.	%	No.	%	
Echocardiography finding	Normal	2	10.5	17	89.5	0.327
	HHD	2	9.5	19	90.5	
	IHD	5	27.8	13	72.2	
	Severe MR	-	-	2	100.0	
EF	Mean±SD	55.78±7.645		59.94±7.596		0.135

## DISCUSSION

The incidence of renal artery stenosis (RAS) observed in hypertensive patients in the present study during coronary angiography is consistent with the available research on the world, which demonstrates a close relationship between hypertension, coronary artery disease (CAD), and renal artery stenosis. Renal artery stenosis was present in 22.5% of hypertensive patients who underwent coronary angiography<sup>22</sup>, and 13% of hypertensive patients<sup>23</sup> had RAS, which was intensified by hypertension, multivessel CAD, and being a female. Mirbolouk et al<sup>24</sup> also emphasized RAS as a factor in the deterioration of the renal function and resistant hypertension in line with the existing evidence that underlines the necessity of RAS screening in hypertensive CAD patients. Kirishcheva et al<sup>25</sup> demonstrated that renal artery endovascular reconstruction enhanced blood pressure and cardiac values, which favor early intervention. Hypertension and low eGFR were also found to be strong predictors to RAS by Dong et al.<sup>26</sup>

The hypertensive patients in this study had mean age of 61.18±6.8 years, mean systolic blood pressure (SBP) of 154.3 mmHg and diastolic blood pressure (DBP) of 90.9 mmHg which showed that they had poor blood pressure control. Approximately 70 percent were uncontrolled hypertension, which is consistent with Ullah et al<sup>27</sup> who reported hypertension as one of the significant predictors of RAS. Sixty percent of the patients were diabetic (mean 11.53 years), and only 18.3% were well-regulated glycemically. According to Tofaha et al<sup>28</sup>, cardiovascular risk is one of the major precipitants of uncontrolled diabetes.

The high CAD burden was seen in 35% of patients who had ischemic heart disease (IHD). All of them lacked chronic kidney disease (CKD), indicating that their renal function was intact despite being at high risk of cardiovascular disease, just like Kayed et al<sup>23</sup>, who observed that multivessel CAD is associated with RAS despite the absence of an overt CKD. Lipid management was not at its best with 65% of the patients having dyslipidemia with only 25% on statins. Mirbolouk et al<sup>24</sup> emphasized the need to follow lipid-lowering therapy. There was also smoking (55%) and sedentary lifestyle (33) which were also considered risk factors to CAD and RAS. Omid et al<sup>29</sup> proved that the sedentary behavior, smoking, and progression of CAD have a strong connection. Also, 65% had a family history of early CAD, which aligns with the report of Kayed et al<sup>23</sup>, who suggested the family history as a significant CAD predeterminant.

Coronary angiography and RAS Correlation: 15% of the patients exhibited abnormal renal angiography, which proves the impressive RAS prevalence. Only 2.9% of hypertensive patients whose coronary angiography was normal exhibited RAS and 32% of hypertensive patients with abnormal coronary angiography exhibited RAS, and this indicates that there is strong correlation between coronary and renal artery disease. These results go hand in hand with Khalaf et al<sup>3</sup>, who discovered that age, hypertension, diabetes, and renal impairment were important predictors of RAS.

The statistical significance of the correlation between abnormal renal and coronary angiography outcomes was statistically significant ( $P = 0.002$ ), which confirms that atherosclerosis is a systemic disease that involves more than one vascular bed as Payami et al,<sup>30</sup>. Nevertheless, there were no significant differences regarding lesion location (ostial or proximal) and coronary outcomes ( $P=0.134$ ), which proves Soliman et al<sup>22</sup> and Mirbolouk et al<sup>24</sup> showed no correlation between RAS and CAD severity.

Control of hypertension helps in the prevention of RAS; diabetes, dyslipidemia, smoking, and echocardiographic data did not play a significant role.<sup>31</sup>

## CONCLUSION

The renal artery stenosis is common in hypertensive patients undergoing coronary angiography, strongly correlates with coronary artery disease, influenced by hypertension control, while diabetes, dyslipidemia, smoking, and echocardiography show no significant association.

### Author's Contribution:

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# Mothers of Autistic Children Insisting Needs

Jaafar S. Al-Showaily<sup>1</sup>, Marwa Jabbar Saiwan<sup>2</sup> and Mohanad. A. Dawood<sup>3</sup>

## ABSTRACT

**Objective:** To identify the needs of those mothers to put the corner stone in diagnosing mothers of autistic children needs and accomplish them.

**Study Design:** A cross sectional descriptive study

**Place and Duration of Study:** This study was conducted at the different places in Nasiriyah city, Thi Qar governorate, Iraq from 1<sup>st</sup> September 2024 to 1<sup>st</sup> December 2024.

**Methods:** The needs questionnaire scale" it is based on previous studies and it was divided into two main parts (the first part contains socio-demographic information, and the second part included questions about the needs of mothers with autistic children). Study instrument contains eleven questions about sociodemographic information and they are, educational level of the mother, the economic status, the age of the mother, the marital status of the mother, the sex of the child, his age, his arrangement among his siblings, the number of all children in the family, The degree of autism disability, the current place of education for the child, and are there any disabilities associated with autism. Part two which is the needs of mothers contains 26 questions to assess the needs of those mothers.

**Results:** There are high, financial needs with mean score 4.4429, high Knowledge and training needs with mean score 4.5375, high societal needs with mean score 4.4557, and high social needs with mean score 4.2850.

**Conclusion:** Mothers with autistic children have high needs in order from the top are, financial needs, knowledge and training needs, societal needs, and social needs.

**Key Words:** Autism spectrum disorder, Needs assessment, Mothers

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## INTRODUCTION

Autism Spectrum Disorders (ASD) are consistently life-long neurodevelopmental disorders characterized by impairments in behavior, communication social interaction accompanied with restricted and repetitive interest and possible sensory disturbances cases taking origin form early childhood.<sup>1</sup> The issue provided by current epidemiological investigations in the preceding 20 years is a rise community incidence of ASD.<sup>2</sup> This is a big group of children, because there are many subjects that suffer from chronic diseases. Forty percent of the world's children are infected by one or more diseases and therefore require special protection (statistics).

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In them, especially disorders that include children's mental and psychological area become of the first important shall be stated autism is one from a lot of these disorder.<sup>3</sup> Children with Autism spectrum disorder (ASD) require whole-care treatment and routine therapy plan for which it is important.<sup>4</sup>

Families of children with ASD are up against more expensive needs, which in any case require additional financial support from their parents. But they do require help from professionals, such as therapists and psychologists to perform developmental or therapeutic examinations of their children, in case these care givers may not have the professional training needed.<sup>5</sup>

Identifying the significant and unmet support needs of parents is important in reducing parenting stress, and potentially improving psychological well-being. Parental Psychological well-being research has found that parental satisfaction with supports is very strongly associated with the behavior of staff working alongside parents.<sup>6</sup>

For mothers of children with autism symptoms studies are presented where the absence of perceived social support has been identified as above all other factors in mental health issues.<sup>7</sup> It is these mothers that give everything to make the structure and process of family as average, ordinary or automatic offering all their capacity into this care business. They practice to look good and mask the pain. Several physical (insomnia, tiredness, headache, back pain and anorexia, dyspepsia

and palpitations) as well emotional problems in the lives of these mothers have been observed.<sup>8,9</sup>

The higher cost of ASD-related special education and treatment that will require a general need to supplement income throughout the course of life, are all important factors in increasing parental fatigue, especially for low-income households.<sup>10</sup> For parents of children with ASD, the five most frequently rated unmet needs were: financial support, my child having friends, help dealing with concerns about my child’s future, ongoing services, and my child’s other friends feeling comfortable around my child. Parents’ unmet needs were also examined in a recent Canadian study of 101 parents of children with ASD aged 6-13 years.<sup>11</sup> Two of their most frequently identified unmet needs were similar to those reported by Kerns and Siklos including social inclusion for their child and services provided on an ongoing basis rather than only in times of crisis.<sup>12</sup>

As far as we know, there are limited studies from Iraq addressing the needs of families for children with ASD. Previous studies have found that mothers of children with ASD report high psychological distress and caregiver burden.<sup>13</sup>

**METHODS**

This cross sectional descriptive study was conducted at different places in Nasiriyah city, Thi Qar governorate, Iraq from 1<sup>st</sup> September 2024 to 1<sup>st</sup> December 2024 vide letter No. 02 dated 8-8-2024. Non-probability (accidental sampling) of 165 mothers of autistic children in Al-Nasiriyah city, Iraq was included.

The needs questionnaire scale" it is based on previous studies and it was divided into two main parts (the first part contains socio-demographic information, and the second part included questions about the needs of mothers with autistic children). Study instrument contains eleven questions about sociodemographic information and they are, educational level of the mother, the economic status, the age of the mother, the marital status of the mother, the sex of the child, his age, his arrangement among his siblings, the number of all children in the family, The degree of autism disability, the current place of education for the child, and are there any disabilities associated with autism. Part two which is the needs of mothers contains 26 questions to assess the needs of those mothers.

Scoring and rating include five points Likert scale applied for rating mother’s needs (happens little, happens a lot, never happened). The data were analyzed with descriptive statistics, levels of need and psychological problems are mild (mean less than 2.333), moderate (mean from 2.34 to 3.67), and high levels (mean between 3.68 and 5). Significance was set at  $p < 0.05$  and CI confidence interval estimated at the 95%

level. Study instrument was checked for its validity and reliability. Sensitivity and specificity of the instrument also checked. The data was entered analyzed through SPSS-25.

**RESULTS**

The demographic information of the participants is shown in Table 1. The mothers need assessment for each domain and total needs is shown in Table 2. Relationship between all the needs of mothers is shown in Table 3.

**Table No. 1: Demographic data of 165 participant in the study (n=165)**

Variable	No.	%
<b>Child gender</b>		
Male	126	76.4
Female	39	23.6
<b>Child age</b>		
4	37	22.4
5	58	35.2
6	39	23.6
7	17	10.3
8	14	8.5
<b>Mothers age</b>		
25-35	138	83.6
36-45	27	16.4
<b>Child order among children</b>		
1	69	41.8
2	41	24.8
3	55	33.3
<b>Disability level</b>		
Sever	14	8.5
Moderate	87	52.7
Mild	64	38.8
<b>Economic status</b>		
Rather enough	71	43.0
Enough	94	57.0
<b>Educational place for autistic child</b>		
Governmental center	17	10.3
Special center	92	55.8
Governmental school	14	8.5
Home	42	25.5
<b>Number of family members</b>		
1	13	7.9
2	18	10.9
3	51	30.9
4	56	33.9
5	27	16.4
<b>Mother educational level</b>		
Illiterate	10	6.1
Primary school	24	14.5
Secondary school	40	24.3
Bachelor’s degree and above	91	55.1

**Table No. 2: Mothers need assessment for each domain and total needs**

	Mean	Std. Deviation	Assessment	Rank
Financial needs	4.4429	0.48305	High	3
Knowledge and training needs	4.5375	0.45224	High	1
Societal needs	4.4557	0.38020	High	2
Social needs	4.2850	0.47957	High	4
Total	4.4303	0.34552	High	

Mild (mean less than 2.333), Moderate (mean between 2.34 and 3.67) High (mean between 3.68 and 5)

**Table No. 3: Relationship between all the needs of mothers**

Domains	Statistical parameters	Financial needs	Knowledge and training needs	Societal needs	Social needs
Financial needs	Pearson Correlation	1	0.861**	0.788**	0.211
	Sig. (2-tailed)		0.000	0.000	0.540
Knowledge and training needs	Pearson Correlation	0.861**	1	0.428*	0.520**
	Sig. (2-tailed)	0.000		0.017	0.002
Societal needs	Pearson Correlation	0.788**	0.428*	1	0.611**
	Sig. (2-tailed)	0.000	0.017		0.000
Social needs	Pearson Correlation	0.211	0.520**	0.611**	1
	Sig. (2-tailed)	0.540	0.002	0.000	

\*\*Correlation is significant at the 0.01 level (2-tailed)

\*Correlation is significant at the 0.05 level (2-tailed).

## DISCUSSION

In fact, all means of the needs are high and even the mean of each item alone, which indicate high needs among mothers and the general mean is (4.4303) which reflecting the high level of needs among mothers, Knowledge and training needs is the highest need among mothers with mean about (4.5375), second comes the societal needs with mean about (4.4557), third needs were financial needs with mean (4.4429), and the fourth needs are social needs with mean (4.2850) which is the last rank.

In fact, to explain these results, it is conveyance that mothers of autistic children have high level of needs because when the child is diagnosed with autism many difficulties will arise, like behavioral problems, the difficult of care as the child needs special care, community acceptance which put more burden on both parents, and high level of stress, especially the mothers as they are the first source of care for the children.<sup>14</sup> Knowledge and training needs come in the first rank is reasonable, as the mothers of the autistic children sees that with autism the biggest problem with their children is learning and development, and it is very difficult to deal with them, unless by the help of special specialist or special center, as the autistic child have problems with communication, learning, eating and even how other family could deal with him in right way, as it is clear from the table 3, highest needs were the needs of mother to learn how to deal with child tantrums, need to learn the child clothing eating and drinking, and the need to learn him social and communication skills, all these needs are fall in knowledge and training needs.<sup>15</sup> Second rank is societal needs, in fact, societal needs can be linked to knowledge and training needs as the mother in

this domain needs the community and governmental support to provide and help her in the special needs of her autistic child with training programs and special centers, as the three highest needs in this domain respectively are, the need of advisory centers or programs to help in decrease stress, the need for special centers and programs to provide entertainment for mothers, and the third need is the need of special centers and programs for educate rehabilitates the autistic child. These needs are high in nature as the mothers need the support from any available services, which it was governmental or special, because of the high burden of raising autistic child.<sup>16</sup> Third ranked need is the financial needs, these needs came in the third place may be because the enough economic status of the participants in table 1, despite this the financial needs were high and they come in the third place, as the medical needs of the autistic child are high and there are a lot of other needs, they all put high burden on mothers especially, needs for special centers with programs, training, and special care they all of high cost.<sup>17</sup> Fourth ranked need is the need for social support which it is high need too, mothers of autistic children need highest available support specially form family, relatives, and neighborhoods as the highest two needs, this domain rank were the fourth may be because mothers need specialist to not only care for their children but also to treat them and made them better.<sup>18</sup> In fact, the order of the needs order is not agreed with<sup>19</sup> which he has societal needs in the first order, knowledge and training needs in the second order, social in the third order and financial needs in the fourth order, may that belong to the differences in culture, social structure and the big differences is in the demographic variables, which created differences in needs. The study of Al-

Kafash is agree which have mentioned that knowledge and training needs are in the first rank.<sup>20</sup> Second question to answer is the relationship between those needs, there is a strong relationship between financial needs and knowledge and training needs, as the knowledge and training need money and financial support to achieve knowledge and training needs.<sup>21</sup> Also, there is a highly relationship between financial and social needs, there are many aspects could link financial needs to social needs, like social inclusion aspects, the higher financial state the easier forming relationships and more friends as they be able to go to special centers and more entertainment places, or even worse which it is the suffering of mothers from abandonment as they have autistic child, first one to leave is the father which made more social and financial burden on mothers in, furthermore, researches have mentioned that women who are alone tend to leave their work, change their work, or modify their work to meet care needs of their autistic children which create more financial needs because of the social needs.<sup>21,22</sup>

In addition, there is significant relationship between knowledge and training and societal needs, knowledge and training are highly linked theoretically as the societal include special centers with special programs and training for the children and their mothers to care for the children and rehabilitates them.<sup>16</sup>

Furthermore, another relationship is between knowledge and training needs and social needs. Actually, these needs are closely connected, as the knowledge and training are for enhance social interaction and social interaction would make better knowledge and successful training.<sup>23</sup>

Final relationship is between social and societal needs, there is high significant relationship between both of them. In fact, societal needs termis interchangeable word to social needs term also mean community needs as it include pointed sheared with knowledge and training needs, in other words societal needs are the basic needs of the mothers and children, if these needs wont met, mothers and children will be socially disabled and inactive.<sup>24,25</sup>

This study recommends offer better and more training and educational programs designed in carful and scientific way to accomplish best available health promotion to the autistic children.

