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Editorial

Muscular Pains and Aches

Prof. Dr. Azhar Masud Bhatti
Editor-in-Chief

Introduction:

Muscle pain is common. It also known as myalgia, can be caused by injuries, infectious diseases, or other health issues. It can be temporary or chronic as well as localized or widespread throughout the body; its intensity varies from person to person. Everyone can experience muscle soreness. People who start a new physical activity regimen can experience delayed-onset muscle soreness, typically occurring 6 to 12 hours after exercise and may persist for up to 48 hours. During this time, you may experience pain as your muscles are recovering.

Muscle pain is evoked by specialized nerve endings (nociceptors). Important stimuli for muscle pain are Adenosine Triphosphate (ATP) and a low tissue pH. Excitation of muscle nociceptors leads to hyperexcitability of spinal sensory neurones (central sensitization). Low frequency activity in muscle nociceptors is sufficient to induce central sensitization.

In the majority 60% to 85% of the population has had nonspecific back pain of muscular origin[1]. Pain evoked by myofascial trigger points has a point prevalence of approximately 30%[2]. More than 7% of all women aged 70 to 80 years suffer from the fibromyalgia syndrome[3]. In an Italian study, musculoskeletal pain was found to be the most common reason that patients consulted a doctor[4].

Muscle pain differs in many ways from pain in the skin or viscera. These differences concern not just the underlying mechanisms, but also a number of subjective features. The main subjective differences between muscle pain and cutaneous pain are listed below:

- In muscle pain electrical nerve stimulation induces only one pain whereas in cutaneous pain it induces a first pain and a second pain.
- Muscle pain is poorly localizable whereas the other is well-localized.
- It has tearing, cramping, pressing quality whereas the cutaneous pain has stabbing, burning, cutting quality.
- It marked tendency toward referral of pain and the cutaneous pain has no tendency toward referral of pain.
- The affective aspect of muscle pain has difficult to tolerate whereas he cutaneous pain it is easier to tolerate.

The main symptoms of muscle pains are muscle soreness, cramps, spasms and joint pain

Types and mechanisms

There are mainly two types of muscle pain and mechanism:

Peripheral mechanisms

Muscle pain is produced by the activation of specific receptors (so-called nociceptors): these receptors are specialized for the detection of stimuli that are objectively capable of damaging tissue and that are subjectively perceived as painful.

Muscle nociceptors contain neuropeptides, including substance P (SP) and calcitonin-gene-related peptide (CGRP). These peptides are released when nerve endings are activated and induce local edema by dilating the local blood vessels and increasing their permeability.

ATP is released in any kind of tissue injury, it can be considered a universal pain-inducing substance[5]. ATP is found in particularly high concentration in muscle cells; it can cause pain in muscle trauma (e.g., a bruise or tear of muscle fibers) as well as in other types of pathological change in muscle (e.g., necrotizing myositis)[6].

Acidic tissue pH is one of the main activating factors leading to muscle pain. Practically all pathological and pathophysiological changes of skeletal muscle are accompanied by a drop in pH, among them

- chronic ischemic states,
- tonic contractions or spasms,
- myofascial trigger points,
- (occupationally induced) postural abnormalities, and
- myositides.

In this way, neurogenic inflammation comes about, characterized by hyperemia, edema, and the release of inflammatory mediators[7]. The inflammatory mediators sensitize the muscle nociceptors and thereby increase neuropathic pain.

It is also the reason why many types of muscle pain respond well to the administration of non-steroidal anti-inflammatory drugs (NSAID), which block prostaglandin synthesis.

Central nervous mechanisms

An influx of nervous impulses from muscle nociceptors into the spinal cord increases the excitability of posterior horn neurons to a greater extent than one from cutaneous nociceptors[8].

Tenderness to pressure and pain on movement or exercise. The over excitability of nociceptive neurons in the CNS is considered the main cause of allodynia and hyperalgesia in patients with chronic muscle pain. The persistent depolarization of the sensitized cells has recently become the target of medications that open potasium channels and thus remove positive charge from the cell[9].

Muscle spasm can be defined as persistent, involuntary muscle contraction (not including spasticity, a phenomenon of central nervous origin). The main

reason why pain arises in muscle spasm is muscle ischemia, which leads to a drop in pH and the release of pain-producing substances such as bradykinin, ATP, and H+.

The vicious-circle concept of muscle spasm – muscle pain causes spasm, which causes more pain, etc. – should now be considered obsolete. Most studies have shown that muscle pain lowers the excitability of the α-motor neurons innervating the painful muscle[10] (a "pain adaptation" model)[11].

Causes

Muscle pains and aches (myalgia) are extremely common. Almost everyone has experienced discomfort in their muscles at some point.

While overuse or injury is common, there are other possible explanations for ongoing discomfort. Some common causes include:

- muscle tension in one or more areas of the body
- overusing the muscle during physical activity
- injuring the muscle while engaging in physically demanding work or exercise
- skipping warmups and cool downs

Some medical explanations for myalgia include:

- fibromyalgia, especially if aches and pains last longer than 3 months
- chronic fatigue syndrome
- myofascial pain syndrome, which causes inflammation in muscular connective tissues called fascia
- infections, such as the flu, polio, or bacterial infections
- autoimmune disorders such as lupus, dermatomyositis, and polymyositis
- use of certain medications or drugs, such as statins, ACE inhibitors, or cocaine
- thyroid problems, such as hypothyroidism or hyperthyroidism
- hypokalemia (low potassium)

In the medical emergency:

- a sudden onset of water retention or a reduction in urine volume
- difficulty swallowing
- vomiting or running a fever
- trouble catching your breath
- stiffness in your neck area
- muscles that are weak
- an inability to move the affected area of the body

Diagnosis

If the cause of your muscle pain is unknown or you experience severe or chronic muscle pain, doctors may order additional tests.

- **Blood tests** can help determine your enzyme, hormone, and electrolyte levels and check for signs of infections.
- **CT scan or MRI** can identify muscle damage.
- **Electromyography (EMG)** can measure the electrical activity in nerves and muscles and evaluate nerve and muscle function.
- **Muscle biopsy.**

These additional tests can help your doctor make a proper diagnosis and treatment plan.

Treatment

Temporary muscle pain can usually be relieved by resting, stretching, or taking pain relievers.

- Rest and elevate the affected area to reduce the strain.
- Apply a cold compress to relieve inflammation and a hot compress to improve blood circulation in the sore muscles.
- Take a warm shower or bath to relax your muscles.
- Take pain relievers

Easing muscle aches at home

Some measures at home you can take to relieve muscle discomfort from injuries and overuse include:

- resting the area of the body where you're experiencing aches and pains
- taking an over-the-counter pain reliever
- applying ice to the affected area to help relieve pain and reduce inflammation

Other measures that may provide relief from muscle pain include:

- gently stretching the muscles
- avoiding high-impact activities until after the muscle pain goes away
- avoiding weight lifting sessions until the muscle pain is resolved
- giving yourself time to rest
- doing stress-relieving activities and exercises such as yoga and meditation to relieve tension

Natural Pain Reliever

People have used essential oils, herbs, and alternative therapies as natural pain relievers for hundreds of years. Researchers have not fully explored these options, but some evidence suggests that certain remedies can help, and that many people find them useful.

Lavender essential oil: Lavender essential oil may help relieve pain naturally. People use lavender oil for pain relief, to help sleep, and to ease anxiety. A small-scale 2012 study found that inhaling lavender oil may relieve pain associated with migraine headaches compared with a placebo. Some research also suggests that lavender oil has pain-relieving, anti-inflammatory, and antioxidant effects.

Peppermint essential oil: Peppermint oil comes from the Mentha piperita L. plant. Some research suggests that the peppermint plant has anti-inflammatory, antimicrobial, and pain-relieving effects. The active compounds in peppermint oil include carvacrol, menthol, and limonene.

People often use diluted peppermint essential oil as a topical treatment, meaning that they rub diluted oil into the area that feels achy or painful.

One 2015 review notes that people have traditionally used peppermint to relieve painful spasms and problems associated with arthritis. The researchers also

report that applying peppermint oil to the temples and forehead may relieve tension headache pain.

Cloves: People have traditionally used cloves, from the Eugenia caryophyllata plant, as a home remedy to relieve pain from toothache. A 2006 study found clove gel to be as effective as benzocaine gel, which is a topical gel that dentists often use to reduce needle pain. The researchers applied clove, benzocaine gel, or a placebo to the inside of the participants' mouths. They reported lower levels of pain with both clove and benzocaine gels, but not with placebos. More research is needed to see how effectively cloves could relieve other sorts of pain. Researchers also believe that clove can have antioxidant, anti-inflammatory, anti-fungal, and anti-viral activity.

Capsaicin: People also use capsaicin, present in chilli peppers, for natural pain relief. This substance can cause a mild burning or tingling sensation when a person applies it topically. A 2011 study notes the important role that capsaicin topical creams and patches play in pain management. Many pain-relieving products contain capsaicin. Researchers are not yet sure why it relieves pain, but some believe that it reduces the skin's sensitivity to pain by working on the nociceptor fibres. These are nerves that carry pain signals.

Ginger: Ginger, or Zingiber officinale, is a root that shows promise as a natural pain reliever. A 2015 systematic review found that ingesting two grams of ginger per day modestly reduced muscle pain from resistance exercise and running when people took it for at least five days. The researchers also suggest that ginger may accelerate recovery and reduce inflammation related to exercise.

Try including ginger in the diet by adding raw ginger to smoothies or teas. People can also use ginger supplements. However, the natural, fresh ingredient may be more healthful.

Turmeric: Curcuma, the active ingredient in the spice turmeric, has pain-relieving qualities. A small-scale 2014 study found that curcuma extract is as effective as ibuprofen for pain management in the treatment of knee osteoarthritis when a person takes it for four weeks. Turmeric is also a common herbal remedy for reducing inflammation. To include turmeric in its natural form in the diet, try adding it to curries, smoothies, or juices.

And also fish oil, vitamin D, calcium, magnesium, Vitamin C, green tea extract and garlic.

Tips for preventing sore muscles

If your muscle pain is caused by tension or physical activity, take these measures to lower your risk of developing muscle pain in the future:

- Stretch your muscles before engaging in physical activity and after workouts.
- Incorporate a warmup and a cool down into all of your exercise sessions, around 5 minutes each.
- Stay hydrated, especially on days when you're active.
- Engage in regular exercise to help promote optimal muscle tone.
- Get up and stretch regularly if you work at a desk or in an environment that puts you at risk for muscle strain or tension.

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Original Article

Recognize the Relationship Between Autoimmune Disease as Rheumatism with Multi Vitamin Deficiency

Mohammed Mousa Atta and Ashraf Fadhil Jomah

ABSTRACT

Objective: To identify associated risk factors in RA. The highest reported prevalence for RA was in the 42-52 years age group, with lower prevalence in over 80-year-old, for whom diagnosis may be more difficult.

Study Design: Cross-sectional case-control study

Place and Duration of Study: This study was conducted at the Thi-Qar Governorate in south of Iraq from 1st February 2025 to 30th June 2025.

Methods: The link between vitamin D deficiency and rheumatoid arthritis and its possible consequences on disease activity and coexisting diseases were assessed. Fifty patients who had been clinically diagnosed with rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria were enrolled from rheumatology clinics and hospitals in the area. A group of healthy subjects, age- and sex-matched and without any autoimmune and chronic inflammatory diseases was also studied for comparisons.

Results: Males had a higher prevalence of Anaplasia compared to females, which might be associated with genetic and immune-related differences between males and females. Diabetic patients were more frequently infected (42%) than hypertensive patients (36%), indicating different effects of comorbidities on the progression of infection. In terms of hematological findings, mild anemia due to chronic inflammation was suspected in all cases, with significant vitamin D3 deficiency identified in more than 80% of cases

Conclusion: Vitamin D has an immunity-regulating role and could be useful in rheumatoid arthritis treatment. A global integrated strategy taking into account comorbid conditions, nutritional deficiencies and demographics in relation to vitamin D supplementation could potentially result better outcomes. In the future, more studies are required to improve the diagnosis and treatment of rheumatoid arthritis.

Keywords: Rheumatoid arthritis, Vitamin D3, Chronic inflammation, Personalized medicine, Hematological markers

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INTRODUCTION

Autoimmune conditions such as RA occur when your body's immune system which is supposed to protect against viruses, bacteria, and other pathogens attacks healthy cells within the body.[1] Rheumatoid arthritis (RA) is a systemic inflammatory disorder with a chronic course that is characterized by synovial inflammation, joint destruction and systemic manifestations including fatigue and cardiovascular disease.[2] It is multifactorial in etiology and includes genetic propensity, environmental factors, level of hormones, and most recently nutritionally condition.[3]

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Vitamin D deficiency is vulnerability for autoimmune disease and is a risk factor for nutritional diseases. Vitamin D, first known for its effects on calcium and bone metabolism, has a strong impact on the immune system.[4] It is involved in both innate immunity, activation of macrophages and dendritic cells, and adaptive immunity through modulation of T cell differentiation and cytokine production.[5] In particular, vitamin D suppresses pro-inflammatory thymic stromal lymphopoietin (Th1 and Th17) cytokines and induces Tregs that promote immune tolerance and prevent autoimmunity.[6]

Surveys of people in various regions of the world have demonstrated that the common the prevalence of deficiency of 25 hydroxy vitamin D (25(OH)D) deficiency in the Middle East is amongst the most common, characterized by low sun exposure (attributed in part to traditional clothing and skin pigmentation and dietary insufficiency.[7] ThiQar is a southern Iraqi governorate, which has the same risk factors of RRMs, but few studies have been carried out on the risk factors linked with VDD and the prevalence of ADs indicate RA particularly.[8] There is a regional gradient that stresses the importance of regional investigation, since

such interaction between IABS and vitamin D status depending on local socio-cultural circumstances is important regarding efficient public health interventions and clinical guidelines.[9]

The immunologic basis to study vitamin D in RA is supported by mechanistic and clinical phenotypic evidence.[10] Mechanistically, stimulation of vitamin D receptor (VDR) in immune cells influences gene expression networks essential in the control of inflammation.[11] Low vitamin D status has been associated with worse disease activity in RA in clinical studies as well as in meta-analyses, and with more pain and lower functional capacity.[12] In addition, some studies, for example of vitamin D supplementation, have found for a possible role of this agent in either symptom relief in RA or in halting its progression findings are controversial.[12,13]

Clasen et al[14] reviewed in meta-analysis of the effect of vitamin D on the risk of rheumatoid arthritis. These workers observed that low circulating levels of 25(OH)D were associated with a slightly increased risk of the incidence of RA, offering a preventive hint to maintain an adequate 25(OH)D status.

Dupuis et al[15] investigated, whether sex has any impact on vitamin D role in autoimmune diseases, including RA. They noted that sex-related effects in vitamin D metabolism and immunity might alter disease risk or presentation and it is critical to account for gender-specific physiological differences in both research and clinical practice when optimizing vitamin D levels with autoimmune disease.

Although an increasing amount of evidence was being collected in this way[16,17], few regional data are available, particularly from Iraqi populations. Yet there has been no large study of vitamin D status among RA patients in ThiQar who were analyzed with respect to demographic factors, seasonal exposure to sunlight, dietary habits, or cultural habits of dress, all of which could skew vitamin D synthesis effects.

The main aim of the present study is to investigate the role of vitamin D deficiency in rheumatoid arthritis and other autoimmune diseases in Thi-Qar province. The goal of this project is to provide insights into the role of vitamin D in the development of autoimmune disease by examining vitamin D levels in healthy and RA individuals and their relevance to the severity and outcome of disease.

METHODS

This cross-sectional case-control study, conducted in Thi-Qar Governorate in south of Iraq from 1st February 2025 to 30th June 2025 vide letter No.202 dated 8-1-2025. The link between vitamin D deficiency and rheumatoid arthritis (RA) and its possible consequences on disease activity and coexisting diseases were assessed. Fifty patients who had been clinically diagnosed with RA according to the 2010 ACR/EULAR classification criteria were enrolled from rheumatology clinics and hospitals in the area. A group of healthy subjects, age- and sex-matched and without any autoimmune and chronic inflammatory diseases was also studied for comparisons. All participants had their venous blood samples taken aseptically. Two portions of the blood samples were separated. White blood cell count (WBC), red blood cell count (RBC), hemoglobin concentration, platelet count, and packed cell volume (PCV) were among the hematologic parameters evaluated by Complete Blood Count (CBC) analysis. Serum from the second part was obtained by centrifugation and kept at -20°C until the levels of 25-hydroxyvitamin D [25(OH)D] and autoimmune markers were analyzed.

Following the manufacturer's instructions, serum 25(OH)-vitamin D levels were measured using a D Xpress ELISA kit, and a Biotek ELX-800 microplate reader was used to measure absorbance. The assay used a monoclonal antibody specific to 25(OH)-vitamin D3 in a competitive ELISA format. The status of vitamin D was categorized as optimal: 30–70 ng/mL; insufficient: 20–30 ng/mL; deficient: <20 ng/mL

Autoimmune Marker Analysis: Commercially available immunoassay kits were used to measure Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPA) in order to confirm the diagnosis and evaluate autoimmune activity. The RA group consisted of only those patients who tested positive for RF and/or ACPA.

Assessment of Disease Activity: **T**he Disease Activity Score 28 (DAS28), which incorporates the sedimentation rate of erythrocytes (ESR), painful and swollen joint counts, and the patient's overall health evaluation was used to assess the progression of rheumatoid arthritis (RA).In order to gather a thorough medical history from the participants, comorbidities such as diabetes mellitus and hypertension which were verified by patient records and ongoing medical treatment were the focus of the interviews.

The data was entered and analyzed through SPSS-26. Vitamin D levels were compared across age and disease activity groups using one-way ANOVA and independent t-tests. Serum vitamin D levels and RA disease activity were compared using Pearson correlation coefficients. A p-value <0.05 was deemed statistically significant.

RESULTS

The findings indicate a higher prevalence of rheumatoid arthritis in males compared to females, with males constituting 62% of the cases (Table 1). The 41–50-year age group accounted for 30% of our series, which is the greatest prevalence among our 50 cases. This was followed by the 51–60 years age group (22% of cases). In comparison, the lowest number (4%) were found amongst those aged under thirty, while those aged 80 years or more made up 2% of the total (Fig. 1).

42% of participants were diagnosed with diabetes, 36% with hypertension, and 22% reported no chronic illnesses. Figure 2 provides an overview of the prevalence of these illnesses within the sample, emphasizing the substantial proportion of persons afflicted by diabetes and hypertension.

Table No. 1: Distribution of rheumatoid arthritis infection according to sexual category (n=50)

Gender	No.	%
Male	31	62
Female	19	38

X^2= 3.84 DF= 1 P<0.016 (Significant)

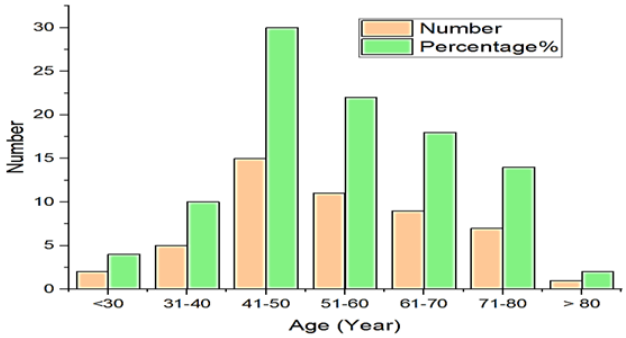

Figure No. 1: Age-wise distribution of rheumatoid arthritis cases

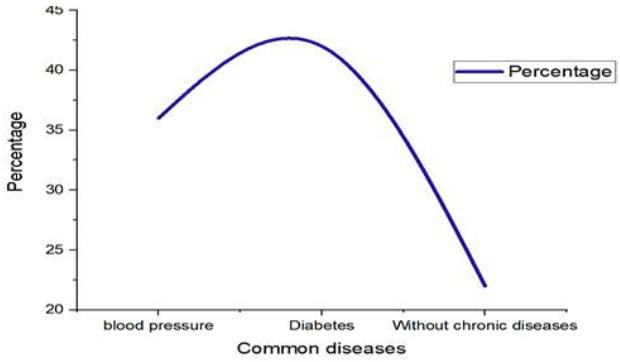

Figure No. 2: The association between rheumatoid arthritis and other common diseases.

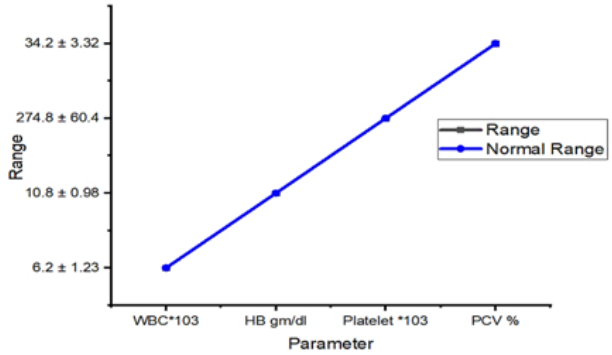

Figure No. 3: Hematological profile of study participants

The Chi-square score of 6.32 exceeds the crucial criterion of 5.99 in the statistical analysis (Fig. 2).

The majority of subjects have blood characteristics within normal limits. However, there were some clinically relevant discrepancies. However, there was a minimal decrease in hemoglobin concentration and packed cell volume (PCV) and this may be suggestive of a mild anemia (Fig. 3).

DISCUSSION

Interesting details regarding the epidemiology and clinical profile of RA were revealed by this investigation. The disease was most common in women aged 42 to 52 (30%). With a 2% prevalence rate in the elderly, the prevalence decline was, nevertheless, highly notable in the older age groups. According to this pattern, middle-aged adults are the ones who are diagnosed with RA the most frequently; underreporting or the presence of conflicting old age symptoms may make it difficult to detect RA in the elderly.[18]

Given the overall epidemiological trend in RA, the high percentage of males in this cohort (62% vs. 38%) is noteworthy. Variations in immune system activity, genetic susceptibility, or other biological and environmental factors that influence disease risk could be reflected in this unexpected sex distribution. The included RA patients' comorbidities were also examined. 42% of RA patients had diabetes mellitus, which seemed to be a serious risk factor. This association is most likely due to the fact that diabetes patients are frequently immunocompromised, which puts them at risk for autoimmune diseases like RA.[19] Although hypertension was found in 36% of patients, it did not appear to have had a comparable impact on immune function; that is, there was a weaker correlation between the development of RA and high blood pressure.[20]

WBCs and platelets, among other hematological parameters, were elevated in the blood (CBC) examination, although they were still within the normal range. Additionally, there were slight drops in hemoglobin and RBC levels, which could be indicators of anemia. One important finding of the present study was that serum 25(OH)-vitamin D levels were significantly lower among patients with RA (80% had vitamin D insufficiency). This finding further substantiates the action of vitamin D on the immune and emphasizes its therapeutic potential in cases of RA. The high insufficiency rate indicates that supplementation might contribute to the adjustment of disease activity and patient outcome. The results emphasize the multifactorial nature of RA, influenced by age, sex, comorbidities, hematological markers, and nutritional condition.[21] These findings reinforce the need for a multidimensional, patient-centered approach to the diagnosis and treatment for RA, considering the

range of clinical and demographic factors that influence disease course and responses to therapy.

The 41–50-year age group accounted for 30% of our series, which is the greatest prevalence among our 50 cases. This was followed by the 51–60 years age group (22% of cases). In comparison, the lowest number (4%) were found amongst those aged under thirty, while those aged 80 years or more made up 2% of the total (Fig. 1). A statistical analysis showed a significant relationship between age and RA prevalence value was greater than the critical table value (12.59) and $p<0.001$). This validates a significant correlation and indicates that age plays an important role in the development and progression of RA. The findings show that most patients with RA had been diagnosed between the ages of 30 to 60, and the group 41–50-year had the highest proportion, which was coincident with the common age of RA onset. The significance of age in RA prevalence, detection, and clinical manifestation is highlighted by these findings. Additionally, they encourage further research on the role of aging-related physiological factors and healthcare access in the onset and diagnosis of RA in older adults.[22]

The total amount of patients with cases of viral rheumatoid arthritis and the associated percentages for each gender (Table 1). There were 31 were male (62%) and 19 were female (38%). The Chi-square value of 5.76 exceeds the crucial value of 3.84; the p-value of 0.016 is statistically significant ($p<0.05$). This indicates a significant sex-specific disparity in the prevalence of rheumatoid arthritis. The findings indicate a higher prevalence of rheumatoid arthritis in males compared to females, with males constituting 62% of the cases.

This does not conform to the usual trend of elevated prevalence of autoimmune illnesses, such as rheumatoid arthritis[23], observed in women. However, it appears that within this particular analyzed population, males exhibit greater susceptibility, since a higher number of instances was identified among them. This may indicate several explanations, including environmental, genetic, or lifestyle factors leading to the heightened frequency of RA in males within this community.

The statistical significance ($P<0.0001$) of this study verifies that the gender distribution in the RA is not attributable to chance. This outcome warrants a comprehensive investigation of the gender disparities in the manifestation and progression of the illness[24], which may enhance the knowledge of the processes driving gender bias in rheumatoid arthritis, thereby facilitating personalized preventative and treatment strategies.

42% of participants were diagnosed with diabetes, 36% with hypertension, and 22% reported no chronic illnesses and the prevalence of these illnesses within the sample, emphasizing the substantial proportion of persons afflicted by diabetes and hypertension. The Chi-square score of 6.32 exceeds the crucial criterion of 5.99 in the statistical analysis. A p-value of 0.042 is statistically significant ($p < 0.05$), indicating that the distribution of chronic illnesses is unlikely to be attributable to chance (Fig. 2). This signifies a substantial correlation between the existence of these chronic illnesses and the study population.

The data indicate that diabetes is the predominant chronic illness in the sample, impacting 42% of individuals, while hypertension affects 36%. This corresponds with overarching public health trends, wherein diabetes and hypertension are significantly widespread worldwide especially among older demographics or those with certain lifestyle variables.[25] The very low number of persons devoid of chronic illnesses (22%) indicates the significant prevalence of these ailments within the sample.

The results summarized in Figure 3 reveal that the majority of subjects have blood characteristics within normal limits. However, there were some clinically relevant discrepancies. However, there was a minimal decrease in hemoglobin concentration and packed cell volume (PCV) and this may be suggestive of a mild anemia. These hematological alterations are commonly observed in chronic inflammatory and immune process such as rheumatoid arthritis (RA).[26]

At the time of testing, there were no hematologic neoplasms, active bleeding, or hypercoagulable state, as evidenced by the WBC and platelet results being within the normal range for age. Despite the fact that these findings are somewhat comforting, they should be interpreted in light of the overall clinical picture, which includes the disease's stage, symptoms, and medication.[27]

CONCLUSION

The low vitamin D levels may exacerbate rheumatoid arthritis severity and activity. The findings clarify the impact of demographic and clinical factors, including age, gender, and comorbidities like diabetes, on the prevalence and progression of rheumatoid arthritis. These findings highlight the importance of vitamin D as both a biomarker and a therapeutic strategy for the optimal management of rheumatoid arthritis.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Mohammed Mousa Atta, Ashraf Fadhil Jomah
Drafting or Revising Critically:	Mohammed Mousa Atta, Ashraf Fadhil Jomah
Final Approval of version:	All the above authors
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Original Article

Relationship Between Malocclusion and Body Mass Index: A Cross-sectional Study in the Tikrit Dentistry Collage

Maha Esam

ABSTRACT

Objective: To determine the effects of obesity and overweight on malocclusion.
Study Design: Cross-sectional study
Place and Duration of Study: This study was conducted at the Tikrit Dentistry Collage from 1st February 2024 to 31st July 2024.
Methods: A total of 103 adults, aged between 19-24 years were part of this study. The following adult subjects were excluded from this work: Subjects who had undergone, previous orthodontic treatment, subject with habits such as atypical swallowing and lip sucking, systemically compromised students, craniofacially abnormal students (clefts and syndromes). Sample was divided into 3 groups based on their body mass index level, G1 normal weight adults, G2 overweight or obese adults and G3 underweight adults.
Results: There was a significant relationship between body mass index and face height. However malocclusion and crowding were not substantially linked with body mass index.
Conclusion: Dietary status may impact craniofacial development and there was no significant link between body mass index and malocclusion or dental crowding.

Key Words: Body mass index (BMI), Growth, Malocclusion, Nutrition, Obesity

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INTRODUCTION

Ideal occlusal scheme is a theoretical concept which is based on the original anatomy of the patient and it is hardly found in nature. This conception was used to a state when the skeletal bases of maxillary archor mandible arch are of the accurate size in relation to one and the other, and the teeth should be in the correct relationship in all three planes of space at rest position.[1,2]

Class I type of malocclusion is the most common kind, much more so than normal one, as there is no clear evidence on its cause.[2-4] Understanding the genesis of this type of malocclusion requires a thorough understanding of how and when it occurs.[5] Class II in the deciduous dentition is characterized by distal terminal plane of the second deciduous molars, distal canine connection, overjet, and substantial overbite.

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Additional abnormalities include a small upper dental arch and maxillary base, as well as inadequate anterior spacing.[6-11] These variables are known to contribute to the development of skeletal malocclusion and facial abnormalities, and they are assumed to be caused by hereditary and/or environmental factors.[12,13] The posterior discrepancy is a significant etiological component in Class III malocclusion.[6] It influences the plane of occlusion. This concept must be revised to provide an acceptable therapeutic approach to the treatment of Class III malocclusion.[7]

Obesity and overweight are considered a global epidemic.[10] It is more than just the result of an unhealthy lifestyle; it is a condition in which weight gain has reached a critical level, posing major health concerns. Obesity can be viewed as both a sickness and a risk element for other disorders.[11] In grown-ups is linked to an increased risk of illnesses that cause significant morbidity.[14,15]

METHODS

This cross-sectional study was conducted at Tikrit Dentistry College, Iraq from 1st February 2024 to 31st July 2024 vide letter No. 23344/QM/Approval/4JKJD8 dated January 8, 2024. A total of 103 subjects were enrolled. The subjects were divided into three groups, G1 normal weight, G2 overweight, and G3 underweight. The exclusion criteria were students who had reported bad habits such as atypical swallowing and lip sucking, students with manifestations illnesses, and

who were undergoing or previously sensed treatment (Fig. 1). The oral examination was done by sitting the students on the dental chair in the college dental clinic, using a disposable mask, gloves, dental mirrors, and dental Vernia to collect the clinical data.[16]

Nutritional status was assessed using BMI, calculated from each participant's height and weight. Weight was measured to the nearest 0.1 kg using a calibrated Beurer scale, with students standing upright and evenly balanced. Height was recorded to the nearest 0.1 cm using a stature meter. Body mass index was then computed using the standard formula: weight (kg) + height² (m). Statistical tests include the use of SPSS version 26. Chi-square association were utilized to analyze the data at P≤0.05.

RESULTS

There was a non-significant changes between them in 23 cases of normal weight 60.5%, 12 cases of overweight 31.5%, and 3 cases of underweight 8% of the abnormal group had malocclusion (Table 1).

There were 11 cases in normal weight, 9 cases in overweight and 1 case in underweight had class II malocclusion while 7 cases in normal weight, 3 cases in overweight and 2 cases in underweight had class III malocclusion. There was a non-significant association between body mass index and class II & III (Table 2, Fig. 2).

Table 1: Association between body mass index and malocclusion

Body mass index	Normal		Abnormal	
	No.	%	No.	%
Normal Weight	31	47.7	23	60.5
Overweight	60	46.2	12	31.5
Underweight	4	6.1	3	8.0

Figure No. 1: Weight categories based on body mass index

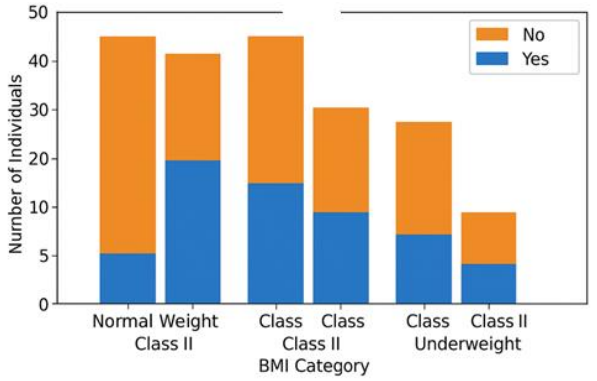

Figure No. 2: Association between body mass index and classes of malocclusion

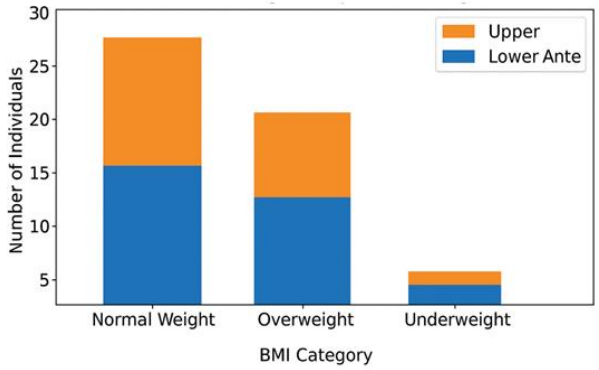

Figure No. 3: Distribution of upper and lower anterior involvement across body mass index categories

Table 3 reveals the relationship between body mass index and crowding, a non-significant association between body mass index and crowding, there are 19 cases in normal weight, 15 cases in overweight, and 5 cases in underweight had crowding in the lower arch, in contrast, 7 cases in normal weight and 4 cases in overweight had crowding in the upper arch.

Six cases of overweight had abnormal lower facial height while 2 cases of overweight had abnormal middle facial height and in 1 case overweight had abnormal upper facial height on other side, in the normal weight group 2, 3, 3 cases had abnormal lower, middle and upper facial height respectively. There was a significant association between BMI and facial height (Table 4).

Table No.2: Association between body mass index and classes of malocclusion

Body mass index	Class II				Total	Class III				Total
	Yes	%	No	%		Yes	%	No	%	
Normal Weight	11	52.4	43	54.4	54	7	58.3	47	51.6	54
Overweight	9	42.9	33	40.3	42	3	25.0	39	42.9	42
Underweight	1	4.7	6	7.3	7	2	16.7	5	5.5	7
Total	21	100.0	82	100.0	103	12	100.0	91	100.0	103
Chi square value	0.189					2.86				
P value	0.910 (NS)					0.362 (NS)				

Table No. 3: Association between body mass index and crowding

Body mass index	Lower Anterior	Percent	Upper Anterior	Percent	Total
Normal weight	19	48.7	7	63.6	26
Overweight	15	38.5	4	36.4	19
Underweight	5	12.8	0	0.0	5
Total	39	100	11	100	50

Chi-square value = 1.787 P value = 0.409 (NS)

Table No.4: Association between body mass index and facial height

Body mass index	Normal	%	Abnormal						Total
			Lower	%	Middle	%	Upper	%	
Normal weight	46	54.8	2	22.2	3	60.0	3	60.0	54
Overweight	33	39.3	6	66.7	1	20.0	2	40.0	42
Underweight	5	5.9	1	11.1	1	20.0	-	-	7
Total	84	100	9	100	5	100	5	100	103

Chi-square value = 5.775 P value = 0.034 (S)

DISCUSSION

Psychological problems are associated with obesity in adults that may affect both compliance and lifestyle. Lastly, the major cause of the increasing prevalence of obesity remains an incorrect lifestyle which would promote the excessive accumulation of body fat, in particular, a high-calorie diet high in fats and fermentable sugars and a reduction in exercise physical.[17,18]

Overweight/obesity (31.5%) cares abnormal malocclusion in the students was non-significant associated ($p>0.05$) (Table1), that means no effect of obesity on malocclusion that was agree with results reported by Dohou et al[18], also no effect on the underweight group (8.0%) that coincidence with some studies.[19,20]

These results found that the overweight group (42.9%) have broad maxilla, large upper teeth with foreword direction, and increase overjet (6-8mm), while narrow mandible, retrusion arch, and also convex facial profile that greater than the underweight group (4.7%), all these features of class II malocclusion. show results that the overweight group (25.0%) have a small upper arch while large and protrusive lower arch, edge-to-edge incisors, reverse overjet, and in some cases reverse overbite or anterior cross bite that also increase in the underweight group (16.7%) but decrease by a half percentage of normal group (58.3%) [Table 2]. The result showed (38.5% lower anterior) (36.4%upper anterior) dental crowding in overweight students; a Non-significant association that disagreed with Thomas et al[21] and symmetry with other studies that found no association between under-weight (12.8% lower anterior) (0.0% upper anterior) and crowding (20-24) [Table 3]. In the present study, the majority of patients with abnormal facial height are from the overweight/obese group lower, upper, and middle thirds (66.7%, 40.0%, and 20.0% respectively). There is also a greater abnormality in the height of the lower facial level in the overweight/obese group (66.7%) compared to the normal weight group (54.8%). However, these results were statistically significant ($p<0.05$). [Table 4].[22-23]

CONCLUSION

A major relation was found between facial heights and obesity and further research is needed to heighten the consistency of these outcomes and upgrade perception.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Maha Esam
Drafting or Revising Critically:	Maha Esam
Final Approval of version:	All the above author
Agreement to accountable for all aspects of work:	All the above author

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

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Original Article

Iron Deficiency Anemia in Children

Frequency of Iron Deficiency Anemia in Children from 6 Months to 5 Years of Age Presented with Pallor in Tertiary Care Hospital

Aalya Farooq, Manzoor Ali Khan, Gulraiz Iqbal, Sughra Latif, Qurba Batool and Tanveer Hussain

ABSTRACT

Objective: To assess the frequency of iron deficiency anemia amongst children from 6 months to 5 years aged group presenting with pallor.

Study Design: Cross sectional descriptive study

Place and Duration of Study: This study was conducted at the Department of Pediatrics, Abbas Institute of Medical Sciences Muzaffarabad Azad Jammu & Kashmir from January 2025 to June 2025.

Methods: A cross sectional descriptive was conducted over a period of six months in the Department of Pediatrics. The study involved 200 children presented with pallor of aged 6 months to 5 years. After informed consent a structural proforma was obtained from parents or legal guardian of the patients. Hemoglobin <11.0g/dL was considered IDA based on Who criteria. Data were analyzed using SPSS 23.0 version. P value <0.05 was considered statistically significant.

Results: In total of 200 children presented with pallor, n= 42 (21.0%) were diagnosed with iron deficiency anemia. Overall, the highest frequency was seen in 37-48 months aged group n=49. Amongst IDA group the most prevalent age group was 49-60 months aged group with n=12. The most dominant gender was female n=104 than male n=96. A statistically significant difference was found between IDA and non-IDA group (p=0.0062). There was no significant association seen between IDA group and age and gender.

Conclusion: This study concluded that high frequency of iron deficiency anemia was seen in children with pallor and most of them in the late 60 months.

Key Words: Iron deficiency anemia, children, pallor, nutritional deficiency, hemoglobin.

