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### **International Journal of Scientific Study**

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### Heterotopic Pregnancy with Ruptured Tubal Ectopic Pregnancy: A Case Report

#### K Nishitha<sup>1</sup>, Jeyarani Kamaraj<sup>2</sup>, K S Maheswari<sup>3</sup>

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#### Abstract

Heterotopic pregnancy is the rare simultaneous occurrence of two pregnancies at different implantation sites with only one located in the uterine cavity. The incidence of heterotopic pregnancies has increased due to the increase in assisted reproductive techniques. Here, we discuss a case of a spontaneous pregnancy who presented with a history of increasing lower abdominal pain with brownish vaginal discharge, nausea, and vomiting episodes for the past day. Transabdominal and trans-vaginal ultrasound were performed and revealed a viable intrauterine pregnancy of gestational age 9 weeks and 2 days, associated with a fluid accumulation in pouch of Douglas. Emergency laparoscopic bilateral salpingectomy was done.

Key words: Ectopic pregnancy, Heterotopic pregnancy, Intrauterine, Spontaneous pregnancy, Transvaginal ultrasound

#### INTRODUCTION

Heterotopic pregnancy describes the occurrence of two pregnancies at different implantation sites simultaneously, mostly manifested as intrauterine and ectopic pregnancies. Heterotopic pregnancy is rare, with an incidence of about 1:30,000 among spontaneous conceptions,<sup>[1]</sup> but when using assisted reproduction techniques (ART), it has a much higher prevalence of 1:100–1:500.<sup>[2]</sup> Even in the era of high-resolution ultrasound (US) imaging and Doppler techniques, most of the time, the diagnosis is based on the presence of acute abdominal symptoms. In the current study, we present a case of first trimester heterotopic pregnancy with ruptured left ectopic pregnancy, diagnosed by US.

#### **CASE PRESENTATION**

A 34-year-old pregnant patient with spontaneous pregnancy and an obstetric score of G2P1 presented with complaints of progressive lower abdominal pain,



brownish vaginal discharge, nausea, and vomiting for the past 24 h. On examination, patient's pulse was 110/min, BP was 100/70 mmHg, respiratory rate was 15 breaths per minute, and her saturation was 97% in room air. Urgent transabdominal and transvaginal USs were carried out, which revealed fluid collection in the pouch of Douglas and a viable intrauterine pregnancy of 9 weeks and 2 days associated with a ruptured left ectopic pregnancy.

After obtaining written informed consent, the patient was transferred to the operating room. After observing aseptic precautions and proper antibiotic cover, an emergency laparoscopy was performed under general anesthesia with continuous cardiac and respiratory monitoring. It revealed that the peritoneal cavity was filled with approximately 1500 mL of blood, there was a ruptured left tubal ectopic with oozing of blood, and the right fallopian tube was bundled and adhered to the pouch of Douglas. After complete suctioning of the peritoneal blood collection, a bilateral salpingectomy was done with the utmost care without touching the uterus. Post-operative abdominal US confirmed a viable intrauterine pregnancy. The patient tolerated the procedure well. Post-operative vitals were stable, and clear urine was drained at the end of the procedure.

#### Follow-Up

At 36 weeks and 3 days, the patient underwent an elective cesarean section (indication: previous lower segment

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caesarean section). An alive male baby was delivered with cord once around the neck. The baby cried immediately after birth. The postoperative period was uneventful.

#### DISCUSSION

Heterotopic pregnancies can be asymptomatic in about half of the cases; otherwise, they can present with variable clinical presentations, mainly abdominal pain, adnexal swelling that may be associated with vaginal bleeding, or even shock due to hypovolemia. Unfortunately, the clinical findings are more frequently presented with tubal rupture.<sup>[3]</sup> When seen in the emergency room, the differentials include ectopic pregnancy, abortion, and ovarian torsion. Transvaginal US has been instrumental for the diagnosis.<sup>[4]</sup> Ectopic pregnancy needs early diagnosis and management to avoid the high probability of tubal rupture.

Approximately 70% of heterotopic pregnancies are diagnosed between 5 and 8 weeks gestational age, 20% between 9 and 10 weeks, and the remaining 10% beyond 11 weeks. The clinical manifestation varies depending on the time of diagnosis, with early diagnosis being decisive and important for modifying the morbidity and mortality of the patient and her reproductive future.<sup>[5]</sup> The prognosis of intrauterine pregnancy depends on early clinical and ultrasonographic diagnosis.<sup>[5,6]</sup> The fetal mortality rate for extrauterine pregnancy is about 98% and for intrauterine pregnancy between 45% and 65%.<sup>[7]</sup>

According to Reece *et al.*,<sup>[8]</sup> the most frequent location of extrauterine pregnancy coexisting with intrauterine pregnancy is the oviducts (93.9%); definitely more rarely, the pregnancy is located in the ovary (6%). More frequent incidence of pregnancies in the left oviduct in comparison to the right oviduct has been observed (31.8% vs. 36.3%). Reece *et al.*,<sup>[8]</sup> submitted for analysis 37 patients with diagnosed heterotopic pregnancy after surgical treatment of extrauterine pregnancy -75.6% gave birth around their expected delivery date, 16.2% prematurely, and 3% of pregnancies ended with a miscarriage. According to Tal *et al.*,<sup>[9]</sup> the major symptoms are abdominal pain -83%, surgical abdomen symptoms and shock -13%, and vaginal bleeding -50% of cases.

Heterotopic pregnancy treatment needs laparoscopy and, most often, a salpingectomy or salpingostomy. However, in hemodynamically unstable cases, laparotomy may be needed. Systemic methotrexate has no role in the management of heterotopic pregnancy due to the presence of a viable intrauterine pregnancy. Some literature describes the use of local injections of potassium chloride and methotrexate, but the success rate is controversial.<sup>[10]</sup> These case reports and literature reviews emphasize focused scanning of the adnexa in patients who have undergone ART and embryo transfer, even in asymptomatic cases. The standard for ruling out heterotopic pregnancy should be the exclusion of extrauterine gestation. In patients having higher than expected levels of serum beta-HCG but having only single intrauterine gestation, close monitoring by repeated serum beta-HCG levels and transvaginal US is advisable.

#### CONCLUSION

Even though heterotopic pregnancy is a rare condition, clinicians should always keep it as a differential diagnosis in patients of any age presenting with abdominal pain and signs or symptoms of ectopic pregnancy. In early pregnancy, a thorough and detailed clinical examination with US visualization of the uterus and adnexa is an important pillar in the diagnosis and early identification of this pathology.

The appendages should be examined in every woman in early pregnancy, especially if the pregnancy is the result of *in vitro* fertilization and when accompanied by clinical symptoms such as abdominal pain, fluid in the pouch of Douglas, or hypovolemic shock. Laparoscopy is described as the safest approach, with fewer complications and can contribute to maintaining intrauterine pregnancy and its successful delivery.

#### **AVAILABILITY OF DATA AND MATERIALS**

The data that support the findings of this study are available on request from the corresponding author.

# ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethical committee of the institution, and informed written consent from the patient included in this study was obtained.

#### **CONSENT FOR PUBLICATION**

All authors read and approved the final manuscript. The patient included in this research gave written informed consent to publish the data contained within this study.

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# Pseudoepitheliomatous Hyperplasia: A Diagnostic Dilemma

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#### Abstract

Pseudoepitheliomatous hyperplasia (PEH), a neglected entity by oral pathologist, possesses utmost importance in the field of research. Of all the investigative challenges, PEH, a reactive epithelial proliferation is seen secondary to lesions with infectious, inflammatory, reactive, and degenerative origin. Small-sized samples, incomplete excision, improper orientation, and dense inflammatory changes render diagnostic confront to the oral pathologist in the exclusion of frankly invasive malignant lesions such as squamous cell carcinoma (SCC) from lesions exhibiting PEH. In this case report, we presented a case which was misdiagnosed as PEH, and due to this negligence, patient underwent extensive surgery of orofacial structures. This case was diagnosed as SCC on the basis of history, findings, and clinical examination, but due to the fear of the patient and negligence, the patient suffered a lifetime loss and compromised quality of life. Emphasis should be made on the amalgamated efforts of the clinician and pathologist to rule out this type of mystify lesion which will help in rendering the appropriate diagnosis and treatment planning.

Key words: Benign proliferation, Pseudoepitheliomatous hyperplasia, Squamous cell carcinoma

#### INTRODUCTION

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Pseudoepitheliomatous hyperplasia (PEH) is taken into account to be a "benign proliferation of the epidermis into irregular squamous strands extending down into the dermis, respectively,<sup>[2]</sup> with no cytological atypia and mitotic figures."<sup>[3]</sup> Dr. Unna (1896) delivered to light the primary case of PEH as "Epidermal proliferation overlying a lesion of lupus." This lesion is additionally referred as pseudocarcinomatous hyperplasia<sup>[3]</sup> (as they mimic epithelial cell carcinoma squamous cell carcinoma [SCC])<sup>[4]</sup> and invasive epidermal hyperplasia, invasive acanthosis, verrucous epidermal hyperplasia, and carcinomatous hyperplasia.<sup>[5]</sup> Clinically, these wounds appear as skin ulcers/wounds, verrucous/

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multinodular growth, cauliflower growths, and domeshaped swelling with smooth/warty surfaces.<sup>[5]</sup> This reactive proliferation of the epithelium occurs secondary to persistent inflammation resulting from the chronic traumatic wound, ulcer, bacterial/fungal infection, degenerative changes, retained foreign material, dermatitis, traumatic implantation of epithelium, and malignancy.<sup>[2,5]</sup> Lesions flaunting PEH are discerned by the gold standard of biopsy from invasive nasty lesions. PEH could be a benign lesion requiring only local conservative excision, whereas nasty lesion needs radical surgery. As this entity is neglected among pathologist, this article is written in view to enlighten the irreversible loss of orofacial structures due to its misdiagnosis.<sup>[1-3]</sup>

#### **CASE REPORT**

A 35-year-old male patient reported to our department of oral medicine and radiology with the chief complaint of pain and swelling in left lower back tooth region for 3–4 days. The patient gave a history of similar type of swelling on the same region which was noticed 4–5 years ago. At that time, the patient visited to the dentist who gave

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him some medications for 5 days (patient does not know the name of the medications), and swelling was subsided at that time. Now, since 1 year, the patient is noticing the similar type of swelling which was painless and present on the left side of tooth region. The patient did not visit to any other doctor for 1 year. The patient started experiencing pain in that swelling since 3–4 days. Pain is continuous and dull aching. Pain is not radiating to any other associated surrounding structures. The patient did not take any overthe-counter medication for pain relief. The patient gave no relevant medical history. The patient has a habit of smoking bidi 2–3 packets per day since 5 years. The patient also has a habit of chewing tobacco 2–3 packets per day since 10 years.

On extraoral examination, there is no swelling present and has a symmetrical face [Figure 1]. On intraoral examination, while inspection, there is ulceroproliferative growth present on interdental and attached buccal gingival of 36, 37, and 38, which is obliterating the buccal vestibule region [Figure 2]. Blanching on bilateral buccal mucosa is appreciable. Homogenous white patch present on the right side of buccal mucosa adjacent to 46 and 47 [Figure 3]. While palpation, there is firm, indurated, sessile growth present on the buccal attached gingiva of the 36, 37, and 38 extending the gingivobuccal sulcus (GBS). There is buccal vestibule obliteration present on the left side. A growth is having a round border which bleeds to touch due to ulceration superimposing the swelling. There was a presence of fibrous bands palpable on the bilateral buccal mucosa. Mouth opening of the patient was normal. An intraoral periapical radiograph and orthopantomogram (OPG) were done which shows nothing significant changes in bone [Figures 4 and 5].

A diagnosis of SCC of GBS at 37 and 38 region was made. Other diagnoses made were OSMF Grade 1 and homogenous leukoplakia on right buccal mucosa. The patient was counseled to quit the habit of smoking and tobacco chewing. The patient was given nicorette 2 mg to be chewed when there is urge to use tobacco. The patient was advised intralesional injections dexamethasone 4 mg (dexona) and hyaluronic acid (Hynidase) twice weekly for the 1 month. Patient was prescribed 0.1% triamcinolone acetonide (kennacort) for topical application in all the surfaces of oral cavity for 3 times a day for 1 month except the white patch which was present on right buccal mucosa. The patient was also prescribed retino a cream to be applied admixed with honey on white patch present on buccal mucosa 3 times a day for 1 month. The patient was prescribed tablet SM Fibro once a day for 1 month. Patient was referred to the department of oral and maxillofacial surgery for incisional biopsy.

Patient reported to our department after 10 days with biopsy report which was came out to be SCC. The patient



Figure 1: Extra oral image



Figure 2: Intra oral image



Figure 3: Pseudoepitheliomatous Hyperplasia

was not convinced and visited to other hospital and stopped all the medications prescribed by us and had frozen section procedure. Report came out to be PEH with no evidence of malignancy. The patient was treated with marginal mandibulectomy with reconstruction with



Figure 4: IOPA



Figure 5: OPG

tongue with buccal fat pad flap on left side, and OPG was taken. Moreover, the specimen was sent for the biopsy after the procedure. The biopsy report came out to be well-differentiated SCC. Patient again came back to our department after 20 days with complaints of swelling in left alveolus region and reduced mouth opening. Now, the patient was referred to the cancer hospital for extensive oral surgery and radiotherapy. Patient remains asymptomatic for the next 2 years. Patient came to our department after 2 years with the complaints of pain in oral cavity and has pain while deglutition. On examination, there were no oral findings, so he was referred to ENT doctor for throat examination. Patient was followed up after the checkup and diagnostic tests that were advised by the ENT specialist. Patient was again diagnosed with malignancy in throat. He was treated for the same in cancer hospital, and now, he is not able to speak. Patient is still under follow-up.

#### DISCUSSION

PEH resembles SCC on histology, but these two entities are totally alike in terms of the patient management, and prognosis is concerned. These two diseases are customarily come across in biopsy specimens from the oral cavity and also from head-and-neck mucosa. If the sample tissue shows inflammation and has poor tissue orientation in the specimen, then it becomes too difficult to differentiate between these two entities.<sup>[6]</sup> PEH is primary, as in primary gingival PEH, or secondary, because of various reasons.<sup>[4]</sup> The differentiation between the PEH and nasty SCC becomes tougher when the deep rete pegs anastomose with each other or are cut tangentially. Furthermore, often patients would have already taken treatment for the oral cavity lesions and are on follow-up and repeat biopsy specimens are submitted where the tissue architecture may well be already distorted giving rise to difficulty in interpretation.<sup>[6]</sup>

Distinguishing PEH from SCC is of utmost importance for further management and prognosis of patients. In the abovementioned case, patient was diagnosed as SCC on the basis of clinical findings. Due to diagnostic dilemma, PEH resemblance to SCC and lack of the knowledge of the pathologists lead the patient to undergo extensive surgery and radiotherapy sessions which affected the patient physically, financially, and mentally. If it was being treated as SCC earlier, then patient would not have lost his speech. Always correlate the diagnosis with clinical findings as well as a history of the patient to save the patient from such disaster.<sup>[4-7]</sup>

#### **CONCLUSION**

PEH may be a benign epithelial proliferation identified microscopically in association with various heterogeneous lesions. The pathogenesis of PEH remains unclear; however, a scientific knowledge of PEH is important to rule out neoplasms. Clinicopathologic correlation remains a gold standard to succeed in the precise diagnosis. Tissues which are tiny in size, inappropriate orientation, and heavy inflammations in numerous lesions revealing PEH is very tough for pathologists to discriminate them from frank most aggressive lesions such as SCC. Adequate excision and sampling depth render in the exclusion of frankly malignant lesions and aid in appropriate treatment to the patient. Collaboration between clinician and pathologist is totally essential to deliver suitable treatment to the patient and avoid undesirable consequences. The diagnosis can occasionally be difficult as they mimic other lesions also, on clinic-pathological assessment. Thus, this text gives an insight regarding the assorted concepts of etiopathogenesis, histopathology, medical diagnosis, and malignant potential of PEH. A combined effort of a clinician and pathologist benefits every patient to rule out malignancy and render appropriate treatment because the only local conservative approach is important to get rid of PEH-associated lesions.

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### **Clinical and Bacteriological Profile of Chronic Dacryocystitis - A Hospital-Based Study**

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#### Abstract

**Background:** Inflammation and fibrosis in patients with nasolacrimal duct obstruction may be brought on by concurrent infectious colonization within the lacrimal sac lumen. To investigate the likelihood of a primary bacterial etiology for the inflammatory response, we looked at the bacterial flora in the lacrimal sac at the confluence of the sac and duct.

**Materials and Methods:** Our study is a prospective hospital-based study of 41 patients suffering from chronic dacryocystitis, conducted in the Eye Department of R. D. Gardi Medical College, Ujjain, India, between January 2021 and December 2021. All patients underwent comprehensive ocular examination as well as laboratory investigation.

**Results:** Forty-one patients suffering from chronic dacryocystitis, out of which 7 patients had both eyes involved, were included in the study. We found that chronic dacryocystitis was more predominantly seen in female patients 58.53% (24). From the 48 samples, patients 100% had epiphora while discharge was seen in 50% (24) of cases and swelling was seen in 18.75% (9) of cases. Out of 48 samples, 45 (93.75%) were positive for culture, of which 4 (8.88%) had multiple isolates. Out of 41 single-isolation cultures, 27 are Gram-positive bacteria and 14 are Gram-negative bacteria. *Staphylococcus* spp. (74.07%) is the most commonly isolated Gram-positive organism. In both single and multiple isolates, the most common Gram-negative bacteria isolated was *Pseudomonas* spp.

**Conclusion:** Majority of adult individuals with chronic dacryocystitis have microorganisms in their lacrimal sacs. Therefore, before arranging any intraocular surgeries, ophthalmologists should carefully check for signs of nasolacrimal blockage.

Key words: Chronic dacryocystitis, Dacryocystorhinostomy, Epiphora, Staphylococcus spp

#### INTRODUCTION

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A chronic inflammation of the lacrimal sac caused by nasolacrimal duct occlusion is known as chronic dacryocystitis. It is a significant contributor to ocular morbidity in both children and adults.<sup>[1]</sup> It is the most frequent cause of epiphora.<sup>[2]</sup> It has been observed to be more prevalent in people between the ages of 40 and 60, with females (80%) being more frequently affected than males (perhaps because of the bony canal's narrow lumen).<sup>[3]</sup> Patients with poor personal hygiene and those from lower socioeconomic groups are more likely to have the condition.



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Infections of the conjunctiva, nasal cavity (retrograde spread), paranasal sinus, allergic rhinitis, or deviated nasal septum are the main sources of infection. Staphylococcus species (spp.), Streptococcus pneumoniae species (spp.), Streptococcus species (spp.), and Pseudomonas species (spp.) are the most often reported etiologic agents. Rarely, dacryocystitis can also be brought on by persistent granulomatous infections such leprosy, syphilis, TB, and, very rarely, rhinosporidiosis. Each year, 1.6–1.9 million cataract operations are performed throughout India,<sup>[4]</sup> many in "camps" or rural peripheral centers.<sup>[4]</sup> Preoperative syringing of the nasolacrimal system is typically done in most clinics before cataract surgery in an effort to rule out chronic dacryocystitis, which is a significant risk factor for postoperative endophthalmitis. Any intraocular procedure that is performed in the presence of undiagnosed dacryocystitis runs the risk of causing panophthalmitis.<sup>[5]</sup>

Establishing contact between the lacrimal sac and nasal mucosa by forming a bone window in a procedure

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known as a dacryocystorhinostomy (DCR) either by an external or nasal approach is the gold standard treatment for dacryocystitis. Bacteriological tests would aid in the selection of appropriate antimicrobial treatments for chronic dacryocystitis and reduce the use of unnecessary antimicrobials prior to surgery.<sup>[6]</sup> Without the proper systemic antibiotics, infection can occur leading to secondary hemorrhage which, in turn, can lead to surgical failure.<sup>[7]</sup> We have conducted a study to identify the current bacteriology of the lacrimal sac in a given population along with the clinical presentation.

#### **MATERIALS AND METHODS**

A prospective analysis of microbiological and clinical data of 48 eyes of 41 patients had undergone external DCR for chronic dacryocystitis between January 2022 and December 2022 conducted in the Department of Ophthalmology, R. D. Gardi Medical College, Ujjain, Madhya Pradesh, India. Prior approval for the study was obtained from the Institutional Ethics Committee.

Written informed consent was obtained from each patient. The preliminary data of patients such as name, age, sex, and occupation were recorded first. A detailed history was taken, with regard to the chief complaint, past history, and any other disease.

There were 24 (58.53%) females and 17 (41.47%) males in the age range of 25–68 years (mean age 46.5 years). Seven cases were bilateral.

The patients were labelled as chronic dacryocystitis on the basis of history of persistent and discharge from affected eye and findings were confirmed by lacrimal syringing.

Specimens were obtained directly from the lacrimal sac under operating microscope during the making of a sac flap for external DCR. The materials were collected with sterile cotton tip applicators and sent for culture to the microbiology laboratory. All samples were cultured on the day of collection, aerobically and anaerobically, onto the appropriate media. The bacterial isolates were identified by standard procedures.

#### **Growth and Identification of Clinical Cultures** *Aerobic cultures*

For the isolation of aerobes, specimens from patients with suspected chronic dacryocystitis were inoculated on trypticase soy agar (with 5% sheep blood), chocolate agar, and MacConkey agar plates. The plates were inoculated at  $35-37^{\circ}$ C in a 5-10% CO<sub>2</sub> atmosphere. The cultured plates

were examined daily for 5 days. Any growth observed was quantified and documented.

#### Anaerobic cultures

A thioglycollate broth (enriched with hemin and Vitamin K) and trypticase soy blood agar plates were inoculated with specimens from patients with chronic dacryocystitis and incubated at  $35-37^{\circ}$ C in a CO<sub>2</sub>-nitrogen atmosphere for the isolation of anaerobes. Anaerobic media were examined after 48 h. If no growth in the broth was observed after 48 h, a blind subculture of the thioglycollate media was then prepared on the 5<sup>th</sup> day of incubation.

#### **Exclusion Criteria**

- Patients who had a history of acute attack of dacryocystitis
- Patients who had a history of any previous lacrimal sac surgery.

#### RESULTS

A total of 48 samples of 41 patients with a clinical diagnosis of chronic dacryocystitis were analyzed. Forty-five samples (93.75%) revealed growth and 3 samples (6.25%) showed no growth of organisms [Figure 1]. The average age of the patients was studied 46.5 years (range: 25–68 years), with a female predominance 58.53% (24) compared to males 41.47% (17).

From the 48 samples, 100% of patients presented with a complaint of epiphora (48) while discharge was seen in 50% (24) of cases and swelling was seen in 18.75% (9) of cases [Figure 2].

A total of 52 organisms were isolated from the 45 samples. Among these 45 samples, 41 (91.11%) had single isolations and 4 (8.88%) samples had mixed bacterial isolations (more than one organism).

Out of 41, single-isolation Gram-positive bacteria were seen in 27 (65.85%) [Table 1] samples, and Gram-negative bacteria were seen in 14 (34.14%) [Table 2] samples. *Staphylococcus* spp. (74.07%) is the most commonly isolated organism followed by *Streptococcus* species (22.22%) among Gram-positive bacteria.

*Pseudomonas* spp. (50%), *Klebsiella* spp. (21.42%), and *Escherichia coli* (10.67%) were the most commonly isolated Gram-negative bacteria.

In multiple isolations out of 11 organisms, Gram-positive bacteria were isolated in (72.72%) samples [Table 2], and Gram-negative bacteria were isolated in (27.27%) samples [Table 3]. *Staphylococcus* spp. (62.5%) was the most commonly isolated, followed by *Streptococcus* spp. (25%) and others (12.5%) among Gram-positive bacteria [Table 4].

### Table 1: Single-isolate Gram-positive bacteria distribution (n=27)

Bacteria isolated	No. of isolates	Percentage
Staphylococcus epidermis	12	44.4
Staphylococcus aureus	8	29.62
Streptococcus viridans	4	14.81
Streptococcus pneumoniae	2	7.4
Enterobacter	1	3.7

### Table 2: Single-isolate Gram-negative bacteria distribution (n=14)

Bacteria isolated	No. of isolates	Percentage
Pseudomonas aeruginosa	7	50
Klebsiella pneumoniae	3	21.42
Escherichia coli	2	14.2
Corynebacterium spp.	1	7.14
Haemophilus	1	7.14

### Table 3: Multiple-isolate Gram-positive bacteria distribution (n=8)

Bacteria isolated	No. of isolates	Percentage
Staphylococcus epidermis	3	50
Staphylococcus aureus	2	25
Streptococcus viridans	2	12.5
Enterobacter	1	12.5

### Table 4: Multiple-isolate Gram-negative bacteria distribution (n=3)

Bacteria isolated	No. of isolates	Percentage
Pseudomonas aeruginosa	2	66.66
Klebsiella pneumoniae	1	33.33

### Table 5: Age-wise distribution of cases in thestudy group (*n*=41 patients)

Age	No. of patients	Percentage		
25–40	9	21.95		
41–55	13	31.70		
56–70	19	46.34		

*Pseudomonas* spp. (66.66%) and *Klebsiella* spp. (33.33%) were isolated among Gram-negative bacteria.