**CONCLUSION**

Mothers of autistic children have high level of needs and are divided from highest to lowest; knowledge and training needs in the first place followed by societal needs in the second place, in the third-place financial needs, and lastly in the fourth place the social needs. Also, study has found a strong relationship between financial needs and knowledge and training needs, also there is a highly relationship between financial and social needs, in addition, there is significant relationship

between knowledge and training and societal needs, and another relationship with social needs. According social and societal needs there is high significant relationship between both of them.

**Author’s Contribution:**

Concept & Design or acquisition of analysis or interpretation of data:	Jaafar S. Al-Showaily, Marwa Jabbar Saiwan
Drafting or Revising Critically:	Mohanad. A. Dawood
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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# Diagnosis and Effectiveness of Calcium Peroxide Nanoparticles Prepared from Capsicum Plant Extract against Colon Cancer

Hassan MA. Al-Redha and Waleed K. Mahdi

## ABSTRACT

**Objective:** To diagnose the function of natural biomolecules in the biological reduction of metal salts during nanoparticle synthesis.

**Study Design:** Experimental study

**Place and Duration of Study:** This study was conducted at the College of Education for Pure Sciences/Ibn Al-Haitham at the University of Baghdad from 1<sup>st</sup> January 2024 to 31<sup>st</sup> March 2025.

**Methods:** Capsicum plant extract was used and treated with a readily available inorganic salt ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ). It was used as a basic material to obtain particles.

**Results:** Calcium peroxide nanoparticles in the form of a yellowish-white powder were confirmed by using, UV, XRD, SEM, TEM, AFM, and EDX, confirmed that the compound is calcium peroxide nanoparticles with an average nano size of 31.288 nm. The effectiveness of these particles against colon cancer (HT-29) was clearly and reliably demonstrated by diagnostic tests and examinations of infected laboratory cells cultured.

**Conclusion:** The use of calcium peroxide nanoparticles represents a novel approach to cancer treatment, focusing on developing imaging and therapeutic methodologies.

**Key Words:** Green chemistry, Plant extract, Calcium peroxide nanoparticles, Cancer resistance

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## INTRODUCTION

Capsicum, a globally prevalent vegetable crop, is utilized in nutrition either in its fresh or processed forms, as well as in numerous specialties, and extracts. The extract is abundant in proteins, phenolic, oils, aromatic molecules, lipids, vitamins, minerals, ascorbic acid compounds, and other chemicals.<sup>1</sup> The components, carotenoids and capsaicinoids, elucidate the significance of red capsicum cultivars and their fat extracts in the food and medicine sectors.<sup>2</sup>

Pepper's spiciness is controlled by capsaicinoids, which are made up of seven similar branched-chain alkyl vanillyl amides.

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The main compounds are capsaicin and dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, and homocapsaicin are found in smaller amounts.<sup>3</sup> In the last twenty years, there has been a huge rise in interest in figuring out and proving the effects of capsaicin. Researchers have looked at how capsaicin can help with analgesia, preventing cancer, controlling body mass via adipose thermogenesis, improving heart and digestive health, lowering blood sugar levels, and treating blood in the urine.<sup>4</sup> Capsaicinoids are very useful because they can be used as natural food ingredients, antimicrobials, and parts of self-defence products.<sup>5</sup>

The compounds that contribute to the profound red hues are capsanthin and capsanthin-5, 6-epoxide. Carotenoids exhibit various significant biological functions. They are powerful antioxidants that function as scavengers of singlet molecular oxygen, reactive nitrogen species, and peroxy radicals.<sup>6</sup> Consuming foods rich in carotenoids diminishes the prevalence of various disorders, including malignancies, cardiovascular diseases, macular degeneration due to age, cataracts, immunological dysfunction-related diseases, and other degenerative conditions.<sup>7</sup>

Nano calcium peroxide is in the form of a white to yellow crystalline powder belonging to the group of superoxides. It is considered a strong oxidizer. Calcium

peroxide exists as ( $\text{CaO}_2 \cdot 8\text{H}_2\text{O}$ ) and begins to lose water of crystallization on heating above  $130^\circ\text{C}$ .<sup>8</sup>

Tumor-induced hypoxia can lead to high cancer mortality rates. Furthermore, most cancer therapies require oxygen to function properly. Nanomaterials have demonstrated significant antitumor activity and low toxicity, due to the combination of chemotherapeutic effects.<sup>9</sup>

The primary global problem in the management and treatment of HT-29 is the premature identification and provision of effective therapeutic techniques. Numerous advancements have effectively utilized nanotechnology in conjunction with radiopharmaceuticals, rendering individualized treatment for HT-29 a feasible future trajectory.<sup>10</sup>

Nanoparticles exhibit distinctive characteristics, including diminutive size, varied forms, heightened sensibility, and tailored chemical formulations based on their nano-formula. These qualities enable their function as contrasting and coating materials in cancer imaging and therapeutics for the delivery of nanodrugs. Furthermore, they augment the biochemical and physiological comprehension of HT-29, rendering them attractive, innovative instruments for HT-29 care. Nonetheless, various hurdles impede the advancement of nanoparticles owing to their intricate pharmacokinetics.<sup>11</sup>

$\text{CaO}_2$  nanoparticles possess capability to function as an in real-time switch for independent thermoelectric dynamics treatment, attributed to their tumour environment (low pH)-specific thermal impact resulting from water release, a phenomenon that remains unexamined. The tumor-specific self-activated thermoelectric nano heterojunction, in conjunction with catalytic therapy, ion interference therapy, and immunotherapy, demonstrates superior anticancer efficacy in female mice. Overcoming these constraints necessitates additional study and exploration into nanoparticle design and the methodologies for radiolabeling in therapeutic applications.<sup>12</sup>

Cancer nanotechnology has revolutionized contemporary treatment modalities by offering enhanced cancer detection and therapies. It can be utilized for early-stage cancer detection and for the targeted delivery of chemotherapeutic agents to malignant cells.<sup>13</sup>

## METHODS

This experimental study was carried out at the College of Education for Pure Sciences/Ibn Al-Haitham at the University of Baghdad from 1<sup>st</sup> January 2024 to 31<sup>st</sup> March 2025 vide letter No. 8360 date 10-11-2023. Ethyl alcohol ( $\text{C}_2\text{H}_5\text{OH}$ ,  $\geq 99.8\%$ ) was purchased from Honeywell (Germany), sodium hydroxide (NaOH) and calcium sulfate ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ) from Romil pure chemistry (United Kingdom), and Sodium borohydrate ( $\text{H}_4\text{BNa}$ ) from Sigma-Aldrich, (USA). The solutions

were prepared with distilled water and chili pepper (capsicum) plant extract after several preparatory procedures. A digital pH meter was utilised to assess pH. All compounds were of analytical quality.

Capsicum extract was obtained after the plant was chopped and washed with water to remove any dirt and impurities. The extract was transferred to a volumetric flask, and 250 mL of distilled water was added. The mixture was heated to  $70^\circ\text{C}$  with continuous stirring for 30 minutes, resulting in a green color. The mixture was filtered while hot, and 100 mL of the filtrate was taken and 50 mL of 0.1 M calcium sulfate dihydrate ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ) at 1:2 was added. The solution was stirred continuously and heated at  $25^\circ\text{C}$ . The color of the solution was light green. 0.1 M sodium hydroxide (NaOH) was added, followed by  $\text{H}_4\text{BNa}$  powder, with continuous stirring, resulting in a yellow precipitate. The precipitate was separated in a centrifuge for 10 min at 4000 rpm. The solution was filtered through filter paper. The precipitate was washed with hot deionized water and hot ethanol. The precipitate was allowed to dry for 24 h and then transferred to a dry oven at  $285^\circ\text{C}$  for 48 h. The final product was white. The data was entered and analyzed through SPSS-24.

## RESULTS

The electronic spectrum showed an absorption peak for  $\text{CaO}_2$  at ( $\lambda \text{ max} = 371.7 \text{ nm}$ ) in the UV region. This indicates that the color of the nano powder is white, yellowish within the visible area (Fig. 1).

In this context, the wavelength is implemented, where  $k$  denotes the form factor (0.9),  $\theta$  signifies the diffraction angles, and  $\beta$  indicates the full width at half maximum. The phase structure of the sample was ascertained by X-ray diffraction (XRD). The XRD pattern exhibited peaks at  $25.18^\circ$ ,  $31.06^\circ$ ,  $36.15^\circ$ ,  $40.58^\circ$ ,  $42.96^\circ$ ,  $48.44^\circ$ , and  $52.00^\circ$  corresponding to the cubic  $\text{CaO}_2$  planes (110), (002), (200), (112), (211), (202), and (220) respectively. These results were compared with JCPDS file 01-085-0514, revealing no detectable impurity phases. The crystallite size of  $\text{CaO}_2$  nanoparticles corresponding to the peak of greatest intensity was ascertained using (220) plane. Size of crystallite was determined using the Scherrer equation, resulting in a measurement of 20 nm. Structural characteristics of the synthesized  $\text{CaO}_2$  nanoparticles were determined using equations derived from XRD data (Table 1). Ideal parameters were determined by the minimal size of particles (25.18 nm) and maximal crystallinity (distinct XRD peaks).

Techniques were used to examine the microstructure and surface characteristics of  $\text{CaO}_2$  nanoparticles. The scanned images obtained via SEM, illustrating a highly homogeneous and fine particle distribution with minimal agglomeration. The dimensions of the  $\text{CaO}_2$  nanoparticles align with TEM images, which depict spherical particles. Nonetheless, aggregated particles

can be observed in the micrographs. Intergranular gaps represent an additional characteristic observable, signifying greater connectivity among the grains.

Using EDX analysis, the production of calcium peroxide nanoparticles, and different regions were identified during the analysis. The presence of calcium peroxide in the produced nanostructure was confirmed by EDX spectroscopy, with atomic ratios of 40% calcium and 55% peroxide. Although the synthesized samples contained impurities of hydrogen, oxygen, and carbon, and 5% plant extract residues (Fig. 2).

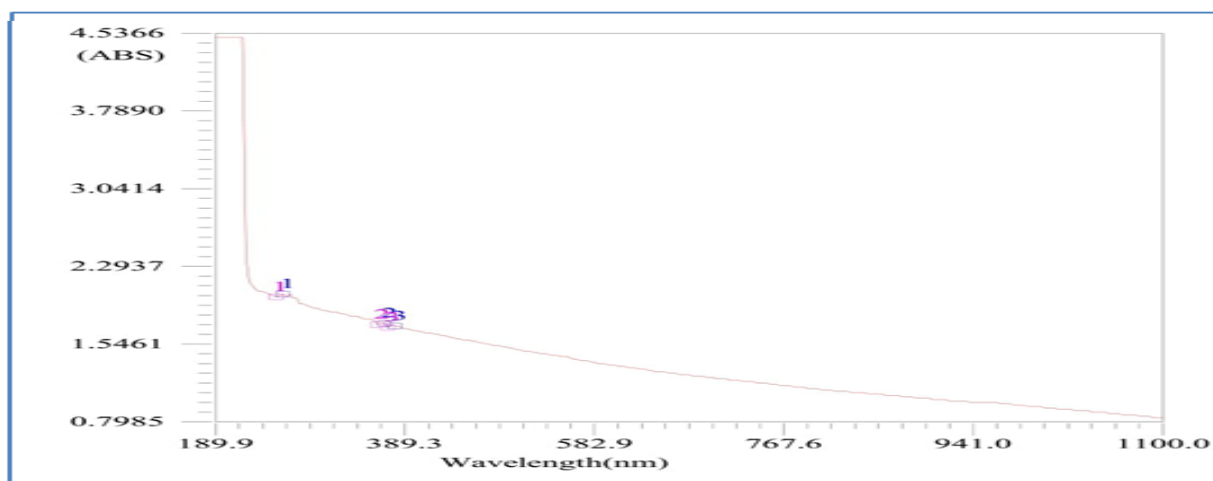
This technique is used to examine the size, shape, and structure of nanomaterials, as well as their dispersion

and aggregation, the AFM histogram and statistical particle analysis of CaO<sub>2</sub>NPs powder.