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INTRODUCTION

The most prevalent form of nutritional anemia across the globe is iron deficiency anemia (IDA). IDA is considered as a major public health issue by WHO.[1,2] Approximately 43% of children less than five years of age worldwide are suffering from anemia in which 50% of cases having iron deficiency.[3] The burden is very high in lower middle income countries and the reason may be due to poor nutrition intake, frequent illness, parasitic infections and lack of public health interventions. The consequences lead to impairment of physical growth, cognitive development, behavior and immunity.[4,5]

Anemia could be defined as the reduction of hemoglobin concentration, hematocrit or red blood cell count below specific age ranges. The anemia diagnosed in children below 5 years old is having hemoglobin concentration less than 11.0g/dL.[6] The causes of anemia vary but the iron deficiency is the most prevalent cause of anemia contributing 60-70% of all pediatric anemia patients. The reason could be due to inadequate intake of iron during the period of rapid growth and increased iron requirements and particularly required in early childhood and infancy. The iron deficiency risk increases exactly after the age of 6 months as the infant now totally dependent on dietary sources while the maternal iron stores are depleted.[5,7,8]

Pallor is one of the most common and first clinical presentation of anemia in children. The pallor can be examined in the palms, conjunctiva, nail beds or oral mucosa. The pallor may or may not be correlated with hemoglobin as it is a subjective sign which are not

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specific therefore further investigations are mandatory. The other clinical presentation includes poor feeding, fatigue, development delay, irritability and tachycardia. Severe cases of anemia lead to congestive heart failure, growth retardation and poor physical endurance.[9,10]

The diagnostic dilemma of iron deficiency includes a combination of clinical examination as well as laboratory investigations.[9] The standard methods of investigations are completed blood count, serum ferritin levels, serum iron,total iron binding capacity, transferrin saturation and peripheral blood smear. Serum ferritin is considered one of the most reliable investigations amongst these which show the iron stores however, it can be seen elevated in the presence of infection or inflammation. The WHO has emphasized the need for early detection and prevention of IDA.[11,12]

The prevalence of anemia in countries like Pakistan, India, Bangladesh and other LMICs are unacceptably high and exceeding 60-70% in some rural areas.[4,8] The significant contributors to anemia in these countries are malnutrition, high birth rates, suboptimal breastfeeding, diarrheal diseases and limited to fortified food access.[8,9] Despite the magnitude of problem, there is a limited data published from hospital based or community level study focusing on children with palor and its correlation with iron status. Therefore, the current study may bridge this gap by determining the frequency of iron deficiency anemia among children aged 6 months to 5 years who present with palor and will help in early diagnosis and treatment while avoiding delayed interventions.

The objective of this study was to determine the frequency of iron deficiency anemia among children aged 6 months to 5 years presenting with palor.

METHODS

A descriptive cross sectional study was carried out in the Department of Pediatrics, Abbas Institute of Medical Sciences Muzaffarabad Azad Jammu & Kashmir from January 2025 to June 2025. Ethical approval was taken from ethical committee of the hospital. The children included in this study were from 5 months to 6 years, clinical pallor which was examined and observed by trained pediatrician and parents or legal guardians who give informed consents. Known or suspected cases of hemolytic anemia, thalassemia, leukemia or chronic systemic disease, recent blood transfusion, children with acute infections or inflammatory conditions and those having congenital anomalies or syndromes which indirectly affect hematological parameters were excluded from this study. The sample size was calculated using the WHO formula for sample size in which the estimated prevalence of 60% children having iron deficiency anemia with pallor was taken.[13] The confidence level was kept at 95% and margin of error was 7 %. The total sample size came with 188 children, to account for non-response or dropouts a final sample size of 200 children was selected through non-probability consecutive sampling technique. Children were diagnosed with IDA if they had hemoglobin < 11.0g/dL.[14] A structural proforma was taken from and informed consent was obtained from parents or guardians of all children. Confidentiality of data was maintained using patients ID.

The data was analyzed using SPSS 23.0 version. Means and standard deviations were calculated for quantitative variables. Frequencies and percentages were obtained for categorical variables. Chi-square was applied to determine association between IDA and categorical variables like age group and gender. Independent t-test was used to compare mean hemoglobin levels between IDA and on-IDA groups. P value of <0.05 was considered statistically significant.

RESULTS

All participants in this study had a clinical pallor were confirmed by a trained pediatrician. The mean age presentation was 32.4±14.7months. Females (n=104) were more than males (n=96) as shown in figure 1.

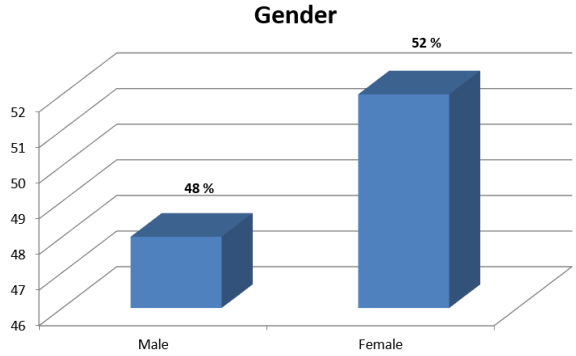

Figure No.1: Percentage of gender distribution.

Table No.1: Distribution of IDA by age.

Age group (months	No IDA group	IDA group	Total	*p*-value
6-12	35	8	43	0.012
13-24	25	10	35	
25-36	33	4	37	
37-48	41	8	49	
49-60	24	12	36	

The iron deficiency anemia was found in 42 children (21.0%) while 158 children were having hemoglobin levels more than 11.0g/dL. Among 104 female 24(57.1%) had IDA while 18(42.9%) males were anemic. Table 1 is showing both groups distribution by age. The chi square statistics revealed that the difference in IDA frequency among age group was not statistically significant (p=0.106). The most prevalent age group 49-60 months (n=12) in IDA group while in

no IDA group 37-48 (n=41) was the most common age group. The chi square statistics showed that there was no association exist between IDA and gender (p=0.45) as shown in table 2.

Table No.2. Association between gender and iron deficiency anemia.

Gender	IDA Present (n=42)	IDA Absent (n=158)	Total (n=200)	χ^2	df	*p*-value
Male	18 (42.9%)	78 (49.4%)	96 (48.0%)	0.56	1	0.45
Female	24 (57.1%)	80 (50.6%)	104 (52.0%)			
Total	42 (100%)	158 (100%)	200 (100%)			

The mean hemoglobin in IDA group children was 9.1±0.6g/dL however in non-IDA group showed the mean hemoglobin level of 10.3±1.3g/dL. The indepdendent t- test showed that the difference in the group was statistically significant (p=0.0062).

DISCUSSION

This was a hospital based study focusing on the children aged 6months to 5 years presenting with clinical pallor. This study revealed a 21 % patients having iron deficiency anemia. The prevalence found in this study is much lower than that national survey figures from Pakistan. A secondary analysis from National Nutrition Survey 2011-2012 demonstrated a 33.2% frequency of iron deficiency anemia in children aged 5 months to 59 months.[15] The difference may be due to that this study focus on clinical subset, children with pallor while that of the survey was done using combined hemoglobin level <11.0g/dL and ferritin <12ug/L. The study analysis of 2018 National Nutritional Survey showed 28.6% iron deficiency anemia frequency in children below five years. The figure is higher than our findings but these are community based surveys whereas this study is mostly symptom-triggered and hospital based.

In another study by Ahmad et al[16] in which they found the prevalence of iron deficiency anemia of 28.8% using hemoglobin <11.0g/dL and ferritin <30ng/mL in children aged 1-15 years presenting with pallor. Their broader age range and high ferritin level likely contribute to the higher proportion but still this study supports our observed burden among symptomatic children.

The frequency of anemia among children below 5 years age was estimated 43% in which iron deficiency was counted for about 50% of cases.[15] World Health Organization data revealed mild to moderate load of iron deficiency in South Asia, severe load (>40% in sub-Saharan Africa and some parts of Asia.[13] In meta-analysis the frequency of iron deficiency anemia ranges from 5.8% to 41% depending on nutritional status and age.[17] The findings of this study fall on the lower end. These figures showed the heterogeneity in iron deficiency anemia epidemiology.

Pallor is the most commonly presenting symptoms however; the diagnostic sensitivity and specificity vary. This study showed that 1 in 5 children with pallor has confirmed iron deficiency anemia. The results are in aligned with other study but pallor can over or underestimate the iron deficiency in those areas where there is a high prevalence of malnutrition or hemoglobinopathies.[15] The findings of this study suggest that higher frequency of IDA was present in aged 49-60 months which is in contrast to the National survey which revealed that children under 24 months have a higher frequency of IDA.[15] the difference may be due to smaller sample size and narrower age distribution. The national survey also suggest the lower number of IDA in female children which contradict this study.[13,15] The reason could be local population or hospital attendance biasis.

The strength of this study are vulnerable age group, symptom based sampling, objective diagnostic criteria, gender and age stratification and laboratory confirmation. The limitations of this study are cross-sectional design, hospital based sampling, limited diagnostic marker and lack of dietary assessment. The inflammation and parasitic load were not measured and socioeconomic factors were not explored which are the further limitations of this study. Future research should be carried out for multicenter with large sample size. The results emphasize on need for targeted screening, nutritional counseling, iron supplementation and fortified food programs.

CONCLUSION

The findings of this study concluded that less than half of the patients with pallor were having iron deficiency anemia. Therefore, symptom based like pallor helps in guiding the suspicion of IDA in children in those areas where there is resource limitations.

Author's Contribution:

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Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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Original Article

Prevalence of Ischemic Changes in Foot Arteries on Doppler Ultrasound in Type 2 Diabetic Patients in a Tertiary Care Hospital

Hafiza Bazarqa, Muhammad Tanveer Alam, Syed Muhammad Kashif, Hari Lal and Muhammad Luqman

ABSTRACT

Objective: To ascertain the frequency of Doppler-confirmed foot ischemia in individuals with type 2 diabetes mellitus (T2DM) and assess its correlation with glycemic control, treatment strategy, comorbid conditions, and disease duration.

Study Design: Analytical-Cross Sectional Study

Place and Duration of Study: This study was conducted at the Dr. Ruth K.M. Pfau Civil Hospital in Karachi between September 2024 and February 2025.

Methods: Consecutive sampling was used to select 107 individuals with type 2 diabetes mellitus (T2DM), ranging in age from 30 to 80. Comorbidities, treatment type, length of illness, and HbA1c levels were among the information gathered. Following lower-limb Doppler ultrasonography, arterial flow was classified as either normal (triphasic) or abnormal (biphasic/monophasic) for each participant. The Chi-square and independent t-tests were used in the statistical analysis, which was carried out using SPSS version 25. A p-value of less than 0.05 was deemed statistically significant.

Results: Among the 107 participants, 78 (72.9%) had abnormal Doppler flow (mean age 56.8 ± 10.2 years; 55.1% male), according to the results. Poor glycaemic control (HbA1c ≥ 7%) was found to be significantly correlated with abnormal flow ($p = 0.03$). The mean length of diabetes was longer in patients with ischaemic changes (12.6 ± 6.1 years vs 8.4 ± 5.7 years; $p = 0.02$). Abnormal flow was more common in oral hypoglycemic users (83.6%) than in insulin users (67.6%), though this difference was not statistically significant ($p = 0.11$).

Conclusion: Most people with type 2 diabetes mellitus had subclinical foot ischaemia, especially those with longer disease duration and poorer glycaemic control. For prompt management and the avoidance of major ischaemic complications, routine Doppler evaluation is highly recommended.

Key Words: Type 2 diabetes mellitus, Doppler ultrasonography, Foot vasculopathy, HbA1c, Peripheral arterial disease.

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INTRODUCTION

Diabetes mellitus (DM) is a rapidly growing public health concern, especially in low- and middle-income nations like Pakistan.

According to recent pooled analyses, the prevalence of diabetes in Pakistan is approximately 13.7% (95% CI: 10.7–17.3) for adults, whereas national surveys like the Second National Diabetes Survey of Pakistan (NDSP 2016–2017) found that the prevalence among adults could reach 26.3%[1,2]. These results demonstrate the staggering prevalence of diabetes in the nation.

Both micro and macrovascular diseases are examples of vascular complications of diabetes that greatly increase morbidity and disability. One of the worst is lower extremity peripheral vascular disease (PVD), which increases the risk of ischaemia, ulceration, and amputation[3,4].

Chronic hyperglycemia, oxidative stress, inflammation, and endothelial dysfunction are all part of the pathophysiology that causes diabetic patients to develop atherosclerosis more quickly[5].

Even in asymptomatic people, Doppler ultrasonography is a sensitive, non-invasive diagnostic technique that enables assessment of flow haemodynamics and early vascular alterations. Its clinical utility in identifying

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lower limb arterial disease in diabetics has been highlighted by recent studies, particularly when paired with other imaging modalities like CT angiography[6,7]. The lack of research on Doppler-detected foot vasculopathy in diabetic patients in Pakistan, however, restricts the potential for early intervention.

Poor glycaemic control (HbA1c), a longer duration of the disease, treatment modalities (oral hypoglycemics vs. insulin), and comorbidities like hypertension and ischaemic heart disease are clinical factors linked to vascular dysfunction in diabetes[8]. Preventing the development of severe vascular disease requires addressing these risk factors.

The current study attempts to ascertain the frequency of Doppler-detected foot ischemia among diabetic patients in Karachi and investigate its correlation with HbA1c, duration of diabetes, and treatment modality, given the high prevalence of diabetes and the dearth of local data.

METHODS

During the six months from September 2024 to February 2025, this cross-sectional analytical study was carried out in the medical department of Dr. Ruth K.M. Pfau Civil Hospital in Karachi. The study used a non-probability consecutive sampling technique to include 107 patients with type 2 diabetes mellitus. As long as they provided written informed consent, adult patients aged 30 to 80 who had a documented history of type 2 diabetes mellitus spanning at least a year were eligible to participate. Patients with severe heart, lung, or kidney conditions unrelated to diabetes that could prevent Doppler examination were not included, nor were those with type 1 diabetes mellitus.

Daniel's formula for prevalence studies was used to determine the minimum necessary sample size, which came out to be 107.

$$Z^2 \times p\,(1\text{-}p)) / d^2 = n$$

in which d = 8% margin of error, Z = 1.96 at 95% CI, and p = 19.9% (expected prevalence of peripheral arterial disease in diabetic patients reported in prior literature)[9].

Clinical and demographic information, such as age, gender, length of diabetes, type of treatment (insulin or oral hypoglycemics), and comorbidities like ischaemic heart disease and hypertension, were gathered using a structured proforma. In order to evaluate glycaemic control, glycated haemoglobin (HbA1c) was measured during the previous three months. Every participant had their lower limb arteries Doppler ultrasonographically examined using a high-frequency linear probe. Atherosclerotic alterations were also noted, and flow patterns were classified as either triphasic (normal) or aberrant (biphasic or monophasic).

Abnormal Doppler flow in one or both lower limb arteries was considered vascular dysfunction for analytical purposes. While the duration of diabetes was stratified into less than 10 years and ≥10 years, glycaemic control was classified as either good (HbA1c < 7%) or poor (HbA1c ≥ 7%). Version 25.0 of SPSS was used to analyse the data. For continuous and categorical variables, respectively, descriptive statistics were displayed as means with standard deviations and as frequencies and percentages. The Chi-square test was used to assess relationships between categorical variables and vascular dysfunction, and the independent sample t-test was used to compare continuous variables. A statistically significant p-value was defined as less than 0.05.

The study received approval from Dow University of Health Sciences' Institutional Review Board (Ref: IRB-2610/DUHS/2024). All participants gave their written informed consent, and patient confidentiality was rigorously upheld during the entire study.

RESULTS

The study included 107 diabetic patients in total. The cohort's mean age was in the mid-50s, and its members ranged in age from young adults to elderly patients, with a male preponderance in the gender distribution. Many participants had a long-standing disease burden, as evidenced by the mean duration of diabetes, which was roughly 10 years. With a mean HbA1c level above 8% and values varying greatly among the group, glycaemic control was generally subpar.

Table No.1: Demographic and comorbidity profile of study participants (N = 107)

Variable / Comorbidity	Frequency (n) / Mean ± SD (Range)	Percentage (%)
Male	73	68.2%
Female	28	26.2%
Age (years)	53.3 ± 9.7 (35–75)	
Duration of diabetes (years)	11.3 ± 5.5 (3–30)	
HbA1c (%)	8.7 ± 2.2 (6.0–16.7)	
No known comorbids	76	71.0%
Hypertension	13	12.1%
Hypertension, Ischemic heart disease	11	10.3%
Hypertension, Chronic kidney disease	4	3.7%
Hepatitis c, Tuberculosis	3	2.8%

The vast majority of patients (71.0%) had no known comorbidities. The most prevalent condition among those with related conditions was hypertension (12.1%), which was followed by hypertension and ischaemic heart disease (10.3%). Lower percentages had a dual

diagnosis of TB and hepatitis C (2.8%) or hypertension with chronic kidney disease (3.7%). Crucially, no patient in this dataset had ischaemic heart disease by itself without hypertension (table 1)

The results of Doppler ultrasonography revealed that only a small percentage of patients had normal triphasic flow, while a significant portion displayed aberrant arterial flow patterns, primarily biphasic and monophasic. On Doppler imaging, a few cases also showed signs of atherosclerotic plaque development (table 2)

Table No. 2: Vascular findings (N = 107)

Finding	Frequency (n)	Percentage (%)
Flow pattern: Triphasic	8	7.5%
Flow pattern: Biphasic	21	19.6%
Flow pattern: Monophasic	63	58.9%
Any abnormal flow (mono/biphasic)	84	78.5%
Any plaque/atherosclerosis	5	4.7%

Table No.3A: HbA1c categories vs abnormal flow

HbA1c Category	Abnormal flow (n, %)	Normal flow (n, %)	Total (n)
<7% (Good control)	12 (54.5%)	10 (45.5%)	22
≥7% (Poor control)	66 (83.5%)	13 (16.5%)	79

Chi-square = 6.66, p = 0.01

Table No.3B: Mean HbA1c by Doppler flow pattern

Flow pattern	Mean HbA1c ± SD
Abnormal (n=78)	8.91 ± 2.25
Normal triphasic (n=23)	7.84 ± 1.93

t-test, p = 0.03 (abnormal vs. normal triphasic)

Table No.4A: Duration of diabetes categories vs abnormal flow (N=107)

Duration of diabetes	Abnormal flow (n, %)	Normal flow (n, %)	Total (n)
<10 years	48 (70.6%)	20 (29.4%)	68
≥10 years	36 (92.3%)	3 (7.7%)	39

Chi-square = 5.7, p = 0.017

Table No. 4B: Mean duration of diabetes by Doppler flow pattern

Flow pattern	Mean duration ± SD (years)
Normal triphasic flow	7.57 ± 3.12
Abnormal flow	12.24 ± 5.45

t-test, p = 0.0 (abnormal vs. normal triphasic)

There were 101 patients with available HbA1c data; most of them had poor glycaemic control, but a smaller number had adequate levels. Patients with poor glycaemic control were more likely to have abnormal arterial flow, and this relationship was statistically significant (Table 3A). The association between poor glycaemic status and vascular dysfunction was further supported by the fact that the mean HbA1c level was higher in people with abnormal Doppler findings than in those with normal triphasic flow (Table 3B).

Doppler findings were found to be significantly correlated with the length of diabetes. Compared to patients who had the disease for a shorter period of time, those who had a longer duration were more likely to show abnormal arterial flow patterns. Those with abnormal Doppler results also had a longer mean duration of diabetes, which supports the association between chronic hyperglycemia and progressive vascular impairment (Tables 4A and 4B).

Of the 107 patients, 73 (68.2%) were taking oral hypoglycemics (OHA) and 34 (31.8%) were taking insulin. 23 out of 34 insulin users (67.6%) and 61 out of 73 OHA users (83.6%) had abnormal Doppler flow. Vascular dysfunction and treatment modality did not statistically significantly correlate (Chi-square = 2.6, p = 0.107). Therefore, although the difference was not statistically significant, abnormal flow seemed to be slightly more common in OHA users than in insulin users.

Table No.5: Treatment modality and abnormal Doppler flow (N=107)

Treatment modality	Abnormal flow (n, %)	Normal flow (n, %)	Total (n)
Insulin (n=34)	23 (67.6%)	11 (32.4%)	34
OHA (n=73)	61 (83.6%)	12 (16.4%)	73

Chi-square = 2.6, p = 0.107

DISCUSSION

This study assessed the prevalence of Doppler-detected foot vasculopathy in patients with type 2 diabetes mellitus in a Karachi tertiary care setting and investigated its relationships with comorbidities, treatment modality, duration of diabetes, and glycaemic control. Vascular dysfunction was present in over two-thirds of diabetic patients, according to the findings, underscoring the substantial prevalence of subclinical peripheral arterial disease (PAD) in this demographic.

According to our research, patients with poor glycaemic control (HbA1c ≥7%) were more likely to have abnormal Doppler flow. This result is in line with earlier studies showing that hyperglycemia raises the risk of PAD by promoting endothelial dysfunction, oxidative stress, and accelerated atherosclerosis[10,11]. In a similar vein, a large cohort analysis from the UK Biobank showed that a graded increase in vascular

complications was linked to every unit increase in HbA1c[12]. HbA1c was also highlighted in a recent review as a trustworthy surrogate marker for estimating macrovascular risk in diabetes[13].

In our study, the length of diabetes was another significant predictor of vascular dysfunction. Individuals who had diabetes for more than ten years experienced abnormal flow much more frequently than those who had the disease for less time. Given that chronic exposure to hyperglycemia gradually worsens vascular damage, this is biologically conceivable[14]. Similar findings were found in a Korean cohort, where PAD was independently predicted by the length of diabetes[15].

Our data revealed an intriguing trend regarding treatment modality: patients taking oral hypoglycemics were more likely to have abnormal flow than those taking insulin, although this difference was not statistically significant. Patients who started taking insulin might have had more stringent monitoring or, at the time of the study, had comparatively better glycaemic control. Other South Asian studies have also reported a similar lack of clear association[16,17].

The high frequency of vascular dysfunction may have been caused by comorbidities, which were common among our patients, especially ischaemic heart disease and hypertension. Endothelial damage is exacerbated by hypertension, and ischaemic heart disease and PAD share an atherosclerotic pathway[18]. These cardiovascular risk factors have been shown to cluster in diabetic patients in a number of studies from Pakistan and nearby nations[19].

In contrast to certain international reports, our study had a higher overall frequency of Doppler-detected foot vasculopathy. This could be because of variations in the study population, diagnostic standards, and baseline risk factors[20]. Crucially, Doppler ultrasonography demonstrated efficacy in detecting vascular dysfunction at an early stage, promoting its use as a useful screening method in high-risk diabetic populations. Early detection enables the use of antiplatelet or lipid-lowering medications to slow the progression of limb-threatening ischaemia, optimise blood pressure and glucose control, and implement lifestyle changes in a timely manner.

The cross-sectional design, single-center setting, and relatively small sample size are the study's primary limitations, which may restrict generalisability. However, it highlights the necessity for more extensive, multicenter studies in Pakistan and offers significant local evidence on the burden of diabetic vasculopathy.

CONCLUSION

Most people with type 2 diabetes mellitus had subclinical foot ischaemia, especially those with longer disease duration and poorer glycaemic control. For prompt management and the avoidance of major ischaemic complications, routine Doppler evaluation is highly recommended.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Hafiza Bazarqa, Muhammad Tanveer Alam, Syed Muhammad Kashif
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Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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Original Article

FNAC-Based Evaluation of Thyroid Lesions: Significance of Hematological and Biochemical Parameters in Untreated Hyperthyroid Patients

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ABSTRACT

Objective: To assess thyroid lesions and biochemical alterations in untreated hyperthyroid patients.
Study Design: Hospital based observational cross-sectional study
Place and Duration of Study: This study was conducted at the MINAR Cancer Hospital, Multan from January 2023 to December 2024.
Methods: A total of 1,000 thyroid disorder patients were enrolled at MINAR Cancer Hospital, South Punjab, Pakistan. Clinical evaluation and thyroid function tests (TFTs) identified 272 hyperthyroid patients, 325 euthyroid controls, and 403 with other thyroid disorders. FNAC was performed in 403 cases and categorized using the Bethesda system. Thyroid scans showed predominantly low radioiodine uptake, enabling stratification into hyperthyroid and FNAC groups. Hematological indices, including WBC, RBC parameters, platelet count, and MPV, were assessed. Statistical analyses employed One-way ANOVA, Student's t-test, Chi-square, Pearson, and Spearman correlations, with $p<0.05$ considered significant.
Results: FNAC analysis showed 35.60% of patients with colloid nodule (Bethesda II), 18.18% with follicular neoplasm (Bethesda IV), 23.07% suspicious for malignancy (Bethesda V), and 18.8% malignant (Bethesda VI). Malignancy was more frequent in patients above 45 years, while residence near the hospital had no effect on malignancy distribution. Hematological findings in untreated hyperthyroid patients revealed significant changes in RBC ($p=0.004$), MPV ($p=0.000$), and platelet count ($p=0.000$). Correlation analysis demonstrated negative associations of T4 with HGB, HCT, MCV, and MCH, and a positive association of MPV with T4 across different subgroups.
Conclusion: FNAC classifies thyroid lesions cytologically, while hematological and biochemical parameters reveal systemic changes, aiding diagnosis and treatment planning independently.
Key Words: Thyroid lesions, FNAC, Thyroid function tests (TFTs), Hematological parameters, Untreated hyperthyroidism

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INTRODUCTION

The thyroid gland derives its name from the Greek word thyreos (shield) due to its resemblance to armor. It secretes hormones that regulate metabolic functions such as energy expenditure, lipid and glucose metabolism, thermoregulation, and basal metabolic rate[1]. Thyroid hormone production is regulated by the hypothalamic pituitary thyroid axis through thyroid-stimulating hormone (TSH)[2]. The thyroid predominantly releases thyroxine (T4, ~85%), while a smaller proportion is secreted as triiodothyronine (T3, ~15%). Structural or functional abnormalities in thyroid growth can lead to various thyroid disorders[3].

Fine-needle aspiration cytology (FNAC) is the key diagnostic tool for Bethesda Category II thyroid nodules, including colloid nodules and Hashimoto's thyroiditis, with a malignancy risk of 0–3%. It shows colloid, follicular cells, lymphocytes, or Hurtles cells, ensuring accurate benign diagnosis, guiding follow-up, reducing unnecessary surgery, and complementing ultrasound findings. FNAC also identifies dense lymphoid infiltrates with occasional oncocytic cells,

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aiding diagnosis of Hashimoto's thyroiditis (Bethesda II/III)[4].

FNAC helps to diagnose Bethesda Category IV thyroid lesions (15–30% malignancy risk), showing hypercellularity, micro follicles, scant colloid. Though 85% accurate, it cannot assess invasion; thus, diagnostic lobectomy and molecular testing refine management. FNAC is also valuable in Bethesda Category V (60–75% malignancy risk), detecting suspicious nuclear or architectural features of carcinoma. Though not definitive, it guides surgical excision, integrates with ultrasound, and shows >90% predictive value for papillary subtypes[5]. In Bethesda Category VI (97–99% malignancy risk), FNAC confirms thyroid cancer with classic nuclear features, enabling prompt total thyroidectomy, radioiodine therapy, staging, and follow-up, achieving up to 98% sensitivity in papillary carcinoma[6].

Hyperthyroidism is a hypermetabolic condition characterized by increased energy expenditure, weight loss, enhanced lipid and glucose metabolism, and altered cholesterol levels. It may also accelerate growth in children and patients with Turner syndrome[3]. Complete blood count (CBC) is a key hematological test performed with automated analyzers, measuring parameters such as white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular values, platelet (PLT) count, and mean platelet volume (MPV). WBCs play a crucial role in host defense[7].

In Graves' disease, WBC counts may remain low, whereas hyperthyroid patients generally show higher leukocyte counts due to increases in corpuscles, granulocytes, and mononuclear cells[8]. RBCs transport oxygen, and thyroid dysfunction influences RBC levels; hypothyroidism is often associated with reduced blood cell counts, while hyperthyroidism may cause relative increases[9]. Thyroid hormone imbalance and iron deficiency can also alter erythrocyte distribution width, sometimes resulting in pernicious anemia. Platelets, an important CBC component, may also be affected in hyperthyroidism, with increased platelet count and reduced lifespan being reported. Thyroid disorders are more common in females, and thyroid hormones influence multiple systems, including the coagulation fibrinolytic pathway. MPV and platelet distribution width (PDW) are therefore considered important markers in assessing platelet function in thyroid disease. Moreover, both hypothyroidism and hyperthyroidism have emerged as significant endocrine factors influencing the clinical course and prognosis of COVID-19.[10,11].

Our study underscores the pivotal role of FNAC in thyroid evaluation, emphasizing its diagnostic yield across Bethesda categories, while also integrating hematological and biochemical parameters in hyperthyroid patients.

METHODS

Laboratory Measurements: Patients visited the nuclear medicine department & diagnostic section of MINAR Cancer Hospital, Multan for diagnostic and therapeutic purposes, and completed a structured form concerning demographic characteristics. Samples were taken in K2-EDTA vials (BD-Vacutainer for TFT'S & CBC analysis)[12,13], after the approval of a local ethical committee of MINAR cancer hospital (Pakistan Atomic Energy **Commission, Ref .No.M-3(13)/2018),** and informed consent of participants. T3, T4,FT3,FT4 and TSH were measured with an electrochemiluminescence immunoassay (Hitachi Modular E411; Roche Diagnostics, Mannheim, Germany), routine hematology testing was performed on the MEK9100 Celltac G Hematology Analyzer. Microscopy was performed through Olympus CX-43.

Statistical Analysis: Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Differences between hyperthyroid patients and the euthyroid control group, as well as between malignant and non-malignant cases, were evaluated using the independent t-test or the Mann Whitney U test, depending on data normality as assessed by the Kolmogorov Smirnov and Shapiro Wilk tests. A significance level of $P < 0.05$ was considered statistically significant. The chi-square test was applied to examine the influence of demographic variables on diagnosis, while correlations between thyroid function tests (TFTs) and complete blood count (CBC) parameters were assessed using Pearson and Spearman correlation analyses.

RESULTS

A total of 1000 patients with thyroid disorders were included in the study. Among them, 597 patients were newly diagnosed and untreated, comprising 272 hyperthyroid patients and 325 euthyroid controls, with ages ranging from 1 to 80 years (mean age 35.02 ± 12.86). FNAC-based categorization according to the Bethesda system showed that 35.60% were colloid nodules (Category II), 18.18% were follicular neoplasms (Category IV), 23.07% were suspicious for malignancy (Category V), 9.79% were malignant (Category VI), and 9.09% were papillary thyroid carcinoma (Category VI), while lymphocytic or granulomatous thyroiditis and oncocytic changes accounted for less than 2% as indicated in figure 1.

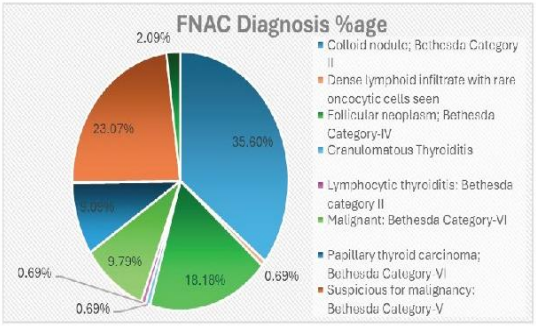
Significant differences were observed between hyperthyroid patients and the euthyroid control group for thyroid function tests, including T3, T4, and TSH (all p=0.000), as well as hematological parameters such as RBC (p=0.004), MPV (p=0.000), and PLT (p=0.000) as indicated in table 1.

Table No.1: Comprehensive Results of TFT'S and CBC parameters

Parameters	Hyperthyroid group	Euthyroid (Control group)	P-value
T3 nmol/L	4.41±2.90	1.98±0.51	[b] **0.000★**
T4 nmol/L	197.8±100.3	111.81±26.14	[b] **0.000★**
TSH µIU/ml	0.06±0.19	1.03±0.81	[b] **0.000★**
WBC×10^3/µL	8.85±3.53	8.97±2.44	[b] 0.269
RBC× 10^6/µL	5.21±0.67	4.50±0.56	[b] **0.004★**
HGB g/dl	12.90±2.32	12.69±1.78	[b] 0.238
HCT%	41.09±6.32	39.62±5.05	[a] 0.076
MCV fL	79.18±10.73	79.80±10.25	[b] 0.404
MCH pg	25.09±3.67	25.59±3.69	[b] 0.100
MCHC g/dl	31.38±3.42	32.04±2.18	[b] 0.156
PLT×10^3/µL	302.74±103.70	350.10±114.16	[b] **0.000★**
RDW%	13.48±1.69	13.09±2.01	[b] 0.045
PCT%	0.23±0.06	0.24±0.09	[b] 0.511
MPV fL	7.92±1.19	7.10±1.54	[b] **0.000★**
PDW%	17.65± 0.96	17.50±1.18	[b] 0.415

[a] Independent t-test, [b] Mann-Witney U Wilcoxon test, ★significant result,

A.



B.

S NO	Diagnosis Through FNAC	%age
1	Colloid nodule; Bethesda Category-II	35.60 %
2	Dense lymphoid infiltrate with rare oncocytic cells seen	0.69%
3	Follicular neoplasm; Bethesda Category-IV	18.18 %
4	Granulomatous Thyroiditis	0.69%
5	Lymphocytic thyroiditis: Bethesda category II	0.69%
6	Malignant: Bethesda Category-VI	9.79%
7	Papillary thyroid carcinoma; Bethesda Category-VI	9.09%
8	Suspicious for malignancy: Bethesda Category-V	23.07 %
9	Suspicious for Papillary thyroid carcinoma: Bethesda Category-V	2.09%

C.

Variable	Benign (mean ± SD)	Malignant (mean ± SD)	t-statistic	p-value
Age	41.3 ± 13.4	50.8 ± 14.6	-3.45	**0.001**
FT3	3.41 ± 12.1	2.53 ± 0.63	0.62	0.54
FT4	1.47 ± 0.55	1.34 ± 0.32	1.36	0.18
TSH	10.5 ± 23.7	11.8 ± 27.1	-0.28	0.78
CEA	5.9 ± 8.1	6.4 ± 9.2	-0.21	0.83

D.

S No	Marker	Colloid nodule; Bethesda Category-II	Follicular neoplasm: Bethesda Category- IV	Suspicious for Malignancy: Bethesda Category-V	Malignant: Bethesda Category-VI	Papillary thyroid carcinoma: Bethesda Category-VI	F-statistic	p-value
1	FT3	7.82±17.51	2.55±0.35	2.64± 0.39	2.65±0.30	-	0.198	0.94
2	FT4	1.40±0.58	1 ±0.1	1.10±0.37	1.45±0.15	1.19±0.09	0.635	0.62
3	TSH	5.94±21.70	1.77 ±1.63	12.14±29.89	17.80±38.66	1.95±1.47	0.501	0.74
4	T3	7.60± 17.61	3.09± 1.08	1.44 ± 0.61	1.70 ± 0.00	1.69± 0.34	3.221	**0.04**
5	T4	-	95.2±39.43	112.24±28.51	104.13±53.13	82.40±8.76	-	-

Figure No.1: A & B FNAC diagnosis percentage, C: Difference between benign and malignant parameters, D: Bethesda category parameters differences

Correlation analysis revealed that, in untreated hyperthyroid patients, T4 was negatively associated with hemoglobin (r=-0.30, p=0.004), hematocrit (r=-0.23, p=0.03), mean corpuscular volume (r=-0.27, p=0.01), and mean corpuscular hemoglobin (r=-0.34, p=0.001), while it showed a positive correlation with mean platelet volume (r=0.23, p=0.03). T3 was negatively correlated with WBC (r=-0.22, p=0.04) and MCH (r=-0.23, p=0.03) overall, whereas gender-specific results indicated a positive association of T3 with MPV in females (r=0.30, p=0.01) and a negative association with MCH in males (r=-0.28, p=0.02) as indicated in table 2.

Age-based analysis further highlighted specific associations. In patients younger than 18 years, TSH was negatively correlated with WBC (r=-0.89, p=0.04), while in young adults (18–35 years), it was negatively correlated with RBC (r=-0.43, p=0.01). In the adult group (36–55 years), MPV was strongly positively associated with T3 (r=0.48, p=0.001), and WBC was negatively associated with T3 (r=-0.38, p=0.01). Moreover, all RBC-related parameters (HGB, HCT,

MCV, and MCH) were negatively correlated with T4, while MPV showed a positive association with T4 (r=0.33, p=0.02). In patients aged 56 years and above, T3 demonstrated a highly significant positive correlation with MCV (r=1.0) as indicated in table 3.

When benign and malignant cases were compared, age was significantly higher in malignant patients (50.8 ± 14.6) compared to benign ones (41.3 ± 13.4) (p=0.001). However, FT3, FT4, TSH, and CEA levels did not show significant differences between the two groups. One-way ANOVA across Bethesda categories revealed that only T3 levels varied significantly (p=0.04), whereas other thyroid function tests did not show notable variation as indicated in figure 1.

Overall, the findings indicate that hyperthyroidism exerts significant effects on thyroid function and hematological parameters, particularly RBC indices and platelet markers. T4 was consistently associated with reduced RBC parameters, while T3 was strongly linked with platelet activity (MPV) and WBC regulation. Age-specific differences suggest that thyroid dysfunction affects hematological parameters more prominently in young adults and middle-aged individuals. Furthermore, FNAC results demonstrated that advanced age is an important risk factor for malignancy, while biochemical markers (FT3, FT4, TSH, and CEA) alone were insufficient to distinguish benign from malignant thyroid disease.

Table No.2: Correlation Table [a] Pearson correlation, [b] Spearman correlation, ★significant result.