Among Gram-positive bacteria, *Staphylococcus epidermidis* was the most common, accounting for 15 (28.84%), followed by *Staphylococcus aureus* 10 (19.23%) and *Streptococcus* spp. 8 (15.38%) for both single and multiple isolations. Among Gram-negative organisms, *Pseudomonas aeruginosa* 9 (17.3%), *Klebsiella pneumoniae* 4 (7.69%), *E. coli* 10 (6.84%), *Enterobacter* 2 (3.84%), and *Corynebacterium* spp. 1 (1.92%) were found in both single- and multiple-isolation cases.



Figure 1: Growth-wise distribution of samples (n=48 samples)



Figure 2: Bar diagram of presenting complaint-wise distribution of cases in the study group (*n*=48 cases)



Figure 3: Pie diagram of sex-wise distribution of cases in the study group (*n*=41 patients)

#### DISCUSSION

With chronic dacryocystitis, infectious changes are always present in all of the lacrimal sacs. In DCR, the infected sac is bypassed in order to access the nasal cavity through a newly formed bone canal. This implies that the patient should receive prophylaxis after surgery to reduce the chance of infection, which could result in problems like secondary hemorrhage. Without the proper antibiotic prophylaxis, even a low-grade infection near the anastomotic site of the sac and mucosa flap might significantly increase the likelihood of failure in an external DCR.

In our study, samples were taken directly from the lacrimal sac while making the sac flap for external DCR under the operating microscope. This method offers a lower risk of contamination than applying pressure to the lacrimal sac or allowing purulent material reflux through the sac while collecting samples.

In our study, females showed a higher incidence [Table 5 and Figure 3] which was similar to Hartikainen *et al.* in 1997 who found a female-to-male ratio of 79%:21%.<sup>[8]</sup>

In the present study, 93.75% of samples were culture positive, which is almost a little less than reported by Chaudhary *et al.* (2005) and higher than previously reported in comparable studies (De Angelis *et al.*, 2001; Hartikainen *et al.*, 1997; Islam *et al.*, 2006; Kuchar *et al.*, 2000; Usha *et al.*, 2006).<sup>[8-12]</sup>

Gram-positive bacteria were found in 65.85% of single isolations and 72.72% of mixed isolations. This is similar to previously reported studies (Chaudhary *et al.*, 2005; Coden *et al.*, 1993; De Angelis *et al.*, 2001; Hartikainen *et al.*, 1997).<sup>[8-10,13]</sup>

*Staphylococcus* spp. is the most commonly isolated from both mixed and single isolations, accounting for 74.07% and 62.5%, followed by *Streptococcus* spp. In the single-isolation groups of Gram-positive bacteria, *S. epidermidis* (44.4%) is the most commonly isolated followed by *S. aureus* (29.62%). Similarly, in mixed isolation, *S. epidermidis* (50%) is the most commonly isolated followed by *S. aureus* (25%). This is similar to Chaudhary *et al.* (2005), Hartikainen *et al.* (1997), and Islam *et al.* (2006).<sup>[8,10,11]</sup>

In cases of Gram-negative bacteria, single isolation reveals *P. aeruginosa* (50%) which accounted for the most commonly isolated bacteria followed by *K. pneumoniae* (21.42%), which is different than Hartikainen *et al.* (1997), who found *Haemophilus influenzae* to be the most common Gram-negative organism isolated.

According to Coden *et al.* (1993), *P. aeruginosa* is the most commonly isolated Gram-negative bacteria.<sup>[13]</sup>

The microbial isolates of chronic dacryocystitis vary with different geographical areas. Reports from Saudi Arabia

(Chaudhary *et al.*, 2005), Toronto (De Angelis *et al.*, 2001), Finland (Hartikainen *et al.*, 1997), China (Sun *et al.*, 2005), and Australia (Sainju *et al.*, 2005) showed predominance of the *Staphylococcus* species, either epidermidis or aureus.<sup>[6,8,9,14,15]</sup> However, studies from the southern part of India (Usha *et al.*, 2006) and Nepal (Badhu *et al.*, 2006) showed predominance of *Streptococcus pneumoniae*.<sup>[16,17]</sup>

According to our study *Streptococcus epidermis* is the most common etiological agent in case of chronic dacryocystitis, while the second most common pathogen is *Staphylococcus aureus*.

#### CONCLUSION

Our study was a hospital-based study, in which 41 patients suffering from chronic dacryocystitis, out of which 7 patients had both eyes involved, were included in the study. We found that chronic dacryocystitis was more predominantly seen in female patients 58.53% (24). From the 48 samples, patients 100% had epiphora while discharge was seen in 50% (24) of cases and swelling was seen in 18.75% (9) of cases. Out of 48 samples, 45 (93.75%) were positive for culture, of which 4 (8.88%) had multiple isolates. Out of 41 single-isolation cultures, 27 are Gram-positive bacteria and 14 are Gramnegative bacteria. *Staphylococcus* spp. (74.07%) is the most commonly isolated Gram-positive organism. In both single and multiple isolates, the most common Gram-negative bacteria isolated was *Pseudomonas* spp.

Our research reveals that the majority of adult individuals with chronic dacryocystitis have microorganisms in their lacrimal sacs, and a sizable proportion of these microorganisms are polymicrobial. The much-increased probability of positive lacrimal sac cultures indicates that, before arranging any intraocular surgeries, ophthalmologists should carefully check for signs of nasolacrimal blockage. Because of the probable danger of endophthalmitis, patients with a history of persistent dacryocystitis should not undergo any intraocular surgeries. Gram-negative organisms, which could be potential pathogens for postoperative intraocular and lacrimal drainage surgery, were present in significant proportions of individuals. Therefore, in addition to the typical precautions, one may think about antibiotic prophylaxis, which also protects against Gram-negative and Gram-positive microorganisms for lacrimal drainage surgery. In patients with chronic dacryocystitis, DCR is recommended before any planned intraocular procedure.

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### Retrospective Analysis of Outcomes of COVID Patients in a District-Level Hospital: CRP Surveillance and Guiding Management in Severe COVID Patients

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#### Abstract

**Background:** Several biomarkers have been explored to predict the severity of various infectious diseases. We aimed to evaluate the outcome of COVID-19 patients and the ability of the C-reactive protein (CRP) to predict the severity of COVID-19 infections.

**Materials and Methods:** A retrospective study on the surveillance of CRP-1 (within 24 h) and CRP-2 (within 48 h) was conducted among 906 patients who were diagnosed with COVID 19 infection via reverse transcription–polymerase chain reaction. The data on demographic characteristics and clinical and laboratory findings were collected from electronic health records. The association between CRP-1 and CRP-2 values and patient characteristics, comorbidity, severity, and outcome was analyzed using Cramer's V test with P < 0.05, which was considered statistically significant. In addition, the sensitivity and specificity of both CRPs (1 and 2) were also analyzed using receiver operating characteristic (ROC) curves for predicting disease severity in COVID-19 infection.

**Results:** The results suggest that age, clinical severity, CT score severity, and final outcome had a significant association with CRP-1 and CRP-2 values. Increased CRP levels in COVID-19 patients are strongly associated with mortality. Furthermore, the ROC curves showed an area under the curve of 0.75 with an overall sensitivity and specificity of 96.15 and 83.33, respectively.

**Conclusion:** In the present study, CRP levels were found to increase dramatically among COVID-19 patients, and our findings suggest that CRP could be utilized clinically to predict COVID-19 prognosis and severity even before disease progression and the manifestation of clinical symptoms.

Key words: Covid 19, Bio marker, C-Reactive protein, Outcomes, Infectious Disease, Cramer's V test

#### **INTRODUCTION**

In December 2019, novel coronavirus emerged in Wuhan City, Hubei Province, China. The coronavirus disease-19 (COVID-19) outbreak is an emerging global health threat across the world.<sup>[1]</sup> As of August 24, 2022, the WHO globally reported 595,219,966 confirmed cases



of COVID-19 and 6,453,458 deaths, in India there are 44,368,195 confirmed cases with 527,452 deaths.<sup>[2]</sup> Many COVID-19 patients exhibit mild symptoms, or sometimes do not exhibit symptoms at all. An emerging challenge is that a small subset of patients with mild or non-severe COVID-19 patients develops into a severe disease course. Therefore, it is important to early identify and give treatment to this subset of patients to reduce the disease severity and improve the outcomes of COVID-19.

The complex pathogenesis of severe acute respiratory syndrome-like cytokine storm, multiorgan disease, and disruption of numerous physiological pathways encompassing fibrinolysis and hemostasis leads to unpredictable clinical progression of the disease,

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which may evolve abruptly and result in critical and life-threatening clinical complications.<sup>[3]</sup> Effective clinical laboratory biomarkers aid in classifying patients according to risk and therefore ensure timely treatment to achieve the desired clinical outcomes. Various inflammatory, biochemical, and hematological biomarkers have been identified in COVID-19 patients, such as procalcitonin, lactate dehydrogenase, urea, liver enzymes, serum amyloid A, cytokines, D-dimer, fibrinogen, ferritin, troponin, creatinine kinase, leukocyte, and platelet counts and lymphocytes.<sup>[2]</sup> C-reactive protein (CRP) is an acute phase that binds to phosphocholine and activates the classical complement pathway of the immune system and regulates phagocytic activity to clear microbes and damaged cells. The normal concentration of CRP in the blood is <10 mg/L; however, it rises rapidly within 48 h from the disease onset and declines abruptly once the infection subsides.<sup>[4-6]</sup> An increase in CRP concentration is associated with acute kidney injury, with an incidence of venous thromboembolism and cardiovascular disease.<sup>[7,8]</sup> Hence, early recognition and timely intervention of COVID-19 are crucial factors for preventing adverse clinical outcomes. Many studies have suggested that CRP can be used as a prognostic biomarker in acute and chronic infections, including malaria, dengue, and hepatitis C.<sup>[9,10]</sup> The current study focused on the outcome of COVID-19 patients and determined the association between CRP levels and disease progression to provide a reference for the clinical management of COVID-19 patients.

#### **MATERIALS AND METHODS**

A total of 2656 patients were diagnosed with COVID-19 infection via reverse transcription-polymerase chain reaction (RT-PCR) at Thangam Hospital, Namakkal, Tamil Nadu. This retrospective study was conducted among 906 patients who were admitted and met both the inclusion and exclusion criteria. The inclusion criteria included patients above the age of 18 years, confirmed cases of COVID-19 with positive RT-PCR results, and patients who were hospitalized in the study center including those with comorbidities. Exclusion criteria included those patients whose clinical and laboratory data were missing and pregnant women. Ethical clearance was obtained from the institutional ethical committee and prior permission was obtained to access the electronic medical records of COVID-19 patients between July 2020 and February 2022.

#### **CRP** Assessment

A CRP level of 6 mg/L was taken as baseline. CRP levels <6 mg/L were considered normal and CRP levels above 6 mg/L were considered to be abnormal. Abnormal CRP

levels from the entry point were used to assess the severity and progression of the illness and to determine its outcome

#### **Clinical Severity Categorization**

- 1. Mild: RT-PCR-positive COVID-19 patients with or without mild symptoms such as fever, cough, and sore throat, with mild changes in chest X-ray, and with abnormal respiratory function with SpO2 >90%
- Moderate: RT-PCR-positive COVID-19 patients with features of dyspnea or hypoxia, moderate changes in chest X-ray, and abnormal respiratory function with SpO<sub>2</sub> of 75–90%
- 3. Severe: RT-PCR-positive COVID-19 patients with clinical symptoms of pneumonia, abnormal changes in chest X-ray, and abnormal respiratory function with  $SpO_2 < 75\%$ .

#### **CT Severity Score**

<8 score - Mild 9–15 - Moderate >15 - Severe.

#### **Statistical Analysis**

Python v3.8 was used to perform all the statistical analyses. Pandas, Numpy, Seaborn, Matplotlib, Sklearn, and SciPy packages were used: The correlation study between CRPs (CRP-1 and CRP-2) and the categorical variables was assessed using Cramer's V test with P < 0.05, which was considered statistically significant. The sensitivity and specificity of both CRP levels (1 and 2) were also analyzed using receiver operating characteristic curves to predict disease severity in COVID-19 patients.

#### RESULTS

A total of 906 patients were included in this study. Among 906 patients, 68.1% were male and 31.9% were female. The mean age of patients included in the study was 54.45. Table 1 demonstrates the demographic data (age and sex) of the patients along with median CRP-1 and CRP-2 levels. The results showed a statistically significant association between CRP level and advanced age. As age increases, CRP levels also increase. Further it shows that males have higher CRP levels when compared to females with median CRP-1 (21.01) and CRP-2 (16.61). The results were considered statistically significant [Table 1].

The patients included in the study presented with comorbidities, such as 2.75% chronic kidney disease (CKD), 7.83% coronary heart disease (CAHD), 33.6% hypertension (HTN), 38.07% diabetes mellitus (DM), 3.53% lung disease, and 2.31% malignancy. 23% of patients had normal CRP 1, n = 213, and 76% of patients had

Table	1: The demographic	c data (age	and sex) of th	ne patie	ents along with the	median CRP	-1 and	CRP-2 levels
S. No.	Patient characteristics	Categories	Median CRP-1	IQR	P-value (Cramer's V)	Median CRP-2	IQR	P-value
1	Age	18–60 years	18	64.465	<0.001 (0.1156)	17.28	44.505	<0.001 (0.256)
		>60 years	39.57	79.065		28.87	68.335	
2	Gender	Female	21.01	56.705	<0.001 (0.1112)	16.61	40.95	<0.001 (0.1112)
		Male	29.98	79.16		23	59.63	

CRP: C-reactive protein

abnormal CRP 1, n = 693. Similarly, 26% of patients had normal CRP-2, n = 238, and 73% had abnormal CRP-2, n = 668. About 0.8% were current smokers while 1.5% had a history of smoking.

In the current study, a percentage of clinically mild, moderate, and severe patients were 28.1%, 31.12%, and 38.19%, respectively. Based on the CO-RADS score, 38.19%, 34.92%, and 27.48% of cases were severe, moderate, and mild, respectively. A total of 77.48% of the patients had a SpO<sub>2</sub> >90, 20% had a SpO<sub>2</sub> of 75–90 and 1.76 had <75. Furthermore, 60.26% of the patients were administered remdesivir, 80.13% were administered steroids, and 2.64% were administered tocilizumab for treatment [Table 2].

Of total patients included in the current study, 39.5% of the patients required oxygen supplement. 7.17% needed high-flow nasal oxygen. 60.26% of the patients were given remdesivir for treatment. 80.13% were given steroids and 2.64% were given tocilizumab. Patients who required oxygen supplement, remdesivir, steroids, tocilizumab, and high-flow nasal oxygen had a significant association with CRP-1 and CRP-2 levels [Table 3].

Table 4 depicts the correlation between clinical severity and CRP-1 and CRP-2 levels in COVID-19 patients. The median CRP-1 for patients who experienced mild clinical severity was 5.63. The median CRP-1 for patients who experienced moderate clinical severity was 23.73. The median CRP-1 for patients who experienced severe clinical severity was 64.1. Similarly, 3.79 was the median CRP-2 for patients with mild clinical severity. The median CRP-2 for patients who experienced moderate clinical severity was 18.485. The median CRP-2 for patients who experienced severe clinical severity was 46.51. The results were statistically significant and suggested that as the clinical severity increased, the disease progressed with an elevation of both CRP-1 and CRP-2 levels. This infers that there was an increase in CRP levels in severe cases than in mild and moderate cases, suggesting that the CRP level may be a biomarker of disease severity and progression in patients with COVID-19.

Table 4 also depicts the correlation of CT score with CRP in COVID-19 patients. The median CRP-1 with mild, moderate, and severe CT scores was 4.98, 22.78,

### Table 2: The percentages of various categoricalvariables in the study

Variable	Category	Frequency	Percent
CT scan (CO-RADS score)	Severe	346	38.2
	Moderate	311	34.3
	Mild	249	27.5
Clinical severity	Severe	369	40.7
	Moderate	282	31.1
	Mild	255	28.2
CRP-1	Abnormal	693	76.5
	Normal	213	23.5
CRP-2	Abnormal	668	73.7
	Normal	238	26.3
Current smoker	Y	7	0.8
	Ν	899	99.2
Past smoker	Y	14	1.5
	N	892	98.5
CAHD			
Y-Yes	Y	835	92.2
N-No	N	71	7.8
CKD (Y/N)	Ν	881	97.2
	Y	25	2.8
HTN (Y/N)	Y	601	66.3
	Ν	305	33.7
DM (Y/N)	Ν	561	61.9
× ,	Y	345	38.1
Lung disease (Y/N)	Ν	874	96.5
	Y	32	3.5
Malignancy	Ν	885	97.7
	Υ	21	2.3

 $\mathsf{CKD}:$  Chronic kidney disease, CAHD: Coronary heart disease, DM: Diabetes mellitus, HTN: Hypertension

and 64.9, respectively. Similarly, the median CRP-2 with mild, moderate, and severe CT scores was 4.15, 19.29, and 45.71, respectively. The results were statistically significant and suggested that as the CT score increases, the disease is progressed and documented with an increase in CRP levels [Table 4].

Table 5 depicts the correlation of patient outcome and CRP-1 and CRP-2 levels. 89% of the patients were alive and healthy, 3.4% of the patients were alive but morbid, and 7.6% were dead. Furthermore, the median CRP-1 and CRP-2 in alive patients were 21.42 and 18.67, respectively. Similarly, the median CRP-1 and CRP-2 in dead patients were 73.07 and 68.5, respectively. This infers that CRP concentrations remain high in expired patients; therefore, CRP could be a promising biomarker for assessing mortality [Table 5].

Fable 3: The treatment modality and median CRP-1 and CRP-2 levels							
Variable	Category	Frequency	Percent	Median CRP-1	Median CRP-2	P-value	
Oxygen requirement (Y/N)	N	548	0.604857	10.93	10.545	<0.001	
	Y	358	0.395143	63.82	45.865	(0.1012)	
Remdesivir (Y/N)	Y	546	0.602649	37.93	28.79	< 0.001	
	Ν	360	0.397351	11.37	11.085	(0.1077)	
Steroids (Y/N)	Y	726	0.801325	37.02	27.39	< 0.001	
	Ν	180	0.198675	5.705	4.745	(0.1178)	
Tocilizumab (Y/N)	Ν	882	0.97351	24.73	20.7	0.024 (0.983)	
	Y	24	0.0264901	80.52	29.49		
High-flow nasal oxygen (Y/N)	Ν	841	0.928256	20.83	18.34	<0.001 (0.980)	
	Y	65	0.0717439	73.07	70.02		

CRP: C-reactive protein

Table 4: Correlation of clinical severity	y and CT score with	h CRP-1 and CRP-2 levels in COVID-19 patient	ts

S. No.	Patient characteristics	Categories	Median CRP-1	IQR	P-value	Median CRP-2	IQR	P-value
1	Clinical severity	Mild	5.63	11.9	<0.001 (0.942)	3.79	10.23	<0.001 (0.863)
		Moderate	23.735	54.67		18.485	33.1	
		Severe	64.12	89.14		46.51	72.38	
2	CT score severity	Mild	4.98	9.43	<0.001 (0.952)	4.15	10.82	<0.001 (0.878)
		Moderate	22.78	54.67		19.29	38.8	
		Severe	64.96	88.465		45.71	72.04	

CRP: C-reactive protein

Table 5: Correlation of patient outcome and CRP-1 and CRP-2 levels									
S. No.	Outcome	Frequency	Percentage	Median CRP-1	IQR	P-value	Median CRP-2	IQR	P-value
1	AH	806	89%						
2	D-Dead	69	3.4%						
3	Am-Alive morbid	31	7.6%						
4	ALIVE	837	92.3%	21.42	66.91	<0.001 (0.1300)	18.67	46.41	<0.001 (0.1265)
5	DIED	69	7.6%	73.07	78.87	. ,	68.5	81.685	<0.001 (0.1265

AH: Alive healthy, CRP: C-reactive protein

Table 6 depicts the association between median CRP levels in patients who are dead while having the comorbidities. The results showed a significant association between CRP-1 and CRP-2 levels in patients who died while having the comorbidities [Table 6].

Figure 1 represents the receiver operating characteristic (ROC) curves of CRP-1 and CRP-2 for predicting the disease severity in COVID-19 patients. Analysis of the ROC curve illustrated an area under the curve 0.75 with overall sensitivity and specificity of 96.15 and 83.33, respectively [Table 5]. The biomarker indicated a high diagnostic value for assessing the clinical severity. The sensitivity and specificity of CRP-1 were 94.23% and 46.79%, respectively. Similarly, the sensitivity and specificity of CRP-2 were 92.3% and 55.04%, respectively [Table 7].

#### DISCUSSION

The current retrospective study evaluated the outcome of 906 COVID-19 patients and the association between CRP and COVID-19 infection. Among the 906 patients, 68.1% were male and 31.9% were female. The mean age of patients included in the study was 54.45. The patients included in the current study presented with comorbidities such as 2.75% CKD, 7.83% with CAHD, 33.6% HTN, 38.07% with DM, 3.53% with lung disease, and malignancy 2.31%.

CRP is an acute-phase protein synthesized by the liver and increases during inflammatory responses. Studies<sup>[11,12]</sup> have shown that CRP levels are increased in viral and bacterial infections. Many studies have suggested that CRP can be used as a prognostic biomarker for acute and chronic infections. Data published in recent studies suggest that severe COVID-19 patients have higher CRP levels than non-severe COVID-19 patients.<sup>[13-17]</sup> CRP levels in COVID-19 patients can effectively predict disease severity, outcomes, prognosis, and mortality. In the current study out of 906 patients, the median CRP-1 for patients who experienced mild clinical severity was 5.63. The median CRP-1 for patients who experienced moderate clinical severity was 23.73. The median CRP-1 for patients who experienced severe clinical severity was 64.1. Similarly,

Table 6: Association between median CRP levels in patients who are dead while having the comorbidities							
Comorbidity	Cat	Median CRP-1 (dead)	IQR	P-value (Cramer's V)	Median CRP-2 (dead)	IQR	P-value (Cramer's V)
DM	Y	94.95	113.45	<0.001 (0.96)	71.985	84.73	<0.001 (0.93)
	Ν	64.12	67.65		51.93	75.43	
CKD	Y	57.78	103.02	<0.001 (0.92)	62.99	85.6	<0.001 (0.91)
	Ν	73.07	85.59		68.5	80.11	
CAHD	Y	81.7	97.945	<0.001 (0.90)	86.995	92.025	<0.001 (0.80)
	Ν	70.76	77.95		66.97	79.34	
HTN	Y	73.185	91.89	<0.001 (0.89)	68.445	87.085	<0.001 (0.83)
	Ν	70.76	76.54		68.5	76.57	
Lung disease	Y	6.53	NA	<0.001 (0.82)	26.67	NA	<0.001 (0.92)
	Ν	73.68	77.38		69.21	79.77	
Malignancy	Y	52.76	NA	<0.001 (0.96)	41.61	NA	<0.001 (0.96)
	Ν	73.185	80.04		69.97	83.26	

CRP: C-reactive protein, CKD: Chronic kidney disease, CAHD: Coronary heart disease, DM: Diabetes mellitus, HTN: Hypertension

Table 7: The sensitivity and specificity	
Results	Percentage
Sensitivity	96.15
Specificity	83.33
Positive likelihood ratio	5.769
Negative likelihood ratio	0.04615



Figure 1: The receiver operating characteristic curves of C-reactive protein-1 and C-reactive protein-2

3.79 was the median CRP-2 for patients with mild clinical severity. The median CRP-2 level in patients with moderate clinical severity was 18.485. 46.51 was the median CRP-2 for patients who experienced severe clinical severity. The results were statistically significant and suggested that as the clinical severity increased, the disease progressed with an elevation of both CRP-1 and CRP-2 levels. This infers that there was an increase in CRP levels in severe cases than in mild and moderate cases, suggesting that the CRP levels in COVID-19 patients can effectively predict disease severity and prognosis. This further helps in step-up or step-down interventions in critical care setting.