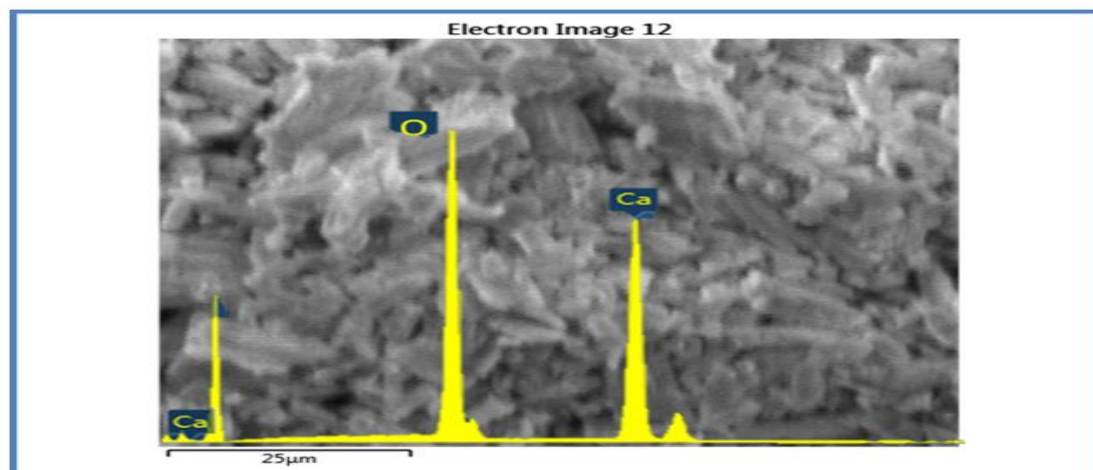
The nanoparticles have a cytotoxic effect against HT-29 cells, and can control untreated HT-289 cells and monitor the morphological changes in HT-29 cells after been treated with CaO<sub>2</sub> NPs. Magnification power 10x (Figs. 3-4. These particles associate with cancer cells by producing reactive oxygen species, which influence protein expression and trigger cell cycle arrest and death. Moreover, they can augment the immune response, rendering them a valuable asset in cancer therapy methodologies.

**Table No. 1: XRD analysis results of CaO<sub>2</sub> powder**

2 Theta (degree)	Hkl	FWHM (deg)	2 Theta (Rad)	FWHM (Rad)	D (nm)	Matched by
25.1802	110	0.2539	0.219738	0.004	32.051	01-085-0514
31.0689	002	0.2962	0.271127	0.005	27.828	
36.157	200	0.3385	0.315529	0.006	24.769	
40.5866	112	0.3385	0.354185	0.006	25.013	
42.9608	211	0.2116	0.374903	0.004	40.338	
48.4496	202	0.2539	0.422802	0.004	34.301	
52.0052	220	0.2539	0.453831	0.004	34.803	



**Figure No. 1: UV – Vis absorption spectrum of CaO<sub>2</sub>NPs powder**



**Figure No. 2: EDX analysis of CaO<sub>2</sub>NPs powder**

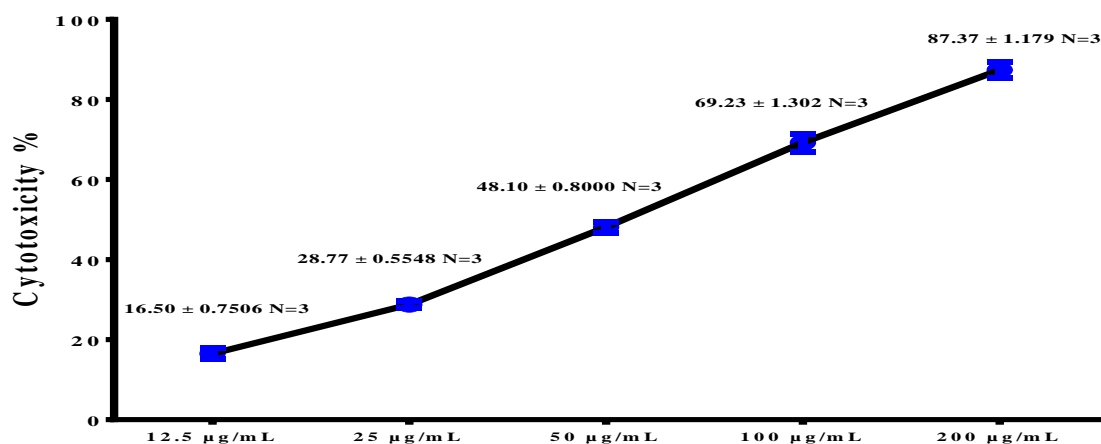


Figure No. 3: Cytotoxicity effect of CaO<sub>2</sub>NPs in HT-29 cells

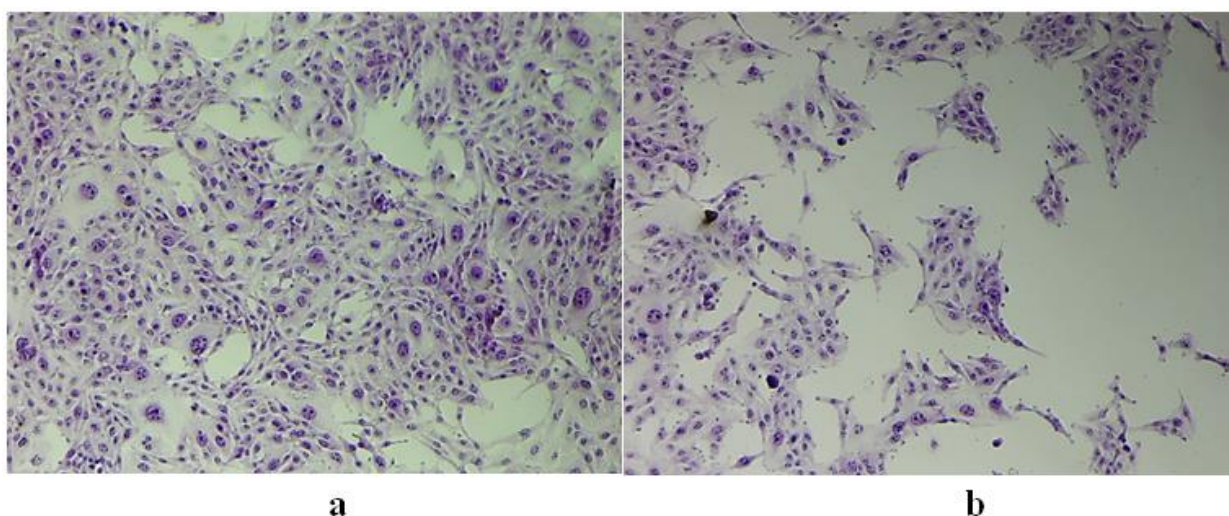


Figure No. 4: (a) Control uninfected HT-29 cells. (b) Morphological alterations in HT-29 cells following treatment with CaO<sub>2</sub> nanoparticles. Magnification power of 10x

## DISCUSSION

The findings of the present study showed that HT-29 ranks among the leading causes of cancer-related mortality globally. The diagnosis and management of this condition encounter multiple hurdles. Traditional diagnostic techniques exhibit diminished accuracy in assessing tumor growth or metastasis, and the resultant treatments sometimes entail adverse side effects stemming from this inaccuracy. The application of calcium peroxide nanoparticles has introduced a novel paradigm in cancer therapy, focused on advancing imaging and treatment methodologies. The biomolecules present in capsicum plant extract of enable eco-friendly procedure and green synthesis for synthesis of CaO<sub>2</sub>NPs. Capsicum plant contains various bioactive compounds

The HT-29 cell line was cultured in RPMI-1640 enriched with 10% fetal calf serum, 100 units/mL of penicillin, and 100 µg/mL of streptomycin. Cells were transmitted with Trypsin-EDTA, reseeded at 80% concentration biweekly, and incubated at 37°C.<sup>14</sup> HT-29 is a form of

cancer that impacts the colon (large intestine) or rectum. It is among the most prevalent forms of cancer globally and can result in significant injury and mortality. The likelihood of getting HT-29 grows with age, predominantly affecting individuals over fifty years old. One of the most important symptoms of this disease is low iron levels in the body.<sup>15</sup> While it may manifest at any age, it typically initiates as diminutive, benign cellular aggregates known as polyps that develop within the colon. Over time, some polyps may progress to colon cancer. In most cases, colon cancer begins as a small clump called an adenomatous polyp.<sup>16</sup> The cytotoxic effect of nanoparticles was assessed using the MTT assay conducted in 96-well plates. HT-29 cells were inoculated at a density of 1×10<sup>4</sup> cells per well. Subsequent to 24 h. Upon achieving a confluent monolayer, HT-29 cells were treated with nanoparticles at varying concentrations. Cell viability was assessed after 72 h and treatment by removing the medium, adding 100 µL of a 2 mg/mL MTT solution, and incubating the cells for 2.5 h at 37°C.<sup>17</sup> Subsequent to the removal of the MTT solution, the residual crystals in the holes were solubilized by the addition of

130 µL of DMSO (Dimethyl Sulphoxide), followed by incubation at 37 °C for 15 min with agitation. The absorbance was measured using a microplate reader at 492 nm; the test was conducted in triplicate.<sup>18</sup>

The use of calcium peroxide nanoparticles in colon cancer therapy is a promising research domain. This study's results emphasize the detection and efficacy of calcium peroxide nanoparticles derived from capsicum plant extract in combating colon cancer. Future research should concentrate on the advancement of more efficient calcium peroxide nanoparticles, specifically for the targeting of colorectal cancer biomarkers, alongside an examination of their safety and efficacy in clinical trials. The application of calcium peroxide nanoparticles in colon cancer therapy may enhance therapeutic efficacy and patient quality of life

## CONCLUSION

The use of calcium peroxide nanoparticles represents a novel approach to cancer treatment, focusing on developing imaging and therapeutic methodologies. Bioactive molecules found in chili pepper extract enable environmentally friendly and green synthesis procedures for the production of calcium peroxide nanoparticles (CaO<sub>2</sub>NPs). Chili peppers contain a variety of bioactive compounds.

### Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Hassan MA. Al-Redha, Waleed K. Mahdi
Drafting or Revising Critically:	Hassan MA. Al-Redha, Waleed K. Mahdi
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

**Conflict of Interest:** The study has no conflict of interest to declare by any author.

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# Comparative Evaluation of Immunohistochemistry and Flow Cytometry in Diagnosing Clonality in B-Cell Lymphoid Malignancies

Bahaulddin Hassan Abbood, Rahem Mahdy Rahem and Kaswr Musa Jaafar Al Tariahi

## ABSTRACT

**Objective:** To assess various methods for clonality detection in patients with B-cell lymphoblastic leukemia.

**Study Design:** A diagnostic study

**Place and Duration of Study:** This study was conducted at the Department of Pathology and Forensic Medicine, Faculty of Medicine, University of Kufa from 1<sup>st</sup> January 2024 to 30<sup>th</sup> June 2024.

**Methods:** Diagnoses were based on the gold-standard flow cytometry test for B-cell acute lymphoblastic leukemia. Patient data, including age, gender, clinical features, complete blood count, blood smear, and bone marrow morphology reports, were collected. Immunohistochemistry panel (CD19, 20, 10, 34, MPO & TdT) was used on BM biopsies.

**Results:** The mean age was 30.74 years, with a male-to-female ratio of 1:2.04. Four diagnostic marker panels, incorporating IHC and cytochemistry, were evaluated. The first panel of five markers (CD10, 19, 20, 34, and TdT) showed a sensitivity of 46.27% and a specificity of 53.73%, second panel with three markers (CD10, 19, 20, and 34), demonstrated 52.24% sensitivity and 47.76% specificity and third panel (CD10, 19, 20, and TdT) yielded 53.73% sensitivity and 46.27% specificity.

**Conclusion:** The four-marker IHC panel (CD10, 19, 20, and TdT) is effective for diagnosing B-cell ALL, especially in settings where flow cytometry is inaccessible or unaffordable offers valuable diagnostic utility in low-resource laboratories lacking access to flow cytometry.

**Key Words:** Clonality detection, B-cell lymphoblastic leukemia, Flow cytometry, Immunohistochemistry, Cytochemical stain

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## INTRODUCTION

Leukemia is a hematologic malignancy characterized by the uncontrolled proliferation of abnormal white blood cells, known as blasts, in the bone marrow and blood. Unlike normal white cells, leukemia cells are immature, rapidly proliferating, and dysfunctional, often replacing healthy blood cells and potentially infiltrating other organs such as the liver and spleen. The major types of leukemia include acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), Acute Myeloid Leukemia (AML), and chronic myeloid leukemia (CML).<sup>1</sup>

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Leukemia is classified based on its rate of progression acute or chronic and the blood cell lineage affected, either lymphoid or myeloid. Acute leukemia progresses quickly, while chronic forms develop more gradually. "Lymphoblastic" or "lymphocytic" leukemia arises from lymphoid stem cells and "myeloid" or "myelogenous" leukemia originates in myeloid progenitors.<sup>2</sup> ALL is a rapidly progressing leukemia derived from immature lymphoid cells. It primarily affects lymphocytes at an early developmental stage and accounts for about 85% of childhood leukemia cases.<sup>3</sup> Subtypes of ALL include B-cell and T-cell ALL, with B-cell ALL being the most common (85% of cases).<sup>3,4</sup> Advances in immunophenotyping have further classified B-cell ALL into Early pre-B (10%), Common ALL (50%), and Mature B-cell ALL (4%).<sup>5</sup> The World Health Organization (WHO) no longer uses the French-American-British (FAB) classification for ALL due to its limited clinical utility and instead relies on immunophenotypic markers to define subtypes.<sup>6</sup> B-ALL is characterized by the overproduction of immature B-cell lymphoblasts. It predominantly affects children aged 1–4 and accounts for 75% of ALL cases.