Categories	Overall Results			Gender-Based Results(Males)			Gender-Based Results(Females)		
Parameters	T3 nmol/L	T4 nmol/L	TSH µIU/ml	T3 nmol/L	T4 nmol/L	TSH µIU/ml	T3 nmol/L	T4 nmol/L	TSH µIU/ml
WBC 10^3/µL	**-0.22(0.04)** [b]★	-0.15(0.14) [b]	-0.13(0.21) [b]	-0.22(0.38) [b]	-0.28(0.26) [b]	-0.14(0.55) [b]	-0.22(0.06) [b]	-0.13(0.26) [b]	-0.12(0.28) [b]
RBC 10^6/µL	0.05(0.61) [b]	-0.06(0.61) [b]	-0.05(0.62) [b]	0.12(0.64) [b]	0.28(0.25) [b]	0.04(0.85) [b]	0.07(0.56) [b]	-0.06(0.59) [b]	-0.11(0.34) [b]
HGB g/dl	-0.14(0.18) [b]	**-0.30(0.00)** [b]★	0.02(0.86) [b]	-0.14(0.58) [b]	-0.23(0.36) [b]	0.16(0.50) [b]	-0.14(0.26) [b]	-0.24(0.05)	-0.05(0.66) [b]
HCT%	-0.08(0.47) [b]	**-0.23(0.03)** [b]★	0.01(0.95) [b]	-0.07(0.78) [b]	-0.18(0.46) [b]	0.22(0.36) [b]	-0.06(0.64) [b]	-0.16(0.18) [b]	-0.09(0.45) [b]
MCV fL	-0.17(0.12) [b]	**-0.27(0.01)** [b]★	0.10(0.33) [b]	-0.27(0.29) [b]	**-0.53(0.02)** [b]★	0.21(0.39) [b]	-0.13(0.27) [b]	-0.17(0.14) [b]	0.06(0.60) [b]
MCH pg	**-0.23(0.03)** [b]★	**-0.34(0.00)** [b]★	0.15(0.16) [b]	-0.24(0.35) [b]	-0.46(0.05)	0.23(0.34) [b]	-0.22(0.06) [b]	**-0.28(0.02)** [b]★	0.11(0.33) [b]
MCHC g/dl	-0.12(0.34) [b]	-0.14(0.17) [b]	0.05(0.61) [b]	-0.04(0.89) [b]	-0.06(0.78) [b]	0.05(0.84) [b]	-0.11(0.39) [b]	-0.13(0.25) [b]	0.06(0.62) [b]
PLT10^3/µL	-0.15(0.15) [b]	-0.10(0.33) [b]	0.02(0.84) [b]	0.04(0.88) [b]	-0.10(0.68) [b]	0.02(0.93) [b]	-0.20(0.09) [b]	-0.19(0.11) [b]	0.05(0.63) [b]
RDW%	0.15(0.15) [b]	0.17(0.09) [b]	-0.17(0.09) [b]	-0.09(0.72) [b]	-0.03(0.91) [b]	0.03(0.88) [b]	0.19(0.10) [b]	0.23(0.06) [b]	-0.23(0.05)
PCT%	-0.00(0.97) [b]	-0.02(0.83) [b]	-0.01(0.88) [b]	0.25(0.34) [b]	0.11(0.64) [b]	-0.15(0.54) [b]	-0.06(0.59) [b]	-0.14(0.22) [b]	0.06(0.60) [b]
MPV fL	0.31(0.00) [b]	**0.23(0.03)** [b]★	-0.08(0.45) [b]	0.35(0.17) [b]	0.48(0.05)	-0.44(0.06) [b]	**0.30(0.01)** [b]★	0.17(0.13) [b]	-0.00(0.98) [b]
PDW%	0.14(0.19) [b]	0.05(0.61) [b]	-0.02(0.81) [b]	-0.17(0.52) [b]	0.12(0.61) [b]	0.04(0.86) [b]	0.21(0.08) [b]	0.08(0.48) [b]	-0.05(0.61) [b]

Table No.3: Correlation Table [a] Pearson correlation, [b] Spearman correlation, ★significant result, °P-value was calculated by Spearman, Level of significance P<0.05

Category	Age Wise Results (<18y)			Young Adult Age : 18-35 y			Adult: 36-55 y			Senior:56 Y and up		
Para-meters	T3 nmol/L	T4 nmol/L	TSH µIU/ml	T3 nmol/L	T4 nmol/L	TSH µIU/ml	T3 nmol/L	T4 nmol/L	TSH µIU/ml	T3 nmol/L	T4 nmol/L	TSH µIU/ml
WBC 10^3/µL	0.61 (0.39)[a]	0.39 (0.61)[a]	**-0.89 (0.04)** [b]★	0.19(0.27) [b]	0.19 (0.25) [b]	-0.10 (0.53) [b]	**-0.38 (0.01)** [b]★	-0.20 (0.16) [b]	-0.06 (0.67) [b]	0.20 (0.80) [b]	0.40 (0.60) [b]	-0.26 (0.74)[b]
RBC 10^6/µL	-0.01 (0.99)[a]	0.18 (0.81)[a]	0.44 (0.45) [b]	-0.00 (0.96) [b]	0.11 (0.51) [b]	**-0.43 (0.01)** [b]★	-0.05 (0.75) [b]	-0.05 (0.72) [b]	-0.01 (0.93) [b]	-0.20 (0.80) [b]	-0.40 (0.60) [b]	-0.77 (0.22)[b]
HGB g/dl	0.03 (0.97)[a]	-0.15 (0.85)[a]	-0.78 (0.12) [b]	0.31 (0.08) [b]	0.30 (0.08) [b]	-0.23 (0.18) [b]	-0.17 (0.25) [b]	**-0.31 (0.03** [b]**)** ★	0.01 (0.96) [b]	-0.20 (0.80)	-0.40 (0.60) [b]	-0.77 (0.22)[b]
HCT%	0.01 (0.99)[a]	-0.08 (0.92)[a]	-0.34 (0.57) [b]	0.28 (0.11) [b]	0.29 (0.09) [b]	-0.12 (0.49) [b]	-0.21 (0.16) [b]	**-0.34 (0.02)** [b]★	0.01 (0.96) [b]	-0.20 (0.80)	-0.40 (0.60) [b]	-0.77 (0.22)[b]
MCV fL	0.01 (0.99)[a]	-0.25 (0.75)[a]	-0.78 (0.12) [b]	0.29 (0.10) [b]	0.17 (0.32) [b]	0.13 (0.45) [b]	-0.18 (0.23) [b]	**-0.32 (0.03)** [b]★	0.04 (0.79) [b]	**1.0**[b] ★	0.80 (0.20) [b]	0.77 (0.22)[b]
MCH pg	0.03 (0.97)[a]	-0.23 (0.77)[a]	-0.78 (0.12) [b]	0.31 (0.07) [b]	0.18 (0.30) [b]	0.04 (0.83) [b]	-0.14 (0.36) [b]	**-0.29 (0.04)** [b]★	0.06 (0.66) [b]	0.80 (0.20) [b]	0.40 (0.60) [b]	0.77 (0.22)[b]
MCHC g/dl	0.03 (0.97)[a]	-0.22 (0.78)[a]	-0.80 (0.10) [b]	0.08 (0.62) [b]	0.08 (0.61) [b]	-0.08 (0.63) [b]	-0.07 (0.63) [b]	-0.12 (0.41) [b]	0.06 (0.69) [b]	0.00 (1.00) [b]	-0.60 (0.40) [b]	-0.26 (0.74)[b]
PLT10^3/µL	-0.07 (0.93)[a]	-0.26 (0.74)[a]	-0.11 (0.86) [b]	-0.28 (0.10) [b]	-0.19 (0.26) [b]	0.15 (0.37) [b]	-0.25 (0.09) [b]	-0.18 (0.21) [b]	0.12 (0.39) [b]	0.20 (0.80) [b]	0.40 (0.60) [b]	-0.26 (0.74)[b]
RDW%	0.52 (0.48)[a]	0.71 (0.28)[a]	0.22 (0.72) [b]	-0.18 (0.31) [b]	-0.09 (0.59) [b]	0.05 (0.77) [b]	0.10 (0.50) [b]	0.21 (0.15) [b]	-0.15 (0.30) [b]	-0.20 (0.80) [b]	-0.40 (0.60) [b]	-0.77 (0.22)[b]
PCT%	-0. 08 (0.92)[a]	-0.09 (0.90)[a]	0.22 (0.72) [b]	-0.20 (0.31) [b]	-0.07 (0.67) [b]	0.22 (0.21) [b]	-0.08 (0.57) [b]	-0.09 (0.54) [b]	0.17 (0.23) [b]	0.40 (0.60) [b]	0.80 (0.20) [b]	0.25 (0.74)[b]
MPV fL	-0.05 (0.95)[a]	0.21 (0.79)[a]	0.34 (0.57) [b]	0.08 (0.64) [b]	0.04 (0.82) [b]	0.06 (0.74) [b]	**0.48 (0.001)** [b]★	**0.33 (0.02)** [b]★	0.05 (0.71) [b]	-0.40 (0.60) [b]	-0.20 (0.80) [b]	0.26 (0.74)[b]
PDW%	0.42 (0.59)[a]	0.51 (0.49)[a]	-0.22 (0.72) [b]	-0.24 (0.17) [b]	-0.23 (0.19 [b])	-0.03 (0.85) [b]	0.24 (0.10) [b]	0.07 (0.63) [b]	0.03 (0.82) [b]	-0.60 (0.40) [b]	0.00 (1.00) [b]	-0.26 (0.74)[b]

DISCUSSION

Thyroid hormones (TH) continue to be recognized as central regulators of metabolism, growth, and hematopoiesis. Recent large-scale studies reinforce the association between thyroid dysfunction and alterations in blood parameters. For instance, a pooled analysis from the Thyroid Studies Collaboration (42,162 individuals) found that both overt hyperthyroidism and hypothyroidism are associated with increased odds of anemia, with lower hemoglobin among those with abnormal thyroid status compared to euthyroid persons[14]. In the Asir region of Saudi Arabia, a cross-sectional study of nearly 10,000 subjects also demonstrated that thyroid abnormalities are strongly linked with anemia, with the prevalence varying by age and gender[15].

In our study of 1000 patients (597 untreated for thyroid disorder vs. euthyroid controls), we similarly observed that hyperthyroid patients exhibit decreased platelet counts (PLT) and increased mean platelet volume (MPV)[16]. These findings align with recent evidence that MPV is elevated in hyperthyroidism and may reflect a hypermetabolic, prothrombotic state. Although fewer recent studies specifically examine MPV in hyperthyroid patients, the gender-based subgroup in our data (adult females) showed a strong positive correlation between T3 and MPV, which is consistent with the role of TH in influencing platelet activation.

Red blood cell (RBC) indices also showed consistent associations: T4 negatively correlated with HGB, HCT, MCV, and MCH, especially in the 36-55 years age group as indicated by previous work[17]. This is supported by local data from Karachi (Ziauddin University) where hyperthyroid patients had significantly lower hemoglobin and hematocrit compared to euthyroid controls[18]. Similarly, studies like "Impact of thyroid dysfunction on red cell indices in Sahiwal" (2022) found changes in MCV and overall red cell indices in thyroid disorders, reinforcing our age-wise observed effects[19].

Our examination of white blood cell (WBC) counts revealed that T3 had a negative correlation with WBC in adults aged 36-55, and TSH had negative association with WBC in the under-18 group. While less commonly reported in recent literature, these findings may tie into broader observations of immune modulation in thyroid disease. Recent investigations (e.g., Saudi and UK Biobank data) show that thyroid dysfunction correlates with systemic inflammation and immune changes, though precise WBC-TH relationships are still under study[20].

A novel and clinically important finding in our cohort was the age-stratified effect: the adult group (36-55 y) showed more pronounced negative associations between T4 and RBC indices, whereas in seniors (≥56 y) we observed a strongly significant positive correlation of T3 with MCV. This suggests that the hematologic impact of TH varies across lifespan, potentially due to shifts in bone marrow responsiveness, co-morbidities, and nutritional status in older age.

We also integrated FNAC (fine-needle aspiration cytology) results from thyroid nodules to assess malignancy risk vis-à-vis hematological / hormonal profiles. Our data confirmed that malignant FNAC (Bethesda VI) cases were significantly older than benign ones, supporting the well-known finding that advancing age is a risk factor for thyroid malignancy. However, as seen in more recent literature (e.g., studies of Bethesda Category III nodules), cytological categories (including those with indeterminate cytology) may carry varying malignancy risk, and integrating age, ultrasound features, and possibly hormone / hematology data strengthens diagnostic stratification[21].

Taken together, our results reinforce that in untreated hyperthyroid patients, T4 is strongly associated with suppression of red cell parameters, while T3 corresponds more to platelet activity and WBC changes, with distinct gender and age patterns. The FNAC data add value: while biochemical markers alone (FT3, FT4, TSH, CEA) often do not reliably differentiate benign vs malignant thyroid disease, the combination of age, cytological findings, and hematological indices may help in risk stratification, especially in indeterminate cases (Bethesda III).

CONCLUSION

In conclusion, our findings demonstrate that hyperthyroidism significantly alters hematological parameters, with T4 strongly linked to suppression of RBC indices and T3 associated with both platelet activity and leukocyte regulation. The observed age- and gender-specific patterns provide important insights for individualized patient management. FNAC results underscore that while cytology remains the gold standard for diagnosis, integration with TFTs and hematological indices may enhance risk stratification, particularly for malignancy. Future studies should explore the utility of combining hematological markers with molecular and cytological data to develop more robust diagnostic and prognostic tools in thyroid disease.

Author's Contribution:

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Original Article

The role of Serum Procalcitonin (PCT) in Predicting 28 Days Mortality in Critically ill Patients with Sepsis Admitted to the Intensive Care Unit

Anum Qader, Zeeshan Ali, Shamim Kausar and Saliha Bano

ABSTRACT

Objective: To assess the relationship between Serum Procalcitonin (PCT) and 28-day mortality in critically ill patients with sepsis admitted to the ICU.

Study Design: Cohort study.

Place and Duration of Study: This study was conducted at the High Definition Unit and Intensive Care Unit at Medical Unit 4, Jinnah Postgraduate Medical Centre Karachi from June 2023 to August 2024.

Methods: Total 142 male and female patients between 18-75 years of age, fulfilling the criteria of sepsis, septic shock, and being critically ill were included. Absence of critical illness, incomplete data and undergone dialysis before admission were not included. The patient was followed for the first seven days of his hospital stay with deterioration or improvement to be assessed till day 28 regardless of the patient being discharged.

Results: Association between PCT levels and mortality it was found that in patients with PCT >7 ng/dl, 48 hours mortality was found to be 25.35%, mortality within 7, 14 and 28 days was 42.25%, 52.11% and 57.75% respectively while in patients with PCT ≤7 ng/dl, it was found to be 12.68%, 23.94%, 29.58% and 33.80% respectively.

Conclusion: In patients hospitalized to the ICU, elevated PCT may be a sign of infection risk and infection-related death.

Key Words: Sepsis, Procalcitonin, Mortality

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction leading to a dysregulated host response as a consequence of infection[1] The prevalence of sepsis recorded in patients at the time of admission or during ICU stay in ICU's worldwide is estimated to be 29.5%.[2] Biochemically PCT is a prohormone of calcitonin and is upregulated by microbial toxins and pro-inflammatory mediators, but is surprisingly reduced by cytokines released in response to viral infection (interleukin-gamma), which showcases its superiority as a marker of bacterial inflicted infection.[3,4] PCT has a rapid release rate of 2-4 hours, reaching a peak at 24 hours[5] as compared to microbial cultures that are most advantageous in aiding the diagnosis but at the cost of a significant time delay of more than 24 hours.[6,7]

A serious consequence of sepsis; septic shock occurs when abnormalities at the cellular and circulatory levels are severe enough to result in all-effect mortality.[8,9]

The sequential Organ Failure Assessment (SOFA Score) is a validated tool widely used to measure organ dysfunction with patients scoring 2 points or more serves as a marker of critical medical illness.[10]

Serum Procalcitonin (PCT) has a well-established role in the diagnosis and management of septic patients. Recruiting such a biomarker can aid in early diagnosis, risk stratification, and initiation of all possible resuscitative measures that pave the way towards a favorable outcome. No proven biomarker yet exists to establish the prognosis of septic shock,[11] and this is where it becomes pertinent to test Serum PCT's ability to serve as a prognostic marker in patients with sepsis in critically ill patients. Thus, the rationale of the present study is to establish the prognostic role of admission Serum PCT, early in the course of their disease in resource-limited settings.

METHODS

After receiving approval from the ethical review committee, this cohort study was carried out from June

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2023 to August 2024. By taking prevalence of 68.5% in PCT>7 ng/dL group and 43.6% in PCT<7 ng/dL of mortality with confidence interval 95% and power of test 80%, the sample size was calculated to be 142 with 71 in each group.[12] Male and female patients between 18-75 years of age, fulfilling the criteria of sepsis, septic shock, and being critically ill were included. Absence of critical illness as per the previous definition of organ dysfunction, incomplete data and undergone dialysis before admission as dialytic treatment tends to falsely reduce PCT levels were not included.

Informed written permission was taken from patients/attendants. Data was collected by retrospectively accessing patient's admission records including treatment sheets and monitoring sheets. Presenting complaint, comorbid conditions (such as HTN, DM, CKD, CLD, malignancy and/or autoimmune disorders but not limited to the following), vital signs, initial Serum PCT levels, physical status including organ or multisystem involvement, duration of hospital stay, and outcome (including death or discharge) were noted. The patient was followed for the first seven days of his hospital stay with deterioration or improvement to be assessed till day 28 regardless of the patient being discharged from ICU with follow-up to be acquired by telephonic communication or physical examination.

Data analysis was done on SPSS version 23. Descriptive analysis was done on variables, chi-square test and independent t-test was used to study the relationship between qualitative and quantitative variables respectively. p-value <0.05 as statistical significance. Effect modifiers included comorbidities such as hypertension, diabetes mellitus, and asthma, malignancy, previously known cardiac disease, previous stroke, malignancy, allergies and smokers. Relative Risk was calculated.

RESULTS

The average age of patients was 46.42 ± 11.43 years. There were 75 (52.82%) females and 67 (47.18%) males. The distribution of patients by various variables is shown in Table 1. Association between PCT levels and mortality it was found that in patients with PCT >7 ng/dl, 48 hours mortality was found to be 25.35%, mortality within 7, 14 and 28 days was 42.25%, 52.11% and 57.75% respectively while in patients with PCT ≤7 ng/dl, it was found to be 12.68%, 23.94%, 29.58% and 33.80% respectively. Despite 48 hours mortality values, all remaining statistics showed significant difference and positive association between PCT values and mortality rate (RR >1) as shown in Table 2. The mean SOFA score for this group was 9.15 ± 3.57, and the majority of patients had either an intra-abdominal infection (38.94%) or a pulmonary infection (47.85%). These patients' median PCT level at admission was 5.74 ng/ml, and those who did not survive had considerably higher PCT levels (p<0.001). Stratification of 28 days mortality with respect to effect modifiers is shown in Table 3.

Table No.1: Distribution of different variables (n=142).

		PCT >7 ng/dL (n=71)	PCT ≤7 ng/dL (n=71)
		Number (%)	Number (%)
Age (years)	18-45	46 (64.79%)	45 (63.38%)
	46-75	25 (35.21%)	26 (36.62%)
Gender	Male	34 (47.79%)	33 (46.48%)
	Female	37 (52.11%)	38 (53.52%)
HTN	Yes	26 (36.62%)	27 (38.03%)
	No	45 (63.38%)	44 (61.97%)
DM	Yes	22 (30.99%)	24 (33.80%)
	No	49 (69.01%)	47 (66.20%)
Asthma	Yes	14 (19.72%)	18 (25.35%)
	No	57 (80.28%)	53 (74.65%)
Malignancy	Yes	11 (15.49%)	15 (21.13%)
	No	60 (84.51%)	56 (78.87%)
Previous stroke	Yes	08 (11.27%)	10 (14.08%)
	No	63 (88.73%)	61 (85.92%)
Previous known cardiac disease	Yes	16 (22.54%)	13 (18.31%)
	No	55 (77.46%)	58 (81.69%)
Allergies	Yes	04 (5.63%)	06 (8.45%)
	No	67 (94.37%)	65 (91.55%)
Smoker	Yes	21 (29.58%)	20 (28.17%)
	No	50 (70.42%)	51 (71.83%)

Table No.2: Serum PCT in predicting mortality in critically ill patients (n=142).

Mortality	PCT >7 ng/dL (n=71)		PCT ≤7 ng/dL (n=71)		P-value	RR
	Yes	No	Yes	No		
Within 48 hours	18 (25.35%)	53(74.65%)	09(12.68%)	62 (87.32%)	**0.062**	**2.00**
Within 7 days	30 (42.25%)	41(57.75%)	17(23.94%)	54 (76.06%)	**0.025**	**1.76**
Within 14 days	37 (52.11%)	34(47.89%)	21(29.58%)	50 (70.42%)	**0.009**	**1.76**
Within 28 days	41 (57.75%)	30(42.25%)	24(33.80%)	47 (66.20%)	**0.006**	**1.71**

Table No.3: Stratification of 28 days mortality with respect to effect modifiers.

		PCT >7 ng/dL (n=71)		PCT ≤7 ng/dL (n=71)		P-value	RR
		28 days mortality		28 days mortality			
		Yes	No	Yes	No		
Age (years)	**18-45**	24 (52.17%)	22 (47.83%)	13 (28.89%)	32 (71.11%)	0.031	1.81
	46-75	17 (68.0%)	08 (32.0%)	11 (42.31%)	15 (57.69%)	0.076	1.61
Gender	**Male**	21 (61.76%)	13 (38.24%)	10 (30.30%)	23 (69.70%)	0.016	2.04
	Female	20 (54.05%)	17 (45.95%)	14 (36.84%)	24 (63.16%)	0.142	1.47
HTN	**Yes**	13 (50.0%)	13 (50.0%)	09 (33.33%)	18 (66.67%)	0.227	1.50
	No	28 (62.22%)	17 (37.78%)	15 (34.09%)	29 (65.91%)	0.012	1.82
DM	**Yes**	15 (68.18%)	07 (81.82%)	10 (41.67%)	14 (58.33%)	0.081	1.64
	No	26 (53.06%)	23 (46.94%)	14 (29.79%)	33 (70.21%)	0.027	1.78
Asthma	**Yes**	07 (50.0%)	07 (50.0%)	03 (16.67%)	15 (83.33%)	0.063	3.00
	No	34 (59.65%)	23 (40.35%)	21 (39.62%)	32 (60.38%)	0.042	1.50
Malignancy	**Yes**	06 (54.55%)	05 (45.45%)	02 (13.33%)	13 (86.67%)	0.048	4.09
	No	35 (58.33%)	25 (41.67%)	22 (39.29%)	34 (60.71%)	0.046	1.48
Previous stroke	**Yes**	05 (62.50%)	03 (37.50%)	01 (10.0%)	09 (90.0%)	0.063	6.25
	No	36 (57.14%)	27 (42.86%)	23 (37.70%)	38 (62.30%)	0.035	1.51
Previous known cardiac disease	**Yes**	11 (68.75%)	05 (31.25%)	07 (53.85%)	06 (46.15%)	0.426	1.28
	No	30 (54.55%)	25 (45.45%)	17 (29.31%)	41 (70.69%)	0.009	1.86
Allergies	**Yes**	02 (50.0%)	02 (50.0%)	01 (16.67%)	05 (83.33%)	0.291	3.00
	No	39 (58.21%)	28 (41.79%)	23 (35.38%)	42 (64.62%)	0.011	1.64
Smoker	**Yes**	12 (57.14%)	09 (42.86%)	07 (35.0%)	13 (65.0%)	0.172	1.63
	No	29 (58.0%)	21 (42.0%)	17 (33.33%)	34 (66.67%)	0.016	1.74

DISCUSSION

The current study set out to assess the association between serum PCT and 28-day mortality in patients with severe sepsis hospitalized in the ICU. A relationship exists between mortality and PCT levels. In patients with PCT >7 ng/dl, mortality was found to be 25.35% within 48 hours, 42.25%, 52.11%, and 57.75% within 7, 14, and 28 days, respectively, while in patients with PCT ≤7 ng/dl, the corresponding mortality rates were 12.68%, 23.94%, 29.58%, and 33.80%. These patients had a median PCT level of 5.74 ng/ml upon admission, and those who did not survive had considerably higher PCT levels ($p < 0.001$).

A retrospective cohort study that included 228 patients admitted to an ICU with a SOFA Score >2 and an overall mortality of 57.5% attempted to assess the prognostic ability of PCT by recording the SOFA scores of septic patients admitted to the ICU, monitoring them for 28 days, and evaluating them based on their life/death status. In order to ascertain whether PCT levels and death within 28 days are related, it was discovered that 40 (31.5%) of the patients with PCT≥7 ng/dl survived the first 28 days, whereas 87 (68.5%) died. In a similar vein, 44 (43.6%) of the patients with PCT≤7 ng/dl were declared expired, while 57 (56.4%) survived. These differences revealed a strong association between higher PCT and the death rate after 28 days (RR 1.572, p value <0.001).[12] Meng et al.'s study[6] found that mortality rates were relatively higher for higher levels of serum PCT on day 1 compared to their study, which found that PCT (day 1) with ranges of 10 ng/ml had a PPV and NPV of 57.1% and 81.8% for sensitivity and specificity of 75.0% and 66.0%, respectively. 78.05% of patients with a severe score of >10 died. It was considerably higher than serum PCT (ng/ml) of 20% of ≤0.5 (normal), 15.28% of >0.5 to 2 (mild), and 21.43% of >2 to 10 (moderate). Moreover, a significantly lower cut-off than that of Meng et al. at 6 ng/ml exhibited enhanced sensitivity and specificity of 72.0% and 79.0%, respectively.[6]

The association between PCT and SOFA scores was established by Suranadi et al., who found that the mean SOFA score was 2.279 higher for PCT> 7ng/dL and 5.85±2.7 for PCT<7ng/dL.[12] According to Sarkar D et al.[13], out of the 70 patients in the research, 87.1% had

serum PCT levels greater than 2 ng/mL, while 12.9% had serum PCT levels less than 2 ng/mL. The death rate among the 75 patients was 7.2% with PCT level <2 and 44.3% with PCT level >2. The specificity is 27.7% and the sensitivity is 96.4%. NPV is 92.9% and PPV is 44.2%. Patients with serum PCT levels more than 2 ng/mL had a statistically significant increased death rate than those with serum PCT levels below 2 ng/mL. The survivors' group had a median serum PCT level of 3.54 and a mean of 3.72±2.18. The group of non-survivors had a median serum PCT level of 8.75 and a mean of 8.8±3.80. The group of non-survivors had considerably higher serum PCT levels than the group of survivors.[13]

The current study's results, however, were different from those of Anand et al[14] who found that non-survivors had lower PCT levels than survivors (11.56 vs. 2.015). In their study, Huang P et al[15] examined PCT levels on the first, third, and fifth days of admission. They found that the group of non-survivors had greater serum PCT values than the survivors. Mustafic et al[16] found a strong correlation between the result and serum procalcitonin levels. Additionally, the study found that serum PCT had a 50% sensitivity and a 98.53% specificity in predicting mortality. The study population was split into three groups by Gupta S et al[17]: control, culture positive, and culture negative. In all three groups, non-survivors had greater serum PCT levels than survivors. Since the findings of this study and previous research are comparable, we may draw the conclusion that serum procalcitonin can be used as a prognostic marker in sepsis.

The highest sensitivity was shown 24 hours after the administration of antibiotics, according to Dolatabadi AA et al.[18] evaluation of procalcitonin serum levels in predicting the mortality. Twenty-four hours after starting treatment, the area under the curve for the 6.5 ng/mL cut-off point for serum procalcitonin levels was 0.789 (95% CI 0.717−0.862). It was able to make predictions with 80% specificity and 67% sensitivity.

The current study was limited in several ways. As this study was conducted at a single location, it may have been skewed by selection. Second, serum PCT levels in septic shock patients were only measured at the time of admission; no dynamic assessments of the relationship between PCT levels over time and mortality risk were performed.

CONCLUSION

In patients hospitalized in the intensive care unit, elevated PCT may be a sign of infection risk and is associated with infection-related death. For these patients, daily monitoring of PCT should be considered, which can help in the prompt diagnosis and treatment of infectious diseases.

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Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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Original Article

Independent Influence of Sleep Quality, Daytime Sleepiness, and Chronotype on Mental Health and Academic Performance among MBBS Students of Mirpur Medical College, AJK

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ABSTRACT

Objective: To study Independent Influence of Sleep Quality, Daytime Sleepiness, and Chronotype on Mental Health and Academic Performance among MBBS Students Mirpur AJK

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Department Of Community Medicine & Medical Education of MBBS Medical College, Mirpur AJK from 1st March 2024 to 30th February, 2025.

Methods: Data were comprehensively collected through a validated questionnaire, which included the Pittsburgh Sleep Quality Index (PSQI) to accurately assess sleep quality, the Epworth Sleepiness Scale (ESS) to objectively evaluate daytime sleepiness, the Depression Anxiety Stress Scale (DASS-21) to precisely determine mental health status, and the Morningness–Eveningness Questionnaire (MEQ) to reliably identify chronotype. Academic performance was objectively measured using Grade Point Average (GPA). Statistical analysis was meticulously performed using SPSS version 21.0, and significance was appropriately set at $p < 0.05$.

Result: Among 200 medical students, poor sleep quality was *negatively associatively* linked with academic performance, as those with poor sleep *academically worse performed* (mean GPA 2.93 ± 0.34) compared to good sleepers (3.44 ± 0.27). Daytime sleepiness *adversely associatively* reduced GPA, *progressively declining* from normal alertness (3.38 ± 0.31) to moderate-to-severe sleepiness (2.78 ± 0.36). Mental health was *statistically significantly* influenced by sleep quality, with poor sleepers more *frequently reporting distress* ($p < 0.001$). Chronotype *correlatively varied*, as morning types *academically better performed* (3.45 ± 0.28), while evening types *academically worse performed* (2.82 ± 0.35). Regression analysis *independently demonstratively* confirmed that poor sleep quality and higher daytime sleepiness *negatively predictively* and *adversely associatively* influenced GPA, collectively showing that disturbed sleep physiology *strongly impactfully* affected both academic performance and mental health.

Conclusion: Overall, reduced sleep quality, increased sleepiness, and late chronotype were negatively and substantially associated with academic success and mental wellness. Therefore, it is strongly suggested that healthy sleep habits and regular sleep schedules,

Key Words: Sleep, Mental Health, Academic Performance

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INTRODUCTION

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Sleep essentially functions to sustain cognitively, emotionally, and physically. Disruptions in sleep quality or circadian rhythm have been consistently associatively with impaired memory consolidation, reduced academic productivity, and deteriorated psychological well-being.[1] allow researchers systematically to investigatively examine the complex interplay between sleep physiology, mental health, and academic performance.[2]

Evidence increasingly demonstrates that medical students particularly suffer vulnerably due to academic pressures, irregular study hours, and psychological stress and impaired academic outcomes.[3] The COVID-19 pandemic additionally exacerbated these conditions,

with medical students reporting worsened sleep quality and elevated psychological distress.[5]Regionally, studies similarly reveal highly prevalent poor sleep, daytime fatigue, and mood disturbances.[4]

Objective assessments such as actigraphy and chronotype questionnaires consistently confirmatively reveal circadian misalignment among students.Experimental sleep restriction demonstratively compromises attention, learning, and memory.[5]Recent studies further emphasize that chronotype, sleep quality, and stress are closely interconnected with academic achievement.[9]

Technological advancements now permit consumer actigraphy to be validated practically for sleep monitoring. Mental health problems has been strongly documented.[6] Lifestyle factors, including smartphone overuse and irregular schedules, additionally aggravate sleep disruption .Neurophysiological investigations fundamentally demonstrate that circadian and homeostatic regulation orchestrates emotional stability and cognitive efficiency.[7]Ultimately, poor-quality sleep consistently associates directly with reduced academic and mental health outcomes.[8]

METHODS

A cross-sectional descriptive study was systematically conducted at Mirpur Medical College, Azad Jammu and Kashmir (AJK) to scientifically examine the relationship between sleep quality, sleepiness of day, chronotype, mental health, and academic performance among MBBS students. This Study Was Conducted at The Department Of Community Medicine & Medical Education of MBBS Medical College, Mirpur AJK From 1st March 2024 to 30th February 2025.

Study Population

A total of 200 MBBS students from all academic years were randomly included. Both male and female students were equally represented. Participation was voluntarily ensured, and written informed consent was properly obtained from each participant prior to data collection.

Eligibility Criteria

Inclusion Criteria:

- Students aged 18–28 years were appropriately included.
- Those who willingly participated and completely filled the questionnaire were carefully considered.

Exclusion Criteria:

- Students with previously diagnosed psychiatric disorders or chronic medical conditions were systematically excluded.
- Those regularly using sleep medications or stimulants were also completely excluded from the study.

Data Collection Procedure

Data were accurately collected which was logically divided into five distinct sections:

1. **Demographic Profile:** Information regarding age, gender, academic year, and self-reported GPA was clearly recorded.
2. **Sleep Quality:** The Pittsburgh Sleep Quality Index (PSQI) was reliably utilized to objectively assess sleep quality.
    - A PSQI score ≤5 was classifiably identified as good sleep, while a score >5 was specifically considered poor sleep.
3. **Daytime Sleepiness:** The Epworth Sleepiness Scale (ESS) was scientifically employed to quantitatively evaluate daytime sleepiness.
    - Scores were categorically divided into normal alertness (0–10), mild sleepiness (11–12), and moderate-to-severe sleepiness (≥13).
4. **Mental Health:** It was consistently applied to objectively assess levels of depression, anxiety, and stress by Depression Anxiety Stress Scale (DASS-21)
5. **Chronotype Assessment:** For accurately classify participants as morning type, intermediate type, or evening type in The Morningness–Eveningness Questionnaire (MEQ)

Collected data were systematically entered and statistically analyzed using SPSS version 21.0. Continuous variables such as GPA and age were numerically expressed as mean ± standard deviation (SD). Categorical variables were summarized descriptively as frequencies and percentages. Independent t-tests and one-way ANOVA were appropriately performed to comparatively evaluate GPA across groups. Pearson's correlation was statistically applied to precisely determine relationships in (mental health), (sleep quality) , and (academic)performance. Multiple linear regressions were independently conducted to reliably identify predictors of academic outcomes. A p-value < 0.05 was statistically considered significant.

Ethical approval for this study was formally obtained from Review Board of Mirpur Medical College. Participants were confidentially assured that all responses would remain anonymous. Participation was voluntarily maintained, and students were freely allowed to withdraw at any stage without any disadvantage.

RESULTS

Out of 200 medical students, 32.5% were classifiably placed in the good sleep category (PSQI ≤5), whereas 67.5% were identifiably grouped as poor sleepers (PSQI >5). Academic performance was observably higher among good sleepers (mean GPA 3.44 ± 0.27), while it was notably lower among poor sleepers (mean GPA 2.93 ± 0.34). Thus, poor sleep quality was negatively and significantly associated with academic performance.

Table No. 1. Sleep Quality Classification and Academic Performance among Medical Students (n = 200)

Sleep Quality (PSQI)	Number of Students	Percentage (%)	Mean GPA ± SD	Association with Academic Performance
Good Sleep (≤5)	65	32.5	3.44 ± 0.27	Positively associated
Poor Sleep (>5)	135	67.5	2.93 ± 0.34	Negatively associated

Table No.2: Daytime Sleepiness (ESS Scores) and Academic Performance

Sleepiness Category	Number of Students	Percentage (%)	Mean GPA ± SD	Trend in Academic Performance
Normal Alertness	86	43.0	3.38 ± 0.31	Highest GPA
Mild Sleepiness	54	27.0	3.07 ± 0.33	Moderate GPA
Moderate–Severe Sleepiness	60	30.0	2.78 ± 0.36	Lowest GPA

Table No.3: Relationship between Sleep Quality and Mental Health Status

Sleep Quality	Normal Mental Health (%)	Mild Distress (%)	Moderate Distress (%)	Severe–Extremely Severe Distress (%)	p-value
Good Sleep	71.6	17.8	7.3	3.3	<0.001
Poor Sleep	25.7	19.2	20.8	34.3	<0.001

Table No.4: Chronotype Distribution and Academic Performance

Chronotype Type	Number of Students	Percentage (%)	Mean GPA ± SD	Association
Morning Type	75	37.5	3.45 ± 0.28	Positive
Intermediate Type	87	43.5	3.11 ± 0.32	Neutral
Evening Type	38	19.0	2.82 ± 0.35	Negative

Table No.5: Regression Analysis for Predictors of Academic Performance

Predictor Variable	β Coefficient	95% CI	p-value	Direction of Effect
Poor Sleep Quality	–0.41	–0.54 to –0.29	<0.001	Negative
Daytime Sleepiness	–0.36	–0.50 to –0.18	<0.01	Negative
Morning Chronotype	+0.27	+0.12 to +0.38	0.02	Positive

Daytime sleepiness, as objectively assessed by the Epworth Sleepiness Scale (ESS), progressively increased across categories. Normal alertness was frequently observed in 43.0% of participants, mild sleepiness in 27.0%, and moderate-to-severe sleepiness in 30.0%. GPA steadily declined from 3.38 ± 0.31 in normally alert individuals to 2.78 ± 0.36 among those severely sleepy. Academic outcomes were adversely and proportionally affected as daytime sleepiness gradually worsened.

Sleep quality and mental health were strongly and correlatively related. Among poor sleepers, only 25.7% were mentally normal, compared with 71.6% of good sleepers. Severe-to-extremely severe distress was disproportionately reported by poor sleepers (34.28%) compared with good sleepers (3.3%). The relationship was statistically and significantly demonstrable ($p < 0.001$), confirmingly proving that poor sleep was strongly associated with psychological distress.

Chronotype distribution consistently varied across groups: 37.5% were morning type, 43.5% intermediate, and 19.0% evening type. Morning types academically performed better (mean GPA 3.45 ± 0.28), intermediate types moderately performed (3.11 ± 0.32), and evening types academically performed worse (2.82 ± 0.35). Morning chronotype was positively and correlatively linked with higher GPA, while evening chronotype was negatively and associatively connected with lower outcomes.

Regression modeling independently and significantly confirmed predictors of academic outcomes. Poor sleep quality negatively and predictively influenced GPA ($\beta = –0.41$, $p < 0.001$), while higher daytime sleepiness adversely and associatively reduced GPA ($\beta = –0.36$, $p < 0.01$).

Collectively, sleep quality, daytime sleepiness, and chronotype independently and substantially impacted both mental health and academic performance among medical students.

DISCUSSION

The findings of this study convincingly highlight that sleep physiology profoundly impacts both academic performance and mental health among medical students. Students with poor sleep quality consistently demonstrated lower GPA scores, which clearly underscores the essential role of restorative sleep in sustaining optimal cognitive functioning. Specifically, poor sleepers (mean GPA 2.93 ± 0.34) academically underperformed compared with their peers who

reported good sleep quality (mean GPA 3.44 ± 0.27). This outcome directly aligns with prior evidence indicating that poor sleep quality detrimentally disrupts attention span, working memory, and executive functioning—processes critically required for learning and examination performance.[9] Daytime sleepiness, as objectively assessed by the Epworth Sleepiness Scale (ESS), progressively increased across categories. Normal alertness was frequently observed in 43.0% of participants, mild sleepiness in 27.0%, and moderate-to-severe sleepiness in 30.0%. GPA steadily declined from 3.38 ± 0.31 in normally alert individuals to 2.78 ± 0.36 among those severely sleepy. Academic outcomes were adversely and proportionally affected as daytime sleepiness gradually worsened. Moreover, the results of this study strongly validate the assertion that subjective sleep disturbances, as measured by PSQI, associatively link with academic inefficiency in medical school environments, where effective and consistent study habits are urgently needed.

Daytime sleepiness emerged significantly as another determinant influencing academic outcomes. GPA scores progressively declined across levels of increasing ESS scores, with students reporting moderate-to-severe daytime sleepiness academically performing poorest (mean GPA 2.78 ± 0.36). These findings correspondingly align with literature demonstrating that excessive daytime sleepiness, often arising from insufficient or fragmented nocturnal sleep, negatively impairs attention, psychomotor vigilance, and learning efficiency. This pattern clearly suggests that even when total sleep duration is nominally adequate, poor sleep quality that persistently produces residual sleepiness can substantially compromise academic functioning. For medical students, who typically balance irregular schedules and high workloads, the cumulative effect of sleepiness seriously threatens both short-term learning efficiency and long-term retention of knowledge.[10]

The study also demonstratively revealed that mental health was significantly influenced by sleep quality. Poor sleepers frequently reported higher rates of stress, anxiety, and psychological distress compared with good sleepers. This observation strongly supports the bidirectional relationship in which poor sleep directly exacerbates psychological stress, while heightened stress reciprocally impairs sleep quality. Sleep quality and mental health were strongly and correlatively related. Among poor sleepers, only 25.7% were mentally normal, compared with 71.6% of good sleepers. Severe-to-extremely severe distress was disproportionately reported by poor sleepers (34.28%) compared with good sleepers (3.3%). The relationship was statistically and significantly demonstrable ($p < 0.001$), confirmingly proving that poor sleep was strongly associated with psychological distress. Such reciprocal effects rapidly create a vicious cycle, predictably increasing vulnerability to burnout and depressive symptoms. Since medical students already consistently face academic pressures, clinical duties, and professional expectations, the identification of sleep quality as a modifiable factor practically offers a promising pathway for interventions designed to enhance mental well-being. These findings further reinforce earlier reports that poor sleep not only academically weakens performance but also seriously compromises psychological resilience and long-term professional sustainability.[11]

Chronotype distribution additionally emerged as a crucial factor influencing outcomes. Morning-type students academically performed better (mean GPA 3.45 ± 0.28), whereas evening-type students regularly underperformed (mean GPA 2.82 ± 0.35). This finding clearly correlates with prior research showing that circadian misalignment, irregular sleep schedules, and delayed chronotypes adversely influence both academic success and mental health.[12] Neurophysiological evidence convincingly demonstrates that circadian preference interacts with hormonal rhythms, memory consolidation, and daily alertness patterns, thereby making students with evening chronotypes increasingly prone to poor concentration and inconsistent study habits. Since medical school schedules predominantly operate in the mornings, evening chronotypes may structurally experience academic disadvantages. This scenario strongly indicates the need for institutional flexibility or support strategies to strategically mitigate such chronotype-related penalties.[13]

Regression analysis in this study independently demonstrated that poor sleep quality and higher sleepiness of day was significant predictors of reduced GPA. The independent contribution of each factor clearly underscores the importance of identifying and addressing sleep-related disruptions early in academic training. It was structured time management, stress reduction programs, and wearable device–based monitoring of sleep patterns could be effectively integrated into medical curricula. [14] Implementing such measures may not only substantially improve academic performance but also proactively strengthen psychological well-being and resilience against professional burnout.