The current study correlated the CT scores with CRP levels in COVID-19 patients. The median CRP-1 with mild, moderate, and severe CT scores was 4.98, 22.78,

and 64.9, respectively. Similarly, the median CRP-2 with mild, moderate, and severe CT scores was 4.15, 19.29, and 45.71, respectively. The results were statistically significant and suggested that as the CT score increased, the disease progressed and was documented with an increase in CRP levels. Furthermore, this suggests the usefulness of the CT severity score in triaging the cases. Several studies have documented similar observation.<sup>[18-20]</sup>

Of total patients included in the current study, 39.5% of the patients required oxygen supplement. 7.17% needed high-flow nasal oxygen. 60.26% of the patients were given remdesivir for treatment. 80.13% were given steroids and 2.64% were given tocilizumab. The current study documented higher CRP levels in severe cases requiring oxygen and high-flow nasal oxygen supplement. This suggests that the CRP level may be used as a potential biomarker in assessing the COVID-19 prognosis.

The current study correlated patient outcomes with CRP-1 and CRP-2 levels. Of patients, 89% were alive and healthy, 3.4% were alive but morbid, and 7.6% had died. The median CRP-1 and CRP-2 levels in alive patients were 21.42 and 18.67, respectively. Similarly, the median CRP-1 and CRP-2 in dead patients were 73.07 and 68.5, respectively. Furthermore, a significant association was found between CRP-1 and CRP-2 levels patients who died while having the comorbidities. This infers that CRP concentrations remain high in expired patients as compared to alive patients which indicate that an increase in CRP level is strongly associated with the prognosis of COVID-19 which must be employed within the clinical practice to guide COVID-19 disease severity and predictable marker in assessing mortality rate.

The overall sensitivity and specificity of CRP were 96.15 and 83.33, respectively. The biomarker indicated a high diagnostic value for assessing the clinical severity. The sensitivity and specificity of CRP-1 were 94.23% and 46.79%, respectively. Similarly, the sensitivity

and specificity of CRP-2 were 92.3% and 55.04%, respectively.

#### **CONCLUSION AND LIMITATION**

CRP levels increase during inflammatory responses, and measurement of CRP alone is the most practical tool to monitor disease outcomes in COVID-19 patients. Limitations of the current study include that it is a retrospective study and assessed only CRP-1 (within 24 h) and CRP-2 (within 48 h). Therefore, to confirm our findings, a large multicenter clinical study should be conducted with multiple CRP level measurements measured at different treatment times.

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### **Evaluation of Risk Factors of Recurrent Pregnancy Loss in Kashmiri Women**

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#### Abstract

Recurrent pregnancy loss (RPL) is defined as three or more consecutive, spontaneous pregnancy losses under 20-week gestation. Age of the mother, genetics, uterine abnormalities, hormonal disorders, metabolic disorders, lifestyle, sperm quality, immunological factors, environmental factors, previous pregnancy loss, etc., are commonly associated with RPL. The present observational study was conducted in the Department of Obstetrics and Gynaecology in GMC Srinagar Lall Ded Hospital with the aim to evaluate the risk factors of RPL among Kashmiri women. A total of 50 pregnant Kashmiri women were screened. It was an observational study. There was no conflict of interest. It was observed that the majority of the study subjects were in the age group of 26–30 years (46%), most of the subjects had three abortions (42%), majority of the study subjects had secondary education (32%), and most of the subjects were from urban area (56%). The most common cause of RPL was endocrinal problems (28%), followed by immunological problems (22%), anatomical factors (18%), unknown causes (12%), chromosomal defects (8%), and 4% subjects had other causes. The study concluded that the RPL is a common health issue among women in child-bearing age. In study subjects who had immunological problems, the most common involved factor was APLA (72.72%).

Key words: Abortion, Miscarriage, Pregnancy loss, Pregnancy problems and risk factors

#### INTRODUCTION

Among women of child-bearing age, the pregnancy loss and miscarriage are common problems. Three or more consecutive spontaneously failed pregnancies before 20 weeks of gestation are characterized by recurrent pregnancy loss (RPL).<sup>[1]</sup> The secondary RPL is an incident of pregnancy loss following one or more prior pregnancies advancing beyond 24 weeks of gestation and primary RPL is defined as the pregnancy loss without a prior pregnancy beyond 24 weeks of gestation.<sup>[2]</sup>

It is estimated that approximately 15–25% of pregnancies had RPL. The available data showed that various factors are related to RPL such as age of the mother, genetics, uterine abnormalities, hormonal disorders, metabolic

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disorders, lifestyle, sperm quality, immunological factors, environmental factors, and previous pregnancy loss.<sup>[3]</sup>

The RPL and its causes or associated factors should be investigated to provide better treatment and to achieve a successful pregnancy.

Thus, the present study was conducted to evaluate the risk factors of RPL among Kashmiri women.

#### **MATERIALS AND METHODS**

The present observational study was conducted in the Department of Obstetrics and Gynaecology in GMC SRINAGAR over a period of 6 months (July 2022–December 2022) after taking the permission from the concerned authority.

A total of 50 pregnant Kashmiri women were involved in the study after obtaining the informed consent from them.

#### **Inclusion Criteria**

- 1. Age >18 years
- 2. Pregnant women with a history of 2 or more spontaneous abortions.

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#### **Exclusion Criteria**

- 1. Pregnant women with a history of one spontaneous abortion
- 2. Pregnant women with a history of induced abortions.

A detailed history was collected, and all the study subjects were examined. Demographic variables were analyzed and all the patients were screened for the involved risk factors.

Data were recorded in Microsoft Excel sheet and analyzed with SPSS version 20.0.

#### **OBSERVATIONS AND RESULTS**

Table 1 depicts that the majority of the study subjects were in the age group of 26–30 years (46%), followed by 31–35 years (28%), 21–25 years (18%), >35 years (6%), and  $\leq 20$  years (2%).

It was reported that the majority of the subjects had three abortions (42%), followed by subjects with two abortions (32%), subjects with four abortions (14%), and subjects with five abortions (12%) as shown in Table 2.

In our study, the most of the study subjects had secondary education (32%), followed by subjects with higher education (28%), subjects with primary education (16%), and 16% subjects were illiterate as presented in Table 3.

In our study, the majority of subjects were from urban area (56%) as shown in Table 4.

In Table 5, it is depicted that the majority of the subjects had primary RPL (68%) and 32% had secondary RPL.

It was found that most (62%) of the study subjects were in the first trimester of pregnancy and 38% subjects were in secondary trimester of pregnancy [Table 6].

Table 7 depicts that the most common cause of RPL was endocrinal problems (28%), followed by immunological problems (22%), anatomical factors (18%), unknown causes (12%), chromosomal defects (8%), and 4% subjects had other causes.

Table 8 shows that, in subjects with first trimester of pregnancy, the most common cause of RPL was endocrinal problems (35.48%), followed by immunological problems (29.03%), unknown cause (12.9%), anatomical factors (9.67%), and chromosomal abnormalities and infection (6.45%), respectively, whereas, in subjects with second trimester of pregnancy, the most common cause of RPL was anatomical factors (31.57%), followed by endocrinal problems (15.78%), chromosomal abnormalities,

#### Table 1: Age distribution

Age wise distribution	Number	%
≤20 year	1	2
21–25 year	9	18
26–30 year	23	46
31–35 year	14	28
>35 year	3	6

#### Table 2: Distribution as per number of abortions

Number of abortions	Number	%	
A2	16	32	
A3	21	42	
A4	7	14	
≥A5	6	12	

#### Table 3: Educational status

Education	Number	%
Illiterate	8	16
Primary	12	24
Secondary	16	32
Higher	14	28

### Table 4: Residence

Area/Locality	Number	%
Urban	28	56
Rural	22	44

Table 5: Type of recurrent pregnancy loss					
Types of RPL	Number	%			
Primary	34	68			
Secondary	16	32			

RPL: Recurrent pregnancy loss

Table 6: Trimester				
Trimester	Number	%		
First trimester	31	62		
Second trimester	19	38		

Table 7: Causes of recurrent pregnancy loss				
Etiology of RPL	Number	%		
Anatomical factors	09	18		
Endocrine	14	28		
Chromosomal	04	8		
Immunological	11	22		
Infectious	04	08		
Unknown cause	06	12		
Others	02	04		

RPL: Recurrent pregnancy loss

### Table 8: Causes of recurrent pregnancy loss infirst and second trimester

Etiology of first trimester ( <i>n</i> =31)	Number	%
Anatomical factors	03	9.67
Endocrine	11	35.48
Chromosomal	02	6.45
Immunological	09	29.03
Infectious	02	6.45
Unknown cause	04	12.9
Etiology of second trimester ( <i>n</i> =19)	Number	%
Anatomical factors	06	31.57
Endocrine	03	15.78
Chromosomal	02	10.52
Immunological	02	10.52
Infectious	02	10.52
Unknown cause	02	10.52
Others	02	10.52

Table	9:	Immuno	logical	factors
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Etiology	Number	%
APLA	8	72.72
SLE	1	9.09
Grave's disease	1	9.09
Rheumatoid arthritis	1	9.09



immunological problems, infection, unknown causes, and others (10.52% each, respectively).

It was observed that, among the study subjects who had immunological problems, the most common involved factor was APLA (72.72%), followed by SLE, Grave's disease [Figure 1], and rheumatoid arthritis (9.09% each, respectively) [Table 9].

#### DISCUSSION

In the present study, a total of 50 pregnant Kashmiri [Figure 2] women were evaluated for the associated risk factors



Figure 1: Distribution as per number of abortions



Figure 3: Educational status



Figure 4: Residence

involved in RPL. The data were analyzed and discussed with previously available literature [Figures 3 and 4].

In our study that the majority of the study subjects were in the age group of 26–30 years (46%), most of the subjects



Figure 5: Type of recurrent pregnancy loss



Figure 6: Trimester



Figure 7: Causes of recurrent pregnancy loss

had three abortions (42%), majority of the study subjects had secondary education (32%), and most of subjects were from urban area (56%). These findings are consistent with the study conducted by Chester *et al.* (2022) reported that most of the patients were in the advanced age.<sup>[4]</sup> According to ACOG, it was reported that most of the patients were in advanced age. Similar study conducted by Singh *et al.* (2017) observed that the majority of the study subjects



were in the age groups of 26–30 years, most of the subjects had G4 gravida (37%), majority of the study subjects had higher education (57%), and most of subjects were from urban area (63%).<sup>[5,6]</sup>

The current study found that the majority of the subjects [Figure 5] had primary RPL (68%) and 32% had secondary RPL, whereas most (62%) of the study subjects were in [Figure 6] the first trimester of pregnancy and 38% subjects were in the secondary trimester of pregnancy. These results are comparable with the studies conducted by Jaslow *et al.*, Jivraj *et al.*, and Li *et al.*, found that the most of the study subjects had primary RPL.<sup>[7-9]</sup>

It was observed that, among all the subjects, the most common cause of RPL was endocrinal problems (28%), followed by immunological problems (22%), anatomical factors (18%), unknown causes (12%), chromosomal defects (8%), and 4% subjects had other causes [Figure 7]. Moreover, among the study subjects who had immunological problems, the most common involved factor was APLA (72.72%), followed by SLE, Grave's disease, and rheumatoid arthritis (9.09% each, respectively) [Figure 8]. The findings are correlated with the study conducted by Jaslow *et al.* found that among majority of the subjects had endocrine problems.<sup>[7]</sup> Another study conducted by Noble reported that most of the patients had APLA factors for RPL.<sup>[10]</sup>

#### CONCLUSION

The present observational study concluded that RPL is a common health issue in women (child-bearing age). In our study, the most common cause of RPL was endocrinal problems.

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### Spectrum of Histomorphological Lesions of Gallbladder in Cholecystectomy Specimens: A cross-sectional Study

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#### Abstract

**Background:** Gallbladder (GB) diseases are one of the most common digestive system diseases that include chronic cholecystitis, cholesterolosis, xanthogranulomatous cholecystitis (XGC), and malignant lesions as adenocarcinoma.

**Aims and objectives:** (1) The aim of the study was to study the range of histomorphological lesions in Cholecystectomy specimens, (2) to determine the age and sex distribution among patients with the lesions, (3) to ascertain the frequency of various histopathological benign and malignant lesions in cholecystectomy specimens, and (4) to evaluate the status of epidermal growth factor receptor expression in encountered adenocarcinoma GB cases.

**Materials and Methods:** In present study, we have studied total 170 cases of GB lesion during the period of 18-month study from January 2021 to June 2022 in the Department of Pathology at T.S. Misra Medical College and Hospital, Lucknow.

**Results:** GB lesions were more common in females as compared to male with a male: female ratio of 1:4.15. Among 61–70year age group, males were more than females. In all other age groups, females were more than males. Majority of the subjects presented with Chronic Cholecystitis (48.8%) and Chronic Cholecystitis with cholelithiasis (20.6%) along with few cases of low-grade dysplasia, high-grade dysplasia, poorly differentiated adenocarcinoma GB, and XGC also seen in our study. EGFR was given a score of 2+ in a case of chronic acalculous cholecystitis with high-grade dysplasia. EGFR was given a score of 3+ in both cases of poorly differentiated adenocarcinoma GB staging.

**Conclusion:** There is thus an overarching need for routine histopathological examination of the resected GB specimens to exclude premalignant ailments such as intestinal metaplasia and dysplasia. These lesions may progress to GB adenocarcinoma.

Keywords: Adenocarcinoma, Cholecystitis, Gallbladder

#### **INTRODUCTION**

The prevalence of gallbladder (GB) diseases is variable within India and ranges from 2% to 29%.<sup>[1]</sup> The spectrum of ailments that afflict the GB can be inflammatory, congenital, or neoplastic in nature.<sup>[2,3]</sup> Inflammatory conditions of the



GB are more common than other GB pathologies and encompass a spectrum of ailments including acute, chronic, follicular, or xanthogranulomatous cholecystitis (XGC).<sup>[4,5]</sup> Cholelithiasis is one of the common health problems encountered all over the world causing economic burden in developing countries.<sup>[6]</sup> Cholelithiasis affect 10–20% of adult population in developed countries.<sup>[7]</sup> The risk factors for the development of gall stone disease (GSD) can be categorized as non-modifiable and modifiable.

Gallstones appear to be the most important risk factor, being reported in 70–98% cases of GB carcinoma, a far higher prevalence than that in age-matched general population.<sup>[8]</sup> GSD helps to develop the pathology in GB

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cells or tissues where GB carcinoma (GBC) is most fatal transformation. Hyperplasia and metaplasia of the GB are the precursors of dysplasia and dysplasia itself is a potential condition of carcinoma.<sup>[9]</sup> GB cancer (GBC) is most common malignancy of the biliary tract.<sup>[10]</sup> GB carcinoma ranks 5<sup>th</sup> in the gastrointestinal malignant tumors, and due to non-specific clinical presentation, it is rarely diagnosed at an early stage.<sup>[11]</sup> GB carcinoma is a rare condition. It is not very uncommon as an incidental histological finding following cholecystectomy for gallstone diseases.<sup>[12]</sup>

The incidence of GB carcinoma in India ranges 1.01/100,000 for males and 10.1/100,000 for females.<sup>[13]</sup> The biological behavior of carcinoma GB is based on certain well-established morphological features such as tumor size, site, grade, type, invasion, and metastatic state. Molecular markers, such as EGFR expressions along with other markers such as CEA, EMA, alpha fetoprotein, and CDX2, may also use to determine the behavior of tumor.<sup>[14]</sup> Thus, it is important to study histomorphological changes to determine the incidence, prevalence, and distribution of lesions. The present study was done to study the spectrum of histomorphological lesions of GB in cholecystectomy specimens.

#### **MATERIALS AND METHODS**

This cross-sectional observational study was conducted after clearance from the Board of Studies and Ethical committee in the Department of Pathology at T.S. Misra Medical College and Hospital, Lucknow. The total sample size was determined to be 170 patients. The study included all specimens of cholecystectomy-open and laparoscopic. The study excluded specimens without any clinical details, specimens too tiny or inadequate to evaluate, autolyzed specimens, and post-chemo/radiotherapy cases.

Patient's clinical data comprising clinical features and laboratory investigations reports were collected from medical records in surgically resected specimens. The specimen was fixed in 10% buffered formalin overnight. Gross findings of the outer surface of GB, mucosa, and any other gross lesions were noted. Mucosa was examined whether velvety, bile-stained, flattened with whitish streaks, any growth, ulceration, congestion, or polyp. Wall thickness was noted.

Sections were taken from the fundus, body-and-neck of the GB, additional sections were taken from abnormal appearing mucosa, thickened wall, ulcerated areas, or any growth if present. This were followed by processing with routine histopathological techniques for paraffin embedding and sectioning at 5- $\mu$  thickness. The tissue sections were placed on a slide warmer for deparaffiniation and further deparaffinization using xylene, followed by hematoxylin and eosin.

#### **Inclusion Criteria**

• All specimens of cholecystectomy-open and laparoscopic.

#### **Exclusion Criteria**

- Specimens without any clinical details
- Specimens too tiny or inadequate to evaluate
- Autolyzed Specimens
- Post-chemo/radiotherapy cases.

The following IHC protocol was used

- Score 0 = No staining is observed
- Score 1+ = Faint membrane staining in more than 1% of tumor cells in part of the cell membrane
- Score 2+ = Weak-to- moderate complete membrane staining in over 1% of tumor cells
- Score 3+ = Strong complete membrane staining in over 1% of tumor cells

The statistical tests were applied as follows: quantitative variables in any two groups were compared using independent t-test. Qualitative variables were correlated using Chi-square test/Fisher exact test.

#### RESULTS

Among study population, there were 27.6% of subjects from 18 to 30 years, 29.4% from 31 to 40 years, 20.6% from 41 to 50 years, 17.1% from 51 to 60 years, 4.1% from 61 to 70 years, and 1.2% from above 70 years. The mean age of the study population was  $40.17 \pm 12.52$  (18–77) years [Table 1].

There were 33 (19.4%) males and 137 (80.6%) females with a male: female ratio of 1:4.15 [Table 2].

Among 61–70-year age group, males were more than females. In all other age groups, females were more than males [Table 3].

Table 1: Distribution of study population according	ng
to age groups	

Age groups	Frequency	Percent		
18–30 years	47	27.6		
31–40 years	50	29.4		
41–50 years	35	20.6		
51–60 years	29	17.1		
61–70 years	7	4.1		
Above 70 years	2	1.2		
Mean±SD	40.17±12.52	40.17±12.52 (18–77)		

Majority of the subjects presented with chronic acalculous cholecystitis (48.8%) and chronic cholecystitis with cholelithiasis (20.6%). There were 14 cases of low-grade dysplasia, 1 case of papillary hyperplasia with chronic acalculous cholecystitis and cholesterolosis and high-grade dysplasia and 2 cases of poorly differentiated adenocarcinoma GB each and 3 cases of XGC [Table 4 and Figures 1-3].

### Table 2: Distribution of study population accordingto gender

Gender Frequency		Percent
Male	33	19.4
Female	137	80.6
Total	170	100.0
Male: Female ratio	1:4.1	5

### Table 3: Distribution of study population accordingto age group

Age groups	Male	Female
18–30 years	5	42
-	10.6%	89.4%
31–40 years	8	42
-	16.0%	84.0%
41–50 years	9	26
-	25.7%	74.3%
51–60 years	5	24
-	17.2%	82.8%
61–70 years	5	2
	71.4%	28.6%
Above 70 years	1	1
	50.0%	50.0%

### Table 4: Distribution of study population accordingto diagnosis

Diagnosis	Frequency	Percent
Chronic acalculous cholecystitis	83	48.8
Chronic cholecystitis with cholelithiasis	35	20.6
Chronic cholecystitis with	30	17.7
cholelithiasis and cholesterolosis		
Eosinophilic cholecystitis	1	0.6
Xanthogranulomatous cholecystitis	3	1.8
Papillary hyperplasia with chronic	1	0.6
acalculous cholecystitis and cholesterolosis		
Chronic cholecystitis with	11	6.6
cholelithiasis and low-grade dysplasia		
Chronic acalculous cholecystitis with	1	0.6
xanthogranulomatous reaction		
with low-grade dysplasia		
Acute on chronic cholecystitis	1	0.6
with cholelithiasis and low-grade dysplasia		
Eosinophilic cholecystitis with	1	0.6
low-grade dysplasia and cholelithiasis		
Chronic acalculous cholecystitis	1	0.6
with high-grade dysplasia		
Poorly differentiated adenocarcinoma	2	1.2
gallbladder Staging - T3 N0 Mx		

Chronic cholecystitis with cholelithiasis and low-grade dysplasia was significantly more among 41–50-year age group [Table 5].



Figure 1: Cholesterolosis (×10)



Figure 2: Chronic acalculous cholecystitis with high-grade dysplasia (×40)



Figure 3: Adenocarcinoma gall bladder (×40)

Diagnosis	Age groups					
	18-30 years	31-40 years	41-50 years	51-60 years	61–70 years	Above 70 years
Chronic acalculous cholecystitis	28	19	15	17	3	0
·	59.6%	36.0%	45.7%	58.6%	28.6%	0.0%
Chronic cholecystitis with cholelithiasis	9	12	10	3	1	0
·	19.1%	24.0%	28.6%	10.3%	14.3%	0.0%
Chronic cholecystitis with	8	14	4	5	1	0
cholelithiasis and cholesterolosis	12.8%	20.0%	2.9%	10.3%	0.0%	0.0%
Acute on chronic cholecystitis	0	0	0	1	0	0
with cholelithiasis and low-grade dysplasia	0.0%	0.0%	0.0%	3.4%	0.0%	0.0%
Chronic cholecystitis with	1	1	5	1	1	1
cholelithiasis and low-grade dysplasia	0.0%	2.0%	2.9%	0.0%	0.0%	50.0%
Chronic acalculous cholecystitis	0	0	0	1	0	0
with high-grade dysplasia	0.0%	0.0%	0.0%	3.4%	0.0%	0.0%
Chronic acalculous cholecystitis with	0	1	0	0	0	0
xanthogranulomatous reaction with low-grade dysplasia	0.0%	2.0%	0.0%	0.0%	0.0%	0.0%
Eosinophilic cholecystitis	0	1	0	0	0	0
	0.0%	2.0%	0.0%	0.0%	0.0%	0.0%
Eosinophilic cholecystitis with	0	0	1	0	0	0
low-grade dysplasia and cholelithiasis	0.0%	0.0%	2.9%	0.0%	0.0%	0.0%
Papillary hyperplasia with chronic	0	1	0	0	0	0
acalculous cholecystitis and cholesterolosis	0.0%	2.0%	0.0%	0.0%	0.0%	0.0%
Poorly differentiated adenocarcinoma	0	0	1	0	0	1
gall bladder Staging - T3 N0 Mx	0.0%	0.0%	2.9%	0.0%	0.0%	50.0%
Xanthogranulomatous cholecystitis	1	1	0	0	1	0
-	2.1%	2.0%	0.0%	0.0%	14.3%	0.0%

#### Table 5: Distribution of study population according to age groups

2º value=12.780, P=0.044\*

Chronic cholecystitis with cholelithiasis and low-grade dysplasia was significantly more among females [Table 6].

EGFR was given a score of 0 in a case of chronic cholecystitis with cholelithiasis and low-grade dysplasia.

EGFR was given a score of 1+ in a case of chronic acalculous cholecystitis with high-grade dysplasia

EGFR was given a score of 3+ in both cases of poorly differentiated adenocarcinoma GB staging [Table 7 and Figure 4].

#### DISCUSSION

In current study, there were 27.6% of subjects from 18 to 30 years, 29.4% from 31 to 40 years, 20.6% from 41 to 50 years, 17.1% from 51 to 60 years, 4.1% from 61 to 70 years, and 1.2% from above 70 years. The mean age of the study population was  $40.17 \pm 12.52$  (1877) years. In concurrence to our study, Mondal *et al.*<sup>[9]</sup> found that mean ages for patients with chronic cholecystitis, hyperplasia, metaplasia, dysplasia, and carcinoma were 34.5, 37.2, 42.9, 43.9, and 53 years, respectively. Talreja *et al.*<sup>[15]</sup> reported the average age of patients was  $41.30 \pm 8.43$  years (range: 26–68 years). Sailabala and Kalyani<sup>[16]</sup> reported that the incidence of non-neoplastic lesions was peak in the age group of 41–60 years and Khan and Abilsh<sup>[17]</sup> reported that the most common age group affected was 4<sup>th</sup>–5<sup>th</sup> decade.