However, adults with B-ALL face lower survival rates and higher relapse risks.<sup>7</sup>

The incidence of ALL varies globally, with higher rates in North America and Europe compared to Asia and Africa. Genetic syndromes, such as Down syndrome, and environmental factors like radiation exposure and chemical toxins are associated with increased ALL risk.<sup>8,9</sup> Additionally, the "hygiene hypothesis" suggests that limited childhood infection exposure may influence leukemia risk.<sup>10</sup> Socioeconomic disparities also contribute to incidence and outcomes.<sup>10</sup>

The pathogenesis of B-ALL involves genetic, epigenetic, and microenvironmental factors. Chromosomal translocations, including BCR-ABL1 and MLL rearrangements, are common in high-risk cases.<sup>11</sup> Epigenetic alterations, such as DNA methylation and histone modifications, and dysregulated non-coding RNAs also play critical roles in disease progression.<sup>12</sup> The bone marrow microenvironment supports leukemic cells through stromal cell interactions and cytokines like IL-7, contributing to therapy resistance.<sup>13</sup>

Diagnosis of B-ALL integrates clinical, cytological, and molecular assessments: (1) Clinical evaluation and CBC identifies anemia, thrombocytopenia, and leukocytosis. (2) Peripheral blood smear highlights characteristic lymphoblasts.<sup>14</sup> (3) Bone marrow biopsy confirms leukemic infiltration. (4) Flow cytometry, a gold-standard technique for immunophenotyping markers such as CD19, CD10, CD34, and TdT. It is also used for Minimal Residual Disease (MRD) monitoring.<sup>15</sup> (4) Cytogenetics and molecular testing detect chromosomal translocations and mutations (e.g. Philadelphia chromosome, hyperdiploidy) to guide prognosis and therapy.<sup>16</sup>

IHC aids in diagnosing and subclassifying B-ALL by identifying surface markers such as CD19: A universal B-cell marker, CD10: Indicates early B-cell precursor stages, TdT: Associated with immature lymphoid cells and PAX5 and CD20: Confirm B-cell lineage and guide therapy.<sup>17</sup>

Treatment of B-ALL involves chemotherapy, targeted therapies, and immunotherapies. Chemotherapy regimens include agents like vincristine and asparaginase, while tyrosine kinase inhibitors (TKIs) such as imatinib are effective for Philadelphia chromosome-positive B-ALL.<sup>18</sup> Novel therapies, including CAR T-cell therapy, offer hope for relapsed or refractory cases.<sup>19</sup> Prognosis depends on age, genetic factors, and MRD status. Children aged 1-9 years show high remission rates (>80%), while adults face poorer outcomes due to adverse genetic profiles.<sup>20</sup> Favorable genetic markers like hyperdiploidy improve outcomes, while CNS involvement worsens prognosis.<sup>21</sup>

## METHODS

This study was conducted in the Department of Pathology and Forensic Medicine at the Faculty of Medicine, University of Kufa, from 1<sup>st</sup> January 2024 to 30<sup>th</sup> June 2024 vide letter No. 3234/QM/Approval/JKEIRU dated 2<sup>nd</sup> September 2023. The cases were collected from the Hematology Department at Baghdad Medical City and Baghdad Educational Laboratories. All cases diagnosed as B-cell Acute Lymphoblastic Leukemia (B-ALL) by a hematopathologist using clinical findings, complete blood count, blood film, bone marrow examination, and flow cytometry (FCM) and newly diagnosed patients, of both genders, with no age limitation were included. All patients undergoing treatment, uncertain diagnoses, other malignancies and cases without complete data were excluded. All cases were retrieved with permission from the department, and patient information was kept confidential.

Blood samples and bone marrow aspirates were collected for testing. The following diagnostic methods were used: complete blood count for evaluating general blood parameters, bone marrow aspiration for FCM analysis, bone marrow biopsy to understand the cellular makeup of the bone marrow and immunohistochemistry to detect cellular markers and signs of clonality in paraffin-embedded tissue samples. The IHC markers used were CD19, CD20, CD10, CD34, TdT, and MPO. Sampling including CBC, blood films, BMA, BMB, and FCM results, were collected. Fresh blood films were taken for further staining if needed, along with 2-3 slides of unstained BM aspirates. Paraffin blocks were sectioned into 6-7 slices for IHC analysis.

Immunohistochemistry is a technique used to detect antigens in tissues using specific antibodies. The steps involved in IHC are as follows:

1. Deparaffinization and Rehydration: Removal of paraffin wax and rehydration of tissue sections.
2. Antigen Retrieval: Treating tissue sections to unmask antigens.
3. Blocking: Preventing non-specific antibody binding.
4. Primary Antibody Incubation: Incubating with primary antibodies (e.g, CD10, CD20, CD19, CD34, MPO, TdT).
5. Washing: Removing unbound primary antibodies.
6. Secondary Antibody Incubation: Adding a secondary antibody with an enzyme or fluorophore for detection.
7. Washing: Removing excess secondary antibodies.
8. Detection and Visualization: Adding a substrate to reveal the target antigen.
9. Counterstaining: Optional step to provide contrast.
10. Mounting: Sealing the slide with a mounting medium.

Each marker's expression was evaluated based on staining intensity and distribution in the tissue. Scoring System: Two scoring systems were used to assess marker expression:

- **Positivity Score:** Measures the percentage of cells showing positivity for a specific marker:
  - Score 0: Less than 5% of tumor cells
  - Score 1: 5%-25% of tumor cells
  - Score 2: 26%-50% of tumor cells
  - Score 3: 51%-75% of tumor cells
  - Score 4: More than 75% of tumor cells
- **Intensity Score:** Measures the strength of staining:
  - 0: Negative
  - 1: Weak
  - 2: Intermediate
  - 3: Strong

A final score is calculated by combining the positivity and intensity scores, with values between 0-12. Scores between 0-8 indicate reduced immunoeexpression, and scores between 9-12 indicate strong immunoeexpression.

Statistical analysis was done using SPSS-26. T-tests were used for comparisons between two groups, and ANOVA was used for comparisons across multiple groups. Regression analysis (e.g, linear regression) was performed to explore the relationship between marker expression levels and patient outcomes and  $p < 0.05$  was considered significant.

## RESULTS

The mean age of the patients is 30.74 years, with a standard deviation of 15.79 years, indicating a wide age range among the patients. The youngest patient is 13 years old, while the oldest is 75 years old. The study found that there are 67.16% females (45 patients) and 32.83% males (22 patients), indicating a higher representation of females in this patient group, with ratio (1:2) [Table 1].

Table 2 shows the hematological features of the patients including their hemoglobin (HB) levels, platelet counts, total white blood cell (WBC) counts, absolute neutrophil (NE), absolute lymphocyte (LY), and blast cell percentage.

Table 3 presents the distribution of positive and negative markers among the patients, as identified through Flow Cytometry (FCM) and Immunohistochemistry (IHC). All patients (67) were positive for CD10 using both FCM and IHC, indicating a 100% positivity rate with no negatives. For CD20, FCM also showed 100% positivity, while IHC revealed that 94.02% (63 patients) were positive and 5.33% (4 patients) were negative. Similarly, CD19 showed 100% positivity by FCM, but IHC indicated that 67.16% (45 patients) were positive and 29.34% (22 patients) were negative. CD34 was positive in 85.07% (57 patients) by FCM and 83.58% (56 patients) by IHC, with corresponding negative rates of 13.34% (10 patients)

and 14.67% (11 patients). MPO exhibited 100% negativity with both FCM and IHC. For TDT, FCM showed 85.07% positivity (57 patients) and 13.34% negativity (10 patients), while IHC showed 91.04% positivity (61 patients) and 8% negativity (6 patients). Both flow cytometry and immunohistochemistry demonstrated a 100% positive detection rate for CD10. CD20 showed a 100% positive detection rate with Flow Cytometry, but a slightly lower positive rate of 94.02% with Immunohistochemistry. The positive detection rate for CD19 was 100% with Flow Cytometry; whereas it was 67.16% with Immunohistochemistry. Flow Cytometry detected CD34 in 85.07% of cases, while Immunohistochemistry showed a slightly lower detection rate at 83.58%. Both Flow Cytometry and Immunohistochemistry did not detect MPO. TDT was detected in 85.07% of cases using Flow Cytometry and in 91.04% of cases using Immunohistochemistry (Fig. 1).

Table 4 critically evaluates various biomarkers using different diagnostic methods, specifically Flow Cytometry and Immunohistochemistry. For CD10, CD20, CD19, and TDT assessed by FCM, the results reveal a perfect sensitivity of 100% but a specificity of 0%. This indicates these markers are excellent at identifying true positives, with a high PPV of 90%, but fail to correctly identify true negatives, resulting in an overall accuracy of 90%. In contrast, the IHC method for CD20 demonstrates a more balanced performance with 93.65% sensitivity, 85.71% specificity, 98.36% PPV, 54.55% NPV, and an accuracy of 92.86%. The IHC method for CD19, with a high sensitivity of 98.41% and moderate specificity of 28.57%, achieves a PPV of 92.86% and an accuracy of 90.48%. The CD34 marker shows a similar pattern, with FCM yielding high sensitivity (98.41%) but low specificity (28.57%), resulting in 90.48% accuracy. In contrast, IHC for CD34 achieves lower sensitivity (80.95%) but higher specificity (85.71%), leading to an accuracy of 82.14%. MPO, evaluated by both methods, fails to detect malignancies effectively, with 0% sensitivity, specificity, PPV, NPV, and accuracy.

**Table No. 1: General features of the patients**

Variable	No.	%
<b>Gender:</b> Male	22	32.83
Female	45	67.16
Age (years)	30.74±15.79	

**Table No. 2: Hematological characteristics of the patients**

Parameter	Mean±SD
Hemoglobin	8.16±1.32
Platelets x 109 /L	40.74±21.32
WBC x 109 /L	12.74±10.37
NE %	12.50±6.43
LY %	41.79±14.47
Blast cell %	31.65±10.55

IHC identified 31 cases as positive (46.27%) and 36 cases as negative (53.73%). In terms of sensitivity, the IHC panel correctly identified 46.27% of the cases that were positive according to IHC, meaning it missed 53.73% of the positive cases, indicating low sensitivity.

The specificity of the IHC panel was 53.73%, which implies it correctly identified negative cases 53.73% of the time, suggesting a moderate ability to avoid false positives (Table 5).

**Table No. 3: Number of positives and negatives of IHC markers**

IHC markers		No. Positives	%	No. Negatives	%
CD10	FCM	67	100	-	-
	IHC	67	100	-	-
CD20	FCM	67	100	-	-
	IHC	63	94.02	4	5.33
CD19	FCM	67	100	-	-
	IHC	45	67.16	22	29.34
CD34	FCM	57	85.07	10	13.34
	IHC	56	83.58	11	14.67
MPO	FCM	0	100	67	-
	IHC	0	100	67	-
TDT	FCM	57	85.07	10	13.34
	IHC	61	91.04	6	8

**Table No. 4: Sensitivity, Specificity, PPV and NPV of the markers**

Marker	Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CD10	FCM	100	0	90	N/A
CD10	IHC	100	0	90	N/A
CD20	FCM	100	0	90	N/A
CD20	IHC	93.65	85.71	98.36	54.55
CD19	FCM	100	0	90	N/A
CD19	IHC	98.41	28.57	92.86	66.67
CD34	FCM	98.41	28.57	92.86	66.67
CD34	IHC	80.95	85.71	98.15	30
MPO	FCM	0	0	0	0
MPO	IHC	0	0	0	0
TDT	FCM	100	0	90	N/A
TDT	IHC	90.48	28.57	92.31	25

**Table No. 5: Panel Test for CD10, CD20, CD19, CD34, TDT**

Result	+ve	-ve	Sensitivity	Specificity	NPV	PPV	Total
IHC Panel	31	36	46.27%	53.73%	53.73%	46.27%	67

## DISCUSSION

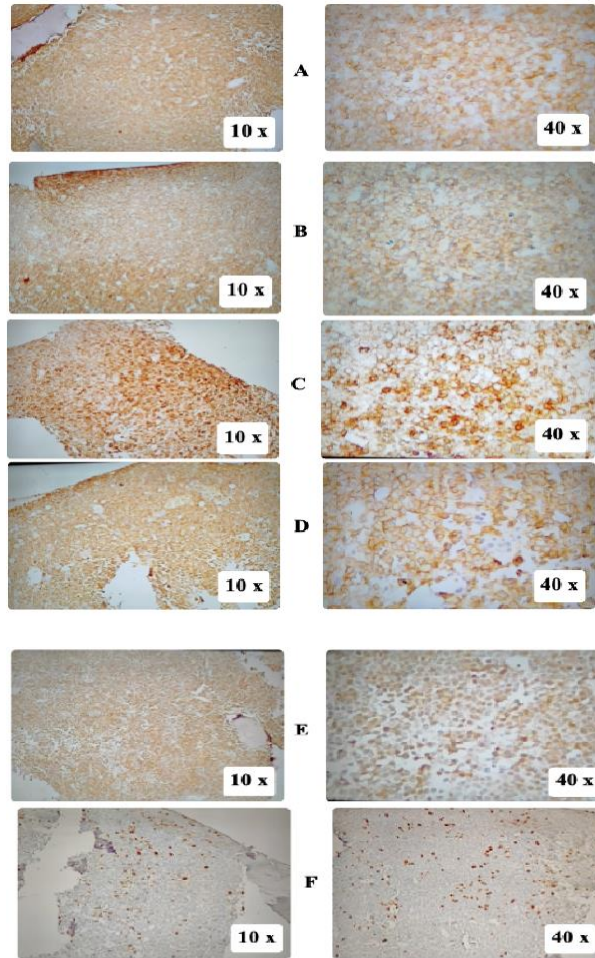
This study explored the efficacy of various diagnostic methods for clonality detection in B-cell lymphoid malignancies. We specifically compared flow cytometry, Immunohistochemistry, to assess their diagnostic reliability. While FCM was confirmed as the gold standard, the integration of IHC helped further diagnosis, particularly in ambiguous cases. These findings highlight the advantage of employing multiple diagnostic tools in combination, rather than relying on a single method.<sup>22,23</sup>

In the present study, mean age was 30.74±15.79 years and 45 (67.16%) were females and 22 (32.83%) males. This sex distribution aligns with typical B-ALL trends, where females are more frequently diagnosed in younger age groups, while males show higher incidence rates in

older age groups. Age is a significant factor in prognosis, as pediatric patients typically benefit from specialized treatment protocols that yield better outcomes, while adult patients face more challenges, particularly those aged over 45.<sup>22</sup> Our results reflect these age-related patterns in B-ALL.

Blood parameters, such as hemoglobin (Hb), neutrophil-to-lymphocyte ratio (NLR), and platelet counts, are increasingly recognized as important prognostic indicators in B-ALL. Low Hb levels, for instance, are associated with more aggressive disease, while an elevated NLR often correlates with poorer outcomes. Platelet abnormalities are common in B-ALL, serving as a marker of bone marrow dysfunction. Although these blood tests can signal potential leukemia, they are not sufficient for a definitive diagnosis and should be followed by more specific methods like FCM and IHC.<sup>24</sup>

The IHC panel used in this study comprising CD10, CD20, CD19, CD34, and TdT demonstrated moderate sensitivity and specificity for B-ALL diagnosis. Of the 67 cases, 31 tested positive (46.27%), and 36 were negative (53.73%). The panel's sensitivity of 46.27% means that it correctly identified less than half of the true positives, while its specificity of 53.73% indicates that it identified just over half of the negative cases correctly. While these results suggest that IHC may not be the most sensitive method, it remains valuable for excluding negative cases. It also provides a cost-effective alternative when more expensive tests like FCM are not accessible.



**Figure No. 1:** (A) Slides of Positive CD10, (B) Slides of Positive CD19, (C) Slides of Positive CD20, (D) Slides of Positive CD34, (E) Slides of Positive TdT, (F) Slides of negative MPO

IHC is supported by several studies, such as the work by Allen et al, which advocate for a streamlined IHC panel to reduce both costs and turnaround time, without compromising diagnostic accuracy.<sup>25</sup> Other research also supports the combination of various markers to improve sensitivity, particularly in cases where other tests are inconclusive.<sup>26</sup> The use of IHC in conjunction with other

diagnostic techniques like FCM can offer more robust results and reduce misdiagnosis.