Collectively, this evidence undeniably highlights the central role of sleep physiology in shaping both academic and psychological outcomes among medical students. Poor sleep quality, mostly sleepiness of day , and unfavorable chronotypes consistently and detrimentally impact cognitive efficiency while simultaneously amplifying susceptibility to stress and emotional disturbances. Interventions designed to promote sleep awareness, encourage structured schedules, and enhance resilience could positively influence academic achievement and mental health stability in this population. Future longitudinal research

should systematically evaluate whether improving sleep quality directly and sustainably translates into academic benefits and psychological resilience, thereby ultimately confirming the causal pathways suggested by these findings.

CONCLUSION

It was observably found that sleep quality significantly influenced both mental health and academic performance among medical students. Higher academic achievement and better psychological well-being were consistently recorded among students maintaining good sleep patterns. Conversely, lower grades and increased mental distress were commonly identified among those experiencing poor sleep quality and greater daytime sleepiness. Academic performance was generally observed to be better among morning-type students as compared to evening types. Overall, reduced sleep quality, increased sleepiness, and late chronotype were negatively and substantially associated with academic success and mental wellness. Therefore, it is strongly suggested that healthy sleep habits and regular sleep schedules should be actively promoted to effectively enhance the overall health and academic performance of medical students.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Amna Ahmed Noor, Farooq Ahmed Noor, Muhammad Shoaib
Drafting or Revising Critically:	Alyia Imtiaz, Ahmed Munir Qureshi, Khuram Shahzad Khan
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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Original Article

Association of Serum Vitamin D Levels with Disease Severity among Patients with Chronic Rhinosinusitis in Mirpur, Azad Jammu and Kashmir

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ABSTRACT

Objective: The objective of the present study was to investigate the association between serum vitamin D levels and the severity of disease among patients with chronic rhinosinusitis(CRS)in Mirpur, Azad Jammu and Kashmir (AJK).

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Community Medicine and ENT Department of MBBS Medical College, Mirpur AJK from 20th March 2024 to 19th February, 2025.

Methods: The present study was ethically approved by the Local Ethics Committee of MBBS Medical College, Mirpur, AJK, and written informed consent was duly obtained from all participants prior to inclusion and this cross-sectional study was Conducted at The Department Of Community Medicine and ENT department of MBBS Medical College, Mirpur AJK Serum 25-hydroxyvitamin D [25(OH)D] concentrations were quantitatively measured using a Euroimmun commercial kit, which was specifically designed based on the enzyme-linked immunosorbent assay (ELISA) principle. Sino nasal symptom severity and its impact on quality of life were assessed comprehensively using the Sino nasal Outcome Test-22 (SNOT-22) questionnaire. All participants were adequately instructed regarding its completion to maximize accuracy

Result: The mean serum vitamin D concentration was measured at 24.7 ± 16.8 ng/mL, indicating an overall tendency toward vitamin D insufficiency. When analyzed separately, a mean level of 23.2 ± 11.6 ng/mL was observed among males, while a mean level of 23.8 ± 19.2 ng/mL was noted among females. A significant negative correlation ($r = –0.22$, $P = 0.034$) was revealed by the Pearson correlation coefficient between serum vitamin D levels and SNOT-22 scores. This inverse relationship indicated that lower serum vitamin D concentrations were associated with higher SNOT-22 scores, thereby reflecting more severe symptoms and a greater negative impact on patients' quality of life.

Conclusion: These findings strongly indicated that the severity of chronic rhinosinusitis was directly correlated with deficiency of vitamin D. Hence, it may be said that the maintenance of adequate levels of vitamin D could be potentially associated with better symptom control & improved life quality among patients distress with rhinosinusitis.

Key Words: vitamin D, chronic rhinosinusitis

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INTRODUCTION

A strong association has been consistently reported between low serum vitamin D levels and increased disease severity in chronic rhinosinusitis (CRS). Patients with vitamin D deficiency have been clinically observed to exhibit higher inflammatory markers, greater mucosal edema, and more pronounced nasal obstruction and discharge,[1]The immunomodulatory role of vitamin D has been experimentally demonstrated, showing that eosinophilic activity is effectively suppressed, and cytokine-mediated inflammation is significantly reduced within the nasal mucosa .2 A systematic review has clearly confirmed that vitamin D deficiency is strongly correlated with the onset, persistence, and recurrence of CRS, thereby indicating that hypovitaminosis D may be potentially regarded as a modifiable risk factor.[3]

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Epidemiological evidence has further revealed that vitamin D deficiency substantially contributes to the chronicity and development of nasal and sinus inflammation, particularly among middle-aged and elderly populations .[4]Clinical investigations have consistently indicated that serum 25-hydroxyvitamin D levels are with healthy control significantly with these levels inversely correlating with symptom severity and radiological grading.[5] The pathogenesis of nasal polyposis has been directly linked to vitamin D deficiency, where tissue remodeling and local inflammatory responses are notably enhanced.[6] Moreover, recent data have demonstratively shown that low vitamin D levels are linked with poorly disease control and adversely influence therapeutic response in CRS with nasal polyps.[7] Conclusively, the evidence collectively implies of deficiency vitamin D adversely contributes to both the pathophysiology and progression of chronic rhinosinusitis. Adequate maintenance of serum vitamin D levels may favorably reduce severity pain of and positively improve clinical outcomes. The association between serum vitamin D levels and disease severity among patients with chronic rhinosinusitis (CRS) was comprehensively evaluated and systematically analyzed in the present study. The mean serum vitamin D concentration (24.7 ± 16.8 ng/mL) was generally found to indicate an overall trend toward insufficiency, consistently aligning with previously documented findings that globally and regionally demonstrated a widespread deficiency in vitamin D among adults[8,9]. Several clinical manifestations of CRSwNP directly stem from a type 2 immune response triggered by multiple environmental and microbial stimuli. Vitamin D functionally inhibits the produced and relief of interleukin, which are commonly regarded as the principal cytokines of the Th2 pathway. These cytokines consequently stimulate the synthesis and secretion of interferon-gamma (IFN-γ), a cytokine predominantly characterizing the Th1 immune response. Moreover, vitamin D significantly enhances the glucocorticoid-mediated cellular response; thus, individuals with vitamin D deficiency frequently require higher doses of glucocorticoids to achieve therapeutically effective outcomes.' Recently, vitamin D increasingly attracted global research attention because it potentially contributes to the pathophysiological mechanisms of numerous chronic inflammatory and autoimmune disorders. Since CRS commonly associates with diseases, vitamin D presumably plays a comparatively similar immunomodulatory role in CRS.

METHODS

The present study was ethically approved by the Local Ethics Committee of MBBS Medical College, Mirpur, AJK, and written informed consent was duly obtained from all participants prior to inclusion. This cross-sectional study was Conducted at the Department of Community Medicine and ENT department of MBBS Medical College, Mirpur AJK from 20th March 2024 to 19th February, 2025 and prospectively included a total of 186 patients, aged 18–66 years, who were diagnosed clinically with chronic rhinosinusitis with nasal polyps (CRSwNP). Participants were systematically recruited from the Ear, Nose, and Throat from Mirpur AJK.

If Patients previously used systemic corticosteroids or vitamin D supplements within one year preceding the study, or were clinically affected by granulomatous issue ,chronic kidney disorders , chronic liver problem, were excluded

Data Collection: Data were systematically collected using a structured questionnaire. The information included (gender), (Height), (weight), (age), and (body mass index) , as well as, time of symptoms, status of smoking (Yes/No), and history of allergy . All responses were recorded accurately to ensure data reliability.

Measurement of Serum Vitamin D: Serum Vitamin]concentrations was quantitatively measured by a Euroimmun commercial kit, which was specifically designed based on the ELISA principle. This technique precisely determined the levels of vitamin D in serum or plasma samples, thereby ensuring standardized and analytically valid results.

Assessment of Sinonasal Symptoms: Sinonasal severity of symptom and its effect on life quality were assessed by Sinonasal Outcome Test-22 comprehensively. All participants were adequately instructed regarding its completion to maximize accuracy. In cases where assistance was needed, an otolaryngology resident carefully completed the questionnaire on behalf of the patient, thereby ensuring consistency and reducing response bias.

A recent study that systematically examined fifteen disease-specific questionnaires for chronic rhinosinusitis (CRS) conclusively identified the SNOT-22 as the most reliable, efficient, and practically applicable instrument for evaluating subjective symptom severity and quality of life among CRS patients.

Statistical Analysis: Serum vitamin D levels and SNOT-22 scores relationship was statistically analyzed using Pearson's correlation coefficient, which was calculated electronically through online statistical software to ensure precision and reproducibility of results.

RESULTS

In this study 186 patients were enrolled, including 110 males (59.1%) and 76 females (40.9%). The mean age was recorded as 37.8 ± 13.7 years (range: 18–66 years), and the participants were mostly represented by young and middle-aged adults.

Vitamin D concentration was measured at 24.7 ± 16.8 ng/mL, indicating an overall tendency toward vitamin D insufficiency. When analyzed separately, a mean

level of 23.2 ± 11.6 ng/mL was observed among males, while a mean level of 23.8 ± 19.2 ng/mL was noted among females. This difference was statistically found to be non-significant (P > 0.05), showing that a nearly equal vitamin D status was shared by both sexes.

Anthropometric and demographic parameters, including age, weight, height, and BMI, were not found to be significantly correlated with either serum vitamin D levels or SNOT-22 scores. It was therefore suggested that physical and age-related factors were not meaningfully influencing these outcomes.

Similarly, mean serum vitamin D levels not significantly differ or SNOT-22 scores when participants were evaluated according to smoking status (P = 0.272) and history of allergy (P = 0.340). Hence, it was indicated that neither smoking habits nor allergic conditions were contributing substantially to variations in vitamin D levels or sinonasal symptom severity.

In contrast, a significant difference in mean SNOT-22 scores was identified between males and females (P = 0.046), where higher scores were reported by female participants. This finding demonstrated that females were more severely affected by sinonasal symptoms and perceived a lower quality of life.

Correlation negative significantly (r = –0.22, P = 0.034) was revealed by the Pearson correlation coefficient between serum vitamin D levels and SNOT-22 scores. This inverse relationship indicated that decreased vitamin D concentrations were linked with increased SNOT-22 scores, thereby reflecting more severe symptoms and it had high impact with negativity on patients' quality of life.

Table No. 1: Demographic and Clinical Characteristics of Study Participants (n = 186)

Variable	Total (n=186)	Male (n=110)	Female (n=76)	P-value
Age (years)	37.8 ± 13.7 (18–66)	—	—	—
Serum Vitamin D (ng/mL)	24.7 ± 16.8	23.2 ± 11.6	23.8 ± 19.2	0.72 (NS)
SNOT-22 Score	40.8 ± 17.5	37.9 ± 14.1	44.8 ± 18.0	0.046 (*)
Smoking Status (%)	—	—	—	0.272 (NS)
Allergy Status (%)	—	—	—	0.340 (NS)

Abbreviations: SNOT-22 = Sino nasal Outcome Test; NS = Not significant; * = P < 0.05 (significant).

According to the SNOT-22 grading system, scores ranging from 8–20 were classified as mildly symptomatic, 21–50 as moderately symptomatic, and above 50 as severely symptomatic. Participants with lower serum vitamin D levels were predominantly found in the moderate to severe categories, which further supported the conclusion that increased sinonasal disease severity was associated with vitamin D deficiency.

Table No.2: Correlation Analysis Between Serum Vitamin D Levels and Disease Severity Scores

Variable Pair	Correlation Coefficient (r)	Interpretation
Vitamin D vs. SNOT-22	−0.22	Inverse correlation (significant)

Table No.3: Multiple Linear Regression Analysis for Predictors of Chronic Rhinosinusitis Severity

Independent Variables	Dependent Variable: SNOT-22 Score (β ± SE)	P-value
Age (years)	0.08 ± 0.04	0.061 (NS)
BMI (kg/m²)	0.05 ± 0.06	0.320 (NS)
Smoking Status (Yes=1, No=0)	1.20 ± 0.98	0.272 (NS)
Allergy Status (Yes=1, No=0)	1.60 ± 1.45	0.340 (NS)
Serum Vitamin D (ng/mL)	−0.42 ± 0.18	0.028 (*)
Constant	41.25	—
Adjusted R^2	0.22	—

Abbreviations: β = Regression Coefficient; SE = Standard Error: SNOT-22 = Sinonasal Outcome Test; NS = Not significant; * = P < 0.05 (statistically significant).

DISCUSSION

Vitamin D has been biologically characterized as an immunomodulatory molecule capable of suppressing pro-inflammatory cytokines, strengthening epithelial barriers, and promoting antimicrobial defense.[10,11]No statistically significant difference in serum vitamin D levels was observably noted between male and female participants, suggesting that both genders were similarly and comparably affected by vitamin D insufficiency. However, SNOT-22 scores were recorded significantly higher among females (P = 0.046), indicating that females were more severely and noticeably affected by sinonasal symptoms. This observation was previously and consistently reported by Mostafa et al. [12] Dysregulation of vitamin D–related enzymes, including 1α-hydroxylase and 24-hydroxylase, was previously and mechanistically demonstrated in sinonasal tissues of CRS patients by Christensen et al. [13] indicating that mucosal inflammation was biologically and metabolically aggravated through vitamin D pathway alteration who collectively explained it hormonally and

immunologically as a gender-related variation in sinonasal inflammation.

Anthropometric and demographic variables, including age, BMI, smoking status, and allergy history, were not significantly or correlatively linked with serum vitamin D levels or SNOT-22 scores. These results were similarly and repeatedly observed by Alipour et al.[9] and Christensen et al. [13] who concluded that vitamin D variability in CRS patients was more immunologically and metabolically determined than physically or behaviorally influenced. Similarly, vitamin D concentrations were reported significantly lower among patients with nasal polyposis and allergic fungal sinusitis, corresponding directly and proportionally with increased clinical severity.[14]The findings of the present study were additionally supported by evidence indicating that lower serum vitamin D levels, characteristically considered as markers of impaired immune regulation, were correlatively associated with increased symptom severity and disease burden. Mucosal inflammation and the extent of sinonasal involvement were objectively and clinically evaluated.[15]

Furthermore, the pathological nature of chronic rhinosinusitis (CRS) was strongly reinforced as a persistently inflammatory disorder. When associatively linked with vitamin D deficiency, it was suggestively implied that reduced vitamin D concentrations could aggravatingly contribute to mucosal inflammation and histological damage, consequently increasing overall disease severity.[16]Experimental studies have conclusively demonstrated that vitamin D supplementation beneficially and effectively reduces sinonasal inflammation and promotes mucosal recovery by modulating immune responses and cytokine balance.[17,18]A statistically significant negative correlation ($r = –0.22$, $P = 0.034$) was clearly identified between serum vitamin D levels and SNOT-22 scores, indicating that lower vitamin D concentrations were inversely and proportionally associated with greater disease severity and poorer sinonasal quality of life. This inverse pattern was previously and consistently emphasized by multiple studies that comprehensively described vitamin D as an immunologically and physiologically essential regulator of mucosal defense. The anti-inflammatory and protective effects of vitamin D were additionally and explicitly highlighted by Cannell et al.[19] who proposed its therapeutic potential as an adjunctive approach in chronic inflammatory airway diseases.

Collectively, the findings of the present study conclusively indicated that vitamin D deficiency was significantly and negatively associated with CRS symptom severity. The absence of association with demographic or lifestyle factors further suggested that local immune and metabolic mechanisms predominantly and independently governed disease progression. Therefore, the routine and clinically integrated assessment of serum vitamin D levels may be beneficially and effectively applied in CRS patients for early identification of deficiency and for guiding targeted therapeutic interventions.

Further large-scale longitudinal studies are strongly and scientifically recommended to validate the causal pathways and to evaluate the therapeutic efficacy of vitamin D supplementation in improving sinonasal health and overall patient quality of life among CRS population.

CONCLUSION

It was clearly demonstrated that more severe sinonasal symptoms were experienced by patients with lower level of vitamin D. Although concentrations of Vitamin D were found to be comparatively similar between males and females, higher symptom severity was reported among female participants. Smoking habits and allergic status were not observed to significantly influence either vitamin D concentrations or SNOT-22 scores.

Author's Contribution:

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Original Article

Integration of Biochemical Markers and Radiological Imaging for the Evaluation of Pulmonary Fibrosis in Mirpur, AJK

Memona Nazir[1], Saqib Ismail[2], Tahira Sanaullah[1], Zahid Saeed[2], Wajahat Ullah Khan[3] and Zahira Bashir[3]

ABSTRACT

Objective: To Integrate Biochemical Markers and Radiological Imaging for the Evaluation of Pulmonary Fibrosis in Mirpur, AJK.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Radiology and Biochemistry & Mohi-ud-Din Islamic Medical College, Mirpur AJK, from 10th April 2023 to 10th March, 2024.

Methods: This cross-sectional study was conducted collaboratively by the Department of Biochemistry and the Department of Radiology, Mirpur AJK. A total of 200 patients with confirmed Chronic Kidney Disease (CKD. Blood samples were collected carefully after overnight fasting. Serum creatinine was measured reliably using the Jaffe kinetic method, while serum sodium, potassium, calcium, and phosphate were analyzed accurately with an automated electrolyte analyzer. Radiological evaluation was performed routinely in the Department of Radiology using ultrasonography with a 3.5–5 MHz convex transducer. Data were analyzed statistically using SPSS 21.

Results: Radiological assessment demonstrated abnormalities occurring predominantly. Reduced renal size was observed commonly in 153 patients (77.3%), while increased cortical echogenicity appeared most frequently, affecting 166 patients (82.6%). Additionally, loss of corticomedullary junction developed notably in 132 patients (66.6%), whereas renal cysts emerged occasionally in 48 patients (24.7%) and hydronephrosis occurred rarely in 22 patients (10.6%). Correlation analysis revealed that serum creatinine correlated inversely and significantly with renal size ($r = –0.63$, $p < 0.001$). Conversely, creatinine correlated positively and strongly with cortical echogenicity ($r = +0.72$, $p < 0.001$) and loss of corticomedullary junction ($r = +0.67$, $p < 0.001$). A moderate positive correlation appeared with renal cysts ($r = +0.31$, $p = 0.012$), whereas hydronephrosis correlated weakly and insignificantly ($r = +0.27$, $p = 0.08$)

Conclusion: When jointly and integratively interpreted, biochemical parameters and radiological features comprehensively and accurately explain CKD progression. This approach not only diagnostically enhances accuracy but also clinically and timely supports decision-making and individually guides patient care

Key Words: Biochemical, Radiological, Pulmonary Fibrosis

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INTRODUCTION

Chronic Kidney Disease (CKD) is globally increasingly recognized as a major public health problem that progressivelly impacts morbidity and mortality.[1]

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It is clinically characteristically manifested by a decline in renal function, which is diagnostically monitored through serum creatinine levels and electrolytic profiles.[2] Serum creatinine serves diagnostically as one of the most widely utilized markers for renal dysfunction, as its concentration indicatively rises with decreasing glomerular filtration rate (GFR).[3] Simultaneously, electrolyte imbalances, including hyperkalemia, hyponatremia, hypocalcemia, and hyperphosphatemia, are frequently observably present in CKD patients, contributing detrimentally to cardiovascular and systemic complications.[4]

Radiological imaging, including ultrasonography, CT, and MRI, is evaluatively employed to provide morphologic insight into renal size, cortical thickness, and structural abnormalities, which correlatively complement biochemical findings.[6]Integration of

biochemical markers with radiological features permits early diagnostical recognition of CKD progression, thereby allowing preventive and therapeutic interventions to be strategically implemented.[5]

In regions like Mirpur, AJK, where access to advanced healthcare facilities is comparatively limited, simple and reliable biochemical parameters such as serum creatinine, along with basic radiological modalities like ultrasound, can be effectively utilized to monitor CKD progression.[6] Previous studies have consistently demonstrated that higher serum creatinine levels correlatively associate with ultrasonographic findings of reduced renal size, cortical thinning, and altered echogenicity.[7] Additionally, electrolyte disturbances have been systemically shown to directly impact radiological changes, highlighting the interplay between metabolic derangements and structural kidney pathology.[8]

Therefore, exploring the correlation of serum creatinine and electrolyte imbalance with radiological changes in CKD patients can provide a cost-effective and regionally relevant approach for diagnostic evaluation, risk stratification, and management planning.[9]

METHODS

This cross-sectional study was conducted collaboratively by the Department of Biochemistry and the Department of Radiology, Mirpur AJK. A total of 200 patients with confirmed Chronic Kidney Disease (CKD), classified systematically into stages 1–5 based on estimated glomerular filtration rate (eGFR), were enrolled. Patients younger than 18 years, those with acute kidney injury, obstructive nephropathy, or concurrent severe systemic disorders, were excluded strictly.

Blood samples were collected carefully after overnight fasting. Serum creatinine was measured reliably using the Jaffe kinetic method, while serum sodium, potassium, calcium, and phosphate were analyzed accurately with an automated electrolyte analyzer.

Radiological evaluation was performed routinely in the Department of Radiology using ultrasonography with a 3.5–5 MHz convex transducer. The parameters were assessed consistently, including renal size, cortical echogenicity, cortico medullary differentiation, cyst formation, and hydronephrosis. Radiological grading of echogenicity and corticomedullary junction visibility was followed meticulously according to standard diagnostic guidelines.

Data were analyzed statistically using SPSS 21. Descriptive statistics were applied appropriately for demographic and biochemical variables. Pearson's correlation coefficient was used analytically to determine the relationship between serum creatinine, electrolyte levels, and radiological findings, with a p-value <0.05 considered statistically significant.

RESULTS

In this study, 200 patients with chronic kidney disease (CKD) were systematically evaluated. The average age was 52.6 ± 13.4 years, with males representing 129 (63%) and females 73 (37%). Hypertension occurred consistently in 127 patients (63.2%), while diabetes mellitus appeared regularly in 83 patients (42.0%). The mean duration of CKD extended steadily to 5.21 ± 2.11 years (Table 1).

Biochemical assessment across CKD stages showed that serum creatinine increased progressively, ranging from 1.21 ± 0.3 mg/dL in stage 1 to 7.21 ± 2.3 mg/dL in stage 5. Electrolyte abnormalities developed gradually with disease advancement. In stage 5, hyponatremia emerged frequently (40.3%), hyperkalemia appeared increasingly (33.4%), hypocalcemia occurred predominantly (47.3%), and hyperphosphatemia presented maximally (52.5%) compared to earlier stages (Table 2).

Table No. 1: Demographic and Clinical Characteristics of CKD Patients (n = 200)

Variable	Value	Percentage (%)
Mean Age (years)	52.6 ± 13.4	–
Gender (Male/Female)	129 / 73	63 / 37
Hypertension	127	63.2
Diabetes Mellitus	83	42.0
Mean Duration of CKD (years)	5.21 ± 2.11	

Radiological assessment demonstrated abnormalities occurring predominantly. Reduced renal size was observed commonly in 153 patients (77.3%), while increased cortical echogenicity appeared most frequently, affecting 166 patients (82.6%).

Table No. 2: Biochemical Profile Across CKD Stages (n = 200)

CKD Stage	Serum Creatinine (mg/dL)	Hyponatremia (%)	Hyperkalemia (%)	Hypocalcemia (%)	Hyper-phosphatemia (%)
Stage 1	1.21 ± 0.3	5.0	3.0	7.1	6.1
Stage 2	2.12 ± 0.5	10.6	7.6	12.1	15.1
Stage 3	3.41 ± 0.9	18.1	15.6	22.1	28.1
Stage 4	5.12 ± 1.4	28.1	25.1	38.1	44.1
Stage 5	7.21 ± 2.3	40.3	33.4	47.3	52.5

Table No. 3: Radiological Findings in CKD Patients (n = 200)

Radiological Feature	Frequency (n)	Percentage (%)
Reduced Renal Size	153	77.3
Increased Cortical Echogenicity	166	82.6
Loss of Corticomedullary Junction	132	66.6
Renal Cysts	48	24.7
Hydronephrosis	22	10.6

Table No. 4: Correlation of Serum Creatinine with Radiological Findings

Radiological Parameter	Correlation Coefficient (r)	p-value
Renal Size	–0.63	<0.001
Cortical Echogenicity	+0.72	<0.001
Loss of Corticomedullary Junction	+0.67	<0.001
Renal Cysts	+0.31	0.012
Hydronephrosis	+0.27	0.08

Table No. 5: Association of Electrolyte Imbalance with Radiological Severity

Electrolyte Abnormality	Radiological Feature Associated	Strength of Association	p-value
Hyponatremia	Severe Cortical Echogenicity	Strong	<0.001
Hyperkalemia	Loss of Cortico-medullary Junction	Strong	<0.001
Hypocalcemia	Parenchymal Atrophy	Moderate	0.003
Hyperphos-phatemia	Loss of Cortico-medullary Junction & Atrophy	Strong	<0.001

Additionally, loss of corticomedullary junction developed notably in 132 patients (66.6%), whereas renal cysts emerged occasionally in 48 patients (24.7%) and hydronephrosis occurred rarely in 22 patients (10.6%) (Table 3).

Correlation analysis revealed that serum creatinine correlated inversely and significantly with renal size ($r = –0.63$, $p < 0.001$). Conversely, creatinine correlated positively and strongly with cortical echogenicity ($r = +0.72$, $p < 0.001$) and loss of corticomedullary junction ($r = +0.67$, $p < 0.001$). A moderate positive correlation appeared with renal cysts ($r = +0.31$, $p = 0.012$), whereas hydronephrosis correlated weakly and insignificantly ($r = +0.27$, $p = 0.08$) (Table 4).

Electrolyte imbalances associated significantly with radiological severity. Hyponatremia associated strongly with severe cortical echogenicity ($p < 0.001$), while hyperkalemia linked strongly with loss of corticomedullary junction ($p < 0.001$). Hypocalcemia correlated moderately with parenchymal atrophy ($p = 0.003$), whereas hyperphosphatemia associated strongly with both corticomedullary loss and parenchymal atrophy ($p < 0.001$) (Table 5).

DISCUSSION

The findings of this research emphatically support the strong correlation between biochemical derangements and radiological abnormalities in CKD. Serum creatinine, as a widely available biochemical marker, has been demonstratively shown to rise progressively with declining renal function, thereby correlatively aligning with radiological evidence of renal atrophy, cortical thinning, and increased echogenicity.[10] This correlation is consistently observable across multiple studies, suggesting that biochemical and radiological assessments should be complementarily employed for reliable evaluation of CKD progression.[11]

Electrolyte imbalance also plays a significantly contributory role in CKD-related morbidity and mortality. Hyperkalemia is clinically dangerously associated with arrhythmias, hyponatremia adversely influences neurological status, while disturbances in calcium and phosphate homeostasis structurally contribute to vascular calcification and renal osteodystrophy.[12] These biochemical abnormalities not only worsen patient outcomes but are also radiologically reflectable in terms of changes in renal parenchymal structure and calcification patterns.[13]

Studies have evidentially shown that ultrasound findings of reduced kidney size, loss of corticomedullary differentiation, and increased echogenicity correlatively match with elevated serum creatinine and electrolyte disturbances.[14]

Importantly, integrating biochemical markers with radiological imaging can significantly strengthen the diagnostic accuracy for CKD. For example, patients with moderate elevations of serum creatinine but with marked ultrasonographic changes may be diagnostically prioritized for earlier intervention.[15] Conversely, electrolyte imbalances in the absence of major radiological abnormalities can be clinically interpreted as early reversible stages of CKD, thereby preventively allowing for lifestyle or pharmacological corrections.

Thus, the combination of serum creatinine, electrolyte profiling, and radiological evaluation represent a synergistically powerful approach for the comprehensive assessment of CKD. This approach is particularly valuable in regions with limited resources, where reliance on readily available tests and imaging can substantially improve diagnostic and therapeutic outcomes.[16]

CONCLUSION

The present study conclusively highlights that serum creatinine and electrolyte disturbances are closely correlatively associated with radiological alterations observed in patients with Chronic Kidney Disease (CKD). Serum creatinine consistently and progressively reflects the decline in renal function, while electrolyte imbalances adversely and significantly contribute to systemic complications that detrimentally aggravate disease outcomes. Radiological imaging, particularly ultrasonography, effectively and complementarily aligns with biochemical findings by structurally and diagnostically evidencing renal parenchymal damage and disease progression.

When jointly and integratively interpreted, biochemical parameters and radiological features comprehensively and accurately explain CKD progression. This approach not only diagnostically enhances accuracy but also clinically and timely supports decision-making and individually guides patient care. For regions such as Mirpur, AJK, where healthcare resources are commonly limited, the combined application of serum creatinine, electrolyte profiling, and radiological evaluation practically, cost-effectively, and reliably demonstrates a diagnostic model. Such integration beneficially strengthens early detection, optimally guides treatment strategies, and ultimately improves patient outcomes.

Author's Contribution:

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Drafting or Revising Critically:	Zahid Saeed, Wajahat Ullah Khan, Zahira Bashir
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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Original Article

Magnetic Resonance Imaging (MRI) Evaluation of Neurological Disorders in Pediatric Patients

MRI Evaluation of Neurological Disorders

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ABSTRACT

Objective: To determine the prevalence and pattern of magnetic resonance imaging-detected structural brain abnormalities among children with developmental delay and to assess their association with demographic features, hypoxic insults, and underlying etiological factors.

Study Design: Prospective observational study

Place and Duration of Study: This study was conducted at the Baghdad Medical City and the Children's Central Teaching Hospital, Iraq from 1st October 2024 to 31st January 2025.

Methods: 65 pediatric patients were enrolled, aged between 1 month and 15 years were recruited. Children with previously confirmed genetic syndromes or metabolic disorders were excluded to ensure a more homogeneous population and to focus specifically on structural and neurological causes of developmental delay. This study provides a unique contribution by combining structured MRI data with a clinical correlation matrix of risk factors in a homogeneous pediatric cohort, offering insights into the predictive potential of imaging for early intervention planning.

Results: Fifty (76.9%) had abnormal magnetic resonance imaging findings. The most common abnormalities were periventricular leukomalacia (56%), cerebral atrophy (30%), and schizencephaly (14%), all significantly associated with developmental delays ($p<0.001$). Hypoxic insults were also strongly correlated with delay ($p<0.001$), whereas mode of delivery had no significant association ($p = 0.164$). The leading etiological contributors were traumatic brain injuries (72%), metabolic disorders (70%), and neurovascular diseases (64%).

Conclusion: Magnetic resonance imaging demonstrated high diagnostic yield in detecting structural brain abnormalities among children with developmental delay. The findings emphasize the importance of early neuroimaging and the recognition of clinical risk factors particularly hypoxic injury, trauma, and metabolic imbalanceas key contributors to neurodevelopmental impairment in pediatric populations.

Key Words: Magnetic resonance imaging, Pediatric neurology, Developmental delay, Periventricular leukomalacia, Traumatic brain injury, Neurovascular disorders, Metabolic disorders

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INTRODUCTION

Magnetic Resonance Imaging (MRI) has emerged as a cornerstone in pediatric neurodiagnostics due to its superior soft-tissue contrast, multiplanar capabilities, and the advantage of avoiding ionizing radiation exposure, making it particularly suitable for use in children.[1,2] It plays a pivotal role in diagnosing a wide spectrum of neurological conditions including developmental delay, congenital malformations, metabolic and degenerative disorders, demyelinating diseases, traumatic brain injury, and brain tumors.[3,4]

Technological advancements have further enhanced the diagnostic scope of MRI through specialized modalities such as Diffusion-Weighted Imaging (DWI), Diffusion Tensor Imaging (DTI), Functional MRI (fMRI), and Magnetic Resonance Spectroscopy (MRS).[5-7] These techniques provide critical structural and functional insights. For instance, DWI is instrumental in identifying early hypoxic-ischemic injury by differentiating between acute and chronic lesions[5,6], while DTI reveals microstructural abnormalities in white matter tracts, facilitating diagnosis of myelin-related pathologies and subtle developmental disorders.[6] fMRI has expanded our understanding of pediatric brain function, and MRS offers biochemical profiles useful in detecting metabolic disturbances linked to neurodevelopmental delays.[7,8]

Despite its diagnostic advantages, performing MRI in young children remains challenging due to their inability to stay still during scanning, often

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necessitating sedation or general anesthesia, which introduces additional clinical risks such as respiratory depression.[9-11] Consequently, pediatric MRI requires rigorous sedation protocols, specialized staff, and infrastructure adapted to the pediatric population to ensure safety and image quality.[8,9] Moreover, standardized imaging protocols and continuous professional training are essential for reliable image interpretation and accurate diagnosis.[9]

The prevalence and pattern of MRI-detected structural abnormalities in pediatric patients with developmental delay, emphasizing conditions such as periventricular leukomalacia (PVL), cerebral atrophy, and neuronal migration disorders like schizencephaly.[10,11] MRI's high diagnostic yield, particularly in contrast to modalities such as CT and ultrasonography, positions it as the gold standard in neurodevelopmental imaging.[12,13] In addition to detecting pathology, MRI also provides valuable prognostic information that can guide early intervention strategies, ultimately improving cognitive and motor outcomes and the overall quality of life in affected children.[13] The current study aims to evaluate the prevalence and pattern of structural brain abnormalities detected by MRI in pediatric patients presenting with developmental delays. Furthermore, it investigates the association of MRI findings with various demographic and clinical factors, such as hypoxic insults, traumatic brain injuries, and metabolic disorders. By addressing these associations, the study provides critical insights into the predictive value of MRI findings, contributing to earlier diagnosis and tailored intervention strategies in pediatric neurological disorders.

METHODS

This prospective observational study was conducted at Baghdad Medical City and the Children's Central Teaching Hospital from 1st October 2024 to 31st January 2025 and approved by the Ethics Committee of the College of Medicine, Al-Iraqia University letter No. 86 dated 6-8-2024. A total of 65 children, aged between 1 month and 15 years were recruited. Children with previously confirmed genetic syndromes or metabolic disorders were excluded to ensure a more homogeneous population and to focus specifically on structural and neurological causes of developmental delay. This study provides a unique contribution by combining structured MRI data with a clinical correlation matrix of risk factors in a homogeneous pediatric cohort, offering insights into the predictive potential of imaging for early intervention planning.

MRI examinations were performed using Siemens MRI scanners, and a selected array of imaging sequences for the highest quality of diagnostic accuracy was employed. The following sequences were used: -

- T1-weighted imaging – anatomical brain structure assessment
- T2-weighted imaging – abnormal white and gray matter detection.
- Fluid-Attenuated Inversion Recovery (FLAIR) – to bring down cerebrospinal fluid signals and bring brain lesions to the forefront.
- Diffusion-Weighted Imaging (DWI) – for finding ischemic and hypoxic changes. T2 Turbo Spin Echo (T2 TSE) – for lesion contrast and tissue characterization.

The first priority was image quality. Therefore, ardent measures needed to be taken, such as sedation (oral or intravenous) or general anesthesia, which was given duly when required, especially in younger children or those who cannot be still for the imaging.

MRI scans were performed using a Siemens 1.5T scanner with the following sequences: axial T1-weighted (TR/TE=500/10 ms), T2-weighted (TR/TE=3000/100 ms), Fluid-Attenuated Inversion Recovery (FLAIR) (TR/TE=9000/114 ms), Diffusion-Weighted Imaging (DWI) with b-values of 0 and 1000 s/mm², and T2 Turbo Spin Echo (T2 TSE). Sedation or general anesthesia was administered as necessary under pediatric sedation protocols to ensure optimal image quality.

Diffusion-Weighted Imaging (DWI) was specifically employed in this study to detect acute ischemic and hypoxic-ischemic brain injuries, enabling the differentiation between cytotoxic and vasogenic edema. This imaging modality provides additional diagnostic insights beyond conventional MRI sequences, particularly in pediatric populations presenting with neurological emergencies.

All MRI images were independently reviewed by two board-certified pediatric neuroradiologists, blinded to the clinical history, to ensure objective interpretation. Structural abnormalities were categorized based on predefined diagnostic criteria and included conditions such as periventricular leukomalacia (PVL), cerebral atrophy, and schizencephaly. The data was entered and analyzed through SPSS-26. Chi-square tests were applied to examine associations between imaging results and clinical variables.

RESULTS

There were 37 (56.9%) males and 28 (43.1%) females. Majority of cases were found under two years of age, 30 (46.2%) cases followed by 2-5 years 22 (33.8%) cases, 6-10 years, 11 (16.9%) cases and more than 10 years, only 2 (3.1%) cases. The evidence of a higher rate of delayed developmental milestones among younger children, particularly children below 2 years old, is the basis for the study's conclusion, which shows the necessity for early diagnosis and targeted therapeutic measures (Tables 1-2).

The majority presented with deviations in MRI, indicating the strong relationship structural brain diseases have with the delayed developmental

milestones. Deviations in 50 patients (76.9%) were found in MRI images, suggesting a link between neuroimaging changes and problems with the child's development. Other than that, 15 patients (23.1%) with standard MRI images that looked typical had delayed early milestones, meaning such people may have diseases that cannot be exactly discovered through a routine MRI scan (Table 3).

The most common aetiology observed was periventricular leukomalacia (PVL), which was detected in 28 patients (56%), thus pointing out the strong association between white matter injury and neurodevelopmental impairment. Cerebral atrophy, which was identified in 15 patients (30%), was the second most common finding, suggesting significant neuronal loss or impaired brain growth as a contributing factor. Schizencephaly, a congenital disorder involving the cortical clefts of the brain, was found in 7 cases (14%), and it is additional evidence of its role in severe developmental delay (Table 4).

All participants aged over 10 years (100%) had delayed milestones. The prevalence was 80% among the children aged <2 years, 77.3% in the 2-5 year range, and 63.6% in the 6-10 year group. Yet, no statistically significant association was identified between age and the delayed milestones (p=0.603). These results indicate that developmental setbacks can be observed at various ages with no evident pattern. In females, the prevalence of abnormal MRI findings slightly increased (82.1%) compared to males (73%). Nevertheless, the difference was not statistically significant (p=0.385), implying that sex does not substantially impact the occurrence of neurological developmental disorders (Table 5).