### Table 6: Distribution of study population accordingto gender

Diagnosis	Gender		
	Female	Male	
Chronic acalculous cholecystitis	68	15	
	49.6%	45.5%	
Chronic cholecystitis with cholelithiasis	30	5	
	21.9%	15.2%	
Chronic cholecystitis with	25	5	
cholelithiasis and cholesterolosis	18.2%	15.2%	
Eosinophilic cholesystitis	1	0	
	0.7%	0.0%	
Acute on chronic cholesystitis with	0	1	
cholelithiasis and low-grade dysplasia	0.0%	3.0%	
Chronic cholecystitis with cholelithiasis	10	1	
and low-grade dysplasia	7.3%	3.0%	
Chronic acalculous cholecystitis	0	1	
with high grade dysplasia	0.0%	3.0%	
Chronic acalculous cholecystitis with	1	0	
xanthogranulomatous reaction	0.7%	0.0%	
with low-grade dysplasia			
Eosinophilic cholecystitis with	0	1	
low-grade dysplasia and cholelithiasis	0.0%	3.0%	
Papillary hyperplasia with chronic	1	0	
acalculous cholecystitis and cholesterolosis	0.7%	0.0%	
Poorly differentiated adenocarcinoma	1	1	
gall bladder staging - T3 N0 Mx	0.7%	1.0%	
Xanthogranulomatous cholecystitis	0	3	
-	0.0%	9.1%	

χ<sup>2</sup> value=8.920, *P*=0.046\*

In present study, there were 19.4% males and 80.6% females with a male: female ratio of 1:4.15. Our study

### Table 7: Distribution of study population accordingto EGFR

Diagnosis	EGFR			
	Score 0	Score 1+	Score 2+	Score 3+
Chronic cholecystitis with cholelithiasis and low-grade dysplasia	1	-	-	-
Chronic acalculous cholecystitis with	-	1	-	-
high-grade dysplasia Poorly differentiated adenocarcinoma	-	-	-	2
gallbladder staging				



Figure 4: Immunohistochemistry of adenocarcinoma gallbladder (×20)

findings agreed with Talreja *et al.*<sup>[15]</sup> reported that most of them were females 70.29%. Almas *et al.*<sup>[18]</sup> found a female predominance among the patient population was observed.

In the current study, majority of the subjects presented with chronic acalculous cholecystitis (48.8%) and chronic cholecystitis with cholelithiasis (20.6%). There were 14 cases of low-grade dysplasia, one case of papillary hyperplasia with chronic acalculous cholecystitis and cholesterolosis, 1 case of high-grade dysplasia, 3 cases of XGC, and two cases of poorly differentiated adenocarcinoma GB.

Kulkarni *et al.*<sup>[19]</sup> reported that chronic calculous cholecystitis (57.76%), followed by chronic acalculous cholecystitis (22.36%). Remaining cases were of acute on chronic cholecystitis (6.21%), acute on chronic cholecystitis with cholelithiasis (4.96%), acute on chronic cholecystitis with perforation peritonitis (1.24%), acute suppurative cholecystitis with perforation peritonitis (0.62%), and biliary atresia (1.24%). In the current study, EGFR was given a score of 0 in a case of chronic cholecystitis with cholelithiasis and low-grade dysplasia. EGFR was given a score of 1+ in a case of chronic acalculous cholecystitis

with high-grade dysplasia. EGFR was given a score of 3+ in both cases of poorly differentiated adenocarcinoma GB staging.

Gomes *et al.*<sup>[20]</sup> studied the expression of EGFR in relation to the variables of interest in the 35 cholangiocarcinoma cases. There was significant EGFR expression in ten (28.6%) of the 35 lesions, being score 3+ in eight patients and 2+ in two patients. In 25 patients (71.4%), EGFR expression was negative, being 1+ in five patients and 0 in 20 patients.

#### **CONCLUSION**

GB disease remains a major indication for cholecystectomy. Postoperative histopathological evaluation of the excised GB specimens divulges a vast spectrum of underlying pathologies. Of these, chronic cholecystitis with or without cholelithiasis/cholesterolosis remain the most prevalent. Furthermore, a macroscopic absence of remarkable features does not preclude the presence of an underlying premalignant or malignant lesion. There is thus an overarching need for routine histopathological examination of the resected GB specimens to exclude premalignant ailments such as intestinal metaplasia and dysplasia. These lesions may progress to GB adenocarcinoma.

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### **Clinicoepidemiological Study of Facial Dermatoses in a Tertiary Care Hospital in South India**

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#### Abstract

**Background:** The face is the most prominent, visible part of the body. The obsession for a flawless skin is increasing in both sexes and all age groups. The appearance of face provides identity to the person. Any spot or lesion, especially over the face, can be alarming and draws the attention of the people. However, these problems are seldom given enough importance. Very common problems such as acne vulgaris and melasma can cause serious psychological impact.

**Aims and Objectives:** The objective of the study was to study the clinical pattern and epidemiological determinants of facial dermatoses among the patients of both the sexes, involving all the age groups.

**Materials and Methods:** Two hundred and fifty patients with facial dermatoses presenting to skin department of a tertiary care center in Bachupally, Hyderabad, are selected for the study. Study design is descriptive and cross sectional, conducted from October 2022 to Febraury2023.

**Results:** 250 consecutive patients with newly diagnosed facial dermatosis attending outpatient department are examined and data were recorded. In this study, most common facial dermatoses are pigmentary disorders (41.4%), of which melasma constituted the most common, followed by acne, rosacea, and perioral dermatitis (24.4%). 14.8% are infections and 11.6% are eczemas. There is a wide variation in the age group of the cases. In this study, we observed that maximum number of cases is students.

**Conclusion:** Facial dermatoses are of a major cosmetic concern in all age groups and both the sexes. Early diagnosis and proper management with the education of patients is important to prevent potential disfiguring complications and psychological sequelae. This study provides an insight into various aspects of facial dermatoses encountered in day-to-day practice.

Key words: Acne, Dermatoses, Melasma, Pigmentary disorders, Rosacea

#### INTRODUCTION

The self-esteem, psychological well-being, and social interactions of an individual are significantly impacted by the face.<sup>[1]</sup> As the face is usually a body part that is visible in most societies, imperfections of its skin are also visible; therefore, its flawed appearance bears the potential to become a source of misery to some.<sup>[2]</sup> The appearance of face provides identity to the person. Lesions on the facial skin evoke anxiety and concern to the patient forcing him to seek early medical



attention. Facial skin diseases can have a tremendous impact on a person's quality of life in general. The face extends superiorly from the hairline in adolescence, inferiorly to the chin and mandible base, and on either side to the auricle.<sup>[3]</sup>

Facial skin differs significantly from the skin of the other regions of the body. The facial skin is studded with most numerous sebaceous glands and small hair follicles, making it prone to the development of dermatoses associated with pilosebaceous units. The epidermis is very thin, and melanocytes are numerous. The rete ridges pattern at dermoepidermal junction is often very poorly developed, which makes a distinction between papillary and reticular dermis often difficult to assess.<sup>[4]</sup> Exposure to various climatic conditions has a major and obvious influence on the incidence, type, and natural history of facial dermatoses. The peculiar and unique nature of the facial skin and

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Figure 1: Age distribution of patients



Figure 2: Chart showing occupational pattern



Figure 3: A case of lip vitiligo

the various disorders that may present on it beckons a detailed study of it. Therefore, it is essential for the early identification and management of facial skin disorders.

There are very few clinical studies of facial dermatoses done in this part of India, and hence this cross-sectional



Figure 4: Mid-facial distribution of Melasma



Figure 5: A child with atopic dermatitis



Figure 6: Keratoacanthoma over the cheek

study is conducted in a tertiary care hospital at Bachupally, Hyderabad of Telangana State. The objective of the study is to study the various dermatological conditions affecting the face.

#### **MATERIALS AND METHODS**

A total of two hundred and fifty patients of all age groups and both the sexes, with facial dermatoses presenting to skin department, at Mamata Academy of medical sciences, Bachupally, are screened after obtaining informed written consent. A detailed clinical history including onset and evolution of lesions, socioeconomic factors, and environmental background of the patients are noted for the study. Study design is observational and is conducted over 5-month duration. They are assessed by available demographic and etiological data, detailed history, and clinical examination. The findings are recorded in a predesigned pro forma. Investigations, including the skin scrapings for potassium hydroxide mount, woods lamp examination, skin biopsy, and relevant investigations, wherever required, are done.

Patients and/or their guardians not giving consent; patients with drug reaction, seriously ill patients, and sexually transmitted infections are excluded.

Ethical clearance is obtained before commencing the study.

#### **Data Entry and Analysis**

Data are entered in Microsoft Excel sheet. The results of the study are tabulated and analyzed. Simple proportions and percentages for comparing different variables such as age and sex are used. Final outcome is expressed as the percentage of facial skin disorders among the study group as a whole and as the percentage of individual facial skin disorders.

#### RESULTS

250 patients satisfying the inclusion criteria are enrolled in the study. Various observations are noted as follows:

In the present study, it is found that the majority of the patients belonged to the age group of 11-20 years (30.4%), followed by 21-30 years (26%), 31-40 years (11.6%), 51-60 years (8.8%), 0-10 years (8.4%), and 41-50 years (7.2%). Least incidence is in the age group above 70 years (2.0%), followed by the age group of 61-70 (5.6%) [Table 1 and Figure 1].

In the present study, it is found that there is an increased female preponderance (52.8%) compared to males (47.2%) [Table 2].

In the present study, the majority of the patients (32.4%) are students, followed by 26.8% housewives/homemakers, 23.2% employees, 12.8% manual laborers, and 4.8% agricultural workers [Table 3 and Figure 2].

#### Table 1: Age distribution of patients

Age group	Number of patients	Percentage
0–10	21	8.4
11–20	76	30.4
21–30	65	26
31–40	29	11.6
41–50	18	7.2
51–60	22	8.8
61–70	14	5.6
71–80	5	2
Total	250	

#### Table 2: Sex distribution of patients

Sex	Number of patients	Percentage
Males	118	47.2
Females	132	52.8
Total	250	100

#### **Table 3: Occupational pattern**

Occupation	No. of cases	Percentage
Home makers	67	26.8
Students	81	32.4
Employees	58	23.2
Manual laborers	32	12.8
Agricultural workers	12	4.8

Table 4: Incidence of facial skin disorders		
Facial dermatoses	Number of cases	Percentage
Infections	37	14.8
Pigmentary disorders	103	41.2
Nevi	6	2.4
Acne, rosacea, perioral dermatitis	61	24.4
Eczemas	29	11.6
Cysts and tumors	3	1.2
Miscellaneous	11	4.4

Of the 250 patients included in this study, 103 (41.2%) patients had pigmentary disorders [Figures 3 and 4]. Among the pigmentary disorders, melasma is the most common, followed by post-inflammatory hyperpigmentation and periocular pigmentation.

This is followed by acne, rosacea, and perioral dermatitis cases which amount to 61 (24.4%) patients.

Infections category includes patients suffering from Tinea faciei, Pityriasis versicolor, Herpes labialis, Molluscum contagiosum, Furunculosis, and Hansen's disease. There are 37 (14.8%) patients in this group.

Eczemas include cases of pityriasis alba, seborrheic dermatitis, Bindi dermatitis, atopic dermatitis [Figure 5], phytophotodermatitis, and cheilitis. 29 patients (11.6%) are in this group.
Conditions which are included in miscellaneous skin disorders are milia, periporitis, hirsutism, urticaria, and DLE. There are 11 patients (4.4%) in this group.

6 patients had nevi (2.4%). 3 patients had cysts and tumors (1.2%) [Figure 6] over the face.

These findings are depicted in Table 4.

### DISCUSSION

In the present study, it is found that thee majority of the patients belonged to the age group of 11-20 years (30.4%). In the study conducted by Bhagwat *et al.*, it is found that the majority of the patients belonged to the age group of 13-22 years (32.0%).<sup>[5]</sup> Sharada and Ashok found the majority of cases 24 (24.0%) in the age group of 20-29 years.<sup>[6]</sup>

In the present study, the majority of the patients (32.4%) are students, followed by 26.8% housewives/homemakers, 23.2% employees, 12.8% manual laborers, and 4.8% agricultural workers. These findings are similar to the study conducted by Sharada and Ashok which showed that maximum patients are students by occupation, i.e., 38% followed by housewives 29%.<sup>[6]</sup>

Of the 250 patients included in this study, 123 patients had pigmentary disorders. Among the pigmentary disorders, melasma is the most common, followed by post-inflammatory hyperpigmentation and periocular pigmentation.

The findings of this study are similar to the study conducted by Kavya and Nataraj<sup>[7]</sup> on facial hyper melanosis, in which melasma is the most common pigmentary disorder. In the study conducted by Sharada and Ashok, out of 100 cases, 26% are pigmentary disorders of which melasma constituted the most common.<sup>[6]</sup>

Jain *et al.* carried out a study among 150 patients who are having dermatoses on the face at the outpatient department. They found that 26.7% of the cases are having pigmentary disorders. The most common etiology of the pigmentation is found to be melasma. Acne is found to be the second leading etiology in 16.7% of the cases. Other dermatoses which are found in their study are cyst, eczema, and nevi.<sup>[8]</sup> These findings are in accordance with the finding of the present study. Hassan *et al.*, found melasma is the most common pigmentary disorder.<sup>[9]</sup> Chintada *et al.*'s conducted a study of facial dermatoses in women. Their study found that, of the 500 patients, 355 patients had pigmentary disorders. Among the pigmentary disorders, melasma is the most common.<sup>[10]</sup>

## CONCLUSION

This cross-sectional study is undertaken to assess the nature and extent of the involvement of the face in various dermatoses in male and female population at different ages and occupational status. In the present study, it is found that the majority of the patients with facial dermatoses belonged to the age group of 11–20 years (30.4%), most of them being students (32.4%). Female preponderance of facial dermatoses (52.8%) was noted. Among the pigmentary disorders, melasma was the most common, followed by post-inflammatory hyperpigmentation and periocular pigmentation.

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# Comparison of Ultrasound-Guided Fascia Iliaca Compartment Block with Femoral Nerve Block for Positioning of Femur Fracture Patients before Spinal Anesthesia

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### Abstract

**Aims:** To compare the ultrasound-guided fascia iliaca compartment block and femoral nerve block (FNB) for positioning of femur fracture patients before spinal anesthesia.

**Objectives:** Primary objectives were patient comfort during positioning for spinal anesthesia, anesthesiologist satisfaction during positioning for spinal anesthesia, and secondary objective was postoperative analgesia.

**Methods:** A prospective, randomized double-blinded controlled study was conducted with 60 patients admitted to Mahatma Gandhi Memorial Government Hospital, Trichirappalli, between the period of February 2020 and September 2021, after satisfying the inclusion and exclusion criteria, aged between 18 and 80 years undergoing elective surgery for fracture femur were included in the study.

**Results:** Significant improvement in Patient Numerical Rating Scale score, anesthesiologist satisfaction score, sensory blockade, and time to first analgesic requirement was observed.

**Conclusion:** Ultrasound-guided FNB was the best anesthetic technique in reducing pain associated with sitting position for subarachnoid block in patients with fracture femur compared to ultrasound-guided fascia iliaca block.

Key words: Fascia iliaca, Femoral nerve, Fracture femur, Pain, Spinal anesthesia, Ultrasound

### INTRODUCTION

Fracture femur is a very painful condition perioperatively and this pain is further exaggerated by movements. Routine analgesics such as pracetamol, NSAIDs, and opioids have their side effects such as nausea, vomiting, constipation, urinary retention, respiratory depression, and nephrotoxicity and these are contraindicated due to their interactions with other drugs.<sup>[1-4]</sup>



Peripheral nerve blocks in lower extremity are increasingly being recommended for the control of pain in patients with fracture femur as it reduces pain, time to first rescue analgesia, need for systemic analgesics, and incidence of delirium and shortens the duration of hospital stays. The femoral nerve block (FNB) and fascia iliaca compartment block (FICB) are the simple methods which require minimal instruments with few absolute contraindications, being hypersensitivity to local anesthetic agents or the presence of vascular or neurological problems in the affected limb. However, these simple techniques are underused in the management of pain relief in femur fracture.<sup>[5-7]</sup>

The hip joint is the largest weight-bearing ball and socket joint and is formed by joining thigh bone or femur and the pelvis and surrounded by muscles, ligaments, and tendons. The main nerves in the hip region include the femoral

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nerve in the front of the femur and the sciatic nerve at the back. The hip is also supplied by a smaller nerve known as the obturator nerve. Fascia iliaca is a thick connective tissue spanning from the lower thoracic vertebrae to the anterior part of the thigh. It lines the posterior part of the abdomen and pelvis, enclosing the psoas and iliacus muscles. Lower, it forms posterior wall of the femoral sheath. Further down, it is covered in the femoral triangle by the fascia lata, blending with it distally.

Contents of fascia iliaca compartment include femoral nerve, lateral femoral cutaneous nerve, obturator nerve, ilioinguinal nerve, and genitofemoral nerve.

### **Aims and Objectives**

To compare the ultrasound-guided FICB and FNB for positioning of femur fracture patients before spinal anesthesia. The primary objectives include patient comfort, anesthesiologist satisfaction during positioning for spinal anesthesia and secondary objective includes post-operative analgesia.

### **MATERIALS AND METHODS**

A prospective, randomized double-blinded controlled study conducted with 60 patients admitted to Mahatma Gandhi Memorial Government Hospital, Trichirappalli, between the period of February 2020 and September 2021, after satisfying the inclusion and exclusion criteria and aged between 18 and 80 years who are undergoing elective surgery for fracture femur were included in the study, after obtaining the institutional ethical committee clearance and after valid written and informed consent from the patient.

Patients were divided into two groups.

- Group A: 30 Patients receiving FNB
- Group B: 30 Patients receiving FICB.

### **Inclusion Criteria**

ASA physical status 1 and 2, Patient posted for elective fracture femur surgery, Age between 18 and 80 years.

### **Exclusion Criteria**

Patients with other bone fractures, psychiatric and neurological illness, inguinal hernia, coagulopathy, local skin infections, severe cardiovascular and respiratory disease, patients allergic to study drugs, and patient on analgesic within 8 h before performing nerve block were excluded from the study.

### Methodology

On arrival of the patient in the operation theater, Numerical Rating Scale (NRS) pain score was assessed using a standard 10-cm NRS, with 0 corresponding to no



Figure 1: Hip joint anatomy



Figure 2: Lumbar plexuses



Figure 3: Contents of fascia iliaca compartment

pain and 10 designating the worst possible pain. The site to be blocked was painted with 5% povidone-iodine and was draped. A linear 7–13 MHz ultrasound probe was used with in-plane approach of 18G needle advancement. Probe was moved laterally or medially and rocked back and forth until a good-quality picture was obtained. Mark on the probe was always kept on the lateral side for image orientation. Optimal gain, depth, and focal point were



Figure 4: Femoral nerve block ultrasound anatomy and procedure



Figure 5: Femoral nerve block ultrasound anatomy and procedure



Figure 6: Fascia iliaca block



Figure 7: Patient satisfaction score



Figure 8: Anesthesiologist satisfaction score



Figure 9: Pin-prick time



Figure 10: Time to first analgesic requirement

set to obtain the best possible view of the concerned anatomical structures.

Group A (n = 30) received ultrasonography (USG) FNB. Landmarks included the identification of femoral nerve lateral to femoral artery at the level of femoral crease followed by the injection of 0.5% ropivacaine 20 mL after careful aspiration adjacent to femoral nerve.

Group B (n = 30) received USG FICB. Landmarks included identification of femoral artery, iliopsoas muscle, fascia iliaca, and sartorius muscle followed by injection of 0.5% ropivacaine 20 mL after careful aspiration between fascia iliaca and iliopsoas muscle.

After the block procedure patient satisfaction before the block procedure, 20 min after the block procedure, during positioning for SAB, and at the end of surgery was assessed, anesthesiologist satisfaction during positioning for spinal anesthesia, pinprick (2 min, 4 min, 6 min, 8 min, 10 min, 15 min, and 20 min), total duration for surgery and time to first analgesics requirement were assessed. Variables were analyzed statistically and expressed as mean  $\pm$  standard deviation. The categorical data were compared using the Chi-square test. Quantitative parametric data were analyzed using unpaired Student's *t*-test, whereas nonparametric data were analyzed using the Mann-Whitney test. *P* = 0.05 was considered statistically significant.

Injection bupivacaine 0.5% heavy 15 mg was given intrathecally using a 25G Quincke needle.

Duration of analgesia was defined as loss of pinprick sensation in the anterior part of thigh after the peripheral nerve block to NRS pain score was assessed every hour postoperatively or when the patient demanded for rescue analgesia. Perioperative patient comfort was assessed postoperatively using the standard NRS scale for comfort, with 0 corresponding to most comfortable and 10 designating the least comfortable state.

Complications such as nausea, vomiting, hypotension, bradycardia, hematoma, and local anesthetic toxicity were carefully monitored. No loss of pinprick sensation in the anterior part of thigh within 20 min of performing the peripheral nerve block was considered as

block failure. Such patients were excluded from the study.

# RESULTS

The patient satisfaction score (NRS). Mean reduction in NRS score for pain before the block procedure, was also more in Group A FNB ( $6.3 \pm 1.1$ ) compared to Group B

FICB (6.6 ± 1.3) (P = 0.3386). Mean reduction in NRS score for 20 min after the block procedure was also more in Group A (1.7 ± 1.2) as compared to Group B (3.8 ± 1.39) which is statistically significant (P = 0.0158). During positioning for spinal anesthesia, the mean reduction in patient satisfaction score was 1.4 ± 0.9 for Group A and 3.6 ± 1.8 for Group B which was statistically significant (0.0003). At the end of the surgery, the patient satisfactory score was 0.33 ± 0.7 for Group A and 0.75 ± 1.3 for Group B (P = 0.1247).

The anesthesiologist satisfaction score during the positioning for spinal anesthesia for the Group A (FNB) was  $2.4 \pm 0.7$  and for the Group B (FICB) was  $1.6 \pm 0.8$ . There found to be significant changes P = 0.0001.

The pinprick in minutes for 4 min; the mean time in minutes was  $0.7 \pm 0.5$  and  $1 \pm 0.6$  for Group A and Group B and its statistically significant (0.0317). At 6 min,  $1.3 \pm 0.4$  and  $1.1 \pm 0.5$  for Group A and Group B. For 8 min, 10 min, 15 min, and 20 min, the pinprick mean minutes were  $1.9 \pm 0.3$  for Group A and  $1.3 \pm 0.4$  for Group B, respectively. It is statistically significant (0.001).

The mean time taken to first analysics requirement for the Group A patients was  $6.8 \pm 1.3$  and for the Group B patients  $4.6 \pm 1.2$ , which was statistically very significant (P = 0.0001).

The time duration taken for the procedure for the Group A (126  $\pm$  15.4) was the mean time in min and for the Group B (141  $\pm$  16.8) was the mean time in min and it was statistically significant (P = 0.0235).

The vitals at the time of block such as heart rate were  $89.8 \pm 10.9$  and  $93.3 \pm 9.5$  for the Group A and Group B, respectively, and systolic blood pressure was  $115.2 \pm 11.2$  and  $111.9 \pm 11.4$  and diastolic blood pressure was  $65.9 \pm 10.3$  and  $64.5 \pm 9.4$  for the Group A and Group B, For SPO<sub>2</sub> 98.8  $\pm$  0.8 and 98.6  $\pm$  0.8 and for respiratory rate  $14.9 \pm 1.4$  and  $14.9 \pm 1.6$  for Group A and Group B, respectively. The vitals during position for spinal anesthesia, heart rate were  $78.8 \pm 5.1$  and  $76.8 \pm 4.1$ for the Group A and Group B, respectively, and the systolic blood pressure was  $118.1 \pm 8.9$  and  $114.1 \pm 8.3$ and diastolic blood pressure was  $71.1 \pm 7.8$  and  $70.3 \pm 7.9$ for the Group A and Group B for SPO<sub>2</sub> 98.5  $\pm 1.04$  and 98.5  $\pm 0.8$  and for respiratory rate  $15.1 \pm 1.4$  and  $14.4 \pm$ 1.1 for Group A and Group B, respectively [Figures 1-10].