## CONCLUSION

The use of 4-panel immunohistochemistry (CD10, 19, 20, TdT) is more suitable in the diagnosis of B-cell acute lymphoblastic leukemia when the flow cytometry method is unavailable or cost-related limitations occur.

### Author's Contribution:

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Drafting or Revising Critically:	Kaswr Musa Jaafar Al tariahi
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Agreement to accountable for all aspects of work:	All the above authors

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# Prevention and Precautions of Hepatitis B and C among Hemodialysis Units

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## ABSTRACT

**Objective:** To evaluate nurses' awareness of hepatitis B and C prevention strategies and precautions at dialysis units in southern Iraqi cities.

**Study Design:** A cross-sectional study

**Place and Duration of Study:** This study was conducted at the dialysis centers in Iraq's southern cities from 15<sup>th</sup> October 2021 to 30<sup>th</sup> December 2021.

**Methods:** Out of four units, 96 nurses were selected as a sample. A developed questionnaire with 42 items divided into five domains was utilized to gather the data, and in-person interviews were employed as the method of interaction. Thirteen experts evaluated the instrument's validity, and the Cronbach's test was used to assess the study tool's reliability.

**Results:** The nurses' understanding of dialysis units varied significantly across four southern cities.

**Conclusion:** Hemodialysis units should employ nurses with the highest educational attainment. Additionally, all nurses should be able to view specific information regarding The walls of the hemodialysis unit are marked with basic precautions and preventative measures for viral hepatitis B and C.

**Key Words:** Prevention, Precautions, Hemodialysis, Hepatitis

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## INTRODUCTION

For individuals with end-stage kidney disease, the most popular type of renal therapeutic alternative therapy is hemodialysis (HD). Patients undergoing HD may be more susceptible to infection, particularly from blood-borne viruses (BBVs).<sup>1</sup>

The primary causes of morbidity and mortality among hemodialysis patients are viral hepatitis B and C infections. These diseases also present care issues in renal dialysis units because patients with chronic kidney failure are unable to adequately eliminate these infectious agents. Hemodialysis centers in southern Iraqi cities were the site of a descriptive cross-sectional investigation. The most common condition that leads to HD treatment is viral hepatitis, including B and C.<sup>2</sup>

Hemodialysis patients are more likely than the general population to develop viral hepatitis B and C. Because of the implementation of prophylactic measures, including as vaccines, serologic screening, and post-exposure treatment, the number of transmissions linked to hemodialysis has significantly decreased.

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The first reports of viral hepatitis spreading in hemodialysis date back to the 1960s and continue to this day.<sup>3</sup>

Hemodialysis patients are more likely than the general population to develop viral hepatitis B and C. Because of the implementation of prophylactic measures, including vaccines, serologic screening, and post-exposure treatment, the number of transmissions linked to hemodialysis has significantly decreased. The first reports of viral hepatitis spreading in hemodialysis date back to the 1960s and continue to this day.<sup>4</sup>

Healthcare professionals have reported contaminated syringes and needles, as well as the little amounts of blood accidentally being inseminated during surgery, are the two ways that HBV and HCV are spread. They must take the right precautions to prevent illness. However, rigorous adherence to accepted microbiological procedures and methods, HBV can be avoided by avoiding pre-vaccine exposure and by regularly taking the proper precautions to shield skin and mucous membranes while handling blood and other bodily fluids for all patients in medical facilities.<sup>5</sup>

Blood transfusions, the length of dialysis, intravenous medication use, and a history of kidney transplantation are risk factors for HBV and HCV in dialysis patients.<sup>6</sup> Hemodialysis requires careful patient care, and a professional nurse is essential in this regard. In addition to providing care that supports management, preventing complications, and giving health advice, they also plan and execute treatments to manage and prevent injuries. The capacity of the nursing specialist to diagnose the patient's symptoms and organize their care based on professional judgment.<sup>7</sup>

To improve the patient's quality of life, the nursing staff frequently provides emotional support to dialysis patients. They do this by looking at the significance that an individual places on their life experiences and trying to determine what the patient expects from the care they receive.<sup>8</sup>

Monitoring, supporting, assessing, and teaching the patient are all crucial tasks performed by the nurse in the dialysis unit. Due to the numerous potential complications, such as clotting of the dialyzer or dialysis tubes, during dialysis, the patient and the dialyzer must be closely watched for air blockage, hypotension, spasms, vomiting, blood leakage, contamination, problems with access tubes, and insufficient or excessive fluid removal.<sup>9</sup>

The requirements of renal failure patients and their relatives throughout their lives are the focus of the specialized nursing field of hemodialysis. The nurse providing this specialist care must exhibit up-to-date specialty knowledge and practice in addition to promoting competent, safe, and ethical care. A vital aspect of nursing practice, patient education enhances people's health and equips them with the information and abilities needed to manage chronic conditions like renal disease. Bringing about long-lasting behavioral changes is the primary objective of patient education by equipping patients with the skills, knowledge, and practices necessary to make independent decisions and take charge of their own care in order to improve their own results.<sup>10</sup>

For nurses, infection prevention measures and protection against needle sticks and severe injuries are crucial. Post-exposure prevention, immunization, and blood-borne transmission education must be put into practice. To fully understand the risk of this potentially dangerous virus to nurses, more research is necessary.<sup>11</sup> Routine monitoring of the patient, dialyzer, and dialysate bath is necessary due to a number of issues, such as blood leakage, cramps, vomiting, hypotension, air embolism, circuit clotting, excessive or insufficient ultrafiltration, contamination, and problems with access and maintaining the vascular access method and providing nursing care to patients are crucial.<sup>12</sup>

## METHODS

This descriptive cross-sectional study was carried out at In the four southern Iraqi cities in hemodialysis units at Al-Hussein Hospital, Emam-Hussein Hospital, Al-Sader Hospital, and Basrah Hospital, educational institutions from 15<sup>th</sup> October 2021 to 30<sup>th</sup> December 2021 vide letter No. 9352/QM/Approval/KJD863 dated January 1, 2021. A total of 96 nurses, both male and female, who work at dialysis units across the four provinces were included in the non-probability (purposive) sample. Data was gathered using a standardized questionnaire and in-person interviewing

methods. There were two primary sections of the questionnaire. Sociodemographic data, part one, while nursing knowledge is covered in part two. It was broken down into five domains and includes 42 items.

The Cronbach's Alpha coefficient test was used to specify the study tool's reliability, and a panel of experts evaluated the instrument's validity to determine its stability and dependability. The following criteria have been used to grade and assess the items on the study questionnaire: 1 = No, 2 = uncertainty and 3 = acceptance. The data was analyzed through SPSS-22. The Chi-square, One-way analysis of variance, and Post-Hoc multiple comparison (Scheffe) test were used and P value <0.05 considered as significant.

## RESULTS

Majority of them (36.5%) hailing from Thi-Qar city. The highest percentage was 66.7% for men aged 26 to 30. The bulk of participants (51.0%) are graduates of the institute, followed by those with 1–5 years of experience (41.7%) and those attending the training session (59.37%) [Table 1]. The average score for each of the five study domains, with general precaution receiving the greatest score (2.55), and dialysis machine equipment receiving the lowest score (1.83) [Table 2].

**Table No. 1: The distribution and sociodemographic traits of the research sample (N = 96)**

Item	No.	%
<b>Province Centre</b>		
Basra	28	29.2
Maysan	22	22.9
Thi-Qar	35	36.5
Muthanna	11	11.5
<b>Gender</b>		
Male	64	66.7
Female	32	33.3
<b>Age (years)</b>		
21-25	22	22.9
26-30	31	32.3
31-35	14	14.6
36-40	15	15.6
41 & more	14	14.6
<b>Level of education</b>		
Secondary students	27	28.1
Institute students	49	51.0
University students	20	20.8
<b>Years of experience</b>		
1–5	40	41.7
6–10	31	32.3
11–15	25	26.0
<b>Training session</b>		
Yes	57	59.37
No	39	40.63

**Table No. 2: Mean of scores for the domains**

Domains	Score				Mean score	Assessment
	Basra	Maysan	Thi-Qar	Muthanna		
Universal precautions	2.40	2.52	2.60	2.68	2.55	Good
Dialysis machine equipment	1.48	1.64	2.01	2.19	1.83	Moderate
Patients surveillance	1.71	2.16	2.31	2.36	2.135	Moderate
Separation of patients	1.76	1.86	2.1	2.19	1.98	Moderate
Immunizations & medications	1.81	2.24	2.32	2.47	2.21	Moderate
Total	1.834	2.082	2.266	2.38	2.14	Moderate
	Moderate	Moderate	Moderate	Good	Moderate	

**Table No. 3: Nurses' Knowledge about Protection and Precautions of Hepatitis B and C**

City	Number	Mean of Score	Standard deviation	F	P- value	Significant
Basra city	28	1.834	0.21477	11.687	0.001	Significant
Maysan city	22	2.082	0.21802			
Thi-Qar city	35	2.266	0.37399			
Muthanna city	11	2.38	0.45135			

**Table No. 4: Multiple comparisons**

Province	Hemodialysis unit	Mean Differences	P-value	Significance
Maysan	Basra	0.27307*	0.030	Significant
Thi-Qar	Basra	0.42759*	0.001	Significant
	Maysan city	0.15451	0.356	Non-significant
Muthanna	Basra city	0.49060*	0.001	Significant
	Maysan city	0.21752	0.322	Non-significant
	Thi-Qar city	0.06303	0.953	Non-significant

With a p-value of 0.001, this table demonstrates that nurses' knowledge in hemodialysis units across four cities varies significantly (Table 3). Basrah differs significantly from the other cities, according to the table above, which displays the results of the Post Hoc multiple comparison (Scheffe) test between southern city hemodialysis centers (Table 4).

## DISCUSSION

The study involved 96 nurses in all who took part in the research. The largest proportion of the sample (36.5%) consisted of people aged 26 to 30 who lived in Thi-Qar city. Of them, men made up the largest percentage (66.7%). This conclusion was corroborated by Mohammed et al<sup>13</sup>, who observed in their study, and Al-Fatlawy<sup>14</sup>, who found that most dialysis unit nurses were men. This result is comparable to that of Dawood et al<sup>15</sup>, who found that men predominated among dialysis unit nurses, with a 56.7% rate. A similar conclusion was reached by the study by Athhi and Mohammad<sup>16</sup>, which also showed that a significant portion (60%) of the participants were men.

More than half of the patients (51.0%) received their degree from a nursing school (Table 1). This can be the result of the relatively limited number of nursing college graduates in these provinces. Most of the study samples

were nursing institute graduates, according to numerous earlier investigations that supported these findings.<sup>17</sup> With a percentage of 41.7%, the current study's findings showed that most nurses have one to five years of experience. These findings also accord with the study by Al-Hchaim and Hamza<sup>18</sup>, which discovered that most study samples had between one and five years of experience.

According to the study, 59.37% of participants are registered in training sessions. This affects nursing expertise since training programs are required to enhance skills and knowledge and keep nurses up to date. The substantial association between nurses' knowledge and prior training sessions, confirm this conclusion.<sup>19</sup>

Nurses in hemodialysis units across four provinces had a modest mean score of 2.14 for their knowledge of five domains pertaining to precautions and prevention strategies against viral hepatitis B and C (Table 2). The mean of score for hemodialysis units in Basra, Maysan, Thi-Qar, and Muthanna provinces were displayed in the table as follows: 1.834, 2.082, 2.266, and 2.38 correspondingly.

Froio et al<sup>20</sup> demonstrated that the most efficient way to stop the transmission of blood-borne viruses is to strictly enforce universal infection control procedures. Garthwaite et al<sup>21</sup> found that in order to successfully prevent the spread of blood or blood-contaminated

material from patient to patient, either directly or indirectly contaminated surfaces or equipment, protocols for infection control must include sanitary measures.

There is no proof that using specialized dialysis equipment is beneficial for individuals with HCV infection.<sup>22</sup> The internal routes of contemporary single-pass dialysis devices have not been demonstrated to be capable of transmitting HCV. While the virus cannot penetrate the intact dialyzer membrane, another study<sup>23</sup> demonstrates that for the virion to spread. It needs to pass through a second patient's dialyzer membrane after moving from the drain tube to the new dialysate circuit. Even in the event of a blood leak, HCV would need to back-filter across the dialyzer membrane to enter the patient's blood compartment after passing through the new dialysate used for a later patient.

According to Zuñiga et al<sup>24</sup>, as long as strict protocols for washing and disinfection are followed between patients, HCV patients do not require specialized equipment. Healthcare professionals should avoid dialyzing patients without an HBV infection concurrently when administering hemodialysis to Hepatitis B-infected patients. The patients must wear personal protective equipment and make sure that every patient is thoroughly decontaminated before moving on to the next, if this is not possible.

Chaves et al<sup>25</sup> reported that patient's total risk is elevated or if they personally go through an event that raises their risk, their need for surveillance should be strengthened. Furthermore, according to his research, HBsAg testing should only be done once a year for patients receiving regular hemodialysis in hospitals who are not susceptible to hepatitis B. But with time, antibody titers may decline, leaving some people vulnerable.

Dialyzing HBV-infected patients in a different area of the dialysis unit from the "clean" area has been shown to reduce the risk of HBV transmission.<sup>26</sup> Dialyzing HCV patients in a different location is not necessary, and infection control and general safety measures are taken.<sup>27</sup> The staff members who interact clinically Patients who have received an HBV vaccination should demonstrate that they are immune and virus-free.<sup>28</sup> Occupational health must clear personnel with an active HBV infection before they can conduct clinical responsibilities and subject to ongoing monitoring. Usually, they aren't given a clinical position in a dialysis facility.

High doses, frequent doses, or both should be utilized in the initial HBV immunization regimen.<sup>29</sup> The legal method (deltoid muscle) is used to administer the immunizations, However, if enough knowledge is acquired, the intradermal approach might work better.

The drug vials should be thrown away after one usage and should not be used again.<sup>30</sup> A single medicine vial is split into multiple dosages and distributed from a central location if it is utilized to treat numerous patients. It is not recommended to puncture single-use intravenous medicine vials more than once since once a needle has

entered a vial marked for single-use, the product's sterility cannot be verified.