Table No. 1: Descriptive statistics

Variable	Mean±SD
Age	1.77±0.84
Hypoxic Insult	0.60±0.49
Traumatic Disease	0.55±0.50
Neurovascular Disease	0.49±0.50
Metabolic Disorder	0.54±0.50
Final Diagnosis Score	2.14±1.21

Table No. 2: Frequency of age (n=65)

Age (years)	No.	%
<2	30	46.2
2-5	22	33.8
6-10	11	16.9
>10	2	3.1

Table No. 3: Classification of patients on MRI findings

MRI Findings	No.	%
Normal	15	23.1
Delay milestone (abnormal MRI)	50	76.9

Table No. 4: **Distribution of diseases leading to delayed milestones**

Disease	No. (%)	p-value
Periventricular leukomalacia	28 (56%)	<0.001
Atrophy	15 (30%)	<0.001
Schizencephaly	7 (14%)	<0.001

Table No. 5: Associate between age and gender with MRI findings

Variable	Normal MRI	Abnormal MRI	p-value
Age (years)			
<2	6 (20%)	24 (80%)	0.603 (NS)
2-5	5 (22.7%)	17 (77.3%)	
6-10	4 (36.6%)	7 (63.6%)	
>10	-	2 (100%)	
Gender			
Male	10 (27%)	27 (73%)	0.385 (NS)
Female	5 (17.9%)	23 (82.1%)	

Table No. 6: Association between mode of delivery and hypoxic insult with MRI findings

Variable	Normal MRI	Abnormal MRI	p-value
Mode of delivery			
Vaginal	12 (23.1%)	40 (76.9%)	0.164 (NS)
Cesarean	2 (16.7%)	10 (83.3%)	
Hypoxic insult perinatal			
Yes	-	35 (100%)	<0.001
No	15 (50%)	15 (50%)	
Natal			
Yes	-	41 (100%)	<0.001
No	15 (62.5%)	9 (37.5%)	
Postnatal			
Yes	-	39 (100%)	<0.001
No	15 (57.7%)	11 (42.3%)	

No statistically significant relationship was found between delivery mode and milestone delays (p = 0.164). The prevalence of abnormal MRI findings was practically the same in the two groups; vaginal delivery: 76.9% of them had abnormal MRI findings. Cesarean section: 83.3% had abnormal MRI findings. Hypoxic events, irrespective of the timing (perinatal, natal, or postnatal), were strongly correlated with the delayed milestones (p < 0.001). Participation in hypoxic events, which led to structural brain abnormalities, was shown by all children (100%), thus confirming the crucial role of oxygen deprivation in neurodevelopmental impairment (Table 6).

White matter abnormalities comprised the dominant observed result, with 49 children (100%) affected, confirming the significant part played by the white matter's viability in the neurodevelopment process. Also, ventricular congenital defects were omnipresent in 32 patients (100%), revealing a strong interrelation with the development delay. Corpus Callosum

abnormalities in 22 patients (100%) were other meaningful structural irregularities. Gray matter abnormalities in 20 (100%) patients, brainstem involvement in 13 (100%) patients, cerebellar abnormalities in 13 (100%) patients were found. All these facts concretely prevail in significant associations with delayed milestones ($p<0.05$). The two most common MRI findings in children experiencing delayed developmental milestones are white matter and ventricular abnormalities, which indicate that periventricular and diffuse white matter damage, are the leading causes of this developmental impairment. The corpus callosum and gray matter anomalies additionally highlight the role of interhemispheric communication and cortical integrity disruption in children suffering from these conditions. Though brainstem and cerebellar involvement are not as frequently observed, they still have a notable association with delayed milestones that could imply possible effects on motor coordination, balance, and autonomic functions. These findings highlight the scope of MRI as a primary tool for diagnosing and as a guide for early intervention in neurodevelopmental disorders [Table 7].

Table No. 7: Magnetic resonance imaging (MRI) structural abnormalities and their significance

MRI Findings	Yes	No	p-value
Ventricular Abnormalities	32 (100%)	-	<0.001
White Matter Abnormalities	49 (100%)	-	<0.001
Corpus Callosum Abnormalities	22 (100%)	-	0.002
Gray Matter Abnormalities	20 (100%)	-	0.003
Brainstem Abnormalities	13 (100%)	-	0.027
Cerebellum Abnormalities	13 (100%)	-	0.027

DISCUSSION

Magnetic resonance imaging has progressively gained its place in the diagnostic field, making it the most important tool for looking at pediatric neurological disorders associated with delayed developmental milestones. In this piece of research, we aim to find out the correlations between the findings in MRIs, the hypoxic injuries, and the developmental problems, and in the end, we advance the knowledge of their causes. The outcomes show highly significant abnormalities of structural MRI, thus confirming MRI's crucial diagnostic role in pediatric neurodiagnostics. It has been found, being the main ratio, that male children who were primarily affected (56.9%) in this study belong to the same category as many studies before this. This is because, as reported in studies of older, adolescent male patients, they are significantly more susceptible to neurodevelopmental disorders than girls, possibly due to factors of genetics, hormones, and brain structure.[14,15] The findings of previous studies also indicate the existence of this gender difference.[16,17]

Even though the occurrence rates of delayed milestones were high in children below five years (46.2% <2 years; 33.8% in 2–5 years), there was no significant statistical association between age and developmental delays ($p=0.603$) in our analysis. The above statement is a contradiction to what Deng et al[18] stated that the perinatal complications affect younger children, especially neonates, more than other age groups, having a higher risk of severe neurodevelopmental deficits. The result of such discrepancies could be related to different study populations, varying timelines of interventions, or discrepancies in MRI interpretation. In our cohort, MRI was abnormal in 76.9% of cases, so its diagnostic significance was again reinforced. The most revealing changes were white matter changes, ventricular enlargement, corpus callosum dysgenesis, gray matter anomalies, and brainstem/cerebellar defects (these were presented in 100% of cases at variance). The observation aligns with studies published in the literature that stressed the significance of white matter and ventricular anomalies in neonatal hypoxic-ischemic injury.[19,20] The finding that the prevalence of brainstem and cerebellar abnormalities (26%) was much higher than the previously reported 10%[21] might be due to improved imaging techniques, better MRI resolution, or different patient selection criteria.

The main causes uncovered were traumatic, metabolic, and neurovascular conditions, which proved the predominant role of hypoxic-ischemic events in perinatal neurodevelopmental disorders. This is in line with Deng et al[18], who identified perinatal asphyxia as a major contributor to white matter damage and cortical dysfunction. However, our findings contradict Wringer et al[22], who asserted that congenital and genetic disorders are dominant factors. The reasons behind such differences could be dissimilar population characteristics and diverse incidences of perinatal complications. On the other hand, it is contradictory to Chauhan et al[17], who, through a weaker correlation, suggested that certain children with mild hypoxia could still develop normally, even if they had anomalies found on MRI. The range in the severity of hypoxia, the duration of follow-up, and the neuroplasticity mechanisms termed compensatory might give ground to this discrepancy.

Our study has not found any significant relationship between the mode of delivery (vaginal delivery vs. cesarean) and developmental delay ($p=0.164$). Mahmood et al[19] rightly say this, as they concluded emergency cesarean deliveries are perhaps introducing perinatal stress but do not have a long-term effect on the development of a child. On the flip side, however, it was reported by Ali et al[16] where it was found that

cesarean deliveries lead to more white matter being associated with the anomalies. This could have been caused by differences in measures of maternal health, complications of the fetus, or differences in the standards of obstetrics set by the authors of the studies.

Clinically, our findings demonstrate the necessity of early MRI screening in infants going through perinatal hypoxic-ischemic events, thus highlighting the predictive role of white matter and ventricular anomalies for cognitive and motor impairment. A comprehensive strategy, including teams of neurologists, pediatricians, and radiologists, is suggested to bring about an early diagnosis and treatment, giving the children a better opportunity for improvement.

In the end, MRI is still the most powerful tool for assessing pediatric patients who exhibit delayed developmental milestones. It highlights structural and functional damage, such as neurodevelopmental abnormalities, and their linkages. The discrepancies that have been found should stimulate more research through longitudinal and multicenter studies, which will help to better refine the predictive utility of the results of MRI in pediatric neurology. Future long-term research is required to comprehend the predictive power of MRI findings in children with neurodevelopmental disorders.

CONCLUSION

Detection of structural brain MRI is best for patients with developmental delays. Targeted MRI screening for affected children is essential for early intervention and individualized treatment.

Author's Contribution:

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Drafting or Revising Critically:	Suha A. Muneam, Umama Ammar
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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Original Article

Synthesis of Kaempferol-Cr (III) Complex and study its Effect on Bax and Bcl-2 Genes Expression in SW480 Cell Lines

Ghadeer Sadeq Jayed[1], Zainab Tuama Al-Dallee[1] and Hiba Najeh Al-Saad[2]

ABSTRACT

Objective: Impact of a kaempferol-Cr(III) complex on the expression of Bax and Bcl-2 genes in the SW480 after 24 hours of treatment and to highlight the complex's potential role in promotion.

Study Design: Experimental study

Place and Duration of Study: This study was conducted at the Department of Pharmacognosy and Medicinal Plants, College of Pharmacy, University of Basrah, Iraq from 1st June 2022 to 30th November 2022.

Methods: Kaempferol and its Cr(III) complex were successfully synthesized and examined through FT-IR, UV-Vis spectroscopy, EI-MS, and HPLC analyses. Their anti-proliferative effects were tested using the MTT assay on SW480 and normal HDFn, with IC50 values calculated to determine cytotoxic activity.

Results: Treatment with the kaempferol–Cr(III) complex significantly suppressed the viability of SW480 colorectal cancer cells more effectively than kaempferol alone, with negligible impact on healthy cells. Gene expression profiling via real-time PCR demonstrated an elevation in Bax levels alongside a reduction in Bcl-2 expression after 24 hours, indicating the induction of apoptosis. These findings point to the complex's ability to trigger programmed cell death through modulation of apoptotic gene expression, supporting its potential as a promising chemotherapeutic agent

Conclusion: Kaempferol-Cr(III) complex exhibits anticancer properties. When compared to ligand alone, this compound has demonstrated a noticeably greater lethal effect in experiments using the SW480 cancer cell line.

Key Words: Kaempferol-Cr(III) complex, Apoptosis, Bax, Bcl-2, SW480 cell line

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INTRODUCTION

Theorists are particularly interested in the development of novel materials. Day by day, the percentage of deaths attributable to cancer illnesses rises.[1] Since the first metal-based chemotherapy medication, cisplatin, was discovered, metal complexes have been employed as antitumor agents.[2] With the development of a multitude of platinum relatives, cisplatin or its derivatives, such as carboplatin or oxaliplatin, are utilized for treating nearly fifty percent of all people with cancer receiving chemotherapy.[3] Flavonoids are secondary metabolites composed of a benzopyrone ring with polyphenolic groups.[4] Their poor absorption and low water solubility have limited biological evaluation for drug development.[5] However, their hydroxyl and carbonyl groups allow interaction with biomolecules and chelation of metal ions, enabling the formation of metal complexes with improved and distinct biological properties.[6]

Kaempferol is a member of the tetrahydroxy flavonoid group because it has four hydroxy groups at positions 3, 5, 7, and 4′.[7] New research has focused on its possible application in cancer treatment since higher consumption was shown to reduce the risk of several cancers, including skin, ovarian, and stomach cancer.[8] Several investigations have shown that kaempferol play a significant part in the apoptosis of carcinoma of the breast.[9] Bcl-2 gene promotes survival of cancer cells by inhibiting apoptosis. On the other hand, cancer cells undergo apoptosis and die when the Bax gene is expressed.[10] Diantini et al[11] found that Kaempferol-3-O-rhamnoside induces death in MCF-7 breast cancer cells by activating the caspase cascade involving caspase-9, caspase-3, and PARP, along with reduced Bcl-2 expression. Nandi et al[12] demonstrated that kaempferol may be effective in treating in vitro triple-negative breast cancer cells. The present study aims to synthesize the kaempferol–Cr(III) complex and evaluate its effect on SW480 cancer cell inactivation by

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assessing the expression of apoptotic genes (BAX and BCL-2) in these cells.

METHODS

The synthesis of the kaempferol complex was performed based with slight modifications. Kaempferol (0.3 g, 1 mmol) was dissolved in 20 mL methanol, followed by the addition of NaOH (0.02 g, 0.5 mmol) in 10 mL methanol. $CrCl_3 \cdot 6H_2O$ (0.1 g, 0.5 mmol) dissolved in 10 mL methanol was then added with stirring.[13] The mixture was stirred at room temperature for 1 hour, then refluxed at 60°C for 4 hours. It was dried at room temperature, washed, and the filtrate was left to dry.

The wavelength (λmax) of kaempferol and kaempferol-Cr(III) complex was determined by preparing standard solutions (1000 µg/mL). Methanol was used to dilute 1 mL of standard solutions to 10 mL, creating the working solution (100 µg/mL).

FTIR spectroscopy was used to kaempferol, and Kaempferol-Cr (III) complex. The KBr sample discs were scanned to obtain infrared spectra in the wavelength range of 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

EI-MSS spectrometry is a potent instrument for metal-flavonoid complex investigation.[14] ACN (0.1% formic acid) and H_2O (0.1% formic acid) was used as mobile phase. EI/MS was performed using a Shimadzu LC/MS 2010 A system in the positive ion mode.

Using HPLC-grade methanol, 1mg.mL^{-1} kaempferol initial solution was made. We then prepared working solutions with concentrations of 100, 90, 70, 40, and 20 µg/mL at the ambient temperature. A calibration plot was then made to illustrate the correlation between peak area and concentration (µg.mL^{-1}). The concentration of kaempferol in the experimental samples was ascertained using the equation for linearity derived from the standard plot.

Dissolved 0.0005 mg of complex in 1mL methanol and the taken 250 µL from solution and added 750 mL from methanol to it. HPLC analysis was then performed on 100 µL of this solution.

HPLC analysis was performed using the German S600 Sykam system with a UV/VIS detector and specimen injector. The column was maintained at 30°C, using methanol (A), acetonitrile (B), and water (C) as eluents. The mobile phase consisted of 20% methanol, 60% acetonitrile, and 20% water (v/v/v) at a flow rate of 1.0 mL/min. An autosampler injected 100 µL of kaempferol and complex solutions, and spectra were recorded at 280 nm.

The Rwafid Alelom Company in Iraq provided the SW480 and HDFn cell lines. 10% FBS was added to RPMI-1640 while the cells were being grown. Every cell was cultivated at 37°C with 5% CO_2 and all media included100U mL of streptomycin and penicillin.

The viabilities of SW480 and HDFn cells were assessed in the presence of kaempferol and its Cr(III) complex. Cells were cultured in triplicate in 96-well plates and incubated for 24 hours at 37 °C with 5% CO_2. After washing with 1X PBS, cells were treated with various concentrations (100, 50, 25, 12.5, 6.25, 3.12 µg/mL) of kaempferol and the metal complex. Untreated cells served as controls. After 24 hours, 200 µL of MTT solution was added, and absorbance at 570 nm was measured after 3 hours. The values were calculated using Excel 2016

The overall RNA Mini Kit (Blood/Cultured Cell) (geneaid) was used to extract total RNA from untreated control cells in accordance with the manufacturer's recommendations, cells (SW480) treated with IC_{50} kaempferol-Cr(III) complex, or kaempferol alone. Total RNA was then treated with RNase-free DNase Sets (Qiagen) and 2 mg of RNA was used for (cDNA) synthesis utilizing the TransScript® Green One-Step qRT- PCR SuperMix, Cat. No. AQ211), as directed by manufacturer.

qRT-PCR was used to measure BAX and BCL-2 gene transcription. A 20 µL reaction mixture contained 6 µL distilled water, 2 µL of each gene-specific primer (Table 1), and 10 µL of green master mix. The reaction was performed using the Cycler96-Roche instrument (Table 2). Gene expression changes were quantified using the $2^{-\Delta\Delta Ct}$ method, with Bax and Bcl-2 expression levels compared to the β-actin reference gene. Three distinct tests are used to calculate the mean standard deviation of the results. The following differences are indicated by asterisks: for $p< 0.0$, two way-ANOVA is utilized.

RESULTS

Kaempferol-Cr (III) complex was created using a straightforward process. The way that compound react, kaempferol, $CrCl_3.6H_2O$, and NaOH in methanol led to the formation crystal-like particle (Fig. 1), Kaempferol, has two unique levels in its electronic spectra. peak I, which represents the cinammoyl component, shows at 365.5 nm, while band II, which represents the benzoyl part arises at 267.0 nm. As a result, both bands underwent a considerable shift due to the chelation of the Cr(III) ion (from 267.0 nm to 350.0 nm for band II and from 365.5 nm to 424.0 nm for band I). As seen in (Fig. 2), band I exhibits a very slight red shift of 58.5 nm, but band II shows a red shift of 83 nm due to the coordination of Cr(III) with kaempferol.

FTIR spectra were recorded in the range of 4000–400 cm^{-1} for both kaempferol and its Cr(III) complex. In the kaempferol spectrum, a broad absorption band was observed between 3400–3000 cm^{-1}, corresponding to O–H stretching vibrations. A sharp peak at 1658 cm^{-1} was attributed to the C=O stretching vibration at position 4 of the kaempferol molecule. In the Cr(III) complex, this peak shifted to 1632 cm^{-1}, indicating a frequency decrease of 26 cm^{-1}.

Table No. 1: Primers sequence utilized

Gene	Sequences of Primer pair	Acquisition number	Reference
Bcl-2 (F)	5'-TCGCCCTGTGGATGACTGA-3'	NM-000633.3	15
Bcl-2 (R)	5'-CAGAGACAGCCAGGAGAAATCA-3'		
Bax (F)	5′GAGCTGCAGAGGATGATTGC-3′	NM-138764.5	16
Bax (R)	5′-AAGTTGCCGTCAGAAAACATG-3′		
β-actin (F)	5′-TCCTCCTGAGCGCAAGTAC-3′	NM-011001.5	16
β-actin (R)	5′-CCTGCTTGCTGATCCACATCT-3′		

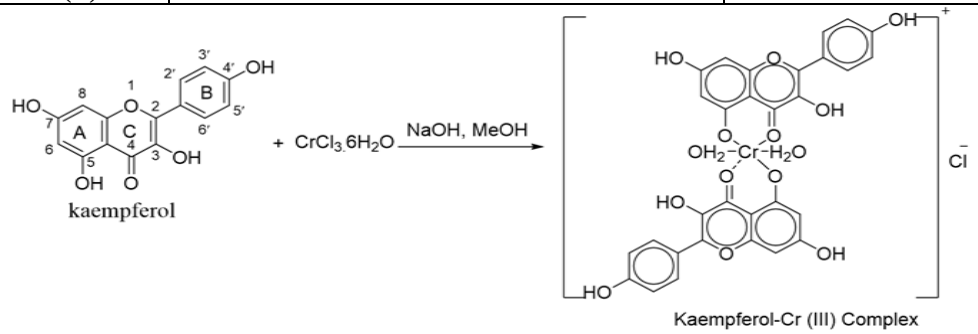

Figure No. 1: Overall reaction

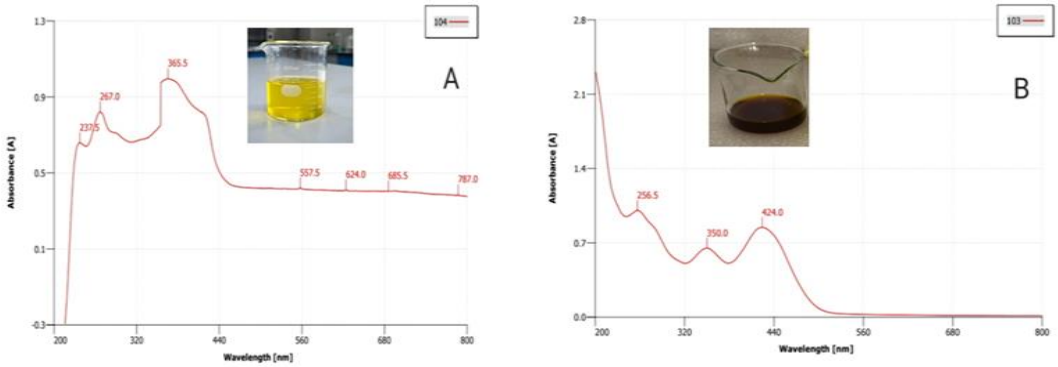

Figure No. 2: A: Uv spectrum of Kaempferol, B: Uv spectrum of kaempferol- Cr(III) complex

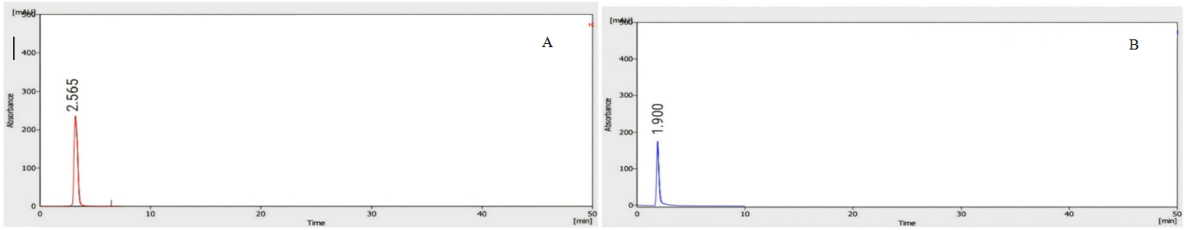

Figure No. 3: HPLC chromatogram A:Kaempferol B:kaempferolCr(III) Complex

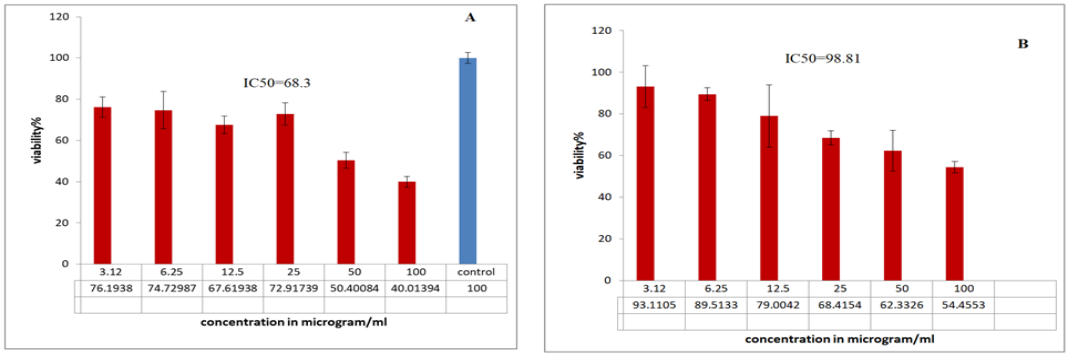

Figure No. 4: Percentage of SW480cells (A) HDFn cells (B) that survived for 24 hour at various complex concentrations

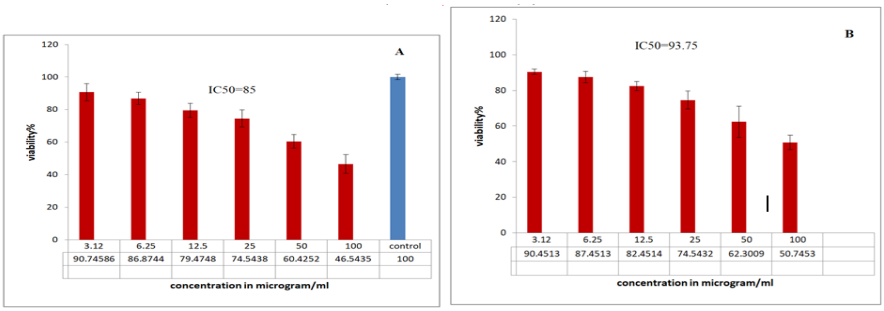

Figure No. 5: Percentage of SW480cells (A) HDFn cells (B) that survived for 24 hour at various kaempferol concentrations

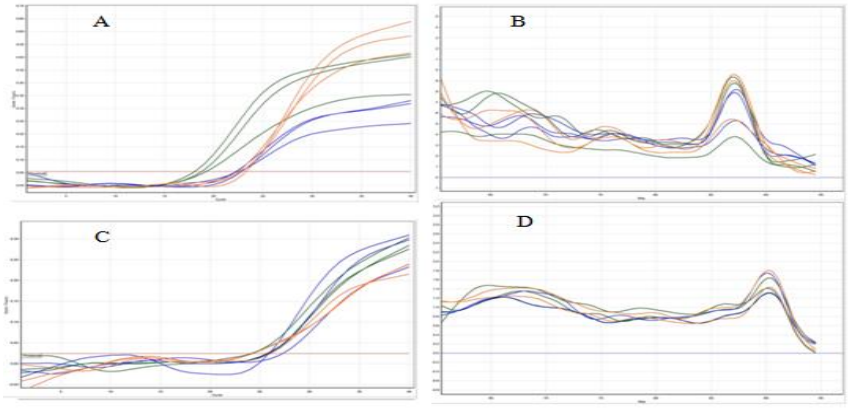

Figure No. 6 :Amplification of Genes in RT-qPCR:Data for β-actin and Bcl genes: A. Fragment duplication, B. Melting curve; Data for β-actin and Bax genes: C. Fragment duplication, D. Melting curve control colored green, blue and orange for kaempferol-Cr(III)complex and kaempferol respectively

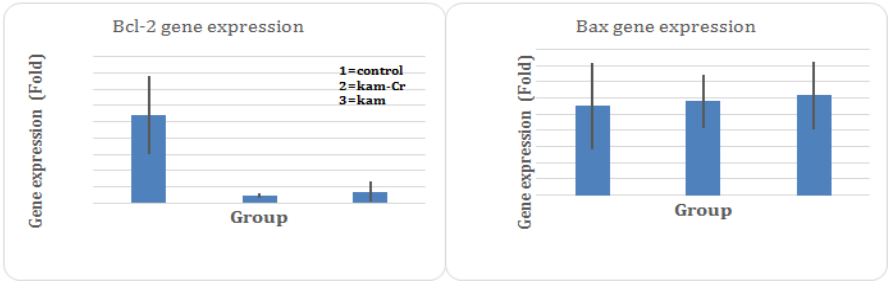

Figure No. 7: Expression rate of Bcl-2 and Bax genes in 24h treatment (p value < 0.05)

Table No.2: PCR steps and repeat cycle

Stage	Temperature (°C)	Time (s)	Number of cycles
Denaturation	94	20	40
Annealing	60	30	
Extension	60	30	

Table No. 3: The main EI/MS data of kaempferol Cr(III) complex

Nominal m/z	Structure
658.5	2 Kaempferol+ Cr(III) +2H_2O
622.47	2 Kaempferol+ Cr(III)
336.23	Kaempferol+ Cr(III)
153 and 165	Fragmentation of kaempferol ring system

The C=C and C–O–C stretching frequencies were observed at 1610 cm^{-1} and 1224 cm^{-1} in kaempferol, and at 1598 cm^{-1} and 1224 cm^{-1} in the complex, respectively. A new peak appeared at 462 cm^{-1} in the complex, which was not present in the free ligand spectrum (Supp. Fig. 1).

EI-MSS spectrometry has been employed to identify chemical structures. (Table 3), displayed the complex's fingerprint. In this case, the ions of m/z 658.5, 622.47, 336.23, 153, and 165 were obtained(Supp. Fig. 2). HPLC was used to analyze both kaempferol and its Cr(III) complex. The chromatogram of kaempferol showed a retention time of 2.565 minutes, while the kaempferol–Cr(III) complex showed a distinct peak at 1.900 minutes as seen in (Fig.3).

MTT assays were employed to assess the impact of 24-hour exposure to kaempferol and the kaempferol-Cr(III) complex on the SW480 cell line's vitality. The IC values were determined to be 85 µg/mL for kaempferol and 68.3 µg/mL for the kaempferol-Cr(III) complex, indicating a stronger cytotoxic effect of the metal

complex. Both compounds significantly reduced the viability of SW480 cells at all tested concentrations (100, 50, 25, 12.5, 6.25, and 3.12 µg/mL). In contrast, neither kaempferol nor the kaempferol-Cr(III) complex caused significant cytotoxicity in normal HDFn cells (Figs. 4-5)

Tables 4-5 present the statistical analyses of the 24-hour administrations with the complex and kampferol with p value < 0.05. This tables show that SW480 cells have the best survival rate at a concentration of 3.12µg/mL. As the concentration rises, SW480 cells become less viable.

Real time PCR: The curve of melting (Fig. 6) demonstrates that the targeted gene fragments were amplified specifically. The control was thought to be β-actin. Primers for the Bcl-2 and Bax genes were used in a real-time PCR experiment following cDNA synthesis. Ct values were calculated using the amplification plot as a guide. Modifications in gene expression were then computed using the 2-ΔΔCT technique (Table 6).

Expression of the genes under investigation in tumer cells subjected to kaempferol-Cr(III) complex and Kampferol: The 2-ΔΔCT method was used to analyze gene expression using Ct values from real-time PCR and the β-actin gene. Treatment with the kaempferol–Cr(III) complex and kaempferol resulted in a notable increase in Bax expression (1.160715 and 1.22837) and a significant decrease in Bcl-2 expression (0.096 and 0.139) with $p<0.05$. Figure 6 shows Bax and Bcl-2 gene expression after 24 hours in SW480 cell lines treated with the kaempferol–Cr(III) complex and kaempferol (Fig. 7).

Table No.4: Average bioavailability of SW480 line using the MTT test for kaempferol-Cr(III) complex and kampferol at varying doses throughout a 24-hour

Compound	Concentration µg/ml					
	3.12	6.24	12.5	25	50	100
Kam-Cr	76.194±2.65	74.7298±2.6	67.6194±3.86	72.91739±5.37	50.400836±4.23	40.01394±9.01
Kam	90.74586±1.55	86.8744±5.72665	79.4748±4.174257	79.4748±4.174257	60.4252±4.357739	46.5435±3.817748

Table No. 5: Average bioavailability of healthy cells using the MTT test for kaempferol-Cr(III) complex and kampferol at varying doses throughout a 24-hour

Com-pound	Concentration µg/ml					
	3.12	6.24	12.5	25	50	100
Kam-Cr	93.1105±2.7082	89.5133±9.7024	79.0042±3.4001	68.4154±14.90102	62.3326±3.024612	54.4553±10.03418
Kam	90.4513±4.025	87.4513±8.8	82.4514±5.079	74.5432±2.5252	62.4009±3.1286	50.7453±1.5316

Table No. 6: Ct value and fold changes in gene expression

	Ct-Bactin	***Ct-Bcl2***	**Fold change**	***Ct-Bactin***	***Ct-Bax***	**Fold change**
Control	19.98666667	18.71	1.08	19.98666667	22.55333333	1.097168333
Kam-Cr	20.17666667	20.37285714	0.096	20.17666667	22.81666667	1.160715333
Kam	20.39121212	21.05207792	0.139	20.39121212	23.29	1.228371333

DISCUSSION

The successful formation of the Kaempferol–Cr(III) complex indicates a strong interaction between the metal ion and the functional groups of kaempferol, which contains several hydroxyl groups. Notably, the A and C rings include 5-hydroxy-4-keto and 3-hydroxy-4-keto groups, while the B ring has its own hydroxyl group. Since the 3-hydroxy and 5-hydroxy sites compete for metal binding, the hydroxy-keto positions on rings A and C are of particular significance. Ligand molecules form more stable compounds by using their most suitable chelation sites. Hydroxy-keto sites, in particular, create strong compounds through additional ring formation and extended conjugation. In contrast, chelation between the 4'-hydroxyl group of ring B and the 3-hydroxyl group of ring C, likely due to the easy ionization of the 4'-hydroxyl group, appears much less certain.[15] As a result, Cr(III) shows notable bathochromic shifts, likely due to its high charge density and strong ligand binding. Band II shows a greater red shift than band I, indicating stronger conjugation at the benzoyl system in ring A compared to the cinnamonoyl system in ring B. The study concludes that, during the formation of the kaempferol–Cr(III) complex, deprotonation occurs at the 5-OH site rather than the 3-OH.[16]

In FTIR, the observed shift of the carbonyl stretching frequency from 1658 cm^{-1} to 1632 cm^{-1} upon complexation suggests coordination of the Cr(III) ion through the carbonyl oxygen of kaempferol.[17] The unaltered frequencies of the C=C and C–O–C bonds imply that the ring oxygen is not involved in metal coordination. The appearance of a new band at 462 cm^{-1} is attributed to the formation of a Cr–O bond, which confirms the complexation between kaempferol and Cr(III).[18]

According to EI-MASS spectrometry, two kaempferol molecules coordinate with one Cr(III) atom through their 5-OH and 4-oxo groups, donating two hydrogen atoms and often binding with two water molecules. The difference in HPLC retention times between kaempferol and its Cr(III) complex indicates successful complex formation (Fig. 3). The shorter retention time of the complex may result from changes in polarity or interactions with the stationary phase due to metal coordination. MTT assay results show that the kaempferol–Cr(III) complex has greater anticancer potential than kaempferol, with a lower IC_{50} and stronger cytotoxic effects at all concentrations. Its selective toxicity toward cancer cells and minimal impact on normal cells suggest it as a promising and safer therapeutic agent.[19]

Apoptosis is a technique of deliberate destruction of cells that preserves homeostasis.[20] The two main mechanisms that mediate apoptosis are the mitochondrial-mediated pathways and the death receptor. They gather at killing pathway, which includes caspase-3 cleavage, nuclear fragmentation, and

the creation of an apoptotic body that is ultimately phagocytosed.[21]

CONCLUSION

Kaempferol-Cr(III) complex exhibits anticancer properties. When compared to ligand alone, this compound has demonstrated a noticeably greater lethal effect in experiments using the SW480 cancer cell line.

Author's Contribution:

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Original Article

Role of Mindfulness-Based Cognitive Therapy in Enhancing Critical Care Nurses' Sense of Personal Accomplishment

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ABSTRACT

Objective: To determine the effect of mindfulness-based cognitive therapy on enhancing the sense of personal accomplishment among critical care nurses.

Study Design: A quasi-experimental study

Place and Duration of Study: This study was conducted at the Critical Care Units of Al-Hussein Medical City and Imam Al-Hassan Al-Mujtaba Teaching Hospital in Karbala, Iraq from 7th June to 13th November 2024.

Methods: This study was conducted with 88 critical care nurses from two Hospitals in Karbala. Due to the specialized nature of critical care units, participants in the intervention group attended sessions comprising 2–5 individuals each. Nurses were randomly allocated to intervention group and control group. The intervention group undertook an eight-week Mindfulness-Based Cognitive Therapy (MBCT) program, while the control group continued with their routine duties. Both groups completed the personal accomplishment subscale of the Maslach Burnout Inventory (MBI) before and after the intervention.

Results: The experimental group showed a significant improvement in personal accomplishment compared with a slight decline in the control group, reflecting a moderate effect size. Within-group analysis confirmed a substantial effect only for the experimental group, which also achieved a markedly higher percentage improvement. Among socio-demographic variables, only family structure was significant, with nurses from nuclear families showing greater gains.

Conclusion: Mindfulness-based cognitive therapy significantly improves personal accomplishment among critical care nurses, enhancing their resilience and reducing burnout.

Key Words: Burnout, Personal accomplishment, Professional, Mindfulness, Cognitive behavioral therapy, Critical care nursing

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INTRODUCTION

Personal accomplishment represents a vital psychological resource that underpins nurses' resilience, motivation, and professional satisfaction.[1,2] Within the framework of burnout, it is one of the three core dimensions identified by Maslach and Jackson, alongside emotional exhaustion and depersonalization.[3,4] A diminished sense of personal accomplishment manifests as negative self-evaluation, feelings of inefficacy, and a perception of reduced competence, which collectively undermine both individual well-being and professional performance.[2] Conversely, a heightened sense of accomplishment fosters engagement, confidence, and commitment to high-quality patient care.[5,6]

Critical care nurses (CCNs) are particularly vulnerable to experiencing reduced personal accomplishment due to the complexity and intensity of their working environment.[7] The pressures, compounded by long shifts, high patient acuity, and frequent exposure to distressing situations, increase the risk of burnout and erode nurses' sense of achievement.[8] Alarm fatigue, staffing shortages, and limited organizational support further exacerbate these challenges, leaving CCNs susceptible to professional dissatisfaction and psychological strain.

The consequences of diminished personal accomplishment extend beyond individual nurses[6], the reduced accomplishment to increased turnover, absenteeism, and job dissatisfaction, all of which compromise continuity of care and contribute to poorer patient outcomes, including higher rates of adverse events, infections, and mortality.[9] Moreover, healthcare organizations bear significant financial costs due to

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high turnover and reliance on temporary staffing. In contrast, cultivating a strong sense of accomplishment enhances resilience, promotes retention, and supports the delivery of safe, compassionate, and efficient care.[10] Addressing personal accomplishment among healthcare providers is crucial for enhancing patient safety and improving the overall quality of care. Interventions that strengthen nurses' sense of personal accomplishment are therefore of particular importance.[11] Mindfulness-Based Cognitive Therapy (MBCT), which integrates cognitive–behavioral strategies with mindfulness practices, has shown promise in reducing emotional exhaustion, alleviating depersonalization, and enhancing personal accomplishment.[12] By cultivating self-awareness, acceptance, and adaptive coping, MBCT enables critical care nurses to reframe their experiences, manage occupational stressors more effectively, and rediscover meaning and fulfillment in their professional roles.[13] The enhancements in resilience and decreases in emotional exhaustion after participation in MBCT[14], while a systematic review corroborated the efficacy of mindfulness-based interventions in alleviating stress and emotional exhaustion among nursing populations.[15] While the benefits of MBCT are well documented in various populations, little is known about its feasibility and impact within high-intensity environments such as critical care units, where nurses contend with complex clinical demands, technological overload, and profound emotional strain.[16]

This research is based on the Neuman Systems Model and Orlando's Nursing Process Theory to help critical care nurses use Mindfulness-Based Cognitive Therapy (MBCT). Neuman's approach posits that stresses disturb the individual's physiological, psychological, and sociocultural systems, which may result in emotional fatigue.[17] MBCT serves as a secondary preventative technique, augmenting the nurse's capacity for self-regulation and adaptive responses to both internal and external stresses. In accordance with Orlando's theory, which underscores the importance of nurses in recognizing and addressing patients' articulated needs through responsive interaction.[18]

METHODS

This quasi-experimental study was conducted at Critical Care Units of Al-Hussein Medical City and Imam Al-Hassan Al-Mujtaba Teaching Hospital in Karbala, Iraq from 7th June to 13th November 2024. The target audience consisted of critical care nurses with a minimum of one year of experience in intensive care units or coronary care units. The sample size was 90 nurses, constituting 76.3% of the qualifying population. Proportional distribution facilitated participation throughout both hospitals and units, yielding 33 ICU and 21 CCU nurses from Al-Hussein Medical City, and 20 ICU and 16 CCU nurses from Imam Al-Hassan Al-Mujtaba Teaching Hospital. During the intervention period, two individuals voluntarily withdrew, resulting in a final sample of 88 critical care nurses. The sample was randomly allocated into two groups: an intervention group (Mindfulness-Based Cognitive Therapy) and a control group. Both males and females nurses with a minimum of one year of professional experience in critical care environments were included. Critical care nurses were excluded if they had previously engaged in Mindfulness-Based Intervention (MBI) training programs, had psychosocial or psychiatric therapy, or did not complete the questionnaire were excluded.

The data of critical care nurses, including demographic factors such as age, gender, residency, and monthly income, alongside clinical features like employment type, years of experience, shift pattern, and patient load. Personal accomplishment subscale of the Maslach Burnout Inventory–Human Services Survey (MBI-HSS) for medical personnel to evaluate the sensation of personal accomplishment was recorded. Responses were evaluated using a seven-point Likert scale from 0 (never) to 6 (every day), enabling participants to indicate the frequency of thoughts, emotions, or actions associated with personal success.The reliability was evaluated by the test–retest procedure, and the findings were analyzed utilizing the Pearson Correlation Coefficient (PCC). The reliability coefficient was 0.81, above the widely recognized criterion of 0.70, therefore indicating good dependability.

Data were evaluated with SPSS-25. Inferential statistics, including independent and paired-samples t-tests, were used to assess group differences, while analysis of variance (ANOVA) with Tukey's HSD post-hoc testing was utilized for variables having three categories, such as age and monthly income. Alongside p-values, effect sizes were computed to provide a more explicit representation of the intervention's effect. Cohen's d was used, with values of $d < 0.5$ signifying a modest impact, $0.5 \leq d < 0.8$ a medium effect, and $d \geq 0.8$ a big effect.

RESULTS

The most common level of education was a bachelor's degree or higher. Most nurses worked 40 hours or less a week, and the majority handled 1-2% patients per shift (Table 1). Prior to the intervention, 55.8% of participants reported low accomplishment, while 30.2% had moderate levels. After the intervention, 51.1% of participants were classified as high personal accomplishment (low burnout), and 20.9% in moderate burnout, with a mean score of 37.2, compared to the control group, which showed minimal change (Table 2).