# DISCUSSION

Peripheral nerve block with spinal anesthesia is the most commonly used anesthetic technique for patients with femur fracture. In fracture femur patients, positioning is a painful condition as evident from NRS pain scores assessed before performing the peripheral nerve block, in our study as well as previous studies. Patients presenting with fracture femur usually are the elderly and have multiple comorbidities, which precludes the use of systemic analgesics. Nerve blocks were used infrequently to aid with positioning. No sedation or analgesia was given for positioning in 15.1% of patients.<sup>[8-13]</sup>

A 2012 survey of three Toronto, Ontario-area hospitals found that regional nerve blocks for hip fractures were performed by only 33% of attending emergency physicians and only 6% performed them often or almost always. A 2009 survey in the United Kingdom found that 55% of emergency departments regularly use regional anesthesia techniques for hip and femur fractures. A 2002 Cochrane systemic review of nerve blocks for hip fractures undertaken shortly after admission to hospital concluded: "Nerve blocks resulted in statistically significant reductions in reported pain levels and in the quantity of parenteral or oral analgesia administered to control pain from the fracture or during surgery. National Institute for Health and Clinical Excellence guidelines says "Consider nerve block for additional analgesia or to limit opioid dosage." Thus, lower limb peripheral nerve blocks may prove to be a useful tool in an anesthetists' armamentarium for not only improving perioperative patient comfort and reducing pain exaggerated by movements but also increasing the ease, success rate and decreasing time for performing subarachnoid block.[14-16]

In our study FNB proves to be significantly more effective than FICB in reducing pain during sitting position for spinal anesthesia. Our study result consistent with the result of Kumar et al. had post-block pain Visual Analog Score (VAS) of 2.94 for FICB, with mean reduction in pain VAS score of 4.56 for (P = 0.01) using 0.5% ropivacaine and Newman et al., who had post block pain VAS score of 4.4 and 5.4 for FNB and FICB, respectively, using 0.5% levobupivacaine. Jain et al. finding reveals that FNB proves to be significantly more effective than FICB in reducing pain during positioning for subarachnoid block was also consistent with our study. Several randomized control trials have also proved the superiority of ultrasound over other techniques. Our study aims to compare FNB with FICB using USG technique as this remains unexplored. Ropivacaine, the S enantiomer of 1propyl 2', 6'pipecoloxylidide, one of the most commonly used long acting local anaesthetics in the peripheral nerve blockade was chosen because it has lower toxicity than the R enantiomer. Reduced central nervous system and cardiac toxicity, along with lower lipid solubility which leads to less propensity for motor blockade than bupivacaine.

The FNB results in anesthesia of the skin and muscles of the anterior thigh and most of the femur and knee joint. The distribution of anesthesia and analgesia that is accomplished with the fascia iliaca block depends on the extent of the local anesthetic spread and the nerves blocked. The block should result in blockade of the femoral nerve in all instances (100%) and lateral cutaneous nerve of the thigh in 80-100% instances. The psoas muscle and pectineus muscle separate the obturator nerve from the femoral nerve along its course, and therefore, this nerve is not reliably blocked by FICB. These blocks are well suited for surgery on the anterior thigh and knee, quadriceps tendon repair, and postoperative pain management after femur and knee surgery. FNB and FICB were earlier performed using landmark or nerve stimulator technique, but the advent of ultrasound overcome their shortcomings and is now a preferred technique.

Deposition of ropivacaine within the vicinity of femoral nerve using ultrasound guidance that gives articular branches to hip joint increases the chances of the nerve getting block. This may be the reason why, in our study, the FNB proved to be more efficacious analgesic than FICB, which requires deposition of large volume of local anesthetic away from the femoral nerve. We observed that FNB and FICB provided longer duration of postoperative analgesia compared to intrathecal 0.5% heavy bupivacaine alone which has a duration of 60-240 min. It will decrease the use of systemic opiates and improves functional recovery and quality of life and decreases duration of hospital stay. Although our results were consistent with the previous studies, the use of USG for performing peripheral nerve blocks was the reasons for no failures and better peri-operative patient comfort in our study.

In resource-limited hospital settings, FICB, which is easy to learn and perform, can be used as it also provides satisfactory analgesia and patient comfort.

Major limitations of our study were assessment of NRS pain score which is subjective and varies with the level of understanding between patient and anesthesiologist.<sup>[17-20]</sup>

### CONCLUSION

In our study, we concluded that ultrasound-guided FNB is the best anesthetic technique in reducing pain associated with positioning for spinal anesthesia in patients with fracture femur compared to ultrasound-guided FICB, nerve blocks performed with patient comfort and without complications and longer duration of post-operative analgesia in the patients undergoing surgery for fracture femur.

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# **ER and PR Receptor Expression in Cases of Endometrial Hyperplasia and Malignancy**

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### Abstract

**Objectives:** The aim of the present study was to evaluate estrogen receptor (ER) and progesterone receptor (PR) expression in the glandular epithelium and stroma of benign and malignant endometrial samples of women in the age group of 30–80 years.

**Materials and Methods:** A total of 87 females underwent D and C, hysterectomy or endometrial biopsy at the King George's Medical University and T S Misra Medical College and Hospital, Lucknow, were included in the study. Patients with the normal menstrual cycle between 30 and 45 years were included as controls. Patients with pregnancy and those with inadequate sample were excluded from the study. Endometrial lesions were histologically classified as benign lesions (endometrial hyperplasia with or without atypia) and malignant lesions. ER and PR expression was evaluated by immunohistochemistry according to cell staining, intensity of nuclear staining, and final H score was calculated.

**Results:** Histopathologically lesions were graded as the type of endometrial hyperplasia and the type of carcinoma. The final H score for receptor expression was compared between the non-malignant and malignant lesions. ER and PR expression was higher in non-malignant as compared to the malignant group. ER and PR H scores were calculated separately for the epithelium and stroma and mean H score was calculated for epithelium an stroma. Statistical analysis of H scores was done separately for ER and PR receptor expression in epithelium and stroma of different lesions of non-malignant and malignant group.

Conclusion: ER PR-positive expression and H score is higher in hyperplasia as compared to malignancy.

Key words: Endometrial carcinoma, Endometrial hyperplasia, Estrogen receptor, Progesterone receptor

### **INTRODUCTION**

Endometrium refers to the inner lining of the uterine lumen. It is composed of a number of glands embedded lying in the connective tissue often termed as stroma.<sup>[1]</sup> In the regular progression of menstrual cycle, the lining of uterus is subject to a pair of steroid hormones, estrogen and progesterone, that exerts an opposing effect



on the endometrial glandular epithelium<sup>[2-4]</sup> are normal and are not considered as any pathological condition and is marked by a normal hormonal profile. However, endometrial hyperplasia, a disordered proliferation of endometrial glands that is considered to be a precursor of endometrial cancer is thought to be resulting from "unopposed estrogenic stimulation of the endometrial tissue with a relative deficiency of the counterbalancing effects of progesterone."[5] Endometrial hyperplasia is characterized by chronic exposure to estrogen coupled with a relative deficiency of progesterone.<sup>[6]</sup> The progression of endometrial hyperplasia to cytological atypia and finally into endometrial carcinoma is marked by a multitude of clinical, pathological and physiological changes. A number of biomarkers viz., "P53, KRAS, PTEN, EGFR, and FGFR, estrogen receptors (ER), progesterone receptors

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(PR), human epidermal growth factor receptor 2, etc." have been shown to have a role in this progression.

In contrast, irregularly in hormone receptor functions can end up in various malignant conditions<sup>[7]</sup> ER exists in two main isoforms, ER alfa and ER beta. They have a distinct pattern of expression in the tissues<sup>[8]</sup> which varies during cellular proliferation and differentiation.<sup>[9]</sup> ER- $\alpha$  binds to estrogens with high affinity and. ER-alfais required for the basic development of estrogen-sensitive tissues. ER-beta inhibits transcription. It is required for the organization and adhesion of epithelial cells and hence for differentiated tissue morphology and its functional maturation.<sup>[10]</sup> Progesterone (PR) also exists in two isoforms PR alfa and PR-beta modulates the anti-proliferative effects of progesterone in the uterus, i.e., estrogen antagonistic PR beta, induces cell growth and thus plays the role of estrogen agonist.<sup>[11]</sup> It is well-documented in the literature that "the transcription of PR gene is induced by estrogen and inhibited by progesterone in the majority of estrogen responsive cells, so the expression of ER and PR is considered to be coordinated."[12,13]

Evaluation of estrogen and progesterone receptors plays an important role in the prognosis of endometrial cancer. They are helpful in determining the survival length and function.<sup>[14,15]</sup> ER/PR positivity helps to determine the need for hormonal treatment for endometrial cancer.<sup>[16]</sup> Study of ER/PR in pre-cancerous and cancerous conditions also helps to study the tumor biological behavior which determines the subsequent pathways for appropriate treatment strategy formulation<sup>[17]</sup> Hence, the present study was planned to study the ER and PR receptor expression in cases of endometrial hyperplasia and malignancy using a cross-sectional design.

### **MATERIALS AND METHODS**

It is the prospective cross-sectional study of the 87 cases of the endometrial tissues obtained from diagnostic and curettage and hysterectomy specimens processed for histopathological examination in the laboratory of T S Misra Medical College and Hospital, Lucknow, India, in collaboration with the King George's medical University, Lucknow, from January 1, 2021 to June 30, 2022 (Total duration 1.5 years). The study included 87 histopathologically proven cases of endometrial hyperplasia and malignancy in the age group (30–80 years). However, those cases with normal endometrium (proliferative and secretary) in the age group (30–45 years) were also included in the study as a control for each batch of immunohistochemical assey. Those cases with inadequate sample or with history of pregnancy were excluded from the study. Informed consent was taken from the patients included in the study. All the demographic details, clinical profile, medical, surgical, obstetric, family and personal history were taken from the clinical records and details of investigations and treatment availed was noted. Immunohistochemistry for ER and PR status was done. ER and PR staining reactions was evaluated as brown nuclear staining in the glandular epithelium and stroma of all cases as a positive reactions. Staining was scored semi quantitatively taking into consideration both intensity as well as percentage of cells staining in glands and the stroma and H-score was calculated as Pi(i+1)/100 i=intensity (0,1,2,3) 0-No staining, 1-weak staining, 2-moderate staining, 3-strong staining, Pi=percentage of stained cells (0–100%) of each tissue component (glands and stoma) in each intensity.

# RESULTS

Majority of cases (n = 65; 74.7%) were non-malignant. There were 22 (25.3%) malignant cases [Table 1].

Among non-malignant cases, (n = 10; 11.5% each) were secretory and proliferative endometrium, respectively. There were 45 (51.7%) cases with endometrial hyperplasia. Among these, maximum were simple hyperplasia without\* atypia (n = 36; 41.4%) followed by simple hyperplasia with atypia (n = 6; 6.9%) and complex hyperplasia without\* atypia (n = 3; 3.4%) respectively [Table 1].

Among 22 malignant cases, maximum (n = 19/22; 86.4%) were endometrial adenocarcinoma. There was 1/22 (4.5%) case each diagnosed with endometrial carcinoma villoglandular type, serous endometrial carcinoma, and endometrioid endometrial carcinoma NOS, respectively.

Out of 22 malignant cases, more than three-fourth (77.3%) were low grade/well differentiated, 4 (18.2%) were moderate grade/moderately differentiated, and only 1 (4.5%) was high grade/poorly differentiated carcinoma [Table 2].

# Table 1: Distribution of women according tohistopathological diagnosis

s	HPE diagnosis	No of	Percentage
No.		women	rereentage
1	Non-malignant	65	74.7
	Proliferative endometrium	10	15.4
	Secretory endometrium	10	15.4
	Simple hyperplasia without atypia	36	55.4
	Simple hyperplasia with atypia	6	9.2
	Complex hyperplasia with atypia	3	4.6
2	Malignant	22	25.3
	Endometrial adenocarcinoma	19	86.4
	Endometrial carcinoma villoglandular	1	4.5
	Serous endometrial carcinoma	1	4.5
	Endometroid endometrial carcinoma NOS	1	4.5

Both ER and PR positivity rates were significantly higher in non-malignant as compared to malignant lesions (P < 0.05) [Figures 1 and 3 and Table 3].

Overall ER/PR status was both ER/PR positive, ER positive PR negative, and ER negative PR positive in 72.7%, 13.6%, and 13.6% malignant cases, respectively, as compared to 98.5%, 0%, and 1.5% non-malignant cases, respectively. Statistically, there was a significant difference between the two groups with respect to overall ER/PR status (P < 0.001) [Figures 1 and 3 and Table 3].

For both epithelium and stroma, mean ER and PR H-scores were significantly higher in non-malignant as compared to malignant lesions (P < 0.001) [Figures 2 and 4 and Table 4].

Both ER and PR H-scores in epithelium as well as stroma were maximum in secretory and proliferative endometrium followed by simple hyperplasia, simple hyperplasia with atypia, and complex hyperplasia with atypia. They were minimum in endometrial carcinoma. These trends were significant statistically too (P < 0.001) [Table 5].

# Table 2: Distribution of cases according to thegrade of malignancy (n=22)

S. No.	History	No. of women	Percentage
1	Low grade/WD	17	77.3
2	Moderate grade/MD	4	18.2
3	High grade/PD	1	4.5

### DISCUSSION

In the past few decades, there has been a high increase in the incidence of endometrial cancer, particularly in developing world, as a result of increasing life-expectancy and changing lifestyle contributing to an increase in obesity which is a recognized risk factor for endometrial cancer.<sup>[18,19]</sup> In the present study, most of the malignant cases 19/22 (86.5%) were endometroid adenocarcinoma; however, one each (4.5%) was villous, serous, and endometroid carcinoma NOS type. Among malignant cases, 17/22 (77.3%) was low grade, 4/22 (18.2%) moderate grade, and 1/22 (4.5%) high grade. Similar to the present study, Kumari et al.<sup>[20]</sup> also reported a dominance of low grade (66%) but had moderate grade as the least common one (12%). However, in the study by Zidan et al.,<sup>[21]</sup> all the cases were endometrioid carcinoma but representation of all the three grades was much homogenous with Grades 1, 2, and 3 being represented by 38.9%, 27.8%, and 33.3% cases, respectively. Furthermore, it has also been seen in some previous studies that given high value of these markers (ER and PR expression in assessing the treatment response and prognosis, they can also be used successfully for differentiation between endometrial cancer and endometrial hyperplasia (and its different types) successfully and could help to stratify their malignant potential too.<sup>[20]</sup>

ER and PR positivity rate in the present study was 98.5% and 100% for non-malignant cases as compared to 86.4% (ER) and 86.4% (PR) for malignant cases. Although Kumari

### Table 3: ER/PR expression status in malignant and non-malignant specimen

S. No.	Receptor	Status	Malignant ( <i>n</i> =22)		Non-m	alignant ( <i>n</i> =65)	Statistical significance	
			No	%	No	%	χ²	' <b>P</b> '
1	ER	Positive	19	86.4	64	98.5	5.485	0.019
		Negative	3	13.6	1	1.5		
2	PR	Positive	19	86.4	65	100	9.180	< 0.001
		Negative	3	13.6	0	0		
3	Overall ER/P	'R status						
	ERP PRP		16	72.7	64	98.5	15.28	< 0.001
	ERP PRN		3	13.6	0	0		
	ERN PRP		3	13.6	1	1.5		

ER: Estrogen receptor, PR: Progesterone receptor

# Table 4: Comparison of ER/PR H-scores in epithelium and stroma between malignant and non-malignant groups

S. No.	Receptor/Source	Malignant (n=22)		Non-malig	gnant ( <i>n</i> =65)	Statistical significance	
		Mean	SD	Mean	SD	't'	'P'
1.	ER						
	Epithelium	1.32	0.50	2.70	0.70	8.506	< 0.001
	Stroma	1.23	0.43	2.54	0.70	8.236	< 0.001
2.	PR						
	Epithelium	1.35	0.48	2.69	0.68	8.518	<0.001
	Stroma	1.26	0.27	2.65	0.59	10.593	<0.001

ER: Estrogen receptor, PR: Progesterone receptor, SD: Standard deviation

# Table 5: Comparison of ER/PR IHC H-scoresin epithelium and stroma among differenthistopathological diagnosis

S.	Receptor	HPE diagnosis	Epithe	lium	Stro	ma
No.			Mean	SD	Mean	SD
1	ER	Proliferative	3.14	0.44	3.23	0.29
		endometrium ( <i>n</i> =10)				
		Secretory	3.01	0.73	2.80	0.74
		endometrium ( <i>n</i> =10)				
		Simple hyperplasia ( <i>n</i> =36)	2.72	0.58	2.51	0.57
		Simple hyperplasia with atypia ( <i>n</i> =6)	1.87	0.58	1.62	0.26
		Complex hyperplasia with atypia $(n=3)$	1.53	0.06	1.53	0.23
		Endometrial	1.32	0.50	1 23	0 43
		carcinoma ( <i>n</i> =22)	1.02	0.00	1.20	0.10
		Statistical	F=26.	963;	F=31	.471;
		significance (ANOVA)	P<0.	001	<i>P&lt;</i> 0.	001
2	PR	Proliferative	2.98	0.29	3.01	0.33
		endometrium ( <i>n</i> =10)				
		Secretory endometrium ( <i>n</i> =10)	2.90	1.04	2.77	0.74
		Simple hyperplasia ( <i>n</i> =36)	2.69	0.59	2.69	0.51
		Simple hyperplasia with atypia ( <i>n</i> =6)	2.32	0.54	2.10	0.43
		Complex hyperplasia with atypia ( <i>n</i> =3)	1.67	0.12	1.63	0.06
		Endometrial	1.35	0.48	1.26	0.27
		carcinoma ( <i>n</i> =22)				
		Statistical	F=19.	281;	F=35	5.03;
		significance (ANOVA)	P<0.	001	<i>P</i> <0.	001

ER: Estrogen receptor, PR: Progesterone receptor, SD: Standard deviation



Figure 1: Endometrial hyperplasia without atypia estrogen receptor strong glandular positivity

*et al.*<sup>[20]</sup> too observed the expression of ER/PR to be significantly higher in hyperplasia as compared to malignant cases, in their study, the expression rate for ER and PR was 58% and 76%, respectively, in malignant as compared to 100% and 100%, respectively, in hyperplasia cases. In the present study, ER and PR positivity and ER and PR H SCORES in epithelium as well as stroma were higher in non-malignant as compared to malignant. ER and PR H SCORES in epithelium and stroma, a decreasing trend is



Figure 2: Atypical hyperplasia faint positivity progesterone receptor



Figure 3: Endometrial CA Endometroid variantrp estrogen receptor (ER) ×20 faint positivity ER



Figure 4: Serous endometrial Ca ×10 negative progesterone receptor

found from normal endometrium to complex hyperplasia with atypia, minimum in endometrial carcinoma and these trends were statistically significant too. Panwar and Gangane<sup>[22]</sup> (2020) have found PR expression to hold a high discriminatory value with all the hyperplasia cases showing a positive expression as compared to only 50% of endometrial carcinoma. The present study do not find such a high discriminatory value on basis of ER and PR status only. In the present study, we used a semi-quantitative criteria, *i.e.*, H-score that looked beyond just positive or negative status but instead evaluated the expression of PR and ER by unifying the number of cells in which expression was seen and intensity of staining.

This quantitative measure has been used previously by some workers<sup>[20,23]</sup> and has been found to have a high discriminatory value too. With adaptation of a quantitative criteria like H-score, the discriminatory power of ER and PR expression increases substantially and it is able to serve to our primary purpose of differentiating between endometrial hyperplasia and endometrial carcinoma as well as between simple hyperplasia and hyperplasia with atypia cases effectively. These findings are in accordance with the observations of Kumari *et al.*<sup>[20]</sup> who also made similar observations. Kaur *et al.* too in their study, despite not using quantitative scores as used in the present study, emphasized that the intensity of expression of ER and PR was helpful in differentiating among histopathological grades of endometrial carcinoma.

### CONCLUSION

ER and PR are the important prognostic biomarkers to predict response to the anti hormonal therapy. The findings of the present study showed that ER/PR expression, particularly quantification of their expression was helpful in not only differentiating between endometrial hyperplasia and endometrial carcinoma but also tended to provide further differentiation and characterization of different endometrial lesions. The study had limitation of sample size and disproportionate representation of different pathologies and grades of carcinoma. Further studies with a larger sample size with adequate representation of different pathologies and grades of carcinoma are recommended to highlight the role of ER/PR expression in differentiation between endometrial hyperplasia and different severity grades.

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# **Topical Solutions for Chronic Lower Limb Ulcers: A Comparative Study of Sucralfate and 5% Povidone-Iodine**

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### Abstract

**Background:** Sucralfate (Aluminum hydroxide salt of the disaccharide sucrose octasulfate) is a medication primarily used to treat active peptic ulcers in the gastrointestinal tract. It is also been found to have potential benefits in wound healing. Studies have shown that sucralfate can promote the growth and repair of skin tissue by stimulating the proliferation of dermal fibroblasts and keratinocytes. In addition, sucralfate has been found to enhance the synthesis of prostaglandin E2 in basal keratinocytes and the release of interleukin-6 from fibroblasts. Applying sucralfate daily to full-thickness wounds has been shown to increase the thickness of granulation tissue, which can help facilitate healing. While sucralfate is primarily used to treat peptic ulcers and gastroesophageal reflux disease, its potential benefits in wound healing warrant further investigation.

**Objectives:** To compare the efficacy of topical sucralfate with that of a control group using 5% povidone-iodine dressing, in the healing of chronic lower limb ulcer.

**Methods:** From October 2020 to November 2022, a comparative study was conducted at BLDE DU Shri BM Patil Medical College Hospital and Research Center, Vijayapura. The study included 224 patients, with 112 assigned to the control group and 112 assigned to the study group. Patients in both groups received daily dressings for 2 weeks, and their progress was monitored for changes in ulcer size, appearance of granulation tissue, and culture sensitivity. The study aimed to compare the outcomes between the two groups using an interventional approach.

**Results:** In our study, complete granulation tissue fill-up was shown in 100 (89.3%) patients in the study group and 71 (63.4%) patients in the control group. In this study, at first visit, positive culture is seen in 89 patients in the study group and 96 patients in the control group and negative culture is seen in 23 patients in the study group and 16 patients in the control group after 14 days Negative culture is seen in 105 patients in the study group and 51 patients in the control group. Study outcomes were better in the study (Sucralfate) group as compared to the control (Betadine) group. The study group showed a significant reduction in mean ulcer surface area (71.8%) as compared to the control group (24.8%).

**Conclusion:** The results suggest that sucralfate dressing may be a promising option for the treatment of chronic lower limb ulcers. Its effectiveness in facilitating wound contraction and promoting early granulation tissue fill-up make it a viable alternative to traditional Betadine dressings.

Key words: 5% povidone iodine solution, Chronic lower limb ulcers, Dressings, Sucralfate

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### INTRODUCTION

The problem of managing chronic wounds continues to be a challenge despite the thousands of years that have passed since mankind first succeeded in deciphering the human genetic code. One of the most frequent surgical conditions a surgeon encounter is chronic wounds, especially those that

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Graph 1: Culture and sensitivity



Graph 2: Percentage reduction of ulcer

do not heal. Doctors have been experimenting with various techniques to heal these types of wounds for a long time.

During the last 20 years, many innovative dressings were introduced in wound healing, such as collagen,<sup>[1]</sup> crystal violet, insulin, mercurochrome, and oxygen therapy. Recent literature says that an ulcer is epithelialized more rapidly when treated with a dressing that allows moist wound healing.<sup>[2,3]</sup>

Studies have shown that topical sucralfate is a superior method for treating diabetic ulcers, as well as decubitus ulcers, venous stasis ulcers, traumatic wounds, burns, and trophic ulcers.<sup>[4]</sup> In preclinical studies, sucralfate has been found to encourage the growth of granulation tissue which in turn encourages the healing of cutaneous ulcers.

Sucralfate is an oral gastrointestinal medicine used primarily to treat active peptic ulcers. It is the aluminum hydroxide salt of the disaccharide sucrose octa sulfate. Peptic ulcers and gastroesophageal reflux disease are both treated with sucralfate.<sup>[5]</sup>

Additionally, it suggests a potential role in the recovery of skin injuries. Dermal fibroblast and keratinocyte proliferation are promoted by sucralfate. Sucralfate increases interleukin-1-stimulated fibroblasts' release

Present/		Gro	up			Total
absent	Cont	rol group	Stud	y group	-	
	Count	% in group	Count %	∕ն in grou	o Count	% in group
Absent	84	75%	84	75%	168	75%
Present	28	25%	28	25%	56	25%
Total	112	100%	112	100%	224	100%

Table	2:	Culture	&	sensitivity	<u> </u>	after	14	day	vs
Table	<u> </u>	Guitare	ч.	SCHORIN	v —	ancor		uu	73

Pus culture		Gr	То	Total		
sensitivity	Contr	ol group	Stud	ly group	_	
(positive/ negative)	Count	% in group	Count	% in grou	o Count %	in group
Negative	51	45.5%	105	93.8%	156	69.6%
Positive	61	54.5%	7	6.2%	68	30.4%
Total	112	100%	112	100%	224	100%

Granulation		Gr	Тс	Total		
tissue fill up	Contro	l group	Study	group	_	
(complete/ partial)	Count%	in group	Count%	in grou	pCount%	in group
Complete	71	63.4%	100	89.3%	171	76.3%
Partial	41 112	36.6% 100%	12 112	10.7% 100%	53 224	23.7% 100%

of interleukin-6 and basal keratinocytes' production of prostaglandin E2.<sup>[6]</sup> Sucralfate enhanced the thickness of granulation tissue when a daily application was made to full-thickness wounds.<sup>[7]</sup>

Numerous types of research demonstrated the effectiveness of sucralfate,<sup>[8]</sup> which resulted in the wound being completely closed and shrinking in size.