There are substantial differences in nurses' expertise in hemodialysis units throughout the cities, with a statistically significant (f) value of 11.687 and a probability value of 0.001. The high mean of score of 2.38 out of 3 degrees for Muthanna were in the largest city (Table 3}. The difference between the nurses' knowledge in the hemodialysis unit in Basrah city and the other dialysis units in the other city, where the probability value originated, is the reason for the statistically significant differences in nurses' knowledge among hemodialysis units (Table 4}. Maysan and Thi-Qar (0.356), Maysan and Muthanna (0.323), and Thi-Qar and Muthanna (0.952) all had probability values more than 0.05, despite the fact that the differences between the hemodialysis units in other cities were not statistically significant.

**Recommendations:** In hemodialysis units, the most highly qualified nurses ought to be allocated. Patients with renal failure receiving hemodialysis therapy should get an instruction handbook on hepatitis B and C prevention and precautions. Basic precautions and preventative measures for hepatitis B and C should be highlighted in special recommendations that are displayed on the hemodialysis unit's walls for all nurses to view. The healthcare director should put continuing education programs into place to raise nurses' knowledge of viral hepatitis B and C in hemodialysis units.

## CONCLUSION

Most of the study nurses were employed at the Basra province's hemodialysis facility(29.2%), were male (66.7), were between the ages of 21 and 25, had graduated from nursing school (51.0%), had one to five years of experience, and were participating in training sessions (59.7%).The study's findings showed that nurses' knowledge of hepatitis B and C precautions and preventive measures was low in the Basra city hemodialysis unit (mean score of 1.834), moderate in Maysan city (mean score of 2.082), moderate in Dhi-Qar city (mean score of 2.266), and good in Muthanna (mean score of 2.38).With a probability value of (.001), the results show that nurses' expertise varies considerably in hemodialysis facilities in four southern Iraqi cities.

### Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Abdulkareem Salman Khudhair
Drafting or Revising Critically:	Abdulkareem Salman Khudhair
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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# Systematic Review & Meta-Analysis of Current Treatment Options for Hydrocele: Hydrocelectomy vs. Sclerotherapy

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## ABSTRACT

**Objective:** We aimed to compare two main treatment approaches - traditional surgery (hydrocelectomy) versus the less invasive sclerotherapy - by examining their effectiveness, safety, and likelihood of recurrence.

**Place and Duration of Study:** This study was conducted at the College of Medicine, Qassim University,

**Methods:** We found the necessary information by searching three major databases—PubMed, Embase, and the Cochrane Library—for papers published between January 2000 and January 2023. Our final set of studies included randomized trials, as well as cohort studies (with a minimum of 20 participants) and case series (with at least 10 patients). Two independent researchers handled the data extraction and assessed the quality of the included articles. We then employed random-effects models to determine pooled risk ratios (RR) with 95% confidence intervals (CIs) and used Chi-squared and I<sup>2</sup> analysis to measure how much the results varied among the studies.

**Results:** From 15 eligible studies, three provided data for statistical analysis (157 total patients). Both treatments showed similar success rates (RR 1.04; 95% CI 0.99–1.09; p=0.13; I<sup>2</sup>=0%). Complications occurred at comparable rates between the two approaches, though the types of complications differed (RR 1.52; 95% CI 0.60–3.84; p=0.38; I<sup>2</sup>=62%). Long-term effectiveness remains unclear because recurrence rates varied widely across the studies. This is supported by the high heterogeneity (I<sup>2</sup>=81%) and the non-significant and imprecise pooled Risk Ratio (RR 1.01; 95% CI 0.03–31.73).

**Conclusion:** Despite surgery being the preferred long-term solution, sclerotherapy provides a viable alternative, especially where resources are scarce. To accurately gauge the long-term efficacy of both treatments, future research must incorporate larger sample sizes and stricter methodological standards.

**Key Words:** Hydrocele, Hydrocelectomy, Sclerotherapy, Treatment Outcome, Randomized Controlled Trial

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## INTRODUCTION

A hydrocele is one of the most common causes of scrotal swelling found in adult men. It occurs when fluid accumulates between the protective layers surrounding the testicle. While many men with hydrocele experience no symptoms, others suffer from pain, discomfort, and concerns about fertility. The condition affects millions worldwide, with particularly high rates in tropical regions where parasitic infections remain common.

With an estimated 25 million men suffering from hydrocele caused solely by lymphatic filariasis, the World Health Organization underscores the massive

worldwide burden of this condition.<sup>[1]</sup> Outside filarial regions, idiopathic hydrocele remains prevalent, especially among older men, where incidence increases with age<sup>[2]</sup>.

Hydrocelectomy, first described in the 19th century, has traditionally been considered the gold standard of treatment<sup>[3]</sup>. Several surgical techniques are available, such as Lord's plication, Jaboulay's eversion, and subtotal excision. Each of these methods has been modified with the goal of minimizing both recurrence and complications.<sup>[4-8]</sup> Despite its durability, hydrocelectomy requires surgical expertise, anesthesia, and perioperative resources that may not be available in low-resource settings.

As a less invasive option, sclerotherapy treats the hydrocele by draining the fluid and subsequently injecting a sclerosant agent (like phenol, tetracycline, or polidocanol) to seal the sac<sup>[9-12]</sup>. Since it is performed without hospitalization, requiring only local anesthesia, this approach has garnered attention in areas with limited resources due to its reduced complexity and lower cost.<sup>[13,14]</sup> However, recurrence remains a major concern, with variable outcomes reported depending on

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the sclerosant used, number of instillations, and follow-up duration<sup>[15]</sup>.

Several randomized controlled trials and observational studies have attempted to compare hydrocelectomy and sclerotherapy. Earlier reviews have suggested broadly comparable short-term efficacy, though hydrocelectomy provides superior long-term outcomes<sup>[16,17]</sup>. More recent systematic reviews and meta-analyses have attempted to address these uncertainties, but heterogeneity in study design, reporting standards, and outcome measures continues to limit definitive conclusions<sup>[18]</sup>.

We conducted this review to systematically evaluate and compare hydrocelectomy and sclerotherapy across three core measures: treatment success, recurrence, and complications. Our analysis seeks to clarify the evidence base for both approaches and determine what further research is required.

## METHODS

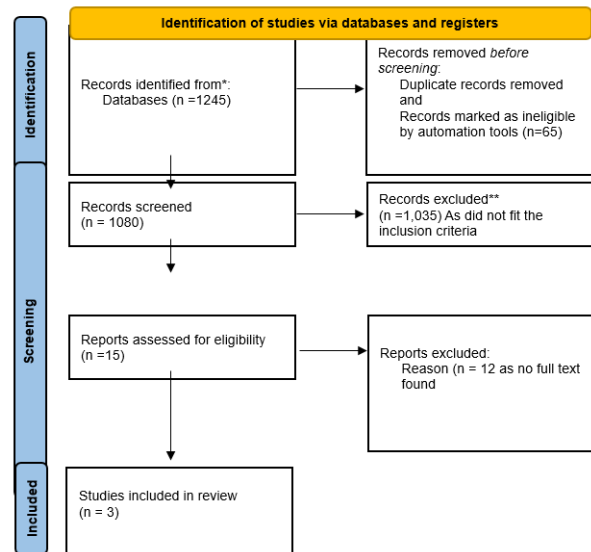
Following the PRISMA guidelines, we conducted a systematic search across PubMed, Embase, and the Cochrane Library for studies published over a 23-year span (January 2000 to January 2023). Our specific search terms combined MeSH terms and keywords related to the condition and its treatments: ("hydrocele" OR "scrotal swelling") AND ("hydrocelectomy" OR "sclerotherapy" OR "minimally invasive procedures"). To minimize bias, two researchers independently reviewed all titles and abstracts, and then assessed the full texts of promising articles. Any discrepancies during the selection process were settled through discussion or by involving a third expert.

Only RCTs and sufficiently sized observational studies (cohort studies with 20 patients or case series with 10 patients) were included, provided they reported results for hydrocelectomy or sclerotherapy. We excluded all case reports, review articles, animal studies, and any research that did not offer quantitative outcome data. The primary outcomes assessed were treatment success, recurrence, and complications.

To maintain the rigor of the review, two independent reviewers screened every title, abstract, and full-text article. Any differences between them were resolved through discussion or by consulting a third party. We then proceeded to extract essential data, including the study design, patient details, treatments used, results, and duration of follow-up. Study quality was evaluated using the Cochrane Risk of Bias (RoB) tool for randomized trials and the Newcastle–Ottawa Scale for observational studies. Statistical pooling was done using random-effects meta-analyses, reporting risk ratios (RR) with 95% CI. Heterogeneity was measured by Chi-squared and  $I^2$ , defined as moderate when  $I^2 > 50$  and substantial when  $I^2 > 75$ .

## RESULTS

Our database search initially yielded 1,245 records. We started by screening 1,080 unique titles and abstracts, immediately ruling out 1,035 of them. We then moved on to assess 45 full-text articles. Of these, 30 were removed because they didn't meet key requirements (e.g., wrong population, non-comparative structure, or poor outcome reporting). This left us with 15 studies for the final qualitative synthesis. Importantly, only three of these studies provided quantifiable data for the meta-analysis (total N=157). See the PRISMA flow diagram for the step-by-step documentation.



### PRISMA FLOW CHART FOR IDENTIFICATION OF STUDIES USING DATABASES

Based on data from three studies (n=157), the overall treatment success rate (defined as resolution without recurrence) was statistically comparable between hydrocelectomy and sclerotherapy. The pooled Risk Ratio was 1.04 (95% CI 0.99–1.09), indicating no significant difference in effectiveness (p=0.13). The 95% confidence interval was narrow and the heterogeneity was negligible ( $I^2=0\%$ ), indicating consistency across studies. This suggests that, in terms of short-term success, both interventions are broadly equivalent (Figure 1).

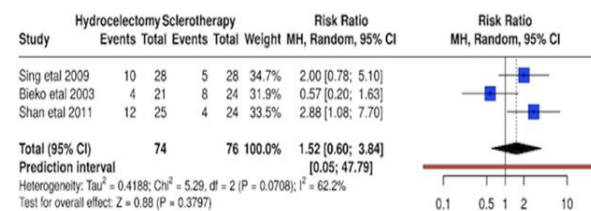
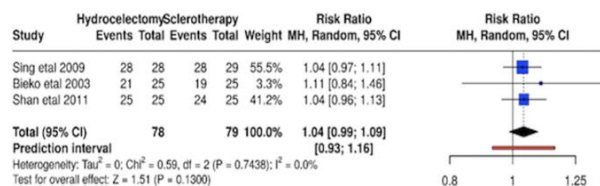


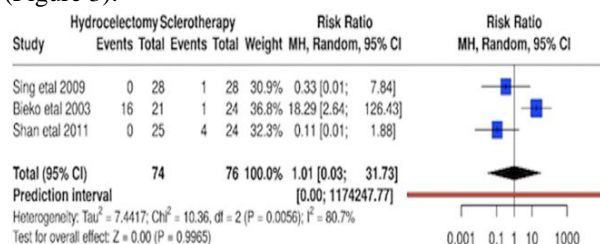
Figure No. 1. Forest plot comparing treatment success between hydrocelectomy and sclerotherapy.

Complication rates were reported in multiple studies, most commonly infection, hematoma, pain, or fever. Pooled results demonstrated no significant difference between hydrocelectomy and sclerotherapy (RR 1.52, 95% CI 0.60–3.84;  $p=0.38$ ). However, heterogeneity was moderate ( $I^2=62\%$ ), suggesting variability in complication definitions and reporting across studies. While the overall risk of complications is comparable, some individual trials reported a slightly higher rate of infection or hematoma with hydrocelectomy, whereas transient pain and inflammation were more frequent after sclerotherapy (Figure 2).



**Figure No. 2. Forest plot comparing complication rates between hydrocelectomy and sclerotherapy**

There was substantial variation in recurrence rates reported across the studies. Despite this variability, the pooled analysis suggested no statistically significant difference in recurrence risk between hydrocelectomy and sclerotherapy (RR 1.01; 95% CI 0.03–31.73). Nevertheless, heterogeneity was substantial ( $I^2=81\%$ ), reflecting the wide variability in follow-up duration, patient populations, and sclerosant agents used. In some individual studies, recurrence after sclerotherapy was notably higher, while others reported results similar to hydrocelectomy. This inconsistency limits firm conclusions but highlights the importance of standardized protocols and long-term monitoring (Figure 3).



**Figure No. 3. Forest plot comparing recurrence rates between hydrocelectomy and sclerotherapy.**

**DISCUSSION**

Our systematic review and meta-analysis, encompassing three studies with 157 patients, indicates similar short-term efficacy and comparable complication rates for both hydrocelectomy and sclerotherapy. The pooled results demonstrated no significant difference in treatment success (RR 1.04, 95% CI 0.99–1.09;  $I^2=0\%$ ) or complications (RR 1.52, 95% CI 0.60–3.84;  $I^2=62\%$ ).

While our findings align with earlier reviews, they also underscore the need for more robust, standardized research to address persistent uncertainties, particularly regarding long-term outcomes and recurrence.

The most notable finding is the consistency in short-term success, as evidenced by the negligible heterogeneity ( $I^2=0\%$ ) for this outcome. This suggests that for a patient seeking immediate symptom relief, both procedures are highly effective. However, the high heterogeneity in recurrence rates ( $I^2=81\%$ ) highlights a critical gap in the current literature. This variability is probably due to variations in surgical techniques, the type of sclerosant agent and concentration used (e.g., phenol, polidocanol, tetracycline), and inconsistencies in follow-up duration. For instance, some studies only followed patients for a few months, whereas others extended follow-up to several years, which is crucial for capturing delayed recurrences. Recurrence after sclerotherapy is a well-documented concern and a primary reason why many urologists still consider hydrocelectomy the gold standard. For example, a meta-analysis found a significantly lower recurrence rate for hydrocelectomy compared to sclerotherapy, reinforcing its superior long-term durability<sup>[19]</sup>. Similarly, a comprehensive review highlighted that while sclerotherapy is a good initial option, patients should be counseled about a higher risk of recurrence, especially with single-injection protocols<sup>[20]</sup>.

While the overall complication rates were comparable between the two methods, the types of complications differed. Following sclerotherapy, patients tend to experience a greater incidence of transient post-procedure discomfort, including pain, swelling, and local inflammation.<sup>[21]</sup> In contrast, hydrocelectomy can result in more serious, though less frequent, complications such as hematoma, infection, and damage to surrounding structures like the testicular artery, which can rarely lead to testicular atrophy. Patient factors must also be considered; sclerotherapy is often preferred for older patients or those with significant comorbidities who may not be suitable candidates for general anesthesia. This less invasive approach is also highly advantageous in resource-limited settings where surgical facilities, trained personnel, and post-operative care resources are scarce<sup>[22,23]</sup>. It's a pragmatic and cost-effective solution for a widespread problem like filarial hydrocele, as highlighted in the World Health Organization's initiatives for tropical diseases<sup>[24]</sup>.