After the intervention, the experimental group showed a significant improvement in personal accomplishment, with a mean score of 37.2±5.9, compared to the control

group's slight decrease of 30.9±7.4. This difference was statistically significant and associated with a moderate between-group effect size (0.71). The experimental group also showed a notable mean change from pretest to posttest, compared to the control group's minimal change (0.511±10.2). The within-group effect size was large for the experimental group (0.63), reflecting a moderate practical effect, while the control group had a negligible effect size (0.07). The percentage change in personal accomplishment was significantly greater in the experimental group (13.4%) compared to the control group (1.5%) [Table 3]

Nurses from nuclear families (husband/wife) reported a pre-test mean of 28.71±6.42 and improved to 39.57±2.99 post-intervention, achieving a significant p-value of 0.035. With respect to the differences in other clinical variables, none of these variations demonstrated statistical significance (Table 4).

Table No. 1: Demographic and clinical characteristics of the participants

Variables		Experimental Group (N=43)		Control Group (N=45)		P value
		No.	%	No.	%	
Age (years)	22-26	24	55.8	23	51.1	0.552 NS
	27-31	11	25.6	16	35.6	
	32-36	8	18.6	6	13.3	
Gender	Male	23	53.5	22	48.9	0.666 NS
	Female	20	46.5	23	51.1	
Marital status	Single	23	53.5	29	64.4	0.296 NS
	Married	20	46.5	16	35.6	
Type of family	Nuclear (Father/Mother)	21	48.9	23	51.1	0.480 NS
	Nuclear (Husband/Wife)	15	34.9	17	37.8	
	Extended	7	16.2	5	11.1	
Monthly income	Sufficient	19	44.2	23	51.1	0.554 NS
	Sufficient to some extent	17	39.5	18	40.0	
	Insufficient	7	16.3	4	8.9	
Academic qualification	Bachelor degree or Higher	22	51.2	24	53.3	0.776 NS
	Nursing diploma	14	32.6	16	35.6	
	Nursing secondary school	7	16.2	5	11.1	
Type of work	Government hospital only	29	67.4	34	75.6	0.399 NS
	Govt. and private hospital	14	32.6	11	24.4	
Current area of assignment	Intensive Care Unit	25	58.1	27	60.0	0.859 NS
	Coronary care Unit	18	41.9	18	40.0	
Years of experience	1-3	34	79.1	32	71.1	0.389 NS
	4-6	9	20.9	13	28.9	
Shift time	Morning	21	48.8	23	51.1	0.831 NS
	Evening	22	51.2	22	48.9	
Weekly hour work	<40 h	25	58.1	27	60.0	0.859 NS
	> 40 h	18	41.9	18	40.0	
Patient load	1-2	39	90.7	38	84.4	0.375 NS
	3-4	4	9.3	7	15.6	

Table No. 2: Comparison of overall personal accomplishment burnout levels among critical care nurses in both study groups before and after the program (Pretest and Posttest)

Variable			Experimental Group (N 43)				Control Group (N=45)				P value
Domains		Score	No.	%	Mean	SD	No.	%	Mean	SD	
Personal Accomplishment (8Q)Min=0, Max= 48	Pre-Test	Low burnout (40-48)	6	14	32.8	7.91	6	13.3	31.4	6.83	0.539 NS
		Moderate burnout (9-30)	13	30.2			12	26.7			
		High burnout (0-33)	24	55.8			27	60			
	Post-Test	Low burnout (40-48)	22	51.1	37.2	5.9	5	11.1	30.9	7.4	0.012 Sig

		Moderate burnout (9-30)	9	20.9			14	31.1			
		High burnout (0-33)	12	28			26	57.8			
Paired testP value			0.024 Sig				0.637 NS				

Table No. 3: Comparison of personal accomplishment burnout before and after the program in both studied group

Time Point	Experimental Group (N=43)		Control Group (N=45)		Effect size between groups	P value
	Mean	SD	Mean	SD		
Pre Test	32.8	7.91	31.4	6.83	0.21	0.539 NS
Post Test	37.2	5.9	30.9	7.4	0.71	<0.001 Sig
Mean difference Pre-Post	-4.34	7.53	0.511	10.2		<0.001 Sig
Effect size within group	0.63	0.07				<0.001 Sig
Percentage change	13.4%	1.5%				<0.001 Sig
P. Value	<0.041sig		0.963			

Table No. 4: Comparison of personal accomplishment scores across sociodemographic and clinical subgroups at pre- and post-test in the experimental group

Variables		Pre-Test (N=43)		Post-Test (n=45)		P value
		Mean	SD	Mean	SD	
Age Group	22-26	33.75	5.98	38.00	5.40	0.982 NS**
	27-31	31.45	4.63	36.18	6.69	
	32-36	32.25	9.25	36.37	6.80	
Sex	Male	32.57	7.05	38.17	5.92	0.244 NS*
	Female	33.25	5.52	36.15	5.88	
Type of family	Nuclear (Fa/Mo)	33.67	6.07	36.24	6.75	0.035 Sig**
	Nuclear (Hus/Wife)	28.71	6.42	39.57	2.99	
	Extended	33.73	6.26	37.53	5.66	
Monthly Income	Sufficient	33.42	6.37	35.95	5.95	0.374 Ns**
	Sufficient to some extent	32.41	6.54	38.35	4.70	
	Insufficient	32.57	6.50	38.00	8.42	
Academic qualification	Bachelor degree or Higher	32.00	8.46	35.71	4.57	0.115 NS**
	Nursing diploma	32.43	6.13	40.14	5.94	
	Nursing secondary school	33.45	5.95	35.86	5.83	
Type of work	Government hospital only	33.59	6.39	38.14	5.81	0.803 NS*
	Government and Private hospital	31.43	6.14	35.36	5.93	
Current Area of Assignment	Intensive Care Unit	34.48	5.54	35.56	6.19	0.061 NS*
	Coronary care Unit	30.67	6.81	39.56	4.78	
Years of Experience	1-3	33.85	6.01	37.41	5.88	0.185 NS*
	4-6	29.22	6.47	36.56	6.38	
Shift time	Morning	32.52	4.94	36.90	6.17	0.979 NS*
	Evening	33.23	7.51	37.55	5.87	
Weekly hour work	40 h or less	34.48	6.68	38.04	6.13	0.425 NS*
	More than 40 h	30.67	5.17	36.11	5.60	
Patient load.	1-2 pt	33.21	6.41	37.23	6.03	0.386 NS*
	3-4 pt	29.75	4.92	37.25	5.50	

*Paired t-test, **ANOVA

DISCUSSION

The study revealed that 55.8% of participants reported diminished levels of personal accomplishment, indicating a markedly high prevalence of burnout. This proportion is considerably greater than the 31% and 28.9% reported by Bruyneel et al[19] and Montoya et al[20] respectively. Such a disparity suggests that the

pressures experienced in CCU environments characterized by relentless demands, intensive patient care, and ongoing emotional strain may exert an especially detrimental effect on nurses' sense of professional fulfillment in the present context. Over time, these conditions erode personal accomplishment and contribute to the broader syndrome of burnout.

In the present study, pretest findings confirmed homogeneity between the experimental and control groups in demographic characteristics, occupational data, and baseline levels of personal accomplishment (32.8±7.91 vs. 31.4±6.83; p = 0.539). This comparability minimizes the risk of confounding influences, thereby strengthening the internal validity of the study and ensuring that post-intervention differences can be attributed to the intervention. Following the intervention, the experimental group demonstrated a significant improvement in personal accomplishment, with mean scores increasing to 37.2±5.9, corresponding to a mean change of 4.34±7.53 and a percentage increase of 13.4%. By contrast, the control group exhibited only a minimal increase of 1.5%. Effect size analysis further substantiated these findings: the between-group effect size (Cohen's d = 0.71) and within-group effect size for the experimental group (Cohen's d = 0.63) both fell within the medium range, indicating that the change was not only statistically significant but also of practical relevance. The control group, in contrast, showed a negligible effect (d = 0.07), reinforcing the absence of meaningful improvement without the intervention.

The observed enhancement in personal accomplishment may be attributed to the role of MBCT in cultivating mindfulness of pleasant emotions, encouraging positive introspection, and broadening cognitive flexibility. By fostering greater awareness of positive experiences, MBCT may expand individuals' perspectives on choices and coping strategies, enabling more adaptive responses to occupational stressors. These findings are consistent with previous research. Xie et al[21], in China, demonstrated that MBCT-based interventions significantly enhanced personal accomplishment and resilience. Similarly, Mealer et al[22] reported improved resilience and reduced burnout symptoms among ICU nurses following an adapted MBCT program, while Mathew et al[23] concluded in their systematic review that mindfulness-based training reduces stress and enhances psychological well-being among nurses. By contrast, Calais[24] reported no significant improvement in personal accomplishment after a six-week mindfulness program, suggesting that intervention duration and contextual factors may influence outcomes.

This study showed that nurses from nuclear families demonstrated substantial improvements in personal accomplishment, with mean scores increasing from 28.71±6.42 to 39.57±2.99; p = 0.035). This study aligns with previous research highlighting the importance of mindfulness-based interventions in alleviating stress and anxiety. Nurses from nuclear families may have fewer inherent support systems compared to those from extended or joint families. Consequently, mindfulness may serve as an additional internal coping resource, rendering its benefits more pronounced.[25] This result may reflect the greater ease of practicing MBCT in quieter environments, with clearer household boundaries and stronger direct family support, compared to extended family settings where competing demands and distractions may hinder engagement.

CONCLUSION

Mindfulness-based cognitive therapy significantly improves personal accomplishment among critical care nurses and the practical value in promoting resilience, psychological well-being, and professional fulfilment. Contextual factors, such as family structure, may influence the effectiveness of MBCT, with nurses from nuclear families showing greater improvements.

Author's Contribution:

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Original Article

Comparative Biochemical Effects of Ferric Carboxymaltose and Iron Sucrose: Focus on Hypophosphatemia and Calcium Homeostasis

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ABSTRACT

Objective: To assess the frequency and severity of hypophosphatemia that arises after treatment with ferric carboxymaltose and consequent hypocalcaemia, compared with iron sucrose, to better understand their safety implications in clinical practice.

Study Design: Comparative study

Place and Duration of Study: This study was conducted at the Al-Diwaniyah Teaching Hospital Diwaniyah, Iraq from 1st October 2024 to 31st May 2025.

Methods: Thirty patients diagnosed with iron deficiency anemia were enrolled. Half received ferric carboxymaltose, while the remaining 15 were treated with iron sucrose. Biochemical evaluations (serum phosphate and calcium) levels were performed before treatment and repeated two weeks after the final infusion to assess potential alterations associated with each therapy.

Results: In ferric carboxymaltose group, a notable decrease in serum phosphate levels and a mild reduction in calcium concentrations were observed, whereas the iron sucrose group maintained stable mineral profiles. These changes suggest that ferric carboxymaltose exerts distinct effects on mineral metabolism, potentially mediated by its pharmacodynamic properties.

Conclusion: The differential impact of FCM and IS on phosphate and calcium homeostasis underscores the importance of individualizing intravenous iron therapy choices. For patients with pre-existing mineral imbalances or risks of hypophosphatemia, careful consideration of metabolic effects is essential to optimize safety and clinical outcomes.

Key Words: Ferric carboxymaltose, Iron deficiency anaemia, Iron sucrose, Hypophosphatemia

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INTRODUCTION

Iron deficiency anemia (IDA) signifies a late-stage consequence of iron depletion, in which diminished iron levels disrupt erythropoiesis, leading to anemia and the emergence of microcytic, hypochromic red blood cells.[1] Hematological and biochemical parameters are essential for the diagnosis of IDA. According to the World Health Organization, anemia is defined as an hemoglobin (Hb) level below 130 g/L in males and below 120 g/L in non-pregnant females.

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A comprehensive assessment of iron status typically includes serum ferritin, serum iron concentration, and transferrin saturation.[2]

Effective management of iron deficiency (ID) begins with identifying the underlying etiology and implementing strategies to restore systemic iron balance. In most clinical scenarios, oral iron supplementation serves as the first-line therapeutic approach, given its cost-effectiveness, broad accessibility, and well-established efficacy in replenishing iron stores.[3]

The clinical application of parenteral iron therapy dates back to the early 20th century, when colloidal ferric hydroxide-based formulations were first introduced. Despite their initial promise, these preparations were soon limited by significant toxicity, primarily due to the uncontrolled release of free iron into the circulation. This concern catalyzed the development of more stable intravenous (IV) iron complexes, characterized by an iron core enveloped within a carbohydrate shell, an innovation designed to modulate iron release and mitigate adverse reactions. By the 1990s, the emergence of iron gluconate and iron sucrose (IS)

marked a pivotal advancement in IV iron therapy. These formulations demonstrated improved safety profiles with lower rates of severe hypersensitivity.[4]

Iron sucrose represents one of the earliest IV iron formulations. It remains among the most extensively utilized parenteral iron therapies in clinical practice. The active pharmaceutical ingredient comprises a polynuclear iron(III) hydroxide core stabilized within a sucrose matrix.[5] Advancements in pharmaceutical technology have enabled the development of third-generation IV iron formulations designed to address the limitations of earlier therapies. These newer agents were specifically engineered to mitigate the toxicity associated with labile iron release and to overcome the dosing constraints inherent to traditional preparations such as iron sucrose. Among the most prominent third-generation IV iron compounds are ferric carboxymaltose (FCM), iron isomaltoside, and ferumoxytol. Each features a highly stable iron-carbohydrate complex that permits the administration of larger single doses over shorter infusion times, thereby enhancing both clinical efficiency and patient convenience.[4] IV iron sucrose necessitates multiple administrations to achieve therapeutic targets. In contrast, FCM is distinguished by its low immunogenic potential, thereby significantly reducing the risk of hypersensitivity and anaphylactic reactions. It permits the delivery of large single doses over brief infusion periods. A growing body of clinical evidence supports the safety and efficacy of FCM in the management of IDA, with studies consistently demonstrating substantial improvements in hemoglobin concentrations and iron indices following treatment.[6]

Since its FDA approval in 2013, the prescribing information for FCM has undergone multiple revisions, some of which have increasingly highlighted the concern regarding hypophosphatemia (HPP) as a notable adverse effect associated with FCM therapy.

Although initially perceived as a mild, transient, and clinically insignificant adverse event, hypophosphatemia associated with FCM emerged as a more serious concern with increased utilization in routine clinical practice. Many cases presented with severe and symptomatic manifestations, occasionally persisting for several months. In some cases, affected individuals required hospital admission for therapeutic correction.[7] Hypophosphatemia induced by FCM often arises due to enhanced urinary phosphate loss. This effect is driven by an increasein circulating levels of the phosphaturic hormone fibroblast growth factor 23 (Fgf23), which begins within the first 24 hours post-infusion. Beyond its role as a phosphaturic hormone, FGF23 suppresses the renal conversion of 25-hydroxyvitamin D (25[OH]D) into its biologically active form. This dual action precipitates a mild decline in serum calcium concentrations. The ensuing hypocalcemia stimulates parathyroid hormone (PTH) secretion as a compensatory response; its inherent phosphaturic activity contributes to the persistence of hypophosphatemia, extending beyond the initial period of elevated Fgf23.[8]

Emerging research highlights a complex interplay between iron metabolism and phosphate homeostasis. In states of ID and inflammation, there is an upregulation of Fgf23 synthesis at both transcriptional and translational levels within bone tissue. However, this elevated Fgf23 expression typically does not result in hypophosphatemia, as it is counterbalanced by enhanced intracellular proteolytic cleavage of the hormone into inactive C-terminal and N-terminal fragments that do not exert phosphaturic effects. Although the underlying mechanism remains incompletely understood, it is postulated that FCM disrupts this regulatory balance, uncoupling Fgf23 production from its cleavage. Consequently, the excessive Fgf23 levels induced by ID lead to an accumulation of biologically active full-length Fgf23 following FCM administration, thereby precipitating hypophosphatemia.[9]

Phosphorus is a key to cellular functions, including structural stability, signaling, and energy metabolism. Its homeostasis is tightly regulated via dietary intake, hormonal control, and renal excretion. Normal adult serum phosphate levels range from 2.48-4.65 mg/dL.[10] Hypophosphatemia spans from mild to critical, defined by serum phosphate levels.[11] Phosphate levels commonly reach their lowest point around day 14 following infusion.[12,13]

METHODS

This prospective interventional study was carried out at Al-Diwaniyah Teaching Hospital in Diwaniyah Iraq from 1st October 2024 to 31st May 2025. Thirty patients with clinically confirmed iron deficiency anemia were recruited into the study, following thorough evaluation and eligibility screening performed by a consulting hematologist. Patients considered eligible for this study were adults aged between 18 and 65 years with a confirmed diagnosis of iron deficiency anaemia; they had not received any form of iron supplementation, oral or IV, for a minimum of one month before evaluation. Patients were excluded if they presented with acute bleeding-related anemia underlying renal impairment, active oncological disease, or current pregnancy or lactation. Furthermore, patients who received agents known to alter electrolyte balance, particularly serum calcium, phosphate, or vitamin D3 levels, such as denosumab. A total of 30 patients were enrolled, the first group of 15 patients were treated with a 500 mg single dose of ferric carboxymaltose while the second (control group) 15 patient received iron sucrose at a dose of 200 mg administered on alternate days, up to a cumulative total of 600 mg within one week.

A-Phosphate measurement: Serum phosphate was measured using a colorimetric method with the Mindray BA-88A analyzer. Phosphate reacts with ammonium molybdate under acidic conditions to form a complex absorbing at 340 nm, allowing accurate quantification.[14]

B-Calcium Measurement: Serum calcium was measured using the ARCHITECT c4000 analyzer via a colorimetric assay. Calcium ions formed a blue-purple complex with Arsenazo III dye, detected at 660 nm, with concentrations automatically computed by the system.[15]

C-Vitamin D3 Measurement: Vitamin D_3 levels were quantified using the ichroma™ II analyzer, following the manufacturer's protocols. The procedure involved sequential mixing of serum with releasing and detection buffers, followed by incubation at 35 °C. After placing the prepared strip into the analyzer, the system performed automated scanning and calculated serum 25(OH)D concentration in ng/mL within 12–15 minutes.

Statistical analysis of biochemical parameters was conducted using SPSS-26. A p-value below 0.05 was interpreted as indicating statistical significance

RESULTS

There were 28 (93.3%) females and only 2 (6.7%) males. The mean gender distribution, coded numerically, was identical in treatment groups, iron sucrose and ferric carboxymaltose (FCM) of 1.07±0.067, yielding a P-value of 1.000. The average age of participants in the iron sucrose group was 31.6±2.72 years, while the FCM group showed a mean age of 31.8±2.75 years (P=0.959). The values of phosphate and calcium before and after treatment with ferric carboxymaltose and iron sucrose are showed in Tables 1-4. The vitamin D3 level at baseline is showed in Table 5.

Table No. 1: Value of phosphate and calcium before treatment with ferric carboxymaltose and iron sucrose

	Groups	Mean	SE mean	P value
Phosphate level before treatment	Iron sucrose	4.053	0.2438	0.349
	Ferric carboxymaltose	4.220	0.1295	
Calcium level before treatment	Iron sucrose	8.753	0.1121	0.342
	Ferric carboxymaltose	8.892	0.1141	

Table No. 2: Value of phosphate and calcium before and after 2week of treatment with ferric carboxymaltose

	Mean	SE mean	P. value
Phosphate level before treatment	4.220	0.1295	0.045
phosphate level after 2 weeks	3.887	0.1142	
Calcium level before treatment	8.892	0.1141	0.042
Calcium level after 2 weeks	8.633	0.1720	

Table No. 3: Value of phosphate and calcium before and after 2 weeks of treatment with iron sucrose

	Mean	SE mean	P. value
Phosphate level before treatment	4.053	0.2438	0.238
phosphate level after 2 weeks	3.987	0.2362	
Calcium level before treatment	8.753	0.1121	0.329
Calcium level after 2 weeks	8.640	0.14266	

Table No. 4: Value of phosphate and calcium after treatment with ferric carboxymaltose and iron sucrose

	Groups	Mean	SE mean	P value
Phosphate level after 2 weeks	Iron sucrose	3.987	0.2362	0.706
	Ferric carboxymaltose	3.887	0.1142	
Calcium level after 2 weeks	Iron sucrose	8.640	0.1466	0.977
	Ferric carboxymaltose	8.633	0.1720	

Table No. 5: Value of vitamin D3 at baseline

	Groups	Mean	SE mean	P value
Baseline vitamin D3	Iron sucrose	13.206	1.7392	0.682
	Ferric carboxymaltose	14.106	1.3027	

DISCUSSION

Before treatment, baseline characteristics were statistically comparable across both groups (p>0.05), supporting the assumption of group equivalence. This comparability is essential for attributing any post-intervention differences to the treatment effects rather than pre-existing disparities. Baseline levels of active vitamin D3 were comparable between the two treatment groups, with no statistically significant difference

observed (p=0.682). This suggests that both groups entered the intervention phase with similar vitamin D status, minimizing its potential role as a confounding factor.

Regarding phosphate levels, treatment with FCM led to a statistically significant reduction post-intervention (p=0.045). This aligns with the established association between FCM and hypophosphatemia, a phenomenon primarily attributed to its influence on FGF23, which enhances renal phosphate excretion. The observed findings like those reported in multiple clinical studies, reinforce the consistency of this safety signal.[7,16,17]

Notably, while serum phosphate levels declined significantly following treatment, none of the participants in this study developed either biochemical or clinically evident hypophosphatemia. This suggests that despite the statistical significance, the reduction did not translate into a measurable clinical impact within the study. The modest reduction in serum calcium levels observed post-treatment with FCM (p=0.042), although remaining within the physiological range, may signal adaptive shifts in mineral metabolism. This response could reflect compensatory mechanisms triggered by phosphate alterations or nuanced changes in vitamin D homeostasis. As outlined in the comprehensive review by Schaefer et al[8], hypophosphatemia can precipitate mild hypocalcemia, primarily through FGF23-driven suppression of 1,25-dihydroxyvitamin D synthesis. This, in turn, impairs intestinal calcium absorption and may contribute to secondary hyperparathyroidism. Although phosphate disturbances were the primary focus of the systematic review by Schaefer et al[18], the analysis also sheds light on key implications for calcium homeostasis. In particular, the review underscores the potential for hypocalcemia, emerging as a downstream effect of disrupted phosphate metabolism.

In the iron sucrose (IS) group, changes in serum phosphate and calcium levels did not reach statistical significance (P>0.05), indicating a relatively neutral impact of IS on mineral metabolism within the studied timeframe. This contrasts with the metabolic alterations observed following ferric carboxymaltose (FCM) administration. Notably, Blazevic et al[19] have highlighted that while mild hypocalcemia may occasionally occur with IS, such events are typically transient and lack clinical relevance. Moreover, IS is consistently associated with a substantially lower incidence of hypophosphatemia compared to FCM.

Following treatment, FCM was associated with a statistically significant reduction in serum phosphate levels, alongside a mild decline in calcium concentrations. However, when directly compared with the iron sucrose group, these changes did not translate into a statistically significant intergroup difference, suggesting comparable impacts on mineral parameters across both treatment modalities.

CONCLUSION

Phosphate levels decreased and calcium levels showed a mild reduction in the FCM group, whereas no such changes were observed with IS. These findings highlight the distinct metabolic effects of FCM, particularly its influence on phosphate and calcium regulation. Such considerations are important when selecting intravenous iron therapies, especially for patients with pre-existing mineral imbalances.

Author's Contribution:

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Original Article

The Role of Biomarkers Vascular Cell Adhesion Molecule-1 (VACM-1), Septin-9, Hypoxia-Inducible Factor-1 (HIF-1) and C-Reactive Protein (CRP) in Distinguishing between Benign and Malignant Male Colon Tumors

Biomarkers, Septin-9, Hypoxia-Inducible and CRP for Differentiate of Colon Tumors

Shaimaa Obaid Mostafa, Haitham L Al-Hayali and Mowafak K. Hasan

ABSTRACT

Objective: To assess the effectiveness of VACM-1, Septin-9, HIF-1, and CRP as potential biomarkers in distinguishing malignant from benign colon tumors in male individuals.

Study Design: Meta-analysis study

Place and Duration of Study: This study was conducted at the Colonoscopy Units in Ibn Sina Teaching Hospital, Aljumhuriy Hospital, Mosul General Hospital, Al-Salam Hospital, and Research Hospitals at Mosul University, as well as from the private clinic of Dr. Abdullah Zuhair Al-Yuzbaki in Mosul City from 1st April 2023 to 31st March 2024.

Methods: A total of 45 patients who underwent colonoscopies were enrolled. Participants ranged in age from 18 to 78 years. Venous samples were collected from each patient before colonoscopy and analyzed for complete blood counts, and tumor markers using ELISA. Samples were classified into benign and malignant tumors, and healthy patients were controls. Tumor markers in the analysis included VCAM-1, Septin-9, HIF-1α, and CRP.

Result: Compared to biopsy groups (before colostomy) results, the lower values observed in the adenoma group suggest a relative stability in the tumor state. Males demonstrated a more pronounced pattern of anemia and immune dysfunction, especially during the initial phases of colon cancer. Statistically significant alterations were observed in blood parameters and tumor markers among male adenoma patients. The variations in immune ratios, including L/M and P/L, underscore the differences in overall immune and inflammatory responses among males at various stages of the disease. VCAM-1, Septin-9, HIF-1α, and CRP also recorded a significant difference in distinguishing between benign and malignant tumors and between adenoma and control groups. VCAM-1, Septin-9, and HIF-1α measures exhibited good effectiveness in identifying various three stages of colon cancer, compared to the adenoma and control groups. This may indicate the effectiveness of alterations in the tumor microenvironment.

Conclusion: Vascular cell adhesion molecule-1, septin-9, and HIF-1α demonstrate high clinical value as biomarkers in tracking the progression and metastasis of colon cancer. Their effectiveness in diagnostically distinguishing between benign and malignant tumors enhances their feasibility as potential clinical evaluation and therapeutic monitoring targets.

Key Words: Adenoma, Colon cancer, Biopsy, VCAM-1, Septin-9, HIF-1α, CRP

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INTRODUCTION

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Benign tumors (adenomas) do not invade surrounding tissues or spread to distant sites, often encapsulated and resemble the original tissue, unlike malignant tumors, which are characterized by aggressive behavior and a harmful effect on the body. Overall, benign tumors are less dangerous and can be surgically removed, however, some have the potential to transform into malignant tumors.[1]

"Malignancy or cancer" refers to the abnormal growth of cells, with the potential to spread and invade other parts of the body, a known as metastasis. Cancer cells can resist apoptosis, and invade surrounding tissues. These cells acquire these characteristics due to complex

genetic changes, contributes to the formation and progression of tumors.[2]

Colon cancer is the third most common type of cancer and the fourth leading cause of cancer-related deaths worldwide for both genders. The disease is challenging to detect in its early stages. It often progresses gradually from benign polyps or cysts to late-stage metastases.[3] Yousif et al[4] also indicated that some biochemical indicators in colon cancer patients were significantly higher than those in the control group. Biomarkers are crucial in the early detection of malignant diseases.

Colon cancer biomarkers are biological molecules found in blood, other body fluids, or tissues that signal the presence or progression of colon cancer. These biomarkers are crucial for the early detection of the disease, assessing its prognosis in patients with colon cancer.[5] Badiwi[6] also indicated that some vital compounds increase by more than 50% in malignant tumors compared to benign tumors. It was observed that tumor marker in the serum of patients of colon cancer, were elevated compared to those in the control group.[7]

VCAM-1 (CD106) is a surface protein belonging to the immunoglobulin family. Evidence suggests its association with angiogenesis and tumor metastasis, particularly in colon cancer. (sVCAM-1) in the serum of cancer patients are an indicator of the tumor environment and contribute to enhancing tumor survival.[8]

The methylated septin-9 (mSeptin-9) is superior to traditional biomarkers such as CEA in diagnosing colorectal cancer at various stages. and after surgery, with a 100% correlation with recurrence or metasta.[9]

HIF-1α is a hypoxia-sensitive transcription factor activated in solid tumor environments, such as colon cancer. It contributes to regulating gene expression associated with cancer cell survival, proliferation.[11] Under hypoxia, it to stabilize and bind to HIF-1β in the nucleus. The resulting complex activates the transcription of genes involved in angiogenesis, metabolism, and cell survival.[10]

C-reactive protein is a diagnostic biomarker and contributor to inflammation associated with colon cancer development. It regulates the signals of immune cells and may influence tumor initiation, progression, and the body's response to it.[11] Elevated levels of are associated with tissue damage resulting from an acute inflammatory response, reflecting a potential role in promoting tumor growth and metastasis.[12]

METHODS

This meta-analysis study was conducted at Colonoscopy Units in Ibn Sina Teaching Hospital, Aljumhuriy Hospital, Mosul General Hospital, Al-Salam Hospital, and Research Hospitals at Mosul University, as well as from the private clinic of Dr. Abdullah Zuhair Al-Yuzbaki in Mosul City, Iraq. A total of 64 patients and ages from 18-78 years were enrolled. 5ml of venous blood samples were collected from the study participants before colonoscopy at the hospitals. 3 ml in gel tubes for tumor marker analysis and 2 ml in EDTA tubes for (CBC) analysis using the MicroCC-20Plus device on the same day of the collection were performed within one hour of sample collection. After serum separation, samples were classified into two main categories based on histopathological biopsy reports: benign tumors and malignant tumors. For the malignant tumor groups, according to the colon cancer staging system, these groups was classified into tumor stages based on histopathological results: Stages II, III, and IV (The serum was stored in deep freeze until the histopathological report of the patients' colectomy was obtained, and the groups were divided into biopsies II, III, and IV), Then the serum was used to measure tumor biomarkers. In addition, 5 ml blood samples were collected from patients whose colonoscopies showed no evidence of tumors or polyps. This group was considered a positive control group; ultimately, and healthy people without any disease symptoms formed the healthy control group. Six tumor markers in the serum using ELISA technology, Labtech Microplate Reader LT-4000, East Sussex, UK were noted. The markers included Vascular Cell Adhesion Molecule 1 (VCAM-1), Septin-9, Hypoxia-Inducible Factor 1 Alpha (HIF-1α), and C-Reactive Protein (CRP), following the guidelines provided by Shanghai Ideal Medical Technology Co., Ltd., China. The differences between groups were analyzed by using the Duncan test, one-way ANOVA at the level of statistical significance $P \leq 0.05$ by SPSS-26.

RESULTS

There were 23 (92%) malignant tumors including 2 samples taken from surgical procedures. Benign tumors accounted for 2 (6%) of all biopsy samples (Fig. 1). Stage IV represented the lowest number, with 5 (21.8%) cases followed by Stage III 8 (34.8%) cases, while Stage II had the highest incidence rate 10 (43.4%) [Fig. 2).

The results showed significant differences between the biopsy groups and the control groups of males in each of (WBC), (LYM), (RBC), (Hb), (MCH), (MCV), (HCT), and (MPV),. In contrast, in (GRA), the significant difference was limited to biopsy II only. There was no significant difference in platelet count except for the adenoma group. The lack of substantial difference between the two control groups is worth noting (Table 1). The L/M% ratio for the fourth-stage patients increased compared to the benign tumor; in contrast, the benign tumor showed an increase in the P/L% ratio (Table 2).

The readings for VCAM-1 and HIF-1α were significantly elevated in biopsy III. Biopsy IV exhibited

a notable increase in Septin-9, while CRP showed an increase in stage III over stage II, but CRP was not statistically significant. There was no significant difference between the two control groups, and a significant difference was found between the three biopsy groups and the two control groups in all biomarkers. A significant difference was observed in VCAM-1, Septin-9, and HIF-1α across the three biopsy groups compared with the control groups. And there was no significant difference between the biopsy groups in CRP (Table 3).

Table No. 1: Complete blood count of male adenoma and biopsy groups

Variable	Healthy control	Control^{+}	Adenoma	Biopsy II	Biopsy III	Biopsy IV
WBC	7.29±0.65	7.30±0.62	6.56±0.65	7.50±1.14	6.02±0.57	6.82±0.15
LYM	2.80±0.42	2.23±0.30	2.01±1.23	1.53±0.17	1.50±0.618	1.67±0.54
MID	0.561±0.07	0.51±0.13	0.640±0.12	0.625±0.07	0.403±0.11	0.467±0.13
GRA	3.92±0.39	4.57±0.72	3.91±0.29	5.35±0.91	4.11±0.30	4.68±0.55
RBC	5.23±0.11	5.32±0.16	3.43±1.13	4.02±0.72	4.33±0.18	4.52±0.17
Hb	14.57±0.44	14.03±1.91	7.90±0.56	9.62±1.45	9.20±2.08	10.00±0.20
MCHC	33.20±0.7	32.21±2.46	31.85±1.82	31.50±0.50	29.70±2.48	30.43±0.65
MCH	27.94±0.76	26.32±3.55	23.20±1.97	24.10±0.83	21.17±3.95	22.10±1.30
MCV	84.26±1.76	81.16±6.71	72.70±9.61	76.52±2.08	70.83±7.91	72.6±2.70
RDW - CV	12.13±0.29	12.73±1.13	14.20±1.69	13.15±0.19	13.83±1.10	13.26±0.45
RDW - SD	42.25±1.23	40.05±3.4	41.80±1.56	40.07±1.92	38.23±2.87	37.13±0.35
HCT	44.62±2.32	43.24±3.79	24.90±1.97	30.55±4.79	30.76±4.6	32.80±1.10
PLT	220±11	222±30.4	278±9.89	209 b ± 39	198±3.51	195±5.0
MPV	7.92±0.25	8.42±0.66	7.10±1.13	7.55±0.58	7.83±0.85	8.70±0.40
PDW	12.70±0.56	14.14±1.58	13.20±1.69	12.90±1.89	14.63±2.05	16.70±0.60
PCT	0.17±0.007	0.186±0.03	0.196±0.007	0.161±0.04	0.149±0.049	0.10±0.009

RBC ($\times 10^6$/µl), Hb (g/dl), PCV and PDW (%), MCV (ϑl), MCH (pg), MCHC (g/L), WBC, Lymph, MID, GRA and PLT ($\times 10^3$/µl). Control+ (Positive control); Biopsy II (Colon cancer stage II), Biopsy III (Colon cancer stage III), Biopsy IV (Colon cancer stage IV). Using the Dun can' test, the different letter indicates the significant difference at the probability level (P≤0.05)

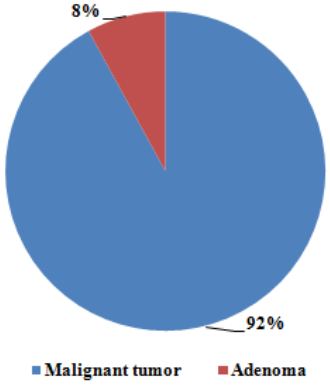

Figure No. 1: Percentage of malignant and benign tumors

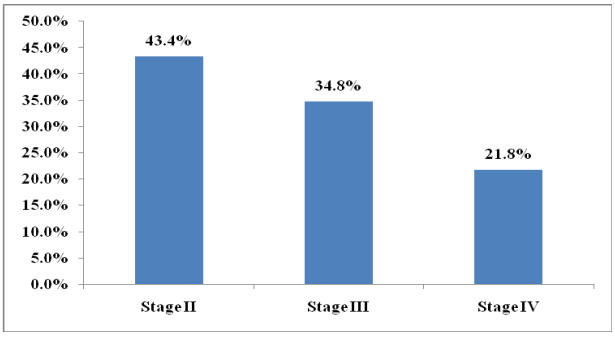

Figure No. 2: Percentage of infections

Table No. 2: The percentage of lymphocytes to monocytes and platelets to lymphocytes in the male groups

Groups	Percent lymphocyte to monocyte ratio	Percent platelets to lymphocyte ratio
Healthy Control	5.6	78.6
Positive Control	4.4	99.6
Adenoma	3.1	134.3
Biopsy II	2.5	136.6
Biopsy III	3.7	132
Biopsy IV	3.6	117

Table No. 3: Differences in tumor markers among control, benign tumor and biopsy groups in males

Variable	Healthy control	Positive control	Adenoma	Biopsy II	Biopsy III	Biopsy IV
VCAM -1	62.5±2	64.3±1.8	38.2±3.5	72.2±2	75.3±1.9	68±2
Septin -9	1.04±0.02	1.07±0.02	0.65±0.05	1.48±0.31	1.88±0.6	2.28±0.4
HIF-1 -alpha	4.3±0.5	4.5±1.3	3.6±0.6	9.4±1.3	13.5±1.2	11.7±0.4
CRP	1.74±0.03	1.81±0.14	1.38±0.11	2.10±0.05	2.11±0.07	2.05±0.04

DISCUSSION

The prevalence of advanced malignancies, including colon cancer, was determined among a German population-based sample of 15,985 participants in colonoscopy screening aged 55–79 years, of whom 7,822 were male. Men had a two-fold increased risk of colon cancer (1.8%) compared to women (1%). Men also had a higher prevalence of advanced and non-advanced adenomas (13.4%) and (24.6%), respectively. It has been suggested that estrogen may reduce the risk of proximal and distal colon cancers by increasing apoptosis in cell lines, which may explain a significant portion of the gender differences in cancer risk.[13]

In a descriptive study conducted by collecting data on 760 male patients who visited the colonoscopy unit in Somalia, it was found that 50 cases of cancer were present, or 8.5% of the cases, and adenomas constituted 40 of the 50 malignant tumors.[14]

The variation in white blood cell counts in mice may be attributed to immune system activation, which induces a positive immune response in the form of increased lymphocytes and monocytes, a hallmark of white blood cell count variations.[15,16]

Wan et al[17] indicated that a high lymphocyte-to-monocyte ratio (LMR) is associated with improved survival rates in cancer patients. LMR is an indicator of antitumor immunity and tumor burden. At the same time, tumor-infiltrating lymphocytes contribute to enhanced immune response, and their low levels are associated with impaired immunity and adverse clinical outcomes.

A recent study by Turri et al[18] showed that a high preoperative white blood cell count and low lymphocyte count were associated with worse postoperative survival outcomes. Our study findings support these observations, as white blood cell counts were 1.5-3.2-fold higher in women in the fourth and second biopsy groups compared to the control group.

Our results showed decreased L/M and P/L ratios in males with advanced disease stages, consistent with the study by Yamamoto et al[19], that demonstrated the importance of LMR and PLR as prognostic indicators in colon cancer, where decreased LMR indicates a severe inflammatory state and decreased overall and disease-free survival rates.

Abd El Kader et al[20] noted that occult blood in the stool is more common in colon cancer patients, reflecting decreased hemoglobin. Monocytes also contribute to tumor-associated inflammation, while lymphocytes play a role in anti-cancer immunity.[21]

Adhesion molecules play a pivotal role in cell growth, differentiation, and migration and contribute to the transmission of cellular signals. Their involvement in these mechanisms is important in tumor progression and vascular spread. Elevated VCAM-1 levels in colon cancer patients are associated with enhanced tumor growth and metastasis by facilitating the interaction of cancer cells with their surrounding environment. Its elevation is an indicator of poor prognosis colon cancer.[8]

Zhang et al[22] reported that VCAM-1 contributes to activating the epithelial-mesenchymal transition (EMT) program, which promotes cancer cell migration and invasion. Its high expression is associated with poor differentiation, increased metastasis, and an aggressive tumor pattern in colorectal cancer, as well as poor survival rates, highlighting its importance as a prognostic factor.

Elevated levels of Septin-9 were observed in males, consistent with the findings of, who linked this to molecular mechanisms related to the cytoskeleton and signaling pathways. The oncogenic form of the protein contributes to enhanced cancer cell invasion by degrading the extracellular matrix (ECM). Also the results are consistent with Qu & Sun.[23] It was mentioned that septin-9 increases with the progression of the disease stages, especially the III and IV Stages.