Because of new research regarding the effectiveness of sucralfate in treating lower limb ulcers, we undertook this study to ascertain if sucralfate administered topically over chronic lower limb ulcers reduces the size of the lesion more effectively than 5% Povidone-iodine treatment.

### **MATERIALS AND METHODS**

This was a prospectively conducted comparative intervention study done during a period of October 2020 to November 2022

Patients who have been hospitalized in surgery wards or who visited outpatient department with lower limb ulcers that have persisted for more than 2 weeks at BLDE[DU] Shri B.M. Patil Medical College, Hospital, and Research

Table 4: Wound contraction							
Variables	Group	n	Mean	SD	Mann-Whitney U-test value	P-value	
Initial area of ulcer in cm <sup>2</sup>	Control group	112	36.116	19.984	6947	0.164	
	Study group	112	33.795	21.883			
Final area of ulcer in cm <sup>2</sup>	Control group	112	28.188	17.051	10610	<0.001	
	Study group	112	10.696	9.63			
% area reduction	Control group	112	0.249	0.16	459	<0.001	
	Study group	112	0.718	0.129			

# Table 5: Wound contraction comparison with otherstudies

Wound contraction	Study group (%)	Control group (%)
Our study	71.8	24.9
Preethi et al.	70.4	29.6
Nagalakshmi <i>et al</i> .	41.97	18.37

Center, Vijayapur after obtaining Institutional ethical committee clearance.

### Aim of the Study

To assess Topical Sucralfate's effectiveness in treating chronic lower leg ulcers in comparison to a control group using a 5% povidone-iodine dressing.

### **Inclusion Criteria**

- 1. Patients in the age range of 12–75
- 2. Lower limb ulcers that have been present for more than 2 weeks
- 3.  $<10 \times 10$  cm in size
- 4. Both diabetic and non-diabetic patients.

### **Exclusion Criteria**

- 1. Vascular insufficiency patients
- 2. Immunocompromised patients
- 3. Osteomyelitis associated with it, ulcers with exposed bone or tendon, or the presence of a Charcot joint, diabetic toe gangrene
- 4. Skin malignancy
- 5. Diabetic ketoacidosis and critically ill patients.

Patients were randomized into two groups of study and control group based on alternate numbers. Out of 224, patients, 112 took treatment in the form of 5% povidine iodine dressings, and 112 took treatment with sucralfate dressing.

The nature of the study was explained to the patients, and written informed consent was obtained from them before enrollment. Photographs of the ulcers both before and after dressing were taken.

The wound area was calculated by multiplying the length by the width following a comprehensive clinical evaluation and ongoing research (the ulcer should be <10 cm  $\times10$  cm).

For both groups, the dressings were changed every other day. 2 weeks of alternate-day follow-up were given to the patients in both groups. Planimetry was used to measure the result, or the area of the target ulcer, using a clear graph sheet. Results were calculated by using the student's *t*-test.

The wounds in both groups were inspected at the time of the first visit and after 14 days, and the wounds were compared in terms of:

- The amount of granulation tissue fill-up
- Reduction in mean ulcer surface area
- Wound culture and sensitivity.

### Sampling

### Sample size: 224.

With the anticipated proportion of area reduction of the wound in conventional dressing and sucralfate in diabetic ulcers at 14.6% and 35% respectively, the study would require a sample size of 112 per group. (i.e., a total sample size of 224 assuming equal group sizes), to achieve a power of 95% for detecting a difference in proportions between two groups at a two-sided P = 0.05.

### **Statistical Analysis**

- The data obtained were entered into a Microsoft Excel sheet, and statistical analysis was performed using a statistical package for the social sciences (version 20).
- Results were presented as Mean ± SD, counts and percentages, and diagrams.
- For normally distributed continuous variables between two groups were compared using an independent t-test for not normally distributed variables Mann Whitney U test was used. Categorical variables between the two groups will be compared using the Chi-square test/ fisher's exact test.
- P < 0.05 was considered statistically significant.

### RESULTS

A total of 224 patients with lower limb ulcers were included in the study and were divided into two groups on an alternate basis; the Study group (Sucralfate group) and the Control group (Betadine group). The age distribution of patients was between 12 and 75 years of age with the highest percentage of the patients belonging to 61–75 years followed by 51–60, 41–50, 31–40, and below 30 years of age groups.

In the present study, the incidence of chronic lower limb ulcers was more in males (81.2%) as compared to females (18.8%), with the maximum incidence of onset being spontaneous (71%) ulcers than traumatic (29%).

In this study, total of 56 (25%) individuals were diabetic and 168 (75%) individuals are non-diabetic with more male predominance [Table 1].

In the study group, 23 were positive for *Staphylococcus aureus* (SA), no patients for *Proteus mirabilis* (PM), 31 for *Pseudomonas aeruginosa* (PA), 8 patients showed *Escherichia coli* (EC), 25 patients showed *Klebsiella pneumonia* (KP), 2 patients showed *Enterococcus faecalis* (EF), and 23 of them did not show any growth. In the control group, 21 of them were positive for SA. 3 of them for PM, 23 for PA, 34 for KP, 1 for AB, 1 for EF, and 13 of them for EC. 16 of the patients did not show any growth on the first visit [Graph 1]. After 14 days, negative culture is seen in 105 patients in the study group and 51 patients in the control group [Table 2].

In this study, complete granulation tissue fill-up was shown in 100 (89.3%) patients in the study group and 71 (63.4%) patients in the control group [Table 3].

The study group had better wound contraction of 71.8% as compared to the control group, the mean wound contraction was 24.9% [Graph 2] (which is statistically significant with P < 0.001 [Table 4].

# DISCUSSION

Every surgeon hopes to find the ultimate dressing, one that facilitates hassle-free chronic ulcer healing. Successful wound care must prevent unfavorable reactions including infection, maceration, and allergies while also keeping the wound moist. Lower leg ulcers are long-lasting lesions that have stopped growing on the surface of the skin.

The mean age group in the study group with chronic lower limb ulcers was 52.33 years and in the control group was 52.44 years. The study conducted by Narwade *et al.* on non-diabetic chronic leg ulcers:<sup>[9]</sup> Etiology and management stated that chronic leg ulcers presented during the sixth decade with a male-to-female ratio of 5:1which show similar results in this study.

In our study, the culture and sensitivity of the ulcers before the commencement of sucralfate dressings were positive for many microorganisms. After sucralfate dressings were given culture obtained on the  $14^{th}$  day surprisingly showed –ve culture in patients in the study group, whereas patients in the control group still had a +ve culture.

This may account for the antimicrobial activity of Sucralfate. A series of experiments was conducted to determine the rate of bacterial growth in a human gastric juice at various pH values with the addition of sucralfate and antacid.

Whereas the addition of antacid resulted in bacterial growth in gastric juice, sucralfate showed an antibacterial effect. This may account for the decreased rate of pneumonia in intensive care.

In our study, it was observed that participants receiving Sucralfate dressing had better wound contraction of 71.8% as compared to the control group in whom the mean wound contraction was 24.9%. These were found to be statistically significant on Mann–Whitney U-test (P < 0.001) suggesting that Sucralfate enhances wound healing in chronic lower limb ulcers. This is similar to a study done by Nagalakshmi *et al.*<sup>[10]</sup> In a study done by Preethi and Dhanasekaran<sup>[11]</sup> on the comparative study of efficacy and cost-effectiveness of topical sucralfate and conventional dressings in diabetic ulcers in 100 patients shows about 70.4% reduction in ulcer surface area whereas control group shows only 29.6% reduction in ulcer surface area [Table 5].

# CONCLUSION

The results suggest that sucralfate dressing may be a promising option for the treatment of chronic lower limb ulcers. Its effectiveness in facilitating wound contraction and promoting early granulation tissue fill-up, makes it a viable alternative to traditional betadine dressings.

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# Assessment of Knowledge, Attitudes, and Practices toward Organ Donation and Transplantation among the General Population of India: A Community-Based Study

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### Abstract

**Background:** Organ donation is yet to gain momentum in India. One of the major concerns of organ shortage in the country is the lack of knowledge among public and various myths and misconceptions. This study aimed to assess the knowledge, attitude, and practices toward organ donation among the general population of India.

**Methods:** It was a cross-sectional study conducted on 800 participants from various parts of India. Data was collected using an online questionnaire on Google Forms which comprised closed and open-ended questions assessing knowledge, attitudes, and practices regarding organ donation in the community.

**Results:** Out of 800 participants, 43.87% were males and 56.12% were females. Majority belonged to the younger age group (72.25%). Most of the respondents (98%) were aware of the term organ donation while only 65.5% actually understood the concept. Despite 48.4% of the respondents showing their willingness to donate, only 10.4% of the participants had pledged. Internet (64.1%) and mass media (57.2%) were the sought-after sources of information regarding organ donation.

**Conclusion:** Several gaps in knowledge, attitudes, and practices were found and reiterates the need for a more intensified interdisciplinary discussion and planning to educate and motivate the general population to pledge to donate their organs.

Key words: Organ donation, Gaps in knowledge, Attitudes, Practices, Religion, Sources of information

### **INTRODUCTION**

Organ transplantation is the process of replacing diseased organs or tissues with healthy one's for therapeutic purposes.<sup>[1]</sup> According to a survey in India, every year about 5 lakh people die because of non-availability of organs, and 1.5 lakh people await a kidney transplant, but only 5,000 among them get it and the bottleneck is the availability of organs.<sup>[2]</sup> Organ donation is yet to gain momentum in India

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and organ donation following brainstem death is abysmally infrequent since the need for organ transplantation is much higher than availability.<sup>[3]</sup> Organ shortage in the country can be attributed to lack of awareness among public, myths, and misconceptions hampering organ donation due to religious and cultural barriers.<sup>[3,4]</sup> Hence, imparting the correct knowledge is quintessential for the success of organ donation program in India. Health-care professionals are the critical link in augmenting public awareness about organ donation. Their attitudes and beliefs can influence the public opinion. Knowledge, attitude, and actions are interrelated and external influences also participate in decision-making.

In India, the Transplantation of Human Organs Act (THOA) was enacted in 1994.<sup>[4]</sup> Yet the rate of organ donation in India is poor (0.08/million population/year) as

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compared to developed countries.<sup>[5,6]</sup> Even after getting on the waiting list there is still a 10–30% chance for not getting a transplant.<sup>[7]</sup> THOA defines brainstem death as "the stage at which all functions of the brainstem have permanently and irreversibly ceased."<sup>[8]</sup> People can sign up as a donor after the age of 18. Any individual under 18 years of age can register as a donor only after family's consent.

This study was conducted with the aim of understanding the knowledge, attitudes, and practices regarding organ donation among the general population. We also evaluated the sociodemographic factors associated with this behavior, to suggest solutions and interventions to overcome them.

### **MATERIALS AND METHODS**

### **Study Setting**

The study based in Goa was conducted on 800 participants from all over India over a period of 3 months (July-October 2020). Based on a review of similar literature, it was found that 56.67% (p) of people were willing to donate their organs.<sup>[9]</sup> Taking a 95% confidence level ( $z\alpha$ ), 2.5% relative error(d) of 56.67% prevalence rate(p), a sample size of approximately 770 participants was calculated by applying the formula:-

$$N = (\boldsymbol{z} \boldsymbol{\alpha})^{2} * \frac{\boldsymbol{p}^{*} \boldsymbol{q}}{\boldsymbol{d}^{2}}$$

### **Study Design**

The study was a descriptive cross-sectional study. The study population included all adults ( $\geq$ 18 years), who gave their consent. The exclusion factors in the study were, if the participant denied giving consent, was not a resident of India or was <18 years. A pre-designed and pretested structured questionnaire was developed and circulated online through the Google Forms portal to abide by the social distancing norms owing to the Covid-19 crisis. The questionnaire was in English and captured the socio-demographic information and assessed the knowledge, attitudes, and practices regarding organ donation in the community.

### Sampling

Data collected were cleaned for any errors and duly transferred into Microsoft Excel 2019 (v.16.0.12026.20174) and SPSS (v.1.0.0.1406). Simple proportions and percentages were calculated and suitable tests of significance were used to study associations between the attributes. *P* value of <0.05 was considered significant. Four major domains in the study were, socio-demographic characteristics which included variables such as name, age, and sex; knowledge of the respondents was assessed through questions regarding meanings of the terms "organ donation" and

"brain death" etc.; attitudes regarding organ donation was determined through questions such as willingness to donate and influence of religion; practices were measured by enquiring about actual donations, possession of organ donor card, etc.

### **Ethical Requirements**

Ethical clearance was obtained from the Institutional Ethics Committee of Goa Medical College, Bambolim, Goa. Confidentiality of responses and informed consent were maintained.

A pilot study was conducted on 10 volunteers, out of which, 5 were males and 5 females; 5 belonged to the younger age group, 3 were middle-aged and 2 were elderly individuals. All the volunteers were made to answer the questionnaire and provide feedback on the same. The suggestions were then studied, and discussed with experts in the field and the questionnaire was suitably modified for the main study.

# RESULTS

Of 822 individuals that were approached in the study, 800 gave their consent and met the criteria. Most of the respondents, 611 (76.4%) were residents of Goa and a few, 189 (23.6%) of them belonged to other states such as Maharashtra (7.5%), Karnataka (4%), and Tamil Nadu (3.6%).

As shown in Table 1, among the respondents, 578 (72.2%) belonged to the younger age group followed by 157 (19.6%) adults and 65 (8.2%) elderly. The sample included 351 (43.8%) males and 449(56.2%) females. As for religion, 612 (77%) were Hindus, 127 (15.5%) were Christians, 39 (4.8%) were Muslims and 15 (1.8%) of the respondents considered themselves to be atheists, along with small proportions of other religions which resemble the religion distribution of our country. Regarding the maximum educational qualification of each respondent of our study, we can conclude that most, i.e., 498 (62.3%) of the respondents have a basic educational degree (undergraduate) and 305 (38.2%) of our respondents were related to the medical field. Out of which, 211(69%) belonged to Allopathic sciences, 35 (11.5%) from Dentistry, 44 (14.4) from the Allied Health Sciences, 10 (3.5%) belonged to Nursing and 5 (1.6%) of the people belong to AYUSH and related disciplines.

### Assessment of Knowledge

Table 2 summarizes the participants' knowledge with regard to organ donation and 784 (98%) were aware of the term "organ donation". Only 524 (65.5%) participants could

Sociodemographic variable	Responses	Frequency ( <i>n</i> =800) (%)
Age group	18–36 years	578 (72.2)
	36–55 years	157 (19.6)
	>55 years	65 (8.2)
Gender	Male	351 (43.8)
	Female	449 (56.2)
Resident of Goa	Yes	611 (76.4)
	No	189 (23.6)
Type of residence	Municipality/Corporation (Urban background)	417 (52.2)
	Village Panchayat (rural background)	383 (47.8)
Marital status	Unmarried	554 (69.2)
	Married	242 (30.2)
	Divorced	4 (0.6)
Employment status	Employed	280 (35)
	Unemployed	520 (65)
Place of work/education from	Belong to the medical field	305 (38.2)
a medical background	Not at all related to the medical field	495 (61.8)
Religion	Hindu	612 (77)
	Christian	127 (15.5)
	Muslim	39 (4.8)
	Atheist	15 (1.8)
	Others	7 (0.9)
Educational qualifications	Professional degree (post graduate/diploma/masters or higher)	202 (25.3)
	Degree (undergraduate/bachelors)	498 (62.3)
	Higher secondary (till 12 <sup>th</sup> grade)	91 (11.4)
	Secondary (till 10 <sup>th</sup> grade)	5 (0.6)
	Primary (literate)	2 (0.2)
	Illiterate	2 (0.2)

Table 1: Socio-demographic	characteristics
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accurately identify that it encompasses all the procedures, i.e., the transfer of tissues or organs from a dead body to a patient in need, the transfer of tissues or organs from a living donor to a patient as well as the removal of organs from the human body for the purpose of immediate transplantation into another body.

As far as having an understanding of consent in organ donation, only 177 (22.1%) respondents had accurate knowledge regarding consent for a living donation, i.e., donor themselves can give consent and the donor's spouse or family members can give consent if the donor is a minor/is of unsound mind. As for consent after brain stem death, only 392 (49%) respondents were aware that donor themselves can pledge beforehand to donate their organs in good faith after their demise, while consent is taken from the donor's spouse/family members.

Most of the respondents of our study, i.e., 747 (93.4%) knew that organ donation is legal and were aware THOA. When asked about the criteria required to qualify as an organ donor, 525 (65.6%) participants rightly identified all the prerequisites while 82 (10.2%) respondents were totally unaware.

As for the understanding of the concept of brain-stem death, only a few i.e., 184 (23%) respondents actually understood brain-stem death as irreversible damage of vital respiratory and cardiac centers of the brain where the patient will not live without external life support. Furthermore, 135 (16.9%) respondents had the false impression that a brain-dead patient can recover from their injuries. When enquired about an ideal situation for organ donation, only 423 (52.9%) participants knew that brain stem death in a controlled ICU setting is conducive.

When asked to arrange in order of priority as the "next of kin" having legal rights over the body of the deceased, only 356 (44.5%) respondents could tell accurately that it is spouse > siblings > parents > friends. Only 28.6% of participants could tell accurately that a single deceased donor can save more than 8 lives.

With regard to certain facts about organ donation, 668 (83.5%) respondents knew that different solid organs upon retrieval have different viability periods beyond which they are rendered useless. Most i.e., 664 (83%) respondents were aware of the severe shortage of available deceased donated organs in our country. A lot many, i.e., 728 (91%) respondents knew that cross-matching of blood is done before transplantation. Out of the respondents, 442 (55.3%) were unfamiliar with the system of green corridors to make way for the organ donation ambulance. Furthermore, 428 (55.5%) respondents were not aware

Knowledge assessment field	Responses	Frequency ( <i>n</i> =800) (%)
Aware of the term organ	Yes*	784 (98)
donation	No	16 (2)
Understands the term organ	Transfer of tissues or organs from a dead body to a patient in need	124 (15.5)
donation	Transfer of tissues or organs from a living donor to a patient in need	29 (3.6)
	The removal of organs from the human body for the purpose of immediate transplantation into another body	112 (14)
	All of the above*	524 (65.5)
	Don't know about organ donation	11 (1.4)
Knows as to who gives	Organs can't be donated before death	24 (3.00)
consent for a living donation	Donor themselves, if not mentally ill or a minor*	687 (85.9)
	Donor's spouse/family members always	73 (9.1)
	Donor's spouse/family only if donor is of unsound mind or is a minor*	221 (27.6)
	Doctor	62 (7.7)
	Don't know	54 (6.7)
Knows as to who gives consent for a donation after	Donor themselves can pledge beforehand to donate their organs in good faith after their demise*	691 (86.3)
death	Donor's spouse/family members or next of kin*	447 (55.9)
	Donor's doctor who certified and confirmed the death	51 (6.2)
	Registrar at municipality/village panchayat who records the death	17 (2.1)
	Don't know	36 (4.5)
Aware if organ donation	Yes, it is legal, and I am aware of the parliamentary THOA which governs the process*	747 (93.4)
and transplantation is legal	Organ donation and transplantation is absolutely illegal in India	8 (1)
in India	Don't Know	45 (5.6)
Knows the criteria to qualify	The donor should be free of any blood borne diseases or STD (e.g., AIDS)	144 (18)
as an organ donor	The donor should not have active metastatic cancer of any kind	33 (4.1)
	The donor should not be badly injured or mutilated	7 (0.9)
	The donor's death should not be related to any active legal police case	9 (1.2)
	All of the above*	525 (65.6)
	Don't know	82 (10.2)
Understands what the term brain stem death means	Brain stem death is similar to a comatose patient where patient's heart and lungs are still functioning	82 (10.3)
	Brain stem death means that there is an irreversible damage of vital respiratory and cardiac centers of the brain and that patient won't live without external life support	184 (23)
	Both A and B encompass brain stem death*	292 (36.5)
	Don't know	242 (30.3)
Is it possible for a declared	Yes	135 (16.9)
brain-dead patient to	No*	406 (50.7)
recover from their injuries?	Don't Know	259 (32.4)
situation for organ	their home	94 (11.8)
donation?	Brain stem death in which an artificial system keeps heart beating so as to maintain circulation and breathing*	423 (52.9)
	Donor is alive and apparently healthy	122 (15.2)
American the fallowing in	Don't know	161 (20.1)
Arrange the following in	Friends>Parents>Siblings>Spouse	7 (0.9)
of kin' boying logal rights of	Siblings>Parents>Spouse>Friends	33 (4.1) 404 (50.5)
the body of the deceased	Spouse>Siblings>Spouse>Friends Spouse>Siblings>Parents>Friends*	404 (50.5) 356 (44.5)
How many individual's lives'	1 only	89 (11.2)
can one deceased organ	1–4	264 (33)
donor improve?	4–8	18 (27.2)
	More than 8*	229 (28.6)

#### Table 2: Knowledge on various aspects about organ donation

The (\*) indicates the most appropriate answer. THOA: Transplantation of human organs act, STD: Sexually transmitted diseases

that the relatives of a deceased, who has pledged to donate their organs before their demise, can still legally revoke the decision of the same.

As far as myths and misconceptions about organ donation, 530 (66.3%) participants were of the impression that possessing an organ donor card also increases one's chances of

receiving organs. A few i.e., 82 (10.3%) respondents thought that one can buy/sell organs. When asked about their views regarding the process leading to the severe disfigurement of the donor's body, 109 (13.7) respondents were in agreement. A vast majority, i.e., 505 (63.1%) participants were of the impression that on the waiting list, financial discrimination prevents eligible patients from getting the transplant they need. Figure 1 depicts the various organs that the respondents thought can be donated after death. Majority of the respondents thought that the kidney 688 (86%), liver 616 (77%), heart 568 (71%), cornea 557 (69.6%), lungs 430 (53.8%), and pancreas 361 (45.1%) can be donated after death; while a few thought that skin (42.6%), bone marrow (39.3%), intestine (23.9%), and nerves and tendons (16.2%) can also be donated and were all correct about their opinions. A few of the respondents thought that the uterus (15.8%) and brain (10.4%), can also be donated and were incorrect.

Figure 2 depicts various organs that the respondents thought can be donated before death. Majority thought that the kidney 712 (89%), liver 442 (55.2%), and skin

338 (42.2%) can be donated. Few respondents thought that heart (9.6%) and brain (3%) can also be donated, while 5.4% were certain that organs cannot be donated when the patient is alive.

Figure 3 shows the various sources of information that the respondents utilize to get information about organ donation. The major sources according to the respondents were the internet 513 (64.1%), followed by television 458 (57.2%), newspaper articles 415 (51.8%), and health-care professionals 392 (49%).

### **Assessment of Attitudes**

Table 3 shows the assessment of the attitudes of the respondents. Majority of the participants, i.e., 797 (99.6%) agreed to the fact that organ donation is a good thing which



Figure 1: Organs that can be donated after death according to the respondents. The (\*) indicates the most appropriate answer



Figure 2: Organs that can be donated before death according to the respondents. The (\*) indicates the most appropriate answer

should be promoted and that, registering as an organ donor can save somebody's life. A large number of respondents, i.e., 653 (81.6%) would be more willing to pledge if they knew their family's opinion.

Most respondents, i.e., 669 (83.6%) believed they would be more willing to donate if more information was available about the viewpoint of their religion. When asked about live donations, 547 (68.4%) respondents were worried - that organ donation might leave them weak/about surgical complications. A small group, i.e., 225 (28.1%) agreed that they did not trust the healthcare system in India with regard to organ donation. A large number of respondents, i.e., 453 (56.6%) were comfortable with organ donation and 648 (81%) were comfortable talking about it. Though the donor has no choice to reflect upon their attitudes,



Figure 3: Preferred sources of information about organ donation. \*HCW: Health care workers

### Table 3: Attitudes toward organ donation

Attitudes assessment field	Responses	
	Agree (%)	Disagree (%)
What the participant felt		
Organ donation is a good thing and should be promoted	797 (99.6)	3 (0.4)
Registering as an organ donor could save somebody's life	797 (99.6)	3 (0.4)
I would be more willing to register as an organ donor		
If I knew my family would have no objection to allowing donation of my organs at the time of my death	653 (81.6)	147 (18.4)
If more information was available about the viewpoint of my religion with regard to organ donation	669 (83.6)	131 (16.4)
Regarding live donation		
I am worried that the organ donation might leave me weak and disabled or about the surgical complications of the same	547 (68.4)	253 (31.6)
I don't trust the healthcare system and believe that it is better to go abroad for organ donation and transplantation	225 (28.1)	575 (71.9)
Statement	Responses	Frequency ( <i>n</i> =800)
Any preference of a recipient for donating your organs if you were to donate your organs?	<ul> <li>Would donate only to a family member or a close friend</li> </ul>	145 (18.1)
	B. Would donate to anyone irrespective of my relation with the same	620 (77.5)
	C. Would donate to someone of the same religion	6 (0.7)
	D Haven't considered donating	29 (37)

respondents were asked about the preferences of a recipient and 145 (18.1%) would donate only to relatives, 620 (77.5%) would donate to anyone and only 6 (0.7%) participants wanted to donate to someone of the same religion.