Our findings reinforce that hydrocelectomy remains the more definitive and durable solution. The various surgical techniques, such as Lord's plication and Jaboulay's eversion, have been refined over decades to minimize complications and recurrence<sup>[25,26]</sup>. The high heterogeneity in recurrence for sclerotherapy points to the need for standardized protocols. This includes determining the optimal sclerosant, its concentration, and the number of instillations required<sup>[27-30]</sup>. For instance, studies by Sigurdsson et al. and Heise et al. found that multiple sclerotherapy sessions significantly improve long-term success rates, though this increases

the overall cost and patient burden<sup>[31,32]</sup>. There's a clear need for future research to focus on optimizing sclerotherapy protocols to close the efficacy gap with surgery.

To resolve the current uncertainty, future studies should focus on conducting large-scale, multicenter RCTs that employ standardized outcomes and extended follow-up periods (2–5 years or more). This rigor is essential for definitively comparing the long-term effectiveness and recurrence rates of treatment approaches. Furthermore, studies must integrate patient-reported outcomes (e.g., quality of life and return to activity) to fully support patient-centered and personalized treatment choices.<sup>[33, 34]</sup> Cost-effectiveness analyses are also essential, particularly in a global health context, to guide policy decisions on which treatment should be promoted in different healthcare environments<sup>[35]</sup>.

### CONCLUSION

while our review demonstrates that both hydrocelectomy and sclerotherapy are effective short-term treatments, the high variability in recurrence rates for sclerotherapy remains a significant concern. Hydrocelectomy offers superior long-term durability and remains the gold standard, particularly in developed healthcare systems. Sclerotherapy offers a valid, non-surgical alternative, especially for patients who are not candidates for hydrocelectomy or when used in resource-limited settings. The decision-making process should be patient-centric, considering the risk tolerance, comorbidities, and access to healthcare resources. Future research must address the heterogeneity in sclerotherapy protocols and provide robust long-term data to better inform clinical practice.

#### Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Muhammad Munir Memon, Zaheera Saadia, Anjuman Gul Memon
Drafting or Revising Critically:	Khalid Shehzad, Emad Abdulrahman Alwashmi, Mariam S Alharbi
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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# Acinic Cell Carcinoma of the Parotid Initially Misdiagnosed as Pleomorphic Adenoma on FNAC: A Case Report

Abdulrahman Altwaijri

## ABSTRACT

Acinic cell carcinoma (ACC) is a rare malignant salivary gland tumour that can closely resemble benign lesions on clinical examination and FNA. A 27-year-old woman presented with a small, tender, mobile parotid mass that was initially diagnosed as pleomorphic adenoma on FNA. She underwent extracapsular excision, but postoperative histopathology revealed ACC, confirmed by GCDFP-15 positivity and absence of myoepithelial cells (p63-negative). This case underscores how ACC can mimic benign parotid tumours and highlights the importance of histopathology and immunohistochemistry for definitive diagnosis.

**Key Words:** Acinic cell carcinoma; Pleomorphic adenoma; Parotid gland tumour; Fine needle aspiration cytology; Salivary gland neoplasm

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## INTRODUCTION

Acinic cell carcinoma (ACC) is a low-grade malignant salivary gland tumour, most often arising in the parotid gland, and can closely resemble benign lesions on cytology<sup>1</sup>. Because its cells appear relatively bland, ACC is frequently underdiagnosed on FNA. This case report describes an ACC that was initially mistaken for pleomorphic adenoma on FNA, emphasizing the need for histopathological and immunohistochemical evaluation for accurate diagnosis.

## CASE REPORT

A 27-year-old female with no known medical illnesses or allergies presented with a three-year history of intermittent right facial pain accompanied by a gradually enlarging swelling. The pain was mild, episodic, and associated with localized tenderness. She denied facial weakness, numbness, xerostomia, fever, weight loss, or any other systemic symptoms. On clinical examination, a firm, mobile, and tender swelling measuring approximately 2 × 1 cm was noted in the right parotid region.

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The overlying skin appeared normal, and there were no signs of inflammation or fixation. Facial nerve function was intact with no evidence of weakness, and there were no sensory deficits or trigeminal nerve-related symptoms. No cervical lymphadenopathy was identified.

Ultrasound imaging revealed a well-defined lesion within the right parotid gland, prompting an ultrasound-guided fine needle aspiration. Cytology smears demonstrated a mixture of epithelial and myoepithelial cells embedded in scattered stromal fragments. The epithelial cells appeared bland, while the myoepithelial component was more prominent. The presence of stromal material contributed to an initial interpretation of a benign neoplasm, and the cytology report concluded that the features were consistent with pleomorphic adenoma.

MRI of the head and neck demonstrated a relatively lobulated, well-defined lesion arising from the superficial lobe of the right parotid gland, measuring approximately 1.3 × 1.6 × 2 cm (AP × TV × CC) (Figure 1). The mass appeared hyperintense on T2-weighted images and intermediate to iso-intense on T1-weighted sequences, with a small internal focus of bright T2 signal. Post-contrast images showed predominantly peripheral enhancement with internal enhancing septations/strands, a pattern commonly associated with benign parotid neoplasms such as pleomorphic adenoma. The lesion also demonstrated relatively increased diffusion signal, a finding that can occur in both benign and low-grade malignant salivary tumours, thus limiting specificity. No definite invasion of adjacent structures was seen, and the contralateral parotid gland appeared normal. A few mildly prominent level IIa and IB lymph nodes were noted but were nonspecific and likely reactive. No evidence of perineural infiltration was observed on the MRI.

Based on the clinical, radiological, and cytological findings, a benign parotid tumour was suspected, and the patient underwent extracapsular excision of the lesion using a modified Blair incision (Figure 2A and 2B). The procedure was uneventful, and the intact specimen was submitted for histopathological examination.

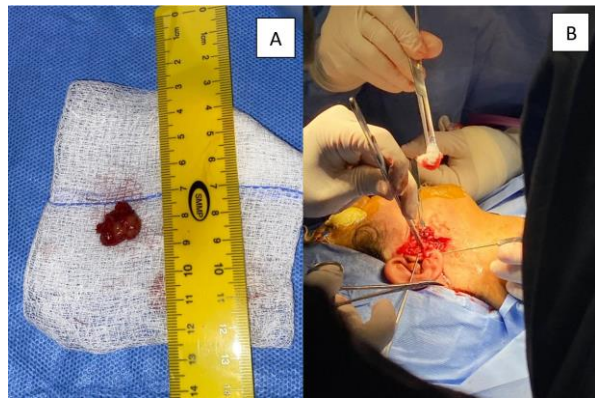
Gross evaluation revealed an unoriented, firm tan tissue mass measuring  $2.3 \times 1.8 \times 1$  cm with a homogeneous gray-tan cut surface. Microscopic examination showed a well-circumscribed mass characterized by prominent basophilia and peripheral lymphoid stroma. The tumour displayed a mixed architectural pattern, including solid, follicular, and microcystic arrangements. Acinar differentiation was evident, with large polygonal cells exhibiting basally located round nuclei and abundant granular basophilic cytoplasm. Occasional tumour cells demonstrated clear cytoplasm due to glycogen or mucin content. Mitotic figures were rare, and importantly, no myoepithelial cells were identified (Figure 3A-3G).

Immunohistochemical staining supported the diagnosis, with p63 negative in tumour cells and positive only in adjacent normal ducts, confirming the absence of myoepithelial differentiation. The tumour cells were strongly positive for GCDFP-15 and negative for S100, consistent with serous acinar differentiation. These findings collectively established the diagnosis of acinic cell carcinoma of the parotid gland.

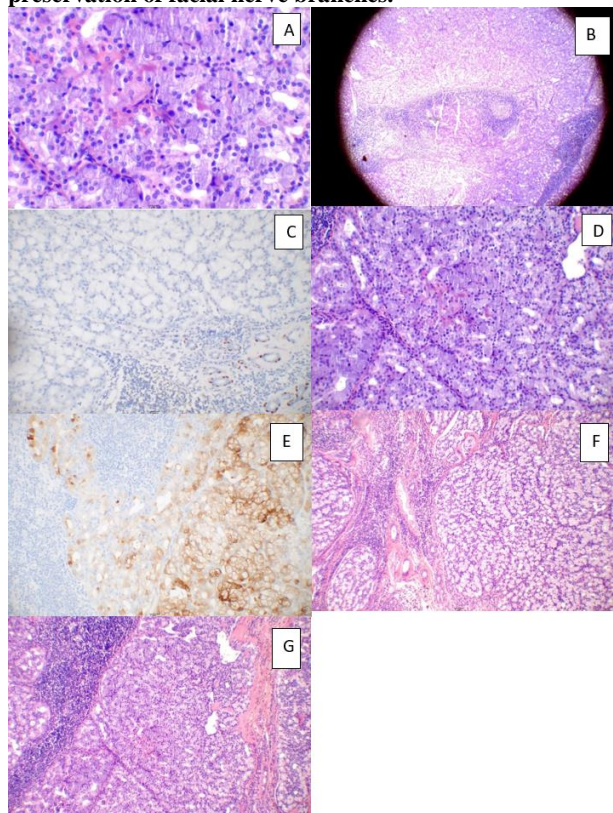
The case was discussed in a multidisciplinary tumour board meeting. Considering the complete excision, low-grade histological features, and absence of adverse prognostic indicators, the board recommended postoperative surveillance as the appropriate management strategy. The patient was advised to undergo regular clinical examinations, periodic imaging, and ongoing monitoring for any evidence of recurrence or nodal involvement.



**Figure No. 1.** T2-weighted MRI image showing a well-circumscribed lesion within the right parotid gland.



**Figure No. 2:** (A) Gross specimen of the excised right parotid lesion showing a well-defined tan nodule. (B) Intraoperative view demonstrating extracapsular excision through a modified Blair incision with careful preservation of facial nerve branches.



**Figure No. 3:** (A) Low-power view showing a well-circumscribed tumour with basophilic cytoplasm and peripheral lymphoid stroma (H&E,  $\times 40$ ). (B) Mixed architectural patterns, including solid, follicular, and microcystic arrangements (H&E,  $\times 100$ ). (C) High-power view demonstrating acinar differentiation with polygonal granular basophilic cytoplasm and basally placed bland nuclei (H&E,  $\times 200$ ). (D) Follicular architecture with clear-cytoplasmic cells, peripheral lymphoid tissue, and adjacent normal ducts (H&E,  $\times 100$ ). (E) High-power image showing basophilic granular cytoplasm and bland nuclei without mitoses or myoepithelial cells (H&E,  $\times 400$ ). (F) p63 immunostain showing absence of myoepithelial cells within the tumour, with positivity restricted to neighbouring normal ducts (p63,  $\times 200$ ). (G) Strong GCDFP-15 positivity in tumour cells confirming serous acinar differentiation (GCDFP-15,  $\times 200$ ).

## DISCUSSION

The acinic cell carcinoma (ACC) is a low-grade malignant tumour of the salivary glands that may closely resemble benign parotid neoplasms regarding both clinical and cytological appearances. ACC can be exhibited on FNA with bland epithelial cells, irregular architecture, and lymphoid-appearing or matrix-like backgrounds and can be confused with pleomorphic adenoma and other benign tumours resulting in false-negative or misdiagnoses<sup>2</sup>. Regular and extensive sample series and reviews of cytology of salivary glands have indicated that ACC is one of the organizations exhibiting the highest false-negative rates on FNA and is often misdiagnosed as benign, especially pleomorphic adenoma<sup>3</sup>.

Cytologic investigations of ACC also underscore its morphologic heterogeneity, and pleomorphic adenoma, Warthin tumour and other benign lesions as alternatives to ACC on the aspiration smears<sup>4</sup>. Accidental overlap between ACC and pleomorphic adenoma also has a good history in histologic and cytologic studies of various differentiations with granular cytoplasm, acinar-like clusters and limited atypia being observed to blur the lines between these two entities<sup>5</sup>. Histopathology is still the gold standard in such a case<sup>6</sup>. Typical characteristics of ACC are serous acinar differentiation and granular basophilic cytoplasm as well as solid, microcystic or follicular forms, and in most cases low mitotic activity<sup>7</sup>. Immunohistochemistry helps further the diagnosis, Serous acinar differentiation is supported by the GCDFP-15 and other acinar markers, and the lack of myoepithelial markers like p63 will help differentiate ACC and pleomorphic adenoma and myoepithelial-rich tumours<sup>8</sup>.

Complete surgical excision is the mainstay of treatment and usually results in a favourable prognosis for low-grade, completely resected ACC, although late local recurrence is well recognised, therefore, long-term follow-up is recommended<sup>9,10</sup>. This case illustrates these known diagnostic pitfalls and reinforces the need for close correlation between cytology, histopathology, and immunohistochemistry when assessing parotid masses that appear benign on initial FNA.

## CONCLUSION

This case emphasizes the limitations of FNA in distinguishing ACC from pleomorphic adenoma. Careful histopathological evaluation, supported by

immunohistochemistry, is essential for accurate diagnosis.

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# Penetrating Cardiac Injury from a Single Stab Wound: Autopsy Findings of a Lethal Left Ventricular Perforation

Penetrating  
Cardiac Injury -  
Autopsy Findings

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## ABSTRACT

Penetrating cardiac injuries are uncommon but carry a high mortality rate, particularly when involving the left ventricle. Survival is rare because of rapid blood loss or cardiac tamponade before medical intervention. This case describes the forensic examination of a 27-year-old man who sustained a single stab wound to the left anterior chest inflicted by an unknown assailant. External examination revealed pallor of the conjunctivae and an open wound on the left chest. Internal examination demonstrated blood infiltration of the left anterior thoracic wall extending to the fourth intercostal space. Approximately 1,000 mL of blood was present in the left pleural cavity and 250 mL within the pericardial sac. The stab wound penetrated the pericardium and left ventricle, causing fatal hemopericardium and cardiac tamponade. This case shows how a single deep chest wound can rapidly cause death and highlights the value of detailed autopsy in determining cause and manner of death.

**Key Words:** cardiac penetrating injury, hemopericardium, cardiac tamponade, stab wound

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## INTRODUCTION

Wounds represent a disruption of tissue integrity caused by external mechanical forces and may affect any part of the body.<sup>1</sup> Among these, sharp force injuries remain a major category encountered in forensic practice, encompassing incised wounds, chop wounds, and stab wounds.<sup>2</sup> A stab wound is typically deeper than its surface length and often results from a pointed weapon such as a knife or dagger. When directed toward the thoracic cavity, the consequences can be devastating, particularly if vital structures such as the heart or great vessels are involved.