As well, Peng et al[24] found that suppressing the expression of Septin-9 nine facilitates cell migration and alters Rho A signaling while having no effect on cell proliferation. Hypermethylation may be linked to the suppression of gene expression, which in turn contributes to cancer cell migration.

Hypermethylation of the SEPT9 gene is a pivotal mechanism in the development of colon cancer, leading to the inactivation of tumor suppressor genes. It can be detected in blood, making it a promising biomarker for diagnosis and monitoring. demonstrated that measuring protein levels before and three months after surgery showed 96.7% sensitivity and 95.5% specificity in distinguishing malignant from non-malignant tumors, which is consistent with the results of our study.[25]

Like others, hypoxia factor HIF-1α is also elevated in male colon cancer patients compared to control subjects. HIF-1α is a master regulator of the cellular response to hypoxia, a common characteristic of solid tumors. This factor is associated with dysregulated cell

proliferation and anti-apoptotic processes, contributing to tumor growth, metastasis, migration, and invasion.[10] C-reactive protein (CRP) elevated CRP has been linked to increased tumor invasiveness as a result of the systemic inflammatory response.[26]

That systemic inflammation assists in assessing risk factors associated with distant metastases in colon cancer. An increase in CRP in breast cancer patients compared to benign tumors, which induce a more significant inflammatory response as a result of tissue invasion and damage, which strengthens the interpretation of the results of our study.[3]

CONCLUSION

Given the role of tumor markers VCAM-1, Septin-9, and HIF-1α it can be used as biomarkers for assessing tumor progression, metastasis and then differentiating between benign and malignant tumors.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Shaimaa Obaid Mostafa, Haitham L Al-Hayali
Drafting or Revising Critically:	Shaimaa Obaid Mostafa , Mowafak K. Hasan
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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Original Article

Knowledge of Rural Iraqi Mothers and its Related Factors on the Care of Children with Common Health Problems

Shoukran Ali and Khamess Bander Obaid

ABSTRACT

Objective: To assess knowledge of rural Iraqi mothers and their related factors on the care of children with common health problems.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Primary Healthcare Centres (PHCCs) in Karbala Iraq from 1st December 2024 to 30th April 2025.

Methods: This cross-sectional study was conducted with 217 mothers referred to the Integrated Management of Childhood Illness (IMCI) unit in the. The samples were selected using a convenience sampling method. Data were collected using a researcher-made questionnaire.

Results: The mean maternal knowledge score was 16.1 ± 2.6. While 89.9% correctly maintained feeding during diarrhoea, 81.1% held misconceptions about antibiotic use. Education level, number of children, and income were significantly associated with knowledge, accounting for 18% of the variance.

Conclusion: The maternal education, economic status, and parenting experience are crucial determinants of mothers' knowledge on the care of children with common health problems

Key Word: Knowledge; Rural mothers; Common health problem

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INTRODUCTION

Children's health is a key public health issue in developing and post-conflict countries like Iraq.[1] In rural areas with limited healthcare services, maternal knowledge and practices significantly affect child health outcomes.[2,3] Many common childhood illnesses, such as diarrhoea and fever, can be managed at home if mothers possess adequate knowledge and skills.[1] However, rural mothers in Iraq often lack this knowledge due to high illiteracy rates, limited access to health information, and traditional practices.[4-7]

Although Iraq has seen improvements in healthcare infrastructure, rural regions still face major service gaps caused by prolonged conflict and instability.[8-11] The absence of targeted community-based education, shortages of trained health staff, and limited access to media further widen the knowledge gap.[12,13] Therefore, culturally sensitive health education and urgent interventions and make program to improve mother knowledge is essential to reduce mortality.[14,15] This study aims to assess rural Iraqi mothers' knowledge of common childhood health problems.

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METHODS

The cross-sectional study was conducted to assess the knowledge of rural mothers about the care of children with common health problems in Karbala, Iraq, from 1st December 2024 to 30th April 2025. Participants were mothers who referred to the Integrated Management of Childhood Illness (IMCI) unit in the primary healthcare centres (PHCCs) in Karbala, Iraq. Three out of six PHCCs in Karbala city, AL-Wand, AL-Hur, and Al-Khayrat PHCCs, were randomly selected for this study. The sample size based on a power analysis to detect a medium effect size at a 95% confidence level and 5% error was determined to be 217 people and data were coded and entered into the SPSS-19.

RESULTS

Most of the participating mothers were over 30 years of age (41%), married (96.7%), and had primary education (47.9%). Illiteracy was observed in 11.5% of the mothers. Employment among the mothers was low, with 94.9% unemployed. The majority of the mothers (94.5%) could walk to the nearest health facility in less than 30 minutes. The results showed that most of children were primarily toddlers (43.3). Common health

problems included fever (47.5%), respiratory tract infections (41%), and diarrhoea (11.5%) [Table 1].

The mean score of mothers' knowledge was 16.1±2.6. Mothers showed varied understanding of child health care. 89.9% knew that feeding should not be stopped during diarrhoea. 81.1% incorrectly believed antibiotics and anti-diarrheal stop diarrhoea early. 75.6% recognized poor hygiene as a cause of diarrhea.68.7% believed rotavirus vaccine prevents all diarrhoea cases. Mothers' knowledge about respiratory infections showed that 96.3% associated dust and smoke with respiratory issues. Most mothers had very good knowledge about managing children's respiratory problems. More over Fever management knowledge was good, with taking an infant to the hospital if the fever lasts more than 3 days (Table 2).

Univariate analysis showed that the mother's educational level (P<0.0001), monthly income (P=0.003) and number of children (r=0.2, P=0.008) had a statistically significant difference in the knowledge of rural mothers in Iraq on the care of children with common health problems (Table 3).

A multivariate analysis with linear regression showed that education level, number of children, and monthly income were statistically significant. The results showed that the knowledge level of illiterate mothers was 2.5 points lower than that of literate ones on the care of children with common health problems (B=-2.56, p<0.0001). Mothers with a diploma or higher had 1.28 points more knowledge than other groups (B=1.28, p=0.03). The number of children (B=0.26, p=0.006) and monthly income (B=-1.41, p=0.003) were statistically significantly associated with increasing mothers' knowledge on the care of children with common health problems. All of these factors determined 18 percent of the knowledge of rural mothers in Iraq (Table 4).

Table No. 1: Sociodemographic characteristics of rural mothers (N=217)

Mothers' Profile		Rural Mothers	
		No.	%
Age	<25 years	57	26.3
	25-30 years	71	32.7
	>30years	89	41.0
Marital status	Married	210	96.7
	Lonely (Divorced, Widowed)	7	3.2
Educational level	Illiteracy	25	11.5
	Primary	122	56.2
	High school	52	24.0
	Diploma and high	19	8.8
Mothers occupation	Employed	11	5.1
	Unemployed	206	94.9
Monthly income	< 300000 ID	99	45.6
	300000-600000 ID	51	23.5
	601000-900000 ID	35	16.1
	>900000 ID	32	14.7
Number of children	< 3	70	32.3
	3-5	112	51.6
	>5	35	16.1
Time to reach the centre on foot	<30 minutes	205	94.5
	More than 30 minutes	12	5.6

Table No. 2: Mothers' Knowledge on the care of children with common health problems

Statements	True		False	
	No.	%	No.	%
Diarrhoea is caused by poor hygiene	164	75.6	53	24.4
Breastfeeding or other feeding should not be stopped during diarrhoea	95	89.9	22	10.1
During diarrhoea, it is necessary to give the child a lot of fluids	141	65	76	35
Vaccines can prevent diarrhoea in children	149	68.7	68	31.3
Zinc is beneficial for children during diarrhoea	105	48.4	112	51.6
Antibiotics and anti-diarrheal medications can stop diarrhoea early	176	81.1	41	18.9
It is important to know how to recognize dehydration due to diarrhoea	162	74.7	55	25.3
Acute respiratory infections can be dangerous if left untreated	196	90.3	21	9.7
Dust and smoke make children more susceptible to respiratory infections	209	96.3	8	3.7

Common symptoms of respiratory infections include fever, cough, runny nose, & difficulty breathing	198	91.2	19	8.8
Chest retraction in a child with fever and cough indicates severe pneumonia	171	78.8	46	21.2
Stridor in a quiet child is a danger sign	149	68.7	68	31.3
Breastfeeding a child with cough and fever should be continued and compensated with more food during recovery	214	98.6	3	1.4
Vaccination helps children be less susceptible to acute respiratory infections	201	92.6	16	7.4
A fever below 40°C is not necessarily harmful to children	126	58.1	91	41.9
To check the temperature of children two years and older, the ear is gently pulled up and back	61	28.1	156	71.93
A lukewarm sponge bath is used 30 minutes after administering fever-reducing medication	113	52.1	104	47.9
When the fever is above 38.3°C and the child is uncomfortable, the child should be woken up to give fever-reducing medicine	177	81.6	40	18.4
If the infant's fever lasts more than 3 days, he should be taken to the hospital	211	97.2	6	2.8
To reduce fever, the child should be placed in a cold bath	59	27.2	158	71.8
To reduce a child's fever, the mother should not give the child a lot of fluids	19	8.8	198	91.2

Table No. 3: Comparison of mean scores of knowledge based on socioeconomic variables

Demographic data			**Mean ± SD**	**P- Value**
Mothers age	<25 years	15.75±2.5	F=2.72	P=0.06
	25-30 years	15.59±2.7		
	>30 years	16.5±2.61		
Mothers marital status	Married	15.41±2.6	T=0.72	P=0.47
	Lonely(Divorced and widowed)	14.71±3.9		
Mother educational level	Illiteracy	13.37±3.6	F=7.96	P<0.0001*
	Primary	15.77±2.3		
	High school	15.57±2.4		
	Diploma and high	15.94±1.32		
Mothers occupation	Employed	16.36±2.7	T=1.33	P=0.21
	Unemployed	15.33±2.6		
Monthly income	< 300000 ID	14.49±2.6	F=4.72	P=0.003*
	300000-600000 ID	15.55±2.8		
	601000-900000 ID	16.67±2.38		
	>900000 ID	15.75±2.6		
Time to reach the centre on foot	<30 minutes	15.39±2.6	T=0.52	P=0.59
	30-60 minutes	15±2.27		
Number of children		r=0.2		P=0.003**

*One Way ANOVA test, Pearson correlation coefficient. A p-value of less than 0.5 was considered significant

Table No. 4: Linear regression model of the factors associated with knowledge in mothers

Independent variable	**Dependent variable is knowledge**				
	B	**Std. Error**	**Beta**	**T**	**p-value***
Constant	15.361	.345		44.552	0.000
Illiterate	-2.56	0.53	-0.302	-4.76	<0.0001
Number of children	0.26	0.09	0.17	2.78	0.006
Monthly income(< 300000 ID)	-1.41	0.46	0.19	-3.03	0.003
Diploma and high	1.281	0.6	0.136	2.13	.03
Explained variance	R=0.42	R^2=0.18		Adjusted R^2=0.164	

*A p-value of less than 0.5 was considered significant

DISCUSSION

This study presents a detailed evaluation of rural mothers' sociodemographic characteristics and their knowledge regarding the management of common child health problems specifically diarrhoea, respiratory tract infections (RTIs), and fever. The findings underscore the impact of education, income, and maternal experience (number of children) on knowledge levels. The demographic profile reveals that most of the mothers were over 30 years of age, married, had

primary education, and were unemployed. Most families had low to moderate income levels, with 45.6% earning less than 300,000 Iraqi Dinars per month. These findings align with patterns observed in rural populations in developing regions, where limited access to education and employment is common among women[1]. Such profiles are critical; as maternal education level has been consistently linked to improved child health outcomes. Good knowledge and practices of caregivers are pivotal to the protection, prevention, and treatment of childhood diarrhoea, hence reducing mortality thereof.[16] Mothers with higher educational attainment are more likely to process health information, practice preventive care, and make informed treatment decisions.

Children presented mostly with fever, RTIs, and diarrhoea. These are common diseases in early childhood, particularly in under-resourced settings.[17] The fact that 94.5% of mothers lived within 30 minutes of a health facility suggests good geographic access to care, yet health outcomes still hinge on maternal knowledge and decision-making, as echoed in studies from Sub-Saharan Africa and South Asia.[18] The average knowledge score was 16.1±2.6 indicating a moderate understanding of child health. While most mothers correctly identified key facts such as the importance of continued feeding during diarrhoea (89.9%) and the role of dust/smoke in RTIs (96.3%), knowledge gaps persisted.[16] Notably, misconceptions about antibiotics and antidiarrheal for stopping diarrhoea early (81.1%) and the low awareness of zinc's benefits (48.4%) suggest areas requiring urgent educational interventions. The management of diarrhea, zinc, culturally appropriate and location-specific messages in the local language had no effect on overall zinc and ORS consumption and reduced antibiotic and antidiarrheal consumption.[19] These results are comparable to regional studies. For instance, a study by Zwisler et al[20] . In rural Jordan found similar misconceptions regarding diarrhoea management, particularly over-reliance on antibiotics and low use of oral rehydration solutions and zinc. The WHO and other international bodies have emphasized that such gaps are common in low-resource settings and need addressing through community-based health education.

The present study showed that there was a significant relationship between maternal education and knowledge on the care of children with common health problems. This is consistent with other studies[27], who noted that maternal education directly influences health literacy and child morbidity.Mothers with lower incomes (ID 601,000-900,000) had significantly less knowledge, which is consistent with other studies[28]. Economic empowerment likely improves access to health information, resources, and services.[21]

The present study showed that there is a positive and significant correlation between the number of children and knowledge on the care of children with common health problems. This suggests thatexperiential learning plays a role in enhancing mothers' health knowledge. A study in Turkey (2007) found that maternal education and number of children were two demographic factors that were significantly associated with maternal knowledge of child development. Mothers with higher education and fewer children had more knowledge of child development.[22]

CONCLUSION

This study confirms that maternal education, economic status, and parenting experience are crucial determinants of mothers' knowledge on the care of children with common health problems. Addressing these through specific community-based interventions among these groups of mothers is essential for improving child health outcomes in rural Iraq and similar contexts. Therefore, there is a need for targeted interventions focusing on health education for illiterate or low-educated and low-income mothers, as well as promoting evidence-based management practices for common childhood diseases.

Author's Contribution:

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Original Article

Effect of a Health Belief Model-Based Intervention on Perceived Susceptibility to Osteoporosis among Female Teachers

Zahraa Fadel Niji[1] and Sarab Nasr Fadhil[2]

ABSTRACT

Objective: To evaluate the effectiveness of a Health Belief Model-based educational intervention in enhancing perceived susceptibility to osteoporosis among female secondary school teachers in Nasiriyah, Iraq.

Study Design: Quasi-experimental pretest-post-test control group study

Place and Duration of Study: This study was conducted at the College of Nursing, University of Baghdad, Iraq from 20th December 2024 to 28th February 2025 vide letter No. 71 dated 12th December 2024.

Methods: A total of 144 female teachers aged 45–65 years were recruited from eight public secondary schools. The participants were divided into an intervention group (n=74) and a control group (n=70). The intervention included structured educational sessions based on Health Belief Model components. Data were collected through validated instruments including the Osteoporosis Health Belief Scale and the Osteoporosis Knowledge Assessment Tool.

Results: There was a statistically significant improvement in the mean scores of perceived susceptibilities in the intervention group across the three time points: pre-test (21.33±6.11), post-test I (26.98±3.37), and post-test II (32.69±1.09). In contrast, the control group showed no significant change over time. Mauchly's test confirmed the significance of changes in perceived susceptibility ($p<0.001$).

Conclusion: The Health Belief Model based intervention effectively enhanced perceived susceptibility to osteoporosis among female teachers, suggesting that targeted educational programs can play a pivotal role in promoting early preventive behaviors. Integrating such models into national health education strategies could improve long-term bone health among at-risk populations in Iraq.

Key Words: Osteoporosis, Health Belief Model, Perceived susceptibility, Educational intervention, female teachers

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INTRODUCTION

Osteoporosis is a silent, progressive skeletal disease characterized by low bone mass and micro-architectural deterioration, leading to an increased risk of fractures, particularly in postmenopausal women. Globally, more than one in three women over the age of 50 will experience osteoporotic fractures in their lifetime, posing a significant burden on health systems.[1] Ahmed et al[2] also emphasized the critical role of enhancing health beliefs - especially perceived susceptibility among nursing staff in Iraq through Health Belief Model (HBM) based interventions, which proved effective in promoting osteoporosis preventive behaviors at the level of primary health care. The HBM provides a widely recognized framework for understanding and modifying health behaviors. It emphasizes key cognitive constructions such as perceived susceptibility, severity, benefits, and barriers that influence individuals' decisions to engage in preventive actions.[3] Among these constructs, perceived susceptibility plays a pivotal role in osteoporosis prevention, especially in asymptomatic individuals who may not recognize their vulnerability. Hosking et al[4] demonstrated that interventions guided by the HBM significantly improved perceived susceptibility and calcium intake among middle-aged women in community settings. However, there remains a paucity of research assessing the impact of such interventions in Middle Eastern countries, including Iraq, where osteoporosis prevention is not yet integrated into national health strategies.

In Iraq, recent work by Al-Mousawi and Al-Ameri[6] examined female teachers' awareness and health beliefs related to osteoporosis. Their findings revealed substantial gaps in perceived personal risk, underscoring the need for theory-based educational programs that specifically address psychological readiness for behavior change. The multiple Iraqi

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studies have demonstrated the applicability and effectiveness of the Health Belief Model in various health contexts. Ahmed et al[2] conducted an HBM-based educational intervention for postmenopausal nurses at primary health care centers in Mosul, revealing significant improvements in participants' beliefs regarding osteoporosis prevention. Similarly, Handhal and Mohammed[6] applied the model to AIDS prevention among Iraqi female university students, showing enhanced health beliefs after the intervention despite the different health topic thus reinforcing the model's versatility.

Additionally, Baktash and Naji[7] reported that HBM-based programs successfully promoted exercise behaviors to prevent stroke among elderly residents in Baghdad. These findings collectively support the model's potential in designing effective, theory-based osteoporosis prevention programs tailored to specific Iraqi populations.

METHODS

This quasi-experimental design with a pretest-posttest control group was conducted at College of Nursing, University of Baghdad, Iraq from 20th December 2024 to 28th February 2025 vide letter No. 71 dated 12th December 2024. The study was conducted in public girls' secondary schools affiliated with the DhiQar Education Directorate in Nasiriyah, Iraq. Eight schools (one from each zone) were randomly selected out of 32 schools using simple random sampling. A total of 144 female teachers aged 45–65 years participated in the study 74 in the intervention group and 70 in the control group. Schools were assigned to either group randomly. The sample size was determined using Krejcie & Morgan's formula with a 95% confidence level and a 5% error margin, based on a population of 71,468. All female teachers aged 45–65 working in public secondary schools and willingness to participate (verbal consent) were included. The teachers with physical immobility or diagnosed with osteoporosis, middle schools and involved in pilot study were excluded. Participants were provided with an overview of the study's scientific purpose and methodology, and those who agreed to participate were given anonymous questionnaires to protect their privacy.

The study instrument consisted of four parts. The first part captured socio-demographic data such as age, educational attainment, occupation of the head of household, income level, residence, height, and weight. The second part addressed the participants' medical history, particularly concerning the family history of osteoporosis and personal history of fractures. The third part used the Osteoporosis Knowledge Assessment Tool (OKAT) to evaluate participants' understanding of osteoporosis, while the fourth part employed the Osteoporosis sub scale of Health Belief Scale (OHBS) developed by Kim et al. to assess perceptions related to susceptibility, regarding osteoporosis prevention. The OHBS utilized a 5-point Likert scale ranging from strongly disagree to strongly agree. Data were analyzed using SPSS-27. Inferential statistics included the Spearman rho correlation to identify associations between variables, the Mann-Whitney U test to compare two groups, and the Kruskal-Wallis test to examine differences across more than two groups.

RESULTS

The mean age was 36.08 years, with the largest proportion 37.5% aged between 29-35 years. The control group has a mean age of 38.73 years, with the highest percentage 26.4% also between 29-35 years. Most participants in both groups hold a bachelor's degree, about 84%, followed by smaller numbers holding master's degrees, diplomas, postgraduate diplomas, and doctoral degrees.

Table No. 1: Participants' sociodemographic characteristics

Variable		Study Group (N = 72)		Control Group (N = 72)	
		No.	%	No.	%
Age (Years)	22-28	14	19.5	10	13.9
	29-35	27	37.5	19	26.4
	36-42	15	20.8	17	23.6
	43-49	8	11.1	16	22.2
	50-57	8	11.1	10	13.9
Level of education	Diploma	3	4.2	4	5.6
	Bachelor's degree	61	84.7	60	83.3
	Postgraduate diploma	2	2.8	3	4.2
	Master's degree	5	6.9	4	5.6
	Doctoral degree	1	1.4	1	1.4
Family's monthly income (Iraqi dinar)	< 300.000	1	1.4	2	2.8
	300.000-600.000	24	33.3	23	31.9
	601.000-900.000	19	26.4	22	30.6
	901.000-1.200.000	10	13.9	7	9.7
	1.201.000-1.500.000	13	18.1	14	19.4

	≥ 1.501.000	5	6.9	4	5.6
Household occupation	Unemployed	6	8.3	11	15.3
	Unskilled worker	4	5.6	3	4.2
	Semi-skilled worker	5	6.9	8	11.1
	Skilled worker	6	8.3	4	5.6
	Clerical, Shop owner, farmer	9	12.5	6	8.3
	Semi-Professional	13	18.1	22	30.6
	Professional	29	40.3	18	25.0

Table No. 2: Descriptive statistics of perceived susceptibility of developing osteoporosis over time

Perceived Susceptibility		**Mean**	**Std. Deviation**	**Number**
Study	Pretest	21.33	6.11	72
	Posttest I	26.98	3.37	72
	Posttest II	32.69	1.09	72
Control	Pretest	20.73	6.61	72
	Posttest I	20.34	6.41	72
	Posttest II	19.23	5.8/0	72

Table No.3: Mauchly's test of Sphericity for perceived Susceptibility of developing osteoporosis

Within Subjects Effect	**Mauchly's W**	**Approx. Chi-square**	**Df**	**Sig.**	**Epsilon**		
					Greenhouse-Geisser	**Huynh-Feldt**	**Lower-bound**
Susceptibility	.344	74.717	2	.000	.604	.609	.500

Table No. 4: Multivariate tests of the perceived susceptibility of developing osteoporosis

Susceptibility		**Value**	**F**	**Hypothesis df**	**Error df**	**Sig.**	**Partial Eta Squared**
Study	Pillai's Trace	.814	153.629	2.000	70.000	.000	.814
	Wilks' Lambda	.186	153.629	2.000	70.000	.000	.814
	Hotelling's Trace	4.389	153.629	2.000	70.000	.000	.814
	Roy's Largest Root	4.389	153.629	2.000	70.000	.000	.814
Control	Pillai's Trace	.186	8.004	2.000	70.000	.001	.186
	Wilks' Lambda	.814	8.00	2.000	70.000	.001	.186
	Hotelling's Trace	.229	8.004	2.000	70.000	.001	.186
	Roy's Largest Root	.229	8.004	2.000	70.000	.001	.186

Table No. 5: Tests of within-subjects effects for perceived susceptibility of developing osteoporosis

Susceptibility		**Type III sum of square**	**Df**	**Mean square**	**F**	**Sig.**	**Partial Eta Squared**
Study	Sphericity Assumed	4646.731	2	2323.366	254.056	.000	.782
	Greenhouse Geisser	4646.731	1.208	3847.711	254.056	.000	.782
	Huynh-Feldt	4646.731	1.217	3817.541	254.056	.000	.782
	Lower-bound	4646.731	1.000	4646.731	254.056	.000	.782
Error	Sphericity Assumed	1298.602	142	9.145			
	Greenhouse-Geisser	1298.602	85.744	15.145			
	Huynh-Feldt	1298.602	86.422	15.026			
	Lower-bound	1298.602	71.000	18.290			
Control	Sphericity Assumed	87.259	2	43.630	1.911	.152	.026
	Greenhouse-Geisser	87.259	1.144	76.276	1.911	.170	.026
	Huynh-Feldt	87.259	1.150	75.846	1.911	.169	.026
	Lower-bound	87.259	1.000	87.259	1.911	.171	.026
Error	Sphericity Assumed	3242.741	142	22.836			
	Greenhouse-Geisser	3242.741	81.224	39.923			
	Huynh-Feldt	3242.741	81.684	39.699			
	Lower-bound	3242.741	71.000	45.672			

Table No. 6: Pairwise comparison of the perceived susceptibility of developing osteoporosis values between study and control groups

Susceptibility	(I)	(J)	Mean difference (I-J)	Std. Error	Sig.	95% Confidence interval for difference	
						Lower Bound	Upper Bound
Study	1	2	-5.653	.439	.000	-6.730	-4.576
		3	-11.361	.674	.000	-13.015	-9.708
	2	1	5.653	.439	.000	4.576	6.730
		3	-5.708	.338	.000	-6.538	-4.879
	3	1	11.361	.674	.000	9.708	13.015
		2	5.708	.338	.000	4.879	6.538
Control	1	2	.389	.968	1.000	-1.985	2.763
		3	1.500	.937	.342	-.799	3.799
	2	1	-.389	.968	1.000	-2.763	1.985
		3	1.111	.294	.001	.389	1.833
	3	1	-1.500	.937	.342	-3.799	.799
		2	-1.111	.294	.001	-1.833	-.389

Around 40% of the study group are professionals, while in the control group approximately 31% are semi-professionals. The rest include skilled workers, semi-skilled workers, clerical workers, shop owners, farmers, unemployed, and unskilled workers. One-third of the study group earn between 300,000 and 600,000 IQD, followed by those earning between 601,000 and 900,000 IQD. The income distribution in the control group is similar, with close proportions in the same income ranges (Table 1).

The findings show a significant and consistent increase in the perceived susceptibility to developing osteoporosis among participants in the study group across the three measurement points (pretest, posttest I, and posttest II). The mean score increased from 21.33±6.11 at pretest to 26.98±3.37 at posttest I and 32.69±1.09 at posttest II (Table 2).

Mauchly's test of Sphericity was significant ($p<0.05$), indicating that the assumption of Sphericity was not violated (Table 3). Repeated multivariate measures revealed a statistically significant effect of the intervention over time (Wilks' Lambda = .186, $F(2, 70) = 153.629$, $p<0.001$, $\eta^2 = .814$), indicating that approximately 81% of the variance in perceived susceptibility was due to the intervention (Table 4). Within-subjects effects were also significant ($F = 254.056$, $p<.001$, $\eta^2 = .782$), indicating strong intervention effects across time (Table 5)

Pairwise comparisons demonstrated that all time points differed significantly from each other ($p<.001$), confirming a progressive improvement in perceived susceptibility after the intervention (Table 6).

DISCUSSION

The demographic characteristics of the study and control groups reveal important patterns that may influence health behaviors and outcomes. The mean age for participants in both groups falls within the range of adulthood where health awareness tends to increase due to personal and family responsibilities. Specifically, the age group 29-35 years was the most represented in both groups. This aligns with global findings indicating that individuals in this age group often demonstrate greater engagement in preventive health behaviors and healthcare utilization,[8]

In addition, the high proportion of participants with bachelor's degrees in both groups (over 83%) indicates a relatively educated population. Research consistently shows that higher educational attainment correlates with better health literacy, improved health outcomes, and increased use of health services.[9] This is particularly relevant in nursing and maternal health contexts, where informed decision-making can significantly impact health practices and care-seeking behavior. Al-Fayyadh et al[10] also reported that majority of nurses demonstrated low knowledge regarding health literacy, more than half had acceptable levels of experience. Similarly, Al-Ashour and Al-Sader[11] identified a statistically significant relationship between health literacy and educational level among patients undergoing hemodialysis, reinforcing the role of higher education in promoting better health literacy.

Regarding occupation, most participants were professionals or semi-professionals. Employment status has been closely linked to socioeconomic stability and mental well-being. Studies suggest that professional employment often provides access to health insurance and resources that promote better health outcomes. Conversely, lower occupational status or unemployment, as seen in some participants, is associated with increased health risks and reduced access to care.[12,14] This factor is further compounded by income levels, with most participants earning between 300,000 and 900,000 IQD monthly, placing them in the lower to middle-income brackets. Income remains a crucial determinant of health, influencing various aspects such as nutrition, living conditions, and access

to quality healthcare. Hassan and Alwan[14] demonstrated that socioeconomic status significantly influenced psychological hardiness and coping mechanisms among nurses. These studies emphasize the role of financial stability in supporting positive health outcomes and the need for targeted interventions to assist low-income groups in accessing essential healthcare services.

Regarding osteoporosis perceptions, the results of Mauchly's test of Sphericity for perceived susceptibility were statistically significant ($W = 0.344$, $\chi^2(2) = 74.717$, $p < .001$), indicating a violation of the sphericity assumption. This implies inconsistency in participants' responses concerning their susceptibility to osteoporosis, potentially due to differing levels of awareness or beliefs about risk. This finding corresponds with Al-Khafaji and Mahmood[15] found low levels of perceived susceptibility among female university students in Baghdad, attributing this to insufficient health education and limited access to screening services. These results underscore the critical need for awareness campaigns targeting at-risk populations, particularly young women, to correct misconceptions and promote proactive health behaviors.

The multivariate analysis showed a significant intervention effect over time on perceived susceptibility (Wilks' Lambda = 0.186, $F(2, 70) = 153.629$, $p < 0.001$, $\eta^2 = 0.814$), indicating that approximately 81.4% of the variance in perceived susceptibility was attributable to the intervention (Table 4). This robust effect validates the efficacy of educational or behavioral programs in enhancing risk perception. These findings echo those of Zhu et al[16], who reported similar outcomes in China, where Health Belief Model-based interventions significantly improved perceived susceptibility to osteoporosis.

In the present study, a significant within-subjects effect in the intervention group ($F(2, 142) = 254.056$, $p<.001$, $\eta^2 = .782$), reflecting a substantial improvement in participants' perception of susceptibility over time (Table 5). No significant effect was detected in the control group ($p=.152$), reinforcing the notion that changes in perception were driven by the educational content. These results parallel findings by Tussing and Chapman-Novakofski[17], who found that theory-based osteoporosis education significantly improved perceived susceptibility and related beliefs in young adults.

This study showed that significant differences across all time points in the intervention group ($p<.001$), indicating progressive and sustained improvement in perceived susceptibility (Table 6). The mean difference from baseline to immediate post-test was −5.653, and from baseline to follow-up was −11.361, suggesting a cumulative intervention effect. Conversely, the control group showed no significant differences except between the second and third time points ($p = .001$), likely due to random variation rather than an intervention effect. These findings are in strong agreement with Abdul-Hameed and Mohammed[18], who reported notable improvements in students' knowledge and osteoporosis awareness following an instructional program. The gradual improvement observed here mirrors the cognitive shifts documented in their study and reinforces the utility of structured educational efforts grounded in theoretical models like the Health Belief Model. Finally, these findings align with Sedlak et al[19], who demonstrated that structured osteoporosis education significantly enhanced perceived susceptibility among college-aged women, with sustained effects during follow-up. The present study thus confirms the long-term value of model-based educational programs in reshaping health beliefs and fostering preventive behaviors related to osteoporosis.

Recommendations : Considering the study findings, it is recommended to integrate HBM-based educational interventions into national health promotion programs targeting middle-aged women, particularly schoolteachers, to improve their awareness and adoption of osteoporosis preventive behaviors. Continuous training workshops should be developed for healthcare professionals and educators to effectively implement behavioral change models in community settings.

CONCLUSION

The HBM-based intervention effectively enhanced perceived susceptibility to osteoporosis among female teachers, suggesting that targeted educational programs can play a pivotal role in promoting early preventive behaviours.

Author's Contribution:

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Drafting or Revising Critically:	Zahraa Fadel Niji, Sarab Nasr Fadhil
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Original Article

Evaluation of Clonality in Patients with B-cell Lymphoid Malignancies by Immunohistochemistry Panel and Flow Cytometry Analysis

Clonality Detection with B-cell Lymphoblastic Leukemia

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: Descriptive 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 October 2023 to June 2024.
Methods: This descriptive diagnostic study was carried out with cases (67 patients) sourced from the Hematology Department of Baghdad Medical City/Educational Lab. Diagnoses were based on the gold-standard flow cytometry test for B-cell acute lymphoblastic leukemia. Age, gender, clinical features, complete blood count, blood smear, and bone marrow morphology reports were collected. Cytochemical tests (Periodic acid-Schiff & Sudan Black B) were performed on fresh bone marrow aspirates.
Results: The mean patient age was 30.74 years, with a male-to-female ratio of 1:2.04. Cytochemical tests, Sudan Black B exhibited high specificity (100%), while periodic acid-Schiff had high sensitivity (65.67%).
Conclusion: The Periodic acid-Schiff cytochemical test, with its high sensitivity, offers valuable diagnostic utility in low-resource laboratories lacking access to immunohistochemistry and flow cytometry.
Key Words: Clonality detection, B-cell lymphoblastic leukemia, Flow cytometry, Immunohistochemistry, Cytochemical stain

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INTRODUCTION

Hematologic cancer, such as acute lymphoblastic leukemia (ALL), is on the rise in healthcare systems as global populations age.[1] This is a fast-growing, aggressive cancer characterized by the proliferation of immature lymphoid cells that infiltrate the blood, bone marrow, and other body tissues. Immunophenotypic profiles can be used to classify ALL into two types: B-cell and T-cell. B-cell ALL (B-ALL) has Early Pre-B ALL (10%), Common ALL (50%), and Mature B-cell ALL (4%), but T-cell ALL subtypes have Pre-T ALL (5-10%), and Mature T-cell ALL (15-20%).[2]
The French-American-British (FAB) system is a classification that all cells are classified according to their morphology, where the L1 cells are small, L2 cells are larger with irregular nuclei, and L3 cells are similar to the Burkitt leukemia. Leukemia refers to the cancer of blood and bone marrow, and it is described as the uncontrolled growth of the abnormal white blood cells (leukemic blasts). These immature cells proliferate and surround the normal cells, causing bone marrow failure and possibly spreading of the disease to other organs like the lymphocytes, liver, and spleen, among others. Leukemia is classified into four major groups which depend on the rate of progression (acute and chronic) and the lineage of the affected blood cell (lymphocytes, lymphocytes): acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myeloid leukem There are two major types of the disease, namely B-cell ALL (85 per cent), and T-cell ALL (15 per cent).[3] French-American-British (FAB) and WHO Classification: ALL may be classified according to cell morphology, with three types: L1 (small lymphoblasts), L2 (larger cells), and L3 (Burkitt leukemia). Nevertheless, currently, immunophenotyping is used by the WHO classification to categorize ALL according to the markers expressed on the leukemia cells. It has resulted in a better understanding and categorization, such as B-cell precursor ALL, T-cell ALL, and Burkitt leukemia.[4,5]

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The most important Diagnostic Methods: The diagnosis of B-ALL is made correctly with the combination of different laboratory tests as flow cytometry (FCM). This test determines the presence of particular B-cell markers, including CD19, CD10, and CD34, to validate the diagnosis. Immunohistochemistry (IHC): This is used to identify the cell lineage by detecting markers, such as CD20, PAX5, and TdT. Cytochemical Stains: Sudan Black B (SBB) and Periodic Acid-Schiff (PAS) Stains could be used to distinguish B-ALL and other forms of leukemia since they are able to identify cytoplasmic lipids and glycogen.[6-8]

Genetic Deficiencies in B-ALL: B-ALL usually has genetic changes, which affect the prognosis. The Philadelphia chromosome (t(9;22)) leading to the formation of the BCR-ABL fusion gene is one of the major genetic abnormalities. This translocation is seen in approximately twenty-five percent of the adult B-ALL cases and has been linked to unfavourable outcomes. Hyperdiploidy, associated with a good prognosis, and hypodiploidy, correlated with poor prognosis, are other important genetic characteristics.[8,9]

Clinical Features and Pathogenesis: The symptoms of B-ALL include bone marrow failure, including anemia (fatigue and pallor), thrombocytopenia (easy bruising, bleeding), and neutropenia (increased risk of infections).[10]

Patients can also show lymphadenopathy, splenomegaly, and hepatomegaly besides bone marrow failure. In a large proportion of cases, CNS involvement with resultant headaches, vomiting, and seizure occurs due to chromosomal translocation, including BCR-ABL, that results in abnormal gene expression and leukemogenesis. B-ALL has a greater susceptibility to genetic syndromes, including Down syndrome, which stimulates Epigenetic factors, including DNA methylation and histone modification, that enhance the survival of leukemic cells.[11]

The primary methods used in the diagnosis of B-ALL are bone Marrow Biopsy: A gold standard, which shows more than 20% lymphoblasts. Flow Cytometry: Is the most accurate immunophenotypic characterization, which is essential in the verification of B-cell lineage and the surveillance of minimal residual disease (MRD). Cytogenetic Analysis: This identifies prominent chromosomal abnormalities, including the Philadelphia chromosome. Molecular Testing: PCR and NGS can detect gene rearrangements, which would help in prognosis and treatment choices.[12]

B-ALL can be treated with chemotherapy (e.g., vincristine, prednisone), targeted therapy (e.g., Philadelphia chromosome-positive cases using tyrosine kinase inhibitors), and immunotherapy such as CAR T-cell therapy. The problems are a lack of effectiveness in treatment, side effects, and the necessity of individual strategies. The prevention of relapse is the monitoring of minimal residual disease (MRD). The continuous study is focused on streamlining interventions and enhancing patient results.[13]

The prognosis of B-ALL is mostly good, particularly in children, with a remission rate of more than 80. The factors that may contribute to prognostics are age, sex, genetic defects (e.g., Philadelphia chromosome), and MRD. Children in the age range of 1 to 9 have the most favorable results, and adults exhibit a more difficult prognosis, necessitating further interventions such as intrathecal chemotherapy.CNS involvement at diagnosis negatively affects the prognosis, and further therapy is necessary in the case of adults.[14]

METHODS

This study was conducted in the Department of Pathology and Forensic Medicine at the Faculty of Medicine, University of Kufa from October 2023 to June 2024 vide letter No. 3234/QM/Approval/JKEIRU dated September 2, 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 (CBC), 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.

Diagnostic Tests and Procedures: Blood samples and bone marrow aspirates were collected for testing. The following diagnostic methods were used. Complete Blood Count (CBC) – for evaluating general blood parameters. Bone Marrow Aspiration (BMA) – for FCM analysis. Bone Marrow Biopsy (BMB) – to understand the cellular makeup of the bone marrow. Immunohistochemistry (IHC) – 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. Additionally, Periodic Acid-Schiff (PAS) and Sudan Black B (SBB) staining were performed for cytochemical analysis.

Patient data, 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.

Cytochemical Staining: Periodic Acid-Schiff (PAS) Staining and Sudan Black B (SBB) Staining were performed to detect specific biochemical components in bone marrow cells: PAS Staining: Detects glycogen, mucopolysaccharides, and glycoproteins. SBB Staining: Identifies lipids, including neutral fats and lipoproteins.

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 immunoexpression, and scores between 9-12 indicate strong immunoexpression. Statistical analysis was done using SPSS software to examine relationships between variables. 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. A significance level of $p<0.05$ was set, and adjustments were made for multiple comparisons to control the error rate.

RESULTS

The average (mean) age of the patients is 30.74 years, and the standard deviation is 15.79 years, showing that the patients have a large age range. The minimum age of the patient is 13 years, and the maximum age is 75 years. The study discovered that they are 67.16 percent female (45 patients) and 32.83 percent male (22 patients), which means that females are overrepresented in this group of patients with the ratio (1:2) [Table 1].