Practices assessment field		Resp	oonses
	Yes		No
Already pledged to be an organ donor and/or have a donor ID card?	83 (10.4%)		717 (89.6%)
Following are certain viewpoints with regard to organ donation, please s	elect whichever vi	iew suits you the n	nost
Statement		Resp	oonses
	Yes (%)		No (%)
I think my donation, whether living or after death is going to impact my life after death in a good way	581 (72.6)		219 (27.4)
Organ donation might increase if social support/financial aid are provided to the family of the deceased	678 (84.8)		122 (15.2)
Opinions of my family members when my organs would be taken after my death preclude me from pledging to donate my organs	422 (52.8)		378 (47.2)
Statement	Respor		ponse
	Yes (%)	No (%)	Don't know (not given a thought yet) (%)
Willing to register as an organ donor Would spread awareness and promote organ donation when the need comes to do so	387 (48.4) 593 (74.1)	23 (2.9) 6 (0.7)	390 (48.8) 201 (25.1)
Religious basis if any, hindering the participants from donating your org	ans /	Beene	2000 (0/ )
Statement		Respo	
A. Not applicable/no religious aspects B. I have personally discussed with a religious leader/clergy C. I have heard a leader talk against it		748 5 ( 7 (	(93.5) (0.6) (0.8)
E. I have discussed it with family and friends	17 (2.1) 27 (3 4)		
F. I know for sure it is against religion or faith		15	(1.9)
Statement	Responses		
	Donated	Received	None of the above
Have family members who have ever donated/recieved any organ before?	35 (4.4%)	17 (2.1%)	748 (93.5%)

### Table 5: Correlation between religion, medical background, age, gender and willingness to donate

Variables		Willingness to donate			Chi square tes	st
	Willing (%)	Not willing (%)	Total (%)	df	X <sup>2</sup> -value	P-value
Religion						
Hindu	306 (38.5)	306 (38.5)	612 (77)	3	13.11	0.004
Christian	56 (7)	71 (8.5)	127 (15.5)			
Muslim	10 (1.2)	29 (3.6)	39 (4.8)			
Others	15 (1.8)	7 (0.9)	22 (2.7)			
Total	387 (48.5)	413 (51.5)	800			
Medical background						
Medical	167 (20.9)	138 (17.3)	305 (38.2)	1	8.03	0.005
Non-medical	220 (27.5)	275 (34.3)	495 (61.8)			
Total	387 (48.4)	413 (51.6)	800			
Age group (in years)						
Young (18–36)	259 (32.3)	319 (39.9)	578 (72.2)	2	10.62	0.005
Adults (37–55)	91 (11.4)	66 (8.2)	157 (19.6)			
Elderly (>55)	37 (4.6)	28 (3.6)	65 (8.2)			
Total	387 (48.3)	413 (51.7)	800			
Gender						
Male	150 (18.7)	201 (25.1)	351 (43.8)	1	7.97	0.005
Female	237 (29.6)	212 (26.6)	449 (56.2)			
Total	387 (48.3)	413 (51.7)	800			

#### **Assessment of Practices**

As shown in Table 4, 387 (48.4%) respondents were willing to register as organ donors, yet only 83 (10.4%) had pledged to do so. None of the respondents had donated/received any organs before our study. Among the respondents, 35 (4.4%) had family members who had donated organs, 17 (2.1%) had family members who had received organs while a large majority i.e., 748 (93.5%) had no relative who had ever donated/received any organs.

Six (0.7%) respondents disagreed to spread awareness and promote organ donation. Only a few respondents, i.e., 52 (6.5%) had a religious bias hindering them from donating their organs. As for reasons for being hesitant to donate, 100 (12.5%) believed that the organs might be misused, 20 (2.5%) opined that the body is sacred even after death and 62 (7.8%) feared that they may be purposely declared brain dead. When asked about their opinion, 678 (84.8%) respondents thought that organ donation might increase, if social support/financial aid is provided to the family of the deceased. More than half, i.e., 422 (52.8%) respondents confirmed that opinions of family members when their organs would be taken preclude them from pledging to donate.

We performed an analysis to look for the associations of socio-demographic variables with attitude of willingness to donate among the respondents; the results of which are provided in Table 5. We found a significant influence of religion (P = 0.004), medical background (P = 0.005), age (P = 0.005), gender (P = 0.005) on the participants' willingness to donate. Table 6 shows the statistical analysis for association of socio-demographic variables with the respondents already having pledged to donate. There was a statistically significant association between religion (P = 0.029), medical background (P = 0.003), age (P = 0.007), gender (P = 0.004) and the respondents having pledged to donate their organs.

## DISCUSSION

Organ donation and transplantation is an important treatment modality of many end-organ diseases.<sup>[1]</sup> According to Shah *et al.*,<sup>[10]</sup> "organ donation is a community service, which saves lives and improves quality of life". Shortage of organ donation is a major problem due lack of awareness and false perceptions about organ donation among the population.<sup>[11]</sup> Thus, our study aimed to assess knowledge, attitudes and practices of the general population of India toward organ donation.

Knowledge is an important determinant for willingness to donate organs.<sup>[12]</sup> Most of the respondents (98%) were aware of the term "organ donation" which is similar to studies done by Jothula and Sreeharshika<sup>[2]</sup> and Vijayalakshmi *et al.*,<sup>[8]</sup> and far better than the results obtained by Dasgupta *et al.*<sup>[12]</sup> The above phenomena can be ascribed to the higher literacy rate and higher number of doctors and medical students in our study. The most preferred sources of information were the internet (64.1%), mass media (TV-57.2%, newspaper articles - 51.8%), and health-care workers (49%). This was in direct correlation with many other studies,<sup>[1,2,7,9,10,12]</sup> which emphasizes their

Table 6: Correlation	between religion,	medical backg	round, age g	proup and ge	ender and the	respondents
having pledged to d	onate					

Variables		Pledged to donate			Chi square te	st
	Pledged (%)	Not pledged (%)	Total (%)	df	X <sup>2</sup> -value	P-value
Religion						
Hindu	67 (8.9)	545 (68.1)	612 (77)	8	802.54	0.029
Christian	13 (1.5)	114 (14)	127 (15.5)			
Muslim	2 (0.2)	37 (4.6)	39 (4.8)			
Others	3 (0.3)	19 (2.4)	22 (2.7)			
Total	85 (10.9)	715 (89.1)	800			
Medical background						
Medical	36 (4.6)	269 (33.6)	305 (38.2)	4	801.72	0.003
Non-medical	49 (6.1)	446 (55.7)	495 (61.8)			
Total	85 (10.7)	715 (89.3)	800			
Age group (in years)						
Young (18–36)	56 (7)	522 (65.2)	578 (72.2)	6	803.44	0.007
Adults (37–55)	22 (2.7)	135 (16.9)	157 (19.6)			
Elderly (>55)	7 (0.9)	58 (7.3)	65 (8.2)			
Total	85 (10.6)	715 (89.4)	800			
Gender						
Male	35 (4.3)	316 (39.5)	351 (43.8)	4	801.28	0.004
Female	50 (6.3)	399 (49.9)	449 (56.2)			
Total	85 (10.6)	715 (89.4)	800			

pivotal role in promoting organ donation. Most of the respondents were aware of the organs that can be donated after brainstem death and by a living donor. However, few thought that the uterus (15.8%) and brain (10.4%) can also be donated which is not true, while 5.4% of respondents believed that organs cannot be donated when the donor is alive. Similar findings were seen in various studies, [1,9,13,14] which infers that some misconceptions and misinformation about organ donation still prevail. A matter of concern was that hardly 22.1% of the respondents understood consent for living donation when donor is alive, which corresponded with a study by Dasgupta et al.[12] where only 20% of respondents understood consent. As for organ donation after death, 49% of respondents were aware as to who gives consent while a better response was seen in a study by Jothula and Sreeharshika<sup>[2]</sup> THOA was enacted in 1994 and 93.4% of the respondents were aware of it, which was far better than other studies.<sup>[1,10,11,15,16]</sup> Regarding criteria for organ donation, 65.6% of respondents were well versed in it, which was similar to a study by Sam et al.[11] As for brain stem death, only 23% of participants were aware of what it entails, while 16.9% were of the belief that a declared brain-dead patient can recover. The responses of our study were better than a previous study done by Vijayalakshmi et al.<sup>[8]</sup> where only 4% of participants knew about brainstem death. However, a relatively poor response was obtained when compared to other studies.<sup>[9,13]</sup> When asked about an ideal situation for organ donation, 52.9% of the respondents thought it to be brain-stem death, in which an artificial system maintains circulation and breathing, which paralleled another study.<sup>[9]</sup> Only 44.5% respondents could arrange the next of kin that gives consent for the deceased donor, which was similar to other studies.<sup>[10,11]</sup> Only 28.6% participants could tell, that multiple lives can be saved by a single deceased donor which was similar to other studies.<sup>[3,9]</sup> A majority of 83.5% respondents knew that solid organs have different viability periods which was better than the study done by Sindhu et al.[1] Most of the respondents (83%) were aware of the shortage of available deceased donated organs. Similar studies, [3,8] had insight into the same. Quite a few (91%) respondents of our study knew that cross-matching is done before transplantation which was consistent with a study by Sindhu et al.<sup>[1]</sup> In our study, 18.5% respondents were unaware that one can register. A similar study was done by Sindhu et al.<sup>[1]</sup> reported that knowledge regarding registration as an organ donor was quite low along with several other studies.<sup>[3,8,14]</sup> Only 46.5% respondents were aware that relatives of the deceased who had pledged before can still revoke the decision, which was similar to a study done by Vijayalakshmi et al.<sup>[8]</sup> Most of the respondents (89.7%) knew that one cannot buy or sell organs, which was consistent with other studies.<sup>[8,10]</sup> In our study, 63.1% of respondents had the

impression that financial discrimination prevents the poor from receiving organs which were similar to a study by Adithyan *et al.*<sup>[3]</sup> Most of the participants (55.3%) were unfamiliar with the system of a green corridor. A vast majority i.e., 66.3% had the impression that possessing an organ donation card also increases one's chances of receiving organs, suggesting a poor level of knowledge regarding organ donation.

Of the participants, 99.6% asserted that organ donation should be promoted and that registering as an organ donor could save lives. This shows a positive attitude as compared to other studies.<sup>[2,7,8,14]</sup> A majority of respondents, i.e., 81.6% would be more willing to register as organ donors if they knew that their families had no objection, which was similar to other studies.<sup>[4,8,11]</sup> Regarding the viewpoint of religion, 83.6% of respondents wanted more information before pledging. In a similar study by Jothula and Sreeharshika<sup>[2]</sup> 88.7% respondents felt that awareness regarding organ donation and knowledge about its procedures is important. Regarding live organ donation, 68.4% respondents felt that organ donation would leave them weak/disabled, while 28.1% felt hesitant to donate because they did not trust the healthcare system. Studies conducted by Dasgupta et al.<sup>[12]</sup> and Devi et al.[4] had similar findings. Another similar study conducted by Sam et al., [11] 13.6% respondents wished not to go through the disfigurement involved and 30% of them did not trust the healthcare system. While 81% respondents were comfortable talking about it, only 56.6% respondents were comfortable donating organs. When asked about preference for a recipient, 18% would donate to their relatives only and 0.7% would donate to someone of the same religion while a majority of 77.5% would donate to anyone irrespective of any relation. In a study done by Dasgupta et al.,<sup>[12]</sup> 55.5% of respondents preferred donating to a family member only while 29% preferred donating to the same religion. In the meanwhile, several studies<sup>[3,8]</sup> showed a majority of respondents ( $\geq$ 85%) being altruistic and willing to donate irrespective of the recipient's religion.

It was interesting that 48.4% of respondents were willing to donate yet only 10.4% possessed a donor card which showed a lack of motivation. Similar findings were seen in other studies,<sup>[4,12,14]</sup> with respondents being uncomfortable to register as a donor. Possible reasons for the unwillingness of participants to pledge could be fear of misuse of organs, objection from family members, lack of knowledge regarding organ donation, myths, and misbeliefs as seen in previous studies.<sup>[2,3,10-12,14,17]</sup> In our study, 74.1% respondents were ready to create awareness and promote organ donation. It was interesting to note that 93.5% of participants were unaffected by religion for donating/receiving an organ. In a study done by Kaistha *et al.*,<sup>[14]</sup> 69.6% wanted to create awareness and promote

organ donation. Studies<sup>[1,4,13]</sup> reveal that religion did not hinder the participants from pledging to donate. As for the reasons for hesitance to donate organs, 12.5% responded that fear of their organs being misused was one of them, which was similar to other studies,<sup>[8,9,13,18]</sup> where the fear prevailed along with a high level of mistrust toward doctors. More than half, (52.8%) respondents confirmed that the opinions of family members, preclude them from pledging to donate, which was similar to other studies.<sup>[1,8,12]</sup> In a study by Seth *et al.*,<sup>[19]</sup> the reason for the refusal of organ donation was lack of consensus among the patient's family members.

There is a strong association between the religion and the participants' willingness and them having pledged to donate which can be attributed to the fact that different religions have a varied outlook on organ donation. Certain religions also condemn the practice and studies by Krupic<sup>[20]</sup> and Oliver et al.[21] showed similar findings. Comparing the willingness to donate organs and participants having pledged to donate, with their medical background, we found a strong association as, 20.9% of participants from a medical background were willing to donate and 4.6% had pledged to donate. Meanwhile, 27.5% and 6.1% of participants from a non-medical background were willing to and had pledged to donate their organs, respectively. This can be attributed to growing awareness regarding organ donation that makes our participants willing to donate, though the awareness isn't enough. This was synonymous to the results obtained by Siddiqui et al.[8] and differed when compared to a study by Jothula and Sreeharshika<sup>[2]</sup> As for the association of age group of our participants with willingness to donate and them having pledged to donate, we found a strong association which can be attributed to fear and lack of knowledge in the elderly regarding organ donation. Contradictory results were seen in other studies by Reynolds et al.[22] and Sarveswaran et al.[23] where they saw an increased willingness in the elderly age group of above 30 years owing to their acuity to accept knowledge. Finally, on comparing the gender of the participants with their willingness to donate and whether they have pledged to donate, we found that a significant correlation exists. In a study evaluating gender bias in organ donation by Bhuwania et al.<sup>[24]</sup> and Vijayalakshmi et al.,<sup>[8]</sup> more males were willing to donate and register as organ donors which is contradicting with our study. This can be attributed to changing trends of literacy rate between males and females. However, majority of the participants from the both the groups were still unsure about signing organ donation cards.

### CONCLUSIONS

A consistent organ donation program can bridge the gap for the shortage of deceased organ donors in India. Our study highlights that knowledge was adequate, yet not enough, and only 10.4% possessed an organ donor card. A considerable number of respondents were victims of myths and misconceptions while many had religious and cultural beliefs hindering them. Thus, well-designed publicity campaigns to address cultural beliefs and correct misconceptions are needed. Two areas of concern were, the lack of understanding of the role of consent before organ donation and the concept of brainstem death. Another setback was the concern about being disabled after a live donation which can be addressed by reassurance about the procedure. A few participants were anxious about their organs being misused and premature termination of medical treatment. Furthermore, according to the World Health Organization, organ trafficking accounts for 5–10% of the kidney transplants annually.<sup>[25]</sup> Ultimately, our findings indicate that organ donation is the need of the hour and a well-organized approach is required to raise awareness about its various aspects to eliminate the paucity of available organs.

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# Early Prediction of High-Flow Nasal Cannula Success or Failure using ROX and Modified ROX Index Incorporating Heart Rate in Patients with Acute Hypoxemic Respiratory Failure

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#### Abstract

**Background and Aim:** The use of high-flow nasal cannula (HFNC) in acute hypoxic respiratory failure decreases intubation rates and lowers mortality. However, early prediction of HFNC failure is very important, as it may delay the much-needed intubation. To address this issue, ROX index and ROX-HR index were calculated and compared.

**Methods:** Thirty patients of either sex in the age group of 18–60 years of ASA grade I & II presenting with acute hypoxemic respiratory failure were put on HFNC after taking informed consent. Baseline hemodynamic parameters, APACHE II, Q SOFA score and Charleson Comorbidity Index, and ABG were noted, and continuous monitoring of the above parameters was done. ROX index and ROX-HR index were calculated at specified intervals in patients of HFNC success and failure and were compared for their sensitivity, specificity, positive predictive value, and negative predictive value in predicting HFNC success or failure.

**Results:** Twenty-one patients were weaned from HFNC and 9 patients were shifted to a higher mode of oxygenation. There was no positive correlation of age with HFNC success and failure. In HFNC success, heart rate (HR) and respiratory rate (RR) improved over time and patients were weaned off. In HFNC failure, HR and RR both had increasing trends and needed vasopressors to maintain blood pressure. ROX and ROX-HR index values improved (>5.90 and >6.90, respectively) at 6 h in HFNC success patients. At 8 h, both indices were equally sensitive. At 6 h, the specificity of ROX-HR was more.

**Conclusion:** ROX index and ROX-HR index are sensitive in the early prediction of HFNC success. ROX-HR index is more specific for the prediction of HFNC failure.

Key words: High-flow nasal cannula, Acute respiratory failure, ROX index, ROX-HR index

### **INTRODUCTION**

High-flow nasal cannula (HFNC) therapy has been gaining attention in the management of acute hypoxemic

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respiratory failure as it delivers heated and humidified oxygen at flow rates of up to 60 L/min, a PEEP of 3–5 cm H<sub>2</sub>O, with the maintenance of constant fraction of inspired oxygen. It reduces anatomical dead space and provides positive end-expiratory pressure,<sup>[1,2]</sup> thereby decreasing respiratory rate (RR) and improving oxygenation.<sup>[3]</sup> The use of HFNC in patients of acute hypoxemic respiratory failure<sup>[4]</sup> decreases the intubation rates and lowers mortality. However, delayed detection of HFNC failure carries the risk of delaying much-needed intubation. To address this problem, various parameters were used for early prediction of HFNC success or failure. ROX index, defined as the

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ratio of oxygen saturation as measured by pulse oximetry to the fraction of inspired oxygen (SpO<sub>2</sub>/FiO<sub>2</sub>) to RR, has been used to predict HFNC success and failure.<sup>[5]</sup> As heart rate is the most commonly measured parameter in the intensive care unit patients and by incorporating it in the ROX index may improve its diagnostic accuracy for prediction of HFNC success and failure. ROX-HR index defined as the ratio of ROX index over heart rate (beats/ min) multiplied by factor 100 was formulated. Heart rate has an inverse ratio to HFNC success as tachycardia as early as 1 h into HFNC therapy is found to be associated with HFNC failure. As nowadays, HFNC is being commonly used in patients of acute hypoxic respiratory failure to delay unwanted intubations.<sup>[6]</sup> It is necessary to formulate certain parameters to monitor the progress of HFNC therapy so that delayed intubations can be avoided. Hence, the present study was designed with the primary aim of evaluating the efficacy of the ROX index and ROX-HR index in early prediction of HFNC success and failure by comparing their sensitivity i.e., the percentage of correctly predicted HFNC success as a proportion of all successful HFNC trial, specificity which is defined as the percentage of correctly predicted HFNC failures as a proportion of all failed HFNC trials, positive predictive value (PPV) i.e., the percentage of all correctly predicted successful HFNC trials as a proportion of all predicted successful HFNC trials and negative predictive value (NPV) i.e., the percentage of correctly predicted failed HFNC trials as a proportion of all predicted failed HFNC trials. Secondary aim was to note the duration of HFNC therapy and the number of patients with HFNC success and failure.[7]

### **MATERIALS AND METHODS**

This prospective observational study was conducted on 30 patients aged 18–60 years of ASA grades I and II presenting with acute respiratory failure after taking informed consent and approval from the institutional ethics committee (3371/D-26/2020 batch).

Patients with acute hypoxemic respiratory failure with a RR >25 breaths/min and a P/F ratio of <300 mmHg on an oxygen device delivering  $\geq$ 10 L/min of oxygen were included in the study. Patients having chronic respiratory failure, hypercapnia (PaCO<sub>2</sub> >45 mmHg), acute respiratory failure secondary to asthma, chronic obstructive pulmonary disease exacerbation, hemodynamic instability requiring vasopressor support, Glasgow Coma Scale (GCS) <12, epistaxis, and recent facial or nasal surgery were excluded from the study. Baseline investigations such as complete blood count, liver function tests, renal function tests, electrolytes, ABG, coagulation profile, chest X-ray, and ECG were done. Baseline heart rate, RR, NIBP, ECG, SpO<sub>2</sub>,

ABG, GCS score, APACHE II score, q SOFA score, mode of oxygen therapy and FiO<sub>2</sub>, and Charleson Comorbidity Index (CCI) were noted before the start of HFNC therapy.

Patients were attached to HFNC and initiated at a minimum flow of 40L/min which was increased to 60L/min and FiO<sub>2</sub> was adjusted to maintain a target SpO<sub>2</sub> of greater than or equal to 92%. After putting on HFNC, patients were monitored for heart rate, non-invasive blood pressure, RR, SpO<sub>2</sub>, ECG, temperature, and ABG at regular intervals. General well-being of the patients was assessed using APACE II, q SOFA score, and CCI on a daily basis. Laboratory investigations were done depending on the condition of the patient. During HFNC therapy, the ROX index and ROX-HR index were calculated at regular intervals by continuous monitoring of RR, HR, SpO<sub>2</sub>, and FiO<sub>2</sub> given. Both were recorded before the initiation of HFNC therapy, and then, after 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 18 h, 24 h, and 48 h; once daily till HFNC therapy continued and 1 h before termination of HFNC.

Oxygenation with HFNC was continued till either HFNC success, i.e., maintaining  $\text{SpO}_2 > 92\%$  with  $\text{FiO}_2 < 60\%$  independent of gas flow or HFNC failure, i.e., worsening respiratory condition or at least two of the following criteria: failure to achieve correct oxygenation (PaO<sub>2</sub> < 60 mmHg or  $\text{SpO}_2 < 90\%$  despite HFNC flow > 30 L/min and FiO<sub>2</sub> of 1), respiratory acidosis (PaCO<sub>2</sub> > 50 mmHg with pH <7.25), RR > 30 breaths/min or inability to clear secretions, and patients were shifted to NIV or invasive ventilation. The total duration of HFNC therapy in days was calculated, and patients weaned or failure from HFNC therapy were noted. Sensitivity, specificity, NPV and PPV of ROX index, and ROX-HR index were calculated.

### **Statistical Analysis**

Required sample size was calculated using an a priori sample size calculator. Input: Tails: 1, slope H1 = 0.15,  $\alpha$ error probability = 0.05, power = 0.95, standard deviation  $\sigma$ -x = 1.9, standard deviation  $\sigma$ -y =0.5. Output: No centrality parameter = 3.3985716, critical t = 1.7171444, and Df = 22. Total sample size = 24.

The data from the present study were systematically collected, compiled, and statistically analyzed using the software IBM SPSS 22.0 to draw relevant conclusions. Data were expressed as means, standard deviation, numbers, and percentages. The intragroup comparison of the parametric data was done using the " $\ell$ " test. The "P"-value was determined to finally evaluate the levels of significance. P < 0.05 was considered significant, and a P < 0.001 was considered highly significant. Power analysis was done to calculate the power of the study. It was 95% by taking  $\alpha$  error 0.05.

### RESULTS

In the present study, 30 patients were put on HFNC therapy. Twenty-one patients were successfully weaned off (HFNC success) and nine patients needed NIV support or mechanical ventilation (considered HFNC failure). The demographic profile, baseline hemodynamic parameters, APACHE II, q SOFA score, and CCI were recorded in patients with HFNC success and failure, as shown in Table 1.