Penetrating cardiac injuries are relatively uncommon but are associated with very high mortality. Most patients die at the scene before reaching definitive care due to massive hemorrhage or cardiac tamponade.<sup>3,4</sup>

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The left ventricle is the most frequently affected chamber in fatal cardiac stab wounds because of its anterior position and proximity to the chest wall.<sup>5</sup> Outcomes are determined by the weapon's characteristics, the force of penetration, and whether major cardiac chambers or vessels are compromised.<sup>6</sup> This report presents the forensic findings of a 27-year-old man who sustained a single fatal stab wound penetrating the left ventricle. The case highlights the mechanism of death resulting from hemopericardium and cardiac tamponade, demonstrating the crucial role of forensic autopsy in establishing both the cause and manner of death.

## CASE REPORT

A 27-year-old man was brought to Bhayangkara Pusdik Gasum Porong Hospital, East Java, Indonesia on August 24, 2021, for forensic examination following a report of suspected homicide. The examination was conducted upon police request (visum et repertum number VER/13/VIII/2021/Reskrim, received at 22:05).

**External Examination:** The conjunctivae appeared pale, and cyanosis was noted on the lips and fingertips. A single open wound was identified on the left anterior chest. The wound measured approximately 2 centimeters in length and 1 centimeter in width, located near the fourth intercostal space. The depth was estimated at 10 centimeters, consistent with a stab wound where the depth exceeded the surface length (Figure 1). No defensive wounds were observed on the upper limbs.

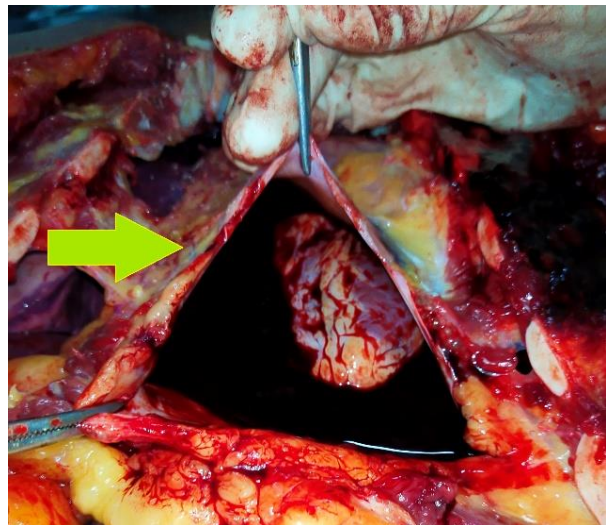
**Internal Examination:** Blood infiltration was found in the soft tissues of the left anterior thoracic wall extending to the fourth intercostal space. Within the thoracic cavity, approximately 1,000 mL of blood was present in the left pleural cavity and 250 mL within the pericardial sac (Figure 2). Examination of the heart revealed a penetrating wound that passed through the pericardium and into the anterior wall of the left ventricle (Figure 3). The wound edges were clean and sharply defined, consistent with a stab injury caused by a pointed, single-edged weapon.

The trajectory of the wound extended inward and slightly downward from the left anterior chest, corresponding to the external wound site. The depth and direction suggested a strong, deliberate thrust consistent with homicide. The cause of death was determined to be hemorrhagic shock and cardiac tamponade secondary to a stab wound that penetrated the pericardium and left ventricle.

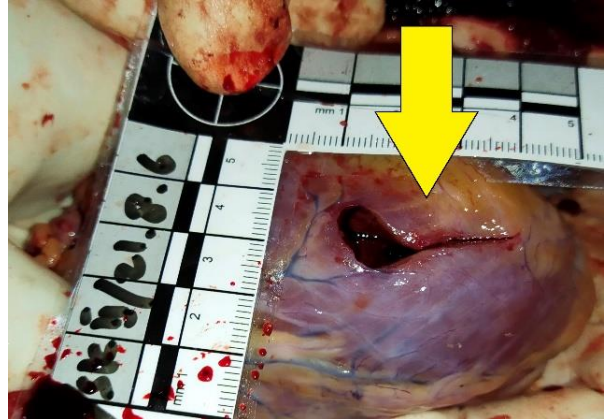
Comparable cases in the literature have described similar fatal outcomes following left ventricular penetration, with survival being exceedingly rare.<sup>5,6</sup> The present findings support that even a single penetrating wound to the heart can cause immediate circulatory collapse through rapid blood accumulation within the pericardial cavity.



**Figure No.1:** The pathway of the stab wound reconstructed from autopsy findings, showing the trajectory from the external chest entry to the left ventricle.



**Figure No.2:** Accumulation of blood and clot within the pericardial space indicating hemopericardium.



**Figure No.3:** Laceration of the anterior wall of the left ventricle observed during internal examination.

## DISCUSSION

The fatal wound in this case measured 2 cm in length, 1 cm in width, and approximately 10 cm in depth, characteristic of a stab injury where penetration exceeds the surface dimension. Stab wounds result from pointed or sharp-edged weapons and differ from incised wounds by their depth and mechanism of entry.<sup>2</sup> The severity of such wounds depends on several factors, including the sharpness of the weapon, the amount of force applied, and the trajectory of penetration. When the thrust strikes vital organs such as the heart, even a single injury can prove rapidly fatal.<sup>1</sup>

Cardiac stab wounds are rare but among the most lethal forms of thoracic trauma. The heart's position within the chest and the potential for massive bleeding or cardiac tamponade make survival uncommon without immediate surgical intervention.<sup>3,4</sup> The left ventricle, being thick-walled and positioned anteriorly, is particularly vulnerable to penetrating trauma. Injuries to this chamber frequently result in sudden hemodynamic

collapse due to loss of cardiac output and rapid accumulation of blood within the pericardial sac.<sup>5</sup> In the present case, the autopsy revealed both hemothorax and hemopericardium. The pericardial blood volume of approximately 250 mL was sufficient to induce cardiac tamponade, compressing the heart and preventing diastolic filling. When this condition develops acutely, even small volumes can cause cardiac arrest. These findings align with previous reports describing similar mechanisms in fatal left ventricular wounds.<sup>6</sup>

Forensic examination remains essential in reconstructing the mechanism of death and determining whether the injury was self-inflicted or homicidal. The downward trajectory, absence of hesitation marks, and the force required to penetrate the left ventricle in this case strongly supported homicidal intent. Beyond its medicolegal significance, this case also illustrates how rapid blood loss and cardiac tamponade can coexist, explaining the immediate fatality often observed in penetrating cardiac trauma.

## CONCLUSION

This case demonstrates how a single penetrating stab wound can lead to rapid death through combined hemothorax and cardiac tamponade. The perforation of the left ventricle resulted in immediate circulatory collapse, emphasizing the lethal potential of chest stab injuries even when inflicted once. Forensic autopsy played a crucial role in determining the mechanism and manner of death, confirming homicide based on the

wound trajectory and absence of hesitation marks. Continuous documentation of such cases remains essential to improve understanding of fatal penetrating cardiac trauma and to support medicolegal investigations.

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# Persistent Somatic Pain Masking Psychiatric Distress in Borderline Personality Disorder and Major Depression: A Case Report

Persistent  
Somatic Pain  
Masking  
Psychiatric  
Distress

Zahra Ibadina<sup>1</sup>, Margarita Maria Maramis<sup>1</sup>, Elisabet Citradewi<sup>1</sup> and Isti Suharjanti<sup>2</sup>

## ABSTRACT

Somatic pain without clear medical explanation is frequently encountered in clinical settings and may reflect underlying psychiatric conditions. This case describes an 18-year-old female with a history of borderline personality disorder and major depressive disorder who presented to the emergency department with acute headache accompanied by nausea, vomiting, and limb weakness. Neurological evaluation, imaging, and laboratory testing were unremarkable, and analgesic therapy produced minimal symptom relief. Persistent severe pain and repeated requests for medical reassurance contrasted with incongruent clinical observations. Psychiatric assessment revealed significant emotional distress associated with an interpersonal conflict. After transfer to the psychiatric ward, intensive psychotherapy incorporating supportive and mindfulness-based approaches resulted in gradual symptom improvement without changes in analgesic medication. This case highlights the importance of a psychiatric perspective in managing persistent somatic complaints and supports a multidisciplinary approach when symptoms exceed expected clinical findings or fail to respond to standard medical treatment.

**Key Words:** somatic symptoms, borderline personality disorder, major depressive disorder, pain perception, psychosomatic, multidisciplinary care

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## INTRODUCTION

Somatic symptoms such as headache, dizziness, and fatigue are commonly encountered in clinical practice and often prompt urgent medical evaluation. Although many physical complaints are associated with identifiable medical conditions, a substantial proportion remain unexplained despite thorough diagnostic assessment.<sup>1</sup> Persistent somatic symptoms without corresponding physical findings may indicate underlying psychological distress or psychiatric disorders. The biopsychosocial framework conceptualizes pain as a multidimensional experience shaped by biological, emotional, and social factors, highlighting the importance of considering psychiatric

contributions when symptoms are disproportionate to clinical findings or fail to respond to standard medical treatment.<sup>1-3</sup> Borderline personality disorder is frequently associated with altered pain perception, emotional dysregulation, and increased healthcare utilization.<sup>4</sup> Individuals with this condition may experience somatic symptoms that intensify during periods of psychosocial stress, complicating diagnostic clarity and treatment planning. Early recognition of psychiatric influences is essential in preventing unnecessary investigations and guiding appropriate multidisciplinary management.<sup>5,6</sup> This case illustrates the importance of psychiatric evaluation in the assessment of persistent somatic pain in a patient with borderline personality disorder and major depressive disorder.

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## CASE PRESENTATION

**Case Presentation:** An 18-year-old female presented to the emergency department with a sudden onset severe headache accompanied by nausea, vomiting, and subjective right upper limb weakness. The symptoms had begun one week prior to admission and emerged during significant interpersonal conflict with her father. The patient had a history of major depressive disorder and borderline personality disorder with multiple previous psychiatric hospitalizations and regular outpatient psychiatric care. On admission to the neurology ward, intravenous analgesics, antiemetics,

and supportive medications were provided. Despite treatment, the patient continued to report severe headache, rating her pain intensity as 9 out of 10, and repeatedly requested medical attention throughout the day. Her subjective pain behavior appeared inconsistent with her physical appearance and facial expression, which showed minimal observable discomfort. Neurological examination, computed tomography of the brain, laboratory tests, and electroencephalography were unremarkable.

After three days of hospitalization, nausea and vomiting resolved, but her headache persisted unchanged. She expressed reluctance to be discharged, stating that she felt safer in the hospital environment. She demonstrated persistent reassurance seeking behavior and had difficulty accepting explanations regarding the absence of neurological pathology. A psychiatric consultation was requested, and the patient was transferred to the psychiatric ward. Intensive psychotherapy incorporating supportive techniques and mindfulness based cognitive behavioral approaches was initiated for four structured sessions. No changes were made to the patient's analgesic regimen. During treatment, emotional conflict surrounding her family relationship emerged as a significant trigger. As she engaged in psychotherapy, her headache gradually improved, and she demonstrated increased emotional regulation. The patient accepted discharge from inpatient care and continued outpatient psychiatric follow up without further somatic escalation.

## DISCUSSION

Persistent somatic pain without clear medical explanation presents a frequent diagnostic and therapeutic challenge in clinical practice. Somatic complaints account for a substantial proportion of outpatient and emergency department visits, and many patients continue to report symptoms despite adequate medical evaluation and treatment.<sup>2</sup> A considerable portion of medically unexplained symptoms reflects underlying psychological or psychiatric distress. The biopsychosocial model supports the understanding that pain is influenced not only by sensory mechanisms but also by emotional regulation and interpersonal context. This framework is particularly relevant when symptom severity appears disproportionate to clinical findings or when persistent pain remains unresponsive to standard analgesic regimens.<sup>2</sup>

In this case, neurological assessment and imaging revealed no structural abnormalities to explain the patient's reported headache intensity. The persistence of severe pain despite adequate treatment, combined with repeated reassurance seeking and reluctance to be discharged, suggested contributions beyond physical pathology. Psychiatric evaluation identified psychosocial stress related to family conflict, which appeared to precipitate and maintain somatic symptom

expression. In individuals with borderline personality disorder, emotional dysregulation, impaired stress tolerance, and altered pain perception may amplify physical symptoms and increase reliance on medical systems.<sup>1,4</sup> Pain may function as a manifestation of psychological distress or as a means of seeking safety and interpersonal support when internal coping resources are strained.<sup>1,3,4</sup>

Research has demonstrated a strong association between somatic complaints and psychiatric conditions such as major depression and personality disorders.<sup>5,6</sup> Individuals with borderline personality disorder may experience heightened sensitivity to internal states and difficulty interpreting bodily sensations, which may intensify symptom reporting.<sup>1,3</sup> Emotional conflict may lower pain thresholds or modify pain modulation pathways, including serotonergic, noradrenergic, and endogenous opioid systems, contributing to disproportionate pain responses.<sup>1,4</sup> Psychotherapeutic interventions targeting emotional regulation and interpersonal functioning have been shown to reduce symptom burden and decrease healthcare utilization.<sup>1,2</sup>

The improvement in symptoms following psychotherapy in this case, without changes to analgesic therapy, supports the role of psychological mechanisms in somatic pain persistence. This highlights the value of early psychiatric involvement when somatic symptoms appear inconsistent with objective findings. Multidisciplinary collaboration between medical and psychiatric teams can reduce unnecessary investigations, prevent iatrogenic risk, and guide patient centered treatment. Understanding the emotional context surrounding symptom presentation is essential for effective management, particularly in patients with personality disorders who may rely on somatic expression to communicate distress.

## CONCLUSION

Persistent somatic pain can serve as an important indicator of underlying psychiatric distress, particularly when symptoms lack medical explanation or fail to respond to appropriate treatment. In individuals with borderline personality disorder, emotional dysregulation and altered pain perception may intensify somatic complaints and result in increased use of healthcare resources. This case underscores the need for early psychiatric assessment within a multidisciplinary care approach to improve diagnostic clarity, guide effective treatment strategies, and reduce unnecessary medical interventions. Psychotherapy focused on emotional regulation and coping skills may significantly reduce symptom severity and improve functioning. Recognizing when physical symptoms reflect psychological suffering is essential for optimizing clinical outcomes and preventing chronic disability.

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**Patient consent:** Informed consent has been obtained by authors from patients prior to submission of the case report.

**Contributors:** All authors were involved in the clinical care of the patient and contributed to the conception, drafting, review and revision of the case report.

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