Table 2 presents the hematological characteristics of the patients: the hemoglobin (HB) level, platelet count, total white blood cell (WBC) count, absolute neutrophil (NE), absolute lymphocyte (LY), and the percentage of blast cells.

A very low positive rate of 5.97% was obtained in Table 3, and this means that SBB positivity is very unlikely in the samples tested. PASCYto has an average positive frequency of 65.67% with a positive rate.

Two cytological tests: SBB CYTO and PAS CYTO: Table 4 performance. In SBB CYTO, the positive results were 4, and this represents 5.97 percent of the total; the negative results were 63, and this represents 94.03 percent of the total. This test has a sensitivity of 6.35 percent, which means that it recognizes 6.35 percent of the true positive cases and a specificity of 100 percent, i.e., it recognizes all true negatives. There is also a positive predictive value (PPV) of 100, which indicates that every positive outcome is a true positive result, but this should be further verified. The negative predictive value (NPV) stands at 51.64 per cent, indicating that the cases of negative outcomes are true negatives 51.64 per cent.

Table No. 1: General features of the patients

Parameter	No.	%
Gender		
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
HB	8.16±1.32
Platelets x 10^9 /L	40.74±21.32
WBC x 10^9 /L	12.74±10.37
NE %	12.50±6.43
LY %	41.79±17.47
Blast cell %	31.65±10.55

Table No. 3: Number of positives and negatives of PAS and SBB

Variable	Positive		Negative	
	No.	%	No.	%
SBB CYTO	4	5.97	63	94.03
PAS CYTO	44	65.67	23	34.33

Table No.4: panel test of PAS and SBB cytochemical stain

	+ve	%	-ve	%	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SBB CYTO	4	5.97	63	94.03	6.35	100	100	51.64
PAS CYTO	44	65.67	23	34.33	65.67	34.33	65.67	34.33

Although PAS CYTO had 44 positive results, which comprise 65.67% of the total, and 23 negative results, which comprise 34.33% of the total. The sensitivity of this test is 65.67, such that it is correct in the identification of 65.67 percent of true positive cases. Its specificity is 34.33, implying that it correctly identifies 34.33 percent of true negatives. The PPV of PAS CYTO equals 65.67, which means that 65.67 of the positive results are true positives, and the NPV is 34.33, which means that negative results are true negatives 34.33 of % time.

DISCUSSION

This study explored the efficacy of various diagnostic methods for clonality detection in B-cell lymphoid

malignancies. We specifically compared Flow Cytometry (FCM), two cytochemical stains, Sudan Black B (SBB), and Periodic Acid-Schiff (PAS) to assess their diagnostic reliability. While FCM was confirmed as the gold standard, the integration of SBB and PAS helped further refine diagnosis, particularly in ambiguous cases. These findings highlight the advantage of employing multiple diagnostic tools in combination, rather than relying on a single method.[15]

In the present study, the mean age was 30.74±15.79 years, with ages ranging from 13 to 75. Among these, 45 were female (67.16%) and 22 were male (32.83%). 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.· 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, IHC, or cytochemical stains for confirmation.

The use of cytochemical stains, SBB, and PAS, in diagnosing B-ALL revealed different strengths. The SBB stain had a sensitivity of 6.35%, meaning it only detected a small proportion of true positives, but it demonstrated excellent specificity (100%), ensuring that all identified negative cases were true negatives. In contrast, PAS had higher sensitivity (65.67%) but lower specificity (34.33%), indicating that it was more effective at identifying true positives but also generated more false positives. Previous study supports the role of PAS in identifying B-ALL, with studies reporting its positive staining in the vast majority of B-ALL cases. A study conducted in India found PAS to be positive in 96% of B-ALL cases, highlighting its high sensitivity and diagnostic utility.[16] Similar findings have been reported in studies from the USA and the UK, where PAS has been shown to effectively distinguish between B-ALL and other forms of leukemia, including myeloid leukemia, underscoring its diagnostic relevance.[17]

CONCLUSION

The value of combining Flow Cytometry (FCM), cytochemical stains (SBB and PAS) for diagnosing B-cell Acute Lymphoblastic Leukemia (B-ALL). While FCM remains the gold standard, the addition of cytochemical stains contributes valuable diagnostic information, particularly when resources are limited. PAS offers good sensitivity, while SBB provides high specificity, further enriching the diagnostic process.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Bahaulddin Hassan Abbood, Rahem Mahdy Rahem
Drafting or Revising Critically:	Bahaulddin Hassan Abbood, Kaswr Musa Jaafar Al Tariahi
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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Original Article

Effectiveness of an Integrated Ethical and Therapeutical Communication Program on Critical Care Unit Nurses' Practices

Ethical and Therapeutical Program on CCU Nurses' Practices

Hasanain Yhiya Shimran and Sahar Adham Ali

ABSTRACT

Objective: (1) To assess critical care unit nurses' practices related to ethical and therapeutic communication. (2) To evaluate the effectiveness of an integrated educational program on improving nurses' knowledge and practices in critical care units.

Study Design: A quasi-experimental study

Place and Duration of Study: This study was conducted at the Hilla Teaching Hospitals, Babylon, Iraq, from 20th March to 10th July 2025.

Methods: One hundred and ten nurses were randomly allocated to experimental (n=55) and control (n=55) groups. The experimental group received an integrated ethics and communication training program, while the control group did not. Data were collected using validated tools: a 72-item knowledge questionnaire (r=0.84) and a 34-itxem practice checklist (r=0.79). Assessments were done before, immediately after, and one month post-intervention.

Results: The experimental group showed significant improvements ($p<0.05$) in knowledge and practices compared with the control group. Posttest results revealed a shift from poor/fair to good levels in ethical decision-making, informed consent, patient autonomy, communication skills, and patient safety. Improvements were retained at one-month follow-up. Age and educational level predicted gains, while sex and experience had no significant effect.

Conclusion: The integrated ethical and therapeutic communication program effectively enhanced critical care nurses' knowledge, practices, and ethical awareness, promoting safer and more compassionate care.

Key Words: Ethical principles, Therapeutic communication, Critical care nursing, Educational program, Nurse practices

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INTRODUCTION

Critical care nursing is a highly specialized field requiring the provision of care to patients with life-threatening conditions that demand immediate, complex medical interventions. These patients often face severe and multifaceted health challenges, necessitating advanced technologies, close monitoring, and continuous support. Critical care units (CCUs) are equipped with sophisticated medical devices and staffed by highly trained professionals capable of managing high-stakes situations where time is critical. Nurses in these units play a pivotal role, coordinating care, ensuring patient safety, and addressing not only physical but also emotional and ethical challenges.[1]

The effectiveness of an integrated ethical and therapeutic communication program for critical care unit (CCU) nurses is crucial for improving both the quality of patient care and the well-being of patients and families. Critical care nurses work in high-pressure environments where life-threatening conditions are common, requiring immediate, complex decisions. Nurses who are well-trained in therapeutic communication and ethical decision-making are better equipped to manage difficult situations, navigate family dynamics, and provide compassionate care that aligns with the patient's needs, preferences, and values.[2]

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METHODS

A quantitative, quasi-experimental pre-post design was conducted to evaluate the effectiveness of an integrated ethical and therapeutic communication program on critical care unit nurses' practices. The study took place at Hilla Teaching Hospitals from 20th March to 10th July

2025 vide letter No. 73 dated 10-3-2025. A purposive non-probability sample of 110 nurses from CCUs was selected and randomly allocated to: Experimental group: 55 nurses and Control group: 55 nurses. Random allocation was applied to reduce selection bias and control confounding variables. A 34-item checklist was developed and validated based on literature review, covering:

1. Demographic data: age, gender, educational level, marital status, years of experience
2. Employment data: total nursing experience, ICU experience, special training
3. Nurses' practices in ethical and therapeutic communication

Validity and Reliability

- **KMO Measure:** 0.815 (adequate for factor analysis)
- **Bartlett's Test:** $\chi^2 = 7.022$, df = 6, p = 0.09
- **Reliability:** r = 0.79 (inter-rater reliability, $p \leq 0.05$)

Participants provided informed consent and could withdraw at any time. Pretest: assessed baseline practices in both groups. Intervention: experimental group attended the educational program

Posttests:

Posttest I: immediately after intervention to assess improvement

Posttest II: one month later to assess practice stability

RESULTS

The trial group demonstrated a clear improvement from pre-test to post-test, with mean scores increasing from a poor to a good level in most items. For example, understanding of ethical principles improved from 1.58±0.534 at pre-test to 2.42±0.720 at post-test, and recognizing ethical dilemmas rose from 1.95±0.524 to 2.52±0.555, both indicating significant progress ($p < 0.05$). The control group, however, showed minimal changes, remaining mostly within the poor to fair range, with mean values such as 1.47±0.539 at pre-test and 1.57±0.550 at post-test for the first item. Overall, the results indicate that the educational or training intervention applied to the trial group was effective in enhancing nurses' knowledge and application of ethical decision-making principles particularly in understanding autonomy, beneficence, non-malfeasance, and justice whereas the control group exhibited no meaningful improvement (Table 1).

The marked improvement in the trial group's performance, with mean scores rising from the poor or fair level in the pre-test to the good level in the post-test for all items. For instance, identifying common ethical dilemmas improved significantly from 1.49±0.690 to 2.70±0.610 (p = 0.012), and applying ethical reasoning in real-time situations increased from 2.15±0.524 to 2.60±0.560, both reaching the good category. Similarly, consulting ethical committees and communicating ethical concerns also showed notable progress, moving from poor to good levels after training. In contrast, the control group displayed minimal change across all items, with mean scores remaining in the poor range (e.g , 1.40±0.683 to 1.50±0.680, p = 0.020). Overall, the findings indicate that the educational intervention was effective in strengthening the trial group's ethical practices in critical care, enhancing their ability to identify, reason, consult, and communicate effectively when facing ethical dilemmas (Table 2).

The experimental (trial) group showed significant improvement in their practices related to patient and family involvement in ethical decision-making after the educational intervention, while the control group showed only minimal change. The trial group's mean scores increased from a poor level in the pre-test (around 1.56–1.65) to a good level in the post-tests (ranging between 2.51–2.70), with statistically significant differences ($p < 0.05$). This improvement indicates that participants became more capable of engaging patients and families in treatment discussions, respecting cultural and religious values, and facilitating conversations about end-of-life care.

Table No. 1: Comparison of experimental and control group responses regarding to ethical decision-making principles (pre and post test)

Item	Control group			P value	Trial Group			P value
	Pre-test	Post-test 1	Post-test 2		Pre-test	Post-test 1	Post-test 2	
Demonstrates understanding of key ethical principles (autonomy, beneficence, non-maleficence, justice) in patient care.	1.47±.539	1.53±.539	1.57±0.550	0.026	1.58±.534	2.35±.700	2.42±0.720	0.006
Obtains informed consent using clear, simple language and ensures patient comprehension	1.55±.603	1.62±.652	1.67±0.670		1.58±.629	2.35±.751	2.42±0.765	
Identifies and respects patient autonomy in decision-making processes.	1.95±.891	1.87±.924	1.92±0.935		2.35±.799	2.73±.560	2.80±0.575	
Recognizes and appropriately addresses ethical dilemmas in nursing practice.	1.62±.593	1.60±.655	1.65±0.665		1.95±.524	2.47±.539	2.52±0.555	
Follows institutional protocols for ethical decision-making and documentation	1.84±.601	1.45±.633	1.50±0.650		1.84±.601	2.55±.603	2.60±0.615	

Table 2: Comparison of experimental and control group responses regarding practices for handling ethical dilemmas in critical care (pre and posttest)

Item	Control group			P value	Trial Group			P value
	Pre-test	Post-test 1	Post-test 2		Pre-test	Post-test 1	Post-test 2	
Identifies common ethical dilemmas in critical care settings (end-of-life decisions, resource allocation, patient confidentiality, etc.)	1.40± .683	1.45± .689	1.50± 0.680	0.020	1.49± .690	2.64± .620	2.70± 0.610	0.012
Applies ethical reasoning and decision-making techniques in real-time situations	1.47± .573	1.47± .634	1.52± 0.630		2.15± .524	2.56± .570	2.60± 0.560	
Consults appropriate ethical committees or senior staff when faced with complex ethical decisions	1.49± .505	1.40± .494	1.45± 0.500		1.55± .603	2.45± .789	2.50± 0.770	
Effectively communicates ethical concerns to the healthcare team, patient, and family	1.82± .611	1.76± .637	1.80± 0.630		1.65± .584	2.44± .714	2.48± 0.700	

Table No. 3: Comparison of experimental and control group responses regarding practices for patient and family involvement in ethical decisions (pre and post test)

Item	Control group			P value	Trial Group			P value
	Pre-test	Post-test 1	Post-test 2		Pre-test	Post-test 1	Post-test 2	
Engages patients and families in discussions about treatment goals and ethical considerations.	1.45± .789	1.53± .790	1.58 ± .800	0.008	1.56± .788	2.51± .814	2.58 ± .824	0.001
Respects cultural, religious, and personal values in ethical decision-making.	1.38± .561	1.58± .658	1.62 ± .668		2.15± .448	2.60± .564	2.64 ± .574	
Facilitates discussions about advance directives, code status, and end-of-life care.	1.55± .503	1.47± .504	1.52 ± .514		1.65± .480	2.64± .589	2.70 ± .599	
Encourages patient and family participation while maintaining professional boundaries.	1.45± .689	1.51± .690	1.56 ± .700		1.56± .688	2.51± .717	2.60± .564	

Table No. 4: Comparison of experimental and control group responses regarding practices for professional integrity and ethical conduct (pre and post test)

Item	Control group			P value	Trial Group			P value
	Pre-test	Post-test 1	Post-test 2		Pre-test	Post-test 1	Post-test 2	
Maintains patient confidentiality and privacy in during interactions.	1.56± .501	1.49± .505	1.55± 0.520	0.002	1.67± .474	2.44± .601	2.50± 0.620	0.008
Reports ethical concerns, conflicts of interest, or breaches in ethical conduct.	1.44± .631	1.56± .714	1.60± 0.730		2.18± .611	2.62± .680	2.68± 0.695	
Demonstrates impartiality, fairness, and non-discriminatory behavior in patient care.	1.27± .651	1.38± .680	1.45± 0.690		1.35± .673	2.64± .649	2.70± 0.660	
Engages in continuous learning and ethical discussions with colleagues.	1.29± .658	1.40± .683	1.48± 0.700		1.38± .680	2.62± .680	2.68± 0.695	

Table No. 5: Comparison of experimental and control group responses regarding therapeutic communications practices through pre test and post test

Item	Control group			P value	Trial Group			P value
	Pre-test	Post-test 1	Post-test 2		Pre-test	Post-test 1	Post-test 2	
Greeting the patient	1.36± .485	1.49± .505	1.59 ±0.555	0.244	1.25± .440	2.71± .685	2.81 ±0.735	0.248
Nurse treats the patient with respect	1.49± .767	1.89± .875	1.99 ±0.915		1.76± .816	2.65± .726	2.75 ±0.766	
Show interest in the patient's thoughts about his/her health status	1.71± .458	1.60± .494	1.69± .635		1.47± .504	2.47± .813	2.57 ±0.863	

Understand patient's concern about their health	1.42± .629	1.56± .631	1.66 ±0.681		1.31± .605	2.45± .878	2.55 ±0.928
Pay attention to patient	1.67± .721	1.76± .693	1.60± .494		1.49± .690	2.38± .913	2.48 ±0.963
Allow the patient to speak without interruption	1.53± .604	1.62± .593	1.69± .635		1.38± .593	2.42± .896	2.52 ±0.946
Provide the patient with the necessary information based on their request	1.69± .960	1.78± .937	1.69 ±.635		1.47± .858	2.45± .899	2.55 ±0.949
Use terms and vocabulary that the patient can Understand	1.55± .789	1.93± .790	2.03 ±0.840		1.60± .807	2.45± .899	2.55 ±0.949
Make sure that the patient is fully understand the nurse during the meeting	1.47± .604	1.64± .677	1.74 ±0.654		1.42± .599	2.60± .564	2.70 ±0.614
Encourage patient to ask question about their health	1.44± .570	1.69± .635	1.64 ±.677		1.51± .605	2.47± .634	2.57 ±0.684
Engage patient to be a part of their treatment plan	1.27± .592	1.38± .623	1.48 ±0.673		1.22± .534	2.55± .633	2.65 ±0.683
Discuss with the patient the next steps in their health follow-up	1.49± .742	1.6± 2.733	1.70 ±0.783		1.42± .712	2.49± .858	2.59 ±0.908
Demonstrate caring and interest for the patient	1.55± .633	1.64±. 620	1.69 ±.635		1.49±. 605	2.45± .812	2.55 ±0.862
Spend enough time with patient	1.47± .663	1.51± .635	1.61 ±0.713		1.55± .689	2.35± .907	2.45 ±0.957
Nurses staff treat patient with respect	1.62± .733	1.53± .766	1.63 ±0.783		1.53± .742	2.49± .879	2.59 ±0.929
The nurse use body language when communicating with patients	1.45± .689	1.55± .715	1.65 ±0.739		1.58±. 712	2.55± .835	2.65 ±0.885
The nurse use facial expression when communicating with patients in CCU	1.49± .742	1.42± .738	1.52 ±0.788		1.44± .714	2.49± .858	2.59 ±0.908

In contrast, the control group's mean scores remained mostly at the poor to fair levels, showing no meaningful progress. Overall, these results confirm that the training program effectively enhanced nurses' ethical practice skills, promoting patient-centered and culturally sensitive involvement in ethical decisions (Table 3).

The experimental (trial) group exhibited a clear and statistically significant improvement in their practices related to professional integrity and ethical conduct after the intervention, while the control group displayed only slight or negligible changes. In the trial group, mean scores increased from poor or fair levels at pre-test (1.67±0.474) to good levels at post-test (2.50±0.620), indicating enhanced awareness and practice of ethical standards.

The highest improvements were seen in maintaining confidentiality (2.50±0.620) and demonstrating fairness and non-discrimination (2.70±0.660), suggesting that participants developed stronger professional ethics and accountability. Conversely, the control group's mean scores remained largely within the poor range (around 1.45–1.60) across all items, showing no meaningful progress (Table 4).

Table 5 indicate that the experimental (trial) group demonstrated notable improvement in their therapeutic communication practices from pre-test to post-test, whereas the control group showed minimal or inconsistent progress. The trial group's mean scores increased across all items from poor levels at pre-test (around 1.25–1.60) to good levels at post-test (ranging from 2.45–2.81), reflecting significant enhancement in communication skills such as greeting patients, showing respect, understanding concerns, encouraging participation, and providing clear information. This improvement suggests that the intervention effectively strengthened nurses' ability to build rapport, express empathy, and communicate clearly with patients. In contrast, the control group's scores remained within the poor to fair range (approximately 1.45–1.99), indicating limited change without the intervention. Overall, the results confirm that the educational program had a positive impact on improving nurses' therapeutic communication, promoting better interaction, understanding, and patient-centered engagement in care.

DISCUSSION

This study showed that a significant improvement in the experimental group's ethical practices after implementation of the integrated ethical and therapeutic communication program. All five items showed statistically significant post-test increases ($p<0.05$). For instance, understanding of key ethical principles (autonomy, beneficence, non-maleficence, justice) improved markedly from 1.58±0.534 to 2.35±0.700 ($p=0.006$), moving from a poor to a good level of practice. In contrast, the control group showed minimal change (1.47±0.539 to 1.53±0.539, $p = 0.026$) [Table 1]. These results align with Rainer et al[3] and

Robichaux[4], who emphasized that structured ethics education enhances nurses' moral reasoning and decision-making in critical care.

Improvements were also noted in obtaining informed consent (1.58→2.35), reflecting enhanced ethical communication skills, consistent with Lavoie et al.[5] Respect for patient autonomy recorded the highest post-test mean (2.73±0.560), confirming Milliken's[6] findings on the centrality of autonomy in ethical nursing practice. Additionally, nurses' ability to recognize ethical dilemmas and follow institutional protocols improved significantly (1.95→2.47 and 1.84→2.55, respectively), demonstrating progress in both ethical awareness and practical application. The control group, however, remained largely unchanged.

The findings of this study showed significant gains in handling ethical dilemmas - specifically in identifying ethical conflicts (1.49→2.64, p = 0.012), applying ethical reasoning, consulting ethics committees, and communicating ethical concerns (Table 2). These results are consistent with studies by Grady et al[7], Oh & Gastmans[8] and Park et al[9], which highlight that ethics-based training enhances nurses' competence and confidence in addressing moral challenges in complex care environments.

A significant improvement in patients and family involvement in ethical decision-making is shown in Table 3. The experimental group showed notable increases in engaging patients and families (1.56→2.51), respecting cultural and religious values (2.15→2.60), facilitating discussions about advance directives (1.65→2.64), and encouraging participation in care decisions (1.56→2.51). These outcomes support findings by Epstein & Street[10], Lachman[11] and Trotochaud et al[12], who emphasized the positive impact of communication-based ethics education on shared decision-making and patient-centered care.

Table 4 highlights the marked improvement in professional integrity and ethical conduct within the experimental group. Scores increased substantially for maintaining confidentiality (1.67→2.44, p = 0.008), reporting ethical concerns (2.18→2.62), demonstrating fairness and non-discriminatory behavior (1.35→2.64), and engaging in continuous ethical learning (1.38→2.62). These results align with Saleh et al[13], Mohamed & El-Sayed[14], Lee et al[15] and Othman & Alshammari[16], who stress that continuous ethics education fosters professional accountability, impartiality, and moral integrity among critical care nurses.

In the present study, the experimental group achieved substantial post-intervention improvements in all 17 items assessing therapeutic communication (Table 2). Scores increased from poor/fair levels (1.22–1.76) to good levels (2.4–3.0) across domains such as greeting patients (1.25→2.71), using clear and understandable language (1.60→2.45), encouraging participation in care (1.22→2.55), and ensuring patient understanding (1.42→2.60). In contrast, the control group showed only minimal or inconsistent changes, indicating that the intervention was the key factor driving improvement. These findings confirm that integrating ethical principles with therapeutic communication strategies significantly enhances nurses' ability to deliver patient-centered care. Improved communication skills lead to better engagement, active listening, empathy, and ethical sensitivity - key components of professional nursing in critical care settings. These results are supported by Abou Zeina & El-Mahdy[17], Yousef & Mahmoud[18], Kourkouta & Papathanasiou[19], Al-Hassan & Al-Sayed[20] and Mohammed et al[21], all of whom emphasized the importance of ongoing structured training in fostering effective communication and ethical competency.

We recommend implementing this program as a standard component of in-service training in critical care units, with modules tailored to different age groups and educational levels. Encouraging participation in ethics training can enhance practical application. Ongoing pre- and post-assessments are advised to maintain program relevance and effectiveness. Future research should examine the long-term impact on nursing practice and patient outcomes

CONCLUSION

The integrated educational program was highly effective in improving critical care nurses' practices in ethical principles and therapeutic communication. Nurses in the trial group showed significant improvement, moving from "poor" to "good," while the control group showed minimal change. Gains were most notable in ethical decision-making, communication skills, and patient safety. Age influenced knowledge gains, and education level correlated with practical skills, whereas sex and years of experience had no significant effect, indicating the program's broad effectiveness.

Author's Contribution:

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Drafting or Revising Critically:	Hasanain Yhiya Shimran, Sahar Adham Ali
Final Approval of version:	All the above authors
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Original Article

Nursing Care of Common Symptoms for Antimicrobial Resistance and Multi-Drug Resistant Strains in Pediatric Typhoid Cases

Oday Faris Washeel and Sarah Talib Kadhim

ABSTRACT

Objective: To evaluate the prevalence of MDR S. enteric typhi strains isolated from children diagnosed with typhoid fever and to describe the most common clinical features of infection and assess the susceptibility of isolates to commonly used antimicrobial agents.

Study Design: Retrospective observational study

Place and Duration of Study: This study was conducted at the General AL-Habbobi Hospital for Children in Nassiriya, Iraq from 1st January 2025 to 30th June 2025.

Methods: One hundred and forty eight children who had been clinically diagnosed with typhoid febrile were enrolled.

Results: Salmonella typhi was present in 42 (28.4%). Thirty nine (92.9%) of the isolates had multi-drug resistance (MDR). They were resistant to ampicillin, gentamicin, cotrimoxazole, co-amoxicillin, ciprofloxacin, and tetracycline, among other antimicrobials. However, 96.6 % of the strains were sensitive to amikacin, furazolidone, levofloxacin, and meropenem, which were all equally efficient against all the strains. Regarding resistant strains of S. typhi, the minimum inhibitory concentration of antimicrobial medicines was (MIC ≥0.25 mg/L). One of the most common types of phage found was type 0. In all pediatric age categories, the rate of S. typhi isolation was comparable to one another overall. In every one of the instances, fever was the primary presenting symptom. Other symptoms that were related to MDR typhoid fever patients that were not complicated after admission were headache (35.7%), enteric fever (30.8%), and stomach pain (18.7%). The incidence reached (21.1%), in addition to various other symptoms. There were (42.9%) of patients who had hepatosplenomegaly.

Conclusion: The high resistance rates to commonly used antibiotics, emphasizing the urgent need for effective antimicrobial stewardshipandadherence to international treatment guidelines.

Key Words: Typhoid fever, Pediatric infections, Bacterial infections, Antibiotic resistance, Nursing care

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INTRODUCTION

Enteric fever is a global health problem. There is a huge disease burden in developing countries due to poor sanitation coupled with lack of food and water safety. In developed countries, it is seen in returning travellers from endemic nations.[1,2] Salmonella typhi and paratyphi, which are the two bacteria that cause typhoid fever, are the most prevalent causes of persistent febrile illness.

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Typhoid fever is a serious public health concern, particularly in poor countries.[3,4] The illness has successfully spread over the whole world and is a significant contributor to both morbidity and death.[3,5] The lack of proper sanitation, a high level of personal cleanliness, and the consumption of contaminated food all contribute to the higher prevalence of the disease in underdeveloped nations.[6,7] An epidemic of illness occurs in urban areas as a consequence of the contamination of the water supply, which is caused by inefficient or insufficient sewage disposal systems.[6,8]

In order to make a diagnosis, it is necessary to isolate Salmonella typhi or paratyphi isolated from a variety of bodily fluids.[9,10] The bone marrow aspirate procedure is invasive and unpleasant,although it consistently produces the greatest isolation rates. The diagnosis of typhoid fever is seldom verified in Iraq, particularly in rural populations where a lack of materials, it is already challenging to perform cultures without the necessary tools and expertise, particularly in the bone marrow

aspiration operation.[11,12] This is especially true in areas with a dearth of personnel, equipment, and expertise. It has been shown that a negative culture of blood might occur in as many as 75% of typhoid febrile patients ascribed to self-medication (the use of antibiotics prior to hospital presentation), particularly in metropolitan settings.[13]

As a consequence of a generic response, a lack of standardization, large amounts of false positives and false negatives, as well as variation among laboratory findings, the Widal test may be of poor value in all regions where typhoid fever is widespread.6. Because of the fluctuating symptoms, the lack of characteristic physical indications, the incidence of sub-clinical infection, and the multiple differential diagnoses, clinical diagnosis continues to be the first line of defense in the treatment of typhoid fever.[14,15] However, this is a challenging area to diagnose because of these factors. The clinical case criteria that the Centers for Disease Control and Prevention (CDC) use to diagnose typhoid fever were used for this study.[16]

It is difficult to distinguish between the symptoms of brucellosis, malaria, and typhoid fever in a clinical setting without scientific evidence, and it is worth noting that malaria is widespread in some regions of Iraq as well.[17,18] The conclusive diagnosis of typhoid fever is made when the typhoid organism is isolated from a patient suspected of having the disease. We decided to look at the Widal test's dependability, risk factors, and pattern of presentation since we've seen a rise in the clinical diagnosis of typhoid fever in hospitalized children.

METHODS

This retrospective observational study with both descriptive and analytical components was conducted at General Al-Habbobi Hospital for Children in Nasiriyah, Iraq from 1stJanuary 2025 to 30th June 2025 vide letter No. 1 dated 1-12-2024. The study included a convenience sample of all children (aged 0–12 years)who were clinically diagnosed with typhoid fever based on the CDC clinical case definition, which includes prolonged fever (≥3 days), abdominal pain, and absence of localized symptoms indicating other specific diseases. Diagnosis was made by licensed pediatricians in the hospital setting after excluding other febrile illnesses such as malaria or brucellosis.[16]

While Laboratory diagnosis was performed via blood and stool cultures collected upon admission, before starting antibiotics. Blood samples were inoculated into Tryptic Soy Broth and incubated up to 14 days. Stool cultures were conducted on selective media. Identification of Salmonella enteric serovar typhi was confirmed through standard biochemical methods and serotyping. Additionally, urine cultures were not routinely performed for all patients. However, each patient underwent a standardized initial clinical assessment upon admission. Outcomes and medications administered at the time of admission were recorded.[17,18]

Phage typing of Salmonella enteric serovar typhi isolates was performed using the standardized method established by the Enteric Reference Laboratory (e.g., Colindale scheme), which employs a panel of specific bacteriophages to differentiate strains based on their susceptibility patterns. Isolates were cultured on nutrient agar, and phage lysis patterns were interpreted following incubation. This method enabled identification of common phage types such as type 0, type A, and Vi-negative strains among others.[15]Data were analyzed using SPSS-25.

RESULTS

By analyzing blood and stool samples, 47 children (36.7%) tested positive for S. typhi. Of the 47 S. typhi strains detected, 42 (or 89.4%) showed resistance to two or more antimicrobial agents, whereas one strain showed resistance to a single drug. On the other hand, every antimicrobial drug often used to treat typhoid fever was effective against 11 strains. At admission, 8 out of 42 patients with multi-drug-resistant typhoid fever exhibited jaundice. During the liver function tests, ALT levels were 1.14-1.45 (NV:0.17-0.92 µkat/L), AST was 1.10-1.33 (NV.: 0.17-0.67 µkat/L), alk. Phosphatase was found to be 1.21-147 (NV.: 0.75-1.92 µkat/L), and serum conjugated bilirubin was 0.94-3.2 (NV:0.2–0.7 mg/dL), and unconjugated bilirubin was 0.90-3.10 (NV:0.2-0.5 mg/dL).

The furazolidone was administered to 10 patients, while the chloramphenicol was given to 3 individuals. Approximately 12 days after the beginning of treatment, the jaundice and fever responded well to the medication administered. Upon admission, eleven more infants who were diagnosed with MDR-typhoid exhibited aberrant different states of mind. In the beginning, they were given ciprofloxacin by intravenous administration. With the elimination of MDR-typhoid inflammation, clinical cure was achieved in 10 patients, which accounts for 90.9% of the total. One patient, accounting for 9.1% of the total, who was in a state of shock at arrival passed away within 24 hours after the beginning of ciprofloxacin treatment. The last step was to analyze the clinical, microbial, and ecological features of 42 infants afflicted with MDR-typhoidwho did not have any complications upon admission.

The isolation of multidrug-resistant S. typhi from probable cases of typhoid fever in children of varying ages is shown in Table 1. Across all age groups of children, the rate of S. typhi isolation was quite consistent. One infant (33.3% of 3) was positive for Salmonella typhi as well. There was a 1.3:1 ratio of male to female children impacted, suggesting that boys were more often affected than girls. Although multi-

drug-resistant typhoid fever patients were detected throughout the year, May and October had very low rates of hospitalization and S. typhi isolation. Among the afflicted youngsters, 73.9% were from lower socioeconomic levels and had poor personal cleanliness, while 68.2% were from rural regions of Nassiriya city. Even though many families lived in cramped quarters, there were examples involving smaller families. No one noticed that any of the typhoid-afflicted kids had ever left the village before.

Isolated from these individuals were eight different kinds of phage-associated Mycoplasma typhi (MRD). At 39.8%, phage type 0 was most common, followed by VI negative at 24.7% and A at 26.5%. In addition to the aforementioned phage types, 3.8%, 2.9%, 1.0%, and 0.5% of the strains tested positive for other phage types. In 68.4% of patients with bacteriologically diagnosed typhoid fever, the Widal test showed an antibody titer against S. typhi 0 antigens of 1:160 or higher.

The S. typhi MRD strains obtained from these patients were composed of eight distinct phage types. Phage categories 0 (39.8%), VI-negative (24.7%), and A (26.5%) were the most prevalent. Additional phage types, including Deg V 1, EOP, and WP109, were identified in isolates comprising 3.8%, 2.9%, 1.1%, and 0.5%, respectively. Antibody titers of 1:160 or higher against S. typhi 0 antigens were detected in 68.4% of patients with bacteriologically confirmed typhoid fever using the Widal test.

The MDR-typhoid febrileindividuals had an average age of (3-7) yr. and an average weight in the body of 16.0±5.0 kg. 18 children (19.0%) were malnourished in grades II–IV, 16 (38.1%) were in normal nutritional condition, and 14 (33.3%) were in grade-I malnutrition. The clinical features of the 42 instances of MRD typhoid fever that were verified by bacteriology are shown in Table 2. All instances fell within the fever range of 37.5 to 41 °C. In 40.3% of patients, the duration of fever before admission was 7-15 days (15.5±10.5). After 60 days of sickness, two individuals (4.8%) admitted to the hospital tested positive for S. typhi in their blood cultures. If there was cold or rigidity, the fever might be intermittent (14.9% of cases), persistent (39.7% of cases), or remittent (41.8% of cases). In (35.7%) of patients, fever was present along with headache. 16 instances (38.1%) were found to have diarrhea when admitted to the hospital, while 41.4% of the children had diarrhea prior to being hospitalized. There was a statistically significant ($P<0.05$) association between typhoid fever and diarrhea in children 1.5–2.5 years old. However, this occurrence declined as people became older. Anorexia (22.4%), vomiting (20.5%), and stomach discomfort (17.2%) were other prevalent characteristics that occurred together. In 28 instances (66.7%), patients exhibited a centrally coated tongue; in 8 cases (19.0%), relative bradycardia was seen. The liver and spleen were both detectable in 38.6% of the cases. 30.7% of patients had palpable liver tissue, whereas 2.9% had palpable spleen tissue alone.

Table No. 1: Separation of Salmonella typhi from various ages

Age (years)	No. of cases febrile examined	No. of positive cases
< 1	2	1 (2.4%)
1—3	34	6 (14.3%)
4-7	88	29 (69%)
8-11	24	6 (14.3%)

Table No. 2: Typhoid fever symptoms induced by MDR S. typhi for fever screening, prior to admission, complaining and symptoms

Variable	No.	%
Fever		
>39-41.2°C	6	14.3
37.5-40.5°C	35	83.3
< 37.5°C	1	2.4
Duration (days)		
1-7	2	4.8
8-15	24	57.1
16-22	11	26.2
23-30	3	7.1
> 30	2	4.8
Complaining		
Chill	11	26.2
Headache	15	35.7
Diarrhea	16	38.1
Anorexia	12	28.6
Puking	11	26.2
Constipation	6	14.3
Abdominal complain	17	40.5
Pallor	6	14.3
Symptoms		
Bradycardia	7	16.7
Hepatosplenomegaly	18	32.9
Hepatomegaly	13	21.0
Splenomegaly	3	7.1

DISCUSSION

The findings of this study highlight a concerning prevalence of multidrug-resistant (MDR) *Salmonella enteric* serovar typhi strains among pediatric patients in Nasiriyah, Iraq. Of the 42 culture-confirmed cases, the vast majority were MDR, resistant to at least three classes of commonly used antibiotics, including ampicillin, co-amoxicillin, ciprofloxacin, and cotrimoxazole. This rate is considerably higher than that reported in several neighboring countries and global surveillance reports, such as those from South Asia and Africa, where MDR rates range from 30% to 70% depending on region and methodology.[1]

The resistance patterns observed in our study suggest ongoing misuse or overuse of broad-spectrum antibiotics in the local healthcare setting, which may contribute to the selection pressure driving the emergence of MDR strains. However, encouragingly, more than 96% of isolates were sensitive to amikacin, furazolidone, levofloxacin, and meropenem. These findings support the potential use of these agents as effective therapeutic alternatives, particularly in complicated or resistant cases.[19]

Clinically, fever was universally present, while other common symptoms included headache, abdominal pain, and diarrhea. The symptom profile aligns with existing literature, although rates of hepatosplenomegaly in our study were slightly higher than in comparable pediatric cohorts in South Asia.[2] These variations may be influenced by nutritional status, delays in seeking care, or regional strain characteristics.

In this study, a notable portion of the febrile pediatric patients screened for typhoid fever were confirmed to have MDR *Salmonella enteric* serovar typhi infection. The age distribution revealed that the majority of confirmed cases occurred among children of early school age, suggesting that this group is particularly vulnerable, likely due to greater environmental exposure, developing hygiene behaviors, and frequent interaction with contaminated sources.This pattern aligns with the findings reported by Khan et al[20] who highlighted that school-aged children face increased risk due to greater mobility and exposure to unsafe sanitation. In contrast, infants accounted for only a minimal proportion of positive cases, likely reflecting reduced environmental exposure and closer parental care, consistent with observations made by Abhilasha et al[21] who conducted a study about "typhoid burden in children: an epidemiological update".

More than half of the affected patients experienced symptoms for approximately one to two weeks before seeking medical attention. This delay in presentation is a concerning issue, as it may contribute to the development of more complicated or resistant forms of typhoid fever. Similar findings were reported by Wain et al[22] who studied "delay in presentation and clinical outcome in typhoid fever" and emphasized that delayed healthcare-seeking behavior remains prevalent in endemic settings, often due to limitations in healthcare access and low symptom awareness. The current results underline the necessity of enhancing community awareness for earlier intervention.

Among the clinical complaints, abdominal pain emerged as the most frequently reported symptom, closely followed by diarrhea and headache. Systemic manifestations, such as chills and anorexia, were also noted, though less commonly.These findings are consistent with recent studies by Guptaet al[23] who conducted a study about " Clinical features and outcomes in pediatric typhoid fever: a tertiary center study" and demonstrated that gastrointestinal symptoms dominate the clinical picture of pediatric typhoid.

Moderate fever was the most common clinical feature observed at admission, affecting the vast majority of patients, whereas only a smaller subset experienced high-grade fever. Hypothermia or absence of fever was an uncommon finding, reaffirming that fever remains a central diagnostic hallmark of typhoid fever. These observations are in agreement with Ochiai et al[24] who studied "pediatric fever patterns in typhoid endemic areas: new insights"and described similar fever patterns among pediatric patients.

On physical examination, a coated tongue and hepatosplenomegaly were the predominant findings, affecting a substantial proportion of cases.These signs reflect systemic dissemination of *Salmonella enteric* serovar typhi infection and are well-recognized clinical features, as also noted by Bhutta[25] who studied" Current management of typhoid fever in children: Challenges and advances" and revealed that their presence can therefore serve as valuable early indicators of typhoid fever in children.

Furthermore, multivariable analysis identified several significant predictors for MDR typhoid fever. Prior antibiotic use, altered consciousness at admission, poor personal hygiene, rural residence, reliance on untreated water sources, and malnutrition each contributed substantially to the increased risk of infection. These current results are supported by the findings of Andrews et al[26] who studied " Antimicrobial resistance in typhoid: Emerging challenges and future directions" and also identified inappropriate antibiotic exposure and poor sanitation as major risk factors.

CONCLUSION

The high resistance rates to commonly used antibiotics, emphasizing the urgent need for effective antimicrobial stewardshipandadherence to international treatment guidelines. A possible preventative strategy may be the provision of clean, drinkable water, health teaching on how to keep you clean, clean environments, and the right way to get rid of waste, since the incidence of 30.0 per 1000 admissions is high.

Author's Contribution:

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Drafting or Revising Critically:	Oday Faris Washeel, Sarah Talib Kadhim
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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