After putting patients on HFNC, continuous monitoring of heart rate was done. Difference in the mean HR in HFNC success and failure was statistically non-significant (P > 0.05) till 6 h. From 8 h onwards, mean HR started increasing in failure patients and was stable in patients who were successfully weaned off (P < 0.05), as shown in Graph 1. RR was high in HFNC failure patients as compared to HFNC success patients but the difference was non-significant (P > 0.05) from initiation of HFNC till 6 h. The value of RR started worsening in failure patients at 8 h and was normal in HFNC success patients (P < 0.05) till the patients were weaned off or shifted to a higher mode of oxygenation, as shown in Figure 1. Systolic and diastolic blood pressure was monitored at regular intervals, patients who failed HFNC therapy had fall in BP from 6 h onward and needed vasopressor support. SBP and DBP from 10 h onwards were significantly low in HFNC failure patients (P < 0.05), as shown in Figure 2. Patients who failed HFNC therapy, baseline APACHE II score, and q SOFA score were high (18.44  $\pm$  4.22 and 1.89  $\pm$  0.93, respectively) as compared to HFNC success (12.56  $\pm$  1.33 and  $1.11 \pm 0.33$ , respectively), and remained on the higher side till the patients were shifted to NIV of MV (P < 0.05). However, CCI at the initiation of therapy and throughout

# Table 1: Comparing baseline demographic,hemodynamic characteristics in patients withacute hypoxemic respiratory failure

Baseline parameters	HFNC success (n=21)	HFNC failure (n=9)	P value
Age (years)	43 (41-50)	41 (39-50)	0.193
Male	11 (36.67)	5 (16.67)	0.871
Female	10 (33.33)	4 (13.33)	0.871
APACHE II score	12.56±1.33	18.44±4.2	0.00
q SOFA	1.11±0.3	1.89±0.93	0.02
CCI	1.44±1.34	1.11±1.05	0.27
Heart rate (beats/min)	93±5.07	96±4.64	0.15
Respiratory rate (breaths/min)	21.62.0±4	22.8±4.31	0.41
SBP (mmHg)	123.81±9.28	130.22±8.17	0.08
DBP (mmHg)	76.29±5.81	78.78±6.89	0.16
SpO <sub>2</sub>	90.00±2.50	90.33±4.12	0.500

\*SBP (systolic blood pressure), DBP (diastolic blood pressure), SpO<sub>2</sub> (oxygen saturation) \*S- Significant (p<0.05), NS- Non significant (p>0.05) therapy was statistically comparable in HFNC success and failure patients. At the initiation of HFNC till 8 h, FiO<sub>2</sub> requirement in patients with HFNC success was lower (84.71 ± 6.99) as compared to HFNC failure (93.89 ± 7.04) but the difference was not significant P > 0.05. From 10 h onward, FiO<sub>2</sub> requirement decreased in patients who were successfully weaned but in HFNC failure patients required significantly more FiO<sub>2</sub> to maintain SpO<sub>2</sub>≥92%, P < 0.05), as shown in Table 2.

ROX index and ROX-HR index were calculated using RR, HR, SpO<sub>2</sub>, and FiO<sub>2</sub> at various time intervals to predict HFNC success (ROX >5.90 and ROX HR >6.90) and failure (ROX <5.90 and ROX HR <6.90). Both ROX and ROX-HR index were comparable from initiation of HFNC till 4 h in HFNC success and failure patients (P > 0.05), but 6 h onward, both started increasing in success patients and were significantly low in failure patients P < 0.05, as shown in Table 3.

ROX and ROX-HR indexes were compared for their ability to early predict HFNC success or failure by comparing their sensitivity, specificity, PPV, and NPV, as shown in



Figure 1: Depicting changes in mean HR and RR in patients with high-flow nasal cannula success and failure at various time intervals



Figure 2: Depicting changes in mean systolic blood pressure and mean diastolic blood pressure at various time intervals in patients with high-flow nasal cannula success and failure Table 4. It was observed that at 2 h, the sensitivity and specificity of ROX and ROX-HR were comparable, started increasing at 4 h, but remained comparable. At 6 h, the sensitivity of both indexes was still comparable but the specificity of ROX-HR increased (77.785%). At 8 h, the sensitivity of both indexes was again comparable but the specificity of the ROX-HR index (77.78%) was more than the ROX index (55.56%). At 10 and 12 h, the sensitivity remained comparable but the specificity was more of the ROX-HR index and thereafter the specificity of ROX-HR index and thereafter the specificity of ROX-HR index and thereafter the specificity of ROX-HR index and thereafter the specificity in patients who were successfully weaned was 2.851 ± 1.118 days and in HFNC failure patients was 3.666 ± 1.118 days (P = 0.205).

# Table 2: FiO<sub>2</sub> changes in patients with HFNC success and failure

	Hfnc success (n=21)	Hfnc failure (N=9)	P-value
FIO2	Mean±SD	Mean±SD	p-value
Initiation	84.71±6.99	93.89±7.04	0.500
1 hour	82.38±8.97	89.89±6.94	0.260
2 hours	78.81±10.33	87.56±6.71	0.170
4 hours	76.10±9.49	83.67±6.20	0.090
6 hours	72.48±10.78	80.56±7.68	0.140
8 hours	69.24±10.65	78.67±8.65	0.320
10 hours	64.67±12.08	78.44±8.63	0.030
12 hours	61.10±12.29	82.33±7.52	0.010
18 hours	55.43±12.81	80.00±7.23	0.000
24 hours	51.24±15.39	78.11±7.96	0.000
2 days	45.83±17.35	74.56±7.95	0.000
3 days	40.77±13.67	72.57±9.29	0.000
4 days	40.00±13.23	69.17±8.01	0.000
5 days	36.67±11.69	77.50±3.54	0.000

\*S– Significant (p<0.05), NS- Non significant (p>0.05)

### DISCUSSION

In the present study, 30 patients were put on HFNC therapy, out of which 21 patients were successfully weaned off from HFNC and 9 patients failed HFNC therapy and required a higher mode of oxygenation either NIV or ventilator support. In the present study, 18–60 years age group patients were included. It was observed that the age of the patient had no positive correlation with HFNC success or failure. Out of 30 patients, 14 were females and 16 were males. Among 14 females, 10 were successfully weaned and among 16 males, 11 were successfully weaned. Hence, the sex of patients had no significant effect on HFNC success and failure. Alshahrani *et al.*<sup>[8]</sup> and Kerai *et al.*<sup>[9]</sup> also observed that the age of the patient have no significant effect on HFNC success and failure.

In the present study, baseline APACHE II score and q SOFA score were high in patients who failed on HFNC therapy (13.44  $\pm$  4.22 and 1.89  $\pm$  0.93, respectively) as compared to patients who were successfully weaned (12.59  $\pm$  1.33 and 1.11  $\pm$  0.33, respectively) and both scores significantly improved over the time in HFNC success patients. Previous studies also observed that patients who had high APACHE II and q SOFA scores before initiation of HFNC therapy needed a higher mode of oxygenation as compared to patients who had lower scores.<sup>[7,9,1011]</sup> Charlson Comorbidity Index (CCI) was used to assess the comorbidities in patients before initiation on HFNC therapy and on subsequent days of therapy. CCI was comparable at all measured intervals in HFNC success and failure patients. Goh et al.[11] assessed CCI before initiation of HFNC therapy and observed that values of CCI were comparable in patients of HFNC success and

Table 3: ROX INDEX and ROX-HR INDEX trend at various time intervals in patients with HFNC success and failure

Time interval		ROX Index			ROX- HR	
	Patients with HFNC success (n=21)	Patients with HFNC failure (n=9)	p-value	Patients with HFNC success (n=21)	Patients with HFNC failure (n=9)	p-value
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
Initiation	5.32±0.51	5.10±1.05	0.418	5.18±0.59	4.89±1.19	0.375
1 hour	5.39±0.79	5.18±0.60	0.385	5.46±0.90	4.91±0.69	0.101
2 hours	5.67±0.65	4.80±0.52	0.080	6.17±0.72	5.87±0.81	0.320
4 hours	6.05±0.87	5.81±0.57	0.455	7.23±1.15	6.86±0.92	0.401
6 hours	6.72±1.38	5.61±0.52	0.010	8.06±1.73	6.26±0.49	0.000
8 hours	7.11±1.28	5.81±0.76	0.000	8.62±1.63	6.19±0.58	0.000
10 hours	7.72±1.55	5.81±0.57	0.000	9.15±2.21	6.34±0.60	0.000
12 hours	8.34±1.81	5.44±0.66	0.000	9.99±2.39	5.96±0.57	0.000
18 hours	9.32±2.14	5.66±0.78	0.000	11.06±3.09	6.29±0.67	0.000
24 hours	10.92±3.50	5.68±0.87	0.000	13.25±4.44	6.22±0.45	0.000
2 days	12.74±4.27	5.77±1.18	0.000	15.41±5.30	6.25±0.67	0.000
3 days	14.30±6.68	5.76±1.47	0.000	17.70±8.02	5.80±0.72	0.000
4 days	13.90±3.67	6.13±1.99	0.000	17.72±5.03	5.93±1.06	0.000
5 days	14.35±1.85	5.00±0.47	0.000	18.26±2.88	5.56±0.52	0.000

\*S-Significant (p<0.05), NS-Non significant (p>0.05)

Table 4: Comparison of ROX and ROX HR index in terms of sensitivity, specificity, PPV, NPV							
ROX and ROX-HR index at time intervals	N	Sensitivity(%)	Specificity(%)	PPV(%)	NPV(%)		
2 hour ROX-HR>6.90	30	57.14	77.78	85.71	43.75		
2 hour ROX>5.90	30	47.62	66.67	76.92	35.29		
4 hour ROX-HR>6.90	30	61.90	66.67	81.25	42.86		
4 hour ROX>5.90	30	52.38	66.67	78.57	37.50		
6 hour ROX-HR>6.90	30	66.67	77.78	87.50	50.00		
6 hour ROX>5.90	30	61.90	55.56	76.47	38.46		
8 hour ROX-HR>6.90	30	71.43	77.78	88.24	53.85		
8 hour ROX>5.90	30	71.43	55.56	78.95	43.45		
10 hour ROX-HR>6.90	30	76.19	66.67	84.21	54.55		
10 hour ROX>5.90	30	76.19	55.56	80.00	50.00		
12 hour ROX-HR>6.90	30	76.19	66.67	84.21	54.55		
12 hour ROX>5.90	30	80.95	44.44	77.27	50.00		
18 hour ROX-HR>6.90	30	80.95	77.78	89.47	63.64		
18 hour ROX>5.90	30	80.91	44.44	77.27	50.00		
24 hour ROX-HR>6.90	30	85.71	88.89	94.74	72.73		
24 hour ROX>5.90	30	85.71	44.44	78.26	57.14		
Day 2 ROX-HR>6.90	24	80.00	88.89	92.31	72.73		
Day 2 ROX>5.90	24	73.33	55.56	73.33	55.56		
Day 3 ROX-HR>6.90	17	80.00	85.71	88.89	75.00		
Day 3 ROX>5.90	17	80.00	57.14	72.73	66.67		
Day 4 ROX-HR>6.90	14	87.50	83.33	87.50	83.33		
Day 4 ROX>5.90	14	75.00	66.67	75.00	66.67		
Day 5 ROX-HR>6.90	06	75.00	50.00	75.00	50.00		
Day 5 ROX>5.90	06	75.00	50.00	75.00	50.00		

\*S– Significant (p<0.05), NS- Non significant (p>0.05)

failure. However Kim *et al.*<sup>[12]</sup> observed that in older age group patients, higher CCI is associated with HFNC failure.

In the present study, mean HR at the initiation of HFNC was comparable in patients with HFNC success  $(93.95 \pm 5.07)$  and HFNC failure  $(96.00 \pm 4.64)$ . In HFNC success patients, the mean heart rate improved from 90.57 beats/min at 1 h to 84.62 beats/min at 8 h to 79 beats/ min, when patients were weaned. However, in patients who failed HFNC therapy showed a worsening trend of HR from 88 beats/min at 1 h to 90.22 beats/min at 8 h to 112 beats/min when patients were shifted to a higher mode of oxygenation. Previous studies were done by Goh et al.,<sup>[11]</sup> Cho et al.,<sup>[13]</sup> Calligaro et al.,<sup>[14]</sup> and Lun et al.<sup>[16]</sup> in patients of acute hypoxemic respiratory failure who were put on HFNC observed that patients who had stable baseline HR and showed an improving trend of HR on subsequent intervals of HFNC therapy responded well and were successfully weaned from HFNC as compared to patients who showed an increasing trend in HR. Mean systolic blood pressure, diastolic blood pressure, and mean arterial pressure at the initiation of HFNC therapy were comparable in patients with HFNC success and failure. However, in patients who failed HFNC therapy, BP started decreasing from 10 h onward and needed more vasopressor support to maintain blood pressure. Kim et al.[12] and Cho et al.[13] and observed that patients who failed on HFNC therapy needed vasopressor support to maintain BP more frequently as compared to patients who were successfully weaned. In the present study, the mean RR before initiation of HFNC therapy was comparable in patients of HFNC success and failure. Mean RR started to decline from 21.62/ min to 16.25/min in patients who were successfully weaned. However, in HFNC failure patients, there was an initial decline but after 8 h into therapy, RR increased till patients were shifted to a higher mode of oxygenation. Previous studies also observed that RR is a good predictor of HFNC success and failure as patients who were successfully weaned showed a decrease in RR after HFNC therapy as compared to patients who failed HFNC showed an increase in RR and needed a higher mode of oxygenation.<sup>[9,10-12,14]</sup>

In all 30 patients, HFNC was started at a flow rate of 40 L/min and gradually increased to 60 L/min if needed, and FiO<sub>2</sub> was adjusted to maintain SPO<sub>2</sub>  $\geq$  92%. It was observed that patients, who failed HFNC therapy, needed high flow rates and FiO<sub>2</sub> as compared to patients who were successfully weaned off, to maintain a target SpO<sub>2</sub> of 92%. Previous studies also supported these findings that patients who required high flow rates and FiO<sub>2</sub> to maintain desired saturation ultimately failed on HFNC, and needed a higher mode of oxygenation.<sup>[9,12-14]</sup>

ROX index and ROX-HR index were calculated. ROX index value <5.90 and ROX-HR index value <6.90 were taken as HFNC failure. ROX index was comparable at 1 h, 2 h, and 4 h in patients with HFNC success and failure patients. From 6 h onwards, the ROX index was >5.90 in patients

who were successfully weaned, whereas in HFNC failure patients, the ROX index was <5.90 from 6 h onward till the patients were either intubated or put on NIV. Previous studies observed that HFNC success was associated with a greater increase in ROX index values.<sup>[9-11,14,15]</sup> Calligaro *et al.*<sup>[14]</sup> and Alshahrani *et al.*<sup>[8]</sup> observed that an improved ROX index value at 6 h is a good predictor of HFNC success. Kerai *et al.*<sup>[9]</sup> observed that the ROX index values at 2, 6, and 12 h of HFNC therapy were higher in HFNC success patients.

ROX-HR index was calculated using SpO<sub>2</sub>, FiO<sub>2</sub>, RR, and HR of patients at various time intervals. ROX-HR index remained comparable at initiation, 1 h, 2 h, and 4 h of HFNC therapy in all patients. From 6 h onward, ROX-HR index values remained on the higher side >6.90 in HFNC success and showed a declining trend of <6.90 in patients who failed HFNC therapy. Calligaro *et al.*<sup>[14]</sup> observed that the ROX-HR index performed better in HFNC success patients (3.44) and was low in HFNC failure patients (2.53). Goh *et al.*<sup>[11]</sup> observed that a ROX-HR index of >6.80 is associated with a lower risk of HFNC failure.

In the present study, it was observed that the sensitivity and specificity of ROX and ROX-HR index were comparable at 2 h and started increasing at 4 h. At 6 h sensitivity of both was comparable but the specificity of the ROX-HR index increased from 8 h onward and remained on the higher side. Therefore, the ROX-HR index is better in the early prediction of HFNC failure. Goh *et al.*<sup>[11]</sup> observed that the ROX-HR index was a better indicator in predicting early failure of HFNC therapy as its specificity was greater than the ROX index.

### Limitations

It was a small sample size. The accuracy of the estimation process increases and the findings could be better extrapolated to the general population if the sample size was large. Another limitation was the age group of the study population which was 18–60 years. Hence, the ability of ROX and ROX-HR index for early prediction of HFNC success and failure in older age groups could not be evaluated.

### CONCLUSION

ROX index and ROX-HR index, both are good in the early prediction of HFNC success, whereas the ROX-HR index

is better in the early prediction of HFNC failure in patients of acute hypoxemic respiratory failure.

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# Cytological and Histological Correlation of Breast Lesions at Tertiary Care Hospital the Cross-Sectional Study

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### Abstract

**Introduction:** In recent years, cytology has emerged as a primary screening modality for suspected breast pathologies promising high accuracy. In this study, we correlate the cytological and histopathological findings.

**Methods:** A total of 108 patients with suspected breast masses (107 women and 1 man; aged 19–70 years) were evaluated using fine-needle aspiration cytology (FNAC), followed by histopathology. The level of agreement between FNAC and histopathology was assessed using Kappa statistics.

**Results:** Mean age of patients was  $37.04 \pm 11.53$  years. As per IAC criteria, C1, C2, C3, C4, and C5 pathologies were detected in 3 (2.8%), 80 (74.1%), 3 (2.8%), 2 (1.9%), and 20 (18.5%) cases, respectively. Histopathological diagnosis was benign, borderline, and malignant in 82 (75.9%), 1 (0.9%), and 25 (23.1%) cases, respectively. There was good agreement between cytology and histopathology for the detection of malignant and borderline pathologies ( $\kappa = 0.974$ ; P < 0.001).

Conclusion: Cytology was a useful diagnostic tool for the evaluation of breast lesions.

Key words: Breast lesions, Fine-needle aspiration cytology, Cytology, Histopathology, Malignant, Benign lesion

### INTRODUCTION

Evaluation of suspected breast lesions involves the use of clinical, imaging, biochemical, cytological, and biopsy for therapeutic planning/histopathological assessment. The primary focus of different diagnostic modalities is to ensure the use of minimally invasive and precise techniques for this purpose. Two most common diagnostic techniques used for breast lumps include fine-needle aspiration cytology (FNAC) and trucut biopsy. In recent years, FNAC has emerged as a very efficient tool for the diagnostic evaluation of palpable breast lumps.<sup>[1]</sup>

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Advantages of FNAC are its easy availability, simplicity of the technique, low cost, and most of all, low risk of complications. However, despite these advantages, it is often criticized for inadequacy. However, despite this limitation, FNAC got wide popularity and today it is considered to be an essential component in the triple test for breast cancer.<sup>[2]</sup>

Keeping in view, the significance of differentiation of breast diseases, particularly in the pre-operative milieu, FNAC holds a high relevance and significance. Hence, the present study was planned to carry out the cytological study of various suspicious breast lesions and to correlate them with histopathology as gold standard.<sup>[3]</sup>

### **MATERIALS AND METHODS**

The present study was carried out at the Department of Pathology in collaboration with the Department of Surgery, TS Misra Medical College and Hospital, Lucknow, after seeking approval from the Institutional Ethics Committee

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and obtaining informed consent from the patients. The present study was descriptive study, and minimum sample size projections were done using the formula  $(4*p*[1-p])/d^2$  (where "p" was taken as 0.5 and d indicated absolute error allowance taken as 10% or 0.1). The calculated sample size was 100, however, we included a total of 108 cases with suspicious breast pathologies (aged 19–70 years; 107 women and 1 man; mean age 37.04 ± 11.53 years) whose cytological smear as well as histological section were available for study. Cases having history of treated malignancy and those with autolyzed/necrozed tissue specimens were excluded from the study.

Detailed history was taken, followed by clinical examination. FNAC was performed on all the cases that came with a history of breast lumps. The aspirate was collected in a 10-mL syringe and was fixed into the plunger and it was pushed so that the contents of the needle were blown gently on the slides. The cellular preparation on the slides was kept thin and even. Cytological smears were prepared, air dried, and stained by Leishman stain. The prepared slides were evaluated under the microscope at both low and high-power fields. FNAC findings were reported as per International Academy of Cytologists (IAC) criteria recommended by the National Health Service Breast Screening Program (NHSBPP)<sup>[4]</sup> as follows:

C1	Inadequate
C2	Benign
C3	Atypia, probably benign
C4	Suspicious of malignancy
C5	Malignant

Specimens of breast lesions for histopathological examination (both mastectomy and biopsy sample) whose cytology was available were received in the histopathology section.

Detailed gross examination was done, and the specimens were fixed in 10% formalin, followed by thorough sampling. Histopathological evaluation was done using the standard protocol. Immunohistochemical staining was done wherever needed.

The data were fed into the computer using MS-Excel 2013 software. Data were analyzed using IBM SPSS 21.0 software. Kappa statistic was calculated to assess the level of agreement. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. "P"<0.05 was considered statistically significant [Figures 2-5].

### RESULTS

Cytologically, the majority (74.1%) of cases were diagnosed as C2 (benign), followed by C5 (malignant) (n = 20; 18.5%). There were 3 (2.8%) cases each diagnosed as inadequate

and atypical (C3), respectively, and 2 (1.9%) diagnosed as suspicious of malignancy (C4). The distribution of different cytological diagnoses is shown in Table 1 and Figure 1.

Histopathologically, a total of 82 (75.9%) cases were diagnosed as benign, 1 case (0.9%) was diagnosed as borderline, and 25 (23.1%) were diagnosed as malignant. Among histopathologically diagnosed benign cases, fibroadenoma (n = 51; 47.2%) and fibrocystic disease (n = 19; 17.6%) were the most common. The single case diagnosed as borderline was identified as cystosarcoma phyllodes. Out of 25 (23.1%) cases diagnosed as malignant, 22 (20.4%) cases were diagnosed as infiltrating ductal carcinoma, 2 (1.9%) as lobular carcinoma, and 1 (0.9%) papillary carcinoma, respectively [Table 2].

# Table 1: Cytological Findings according to IACCriteria

IAC	Finding	No. of	Percentage
category		cases	
C1 (n=3)	(n=3) Inadequate		2.8
C2	Fibroadenoma	53	49.1
( <i>n</i> =80)	Fibrocystic disease	15	13.9
	Breast abscess	2	1.9
	Galactocoele	2	1.9
	Lactating adenoma	2	1.9
	Acute mastitis	2	1.9
	Chronic mastitis	1	0.9
	Phyllodes tumor	1	0.9
	Gynecomastia		0.9
	Epithelial cyst with	1	0.9
	secondary inflammation		
C3 (n=3)	Atypical ductal hyperplasia	2	1.9
	Atypical ductal cell	1	0.9
C4 (n=2)	Suspicious malignancy	2	1.9
C5	Ductal carcinoma	17	15.7
( <i>n</i> =20)	Lobular carcinoma	2	1.9
	Papillary carcinoma	1	0.9






Figure 2: Cytological smear - Benign breast disease fibroadenoma breast (Giemsa stain ×40)



Figure 3: Cytological smear - Ductal carcinoma breast (Giemsa stain ×40)



Figure 4: Fibroadenoma breast (H and E ×10)

Statistically, there was a strong association between cytological and histopathological diagnosis (P < 0.001) [Table 3].



Figure 5: Infiltrating ductal carcinoma (H and E ×10)

# Table 2: Histopathological diagnosis

Finding	No. of	Percentage
	cases	•
Benign	82	75.9
Fibroadenoma	51	47.2
Fibrocystic disease	19	17.6
Acute mastitis	2	1.9
Breast abscess	2	1.9
Galactocoele	2	1.9
Lactating adenoma	2	1.9
Chronic mastitis	1	0.9
Gynecomastia	1	0.9
Epithelial cyst with secondary inflammation	1	0.9
Phyllodes tumor	1	0.9
Borderline	1	0.9
Cystosarcoma phyllodes	1	0.9
Malignant	25	23.1
Infiltrating ductal carcinoma	22	20.4
Lobular carcinoma	2	1.9
Papillary carcinoma	1	0.9

Histopathologically, a total of 26 cases were diagnosed as malignant/borderline malignant and 79 as benign. The sensitivity and specificity of cytology for diagnosis of malignant/borderline breast lesions were 96.2% and 100%, respectively. Cytology had 100% positive and 98.8% negative predictive values. Cytology had 99% accuracy in the detection of malignant/borderline lesions [Table 4].

# DISCUSSION

The present study had an inadequacy rate of only 2.8%. According to IAC criteria, the majority (74.1%) of cases were diagnosed as C2 (benign), followed by C5 (malignant) (18.5%). There were three (2.8%) cases each identified as inadequate (C1) and atypical (C3), respectively. A total of two (1.9%) were diagnosed as suspected of malignancy (C4). Similar to the present study, Vasavada and Kher<sup>[5]</sup> in their study found C2 and C5 as

# Table 3: Correlation of IAC cytology categorieswith histopathological diagnostic categories

HPE	IAC Cytology Category							
Diagnosis	C1	C2	C3	C4	C5			
Benign	3 (3.7%)	79 (96.3%)	0	0	0	82		
Borderline	0	0	1 (100%)	0	0	1		
Malignant	0	1 (4.0%)	2 (8.0%)	2 (8.0%)	20 (80%)	25		
Total	3	80	3	2	20	108		

 $\chi^2$ =135.55; P<0.001; percentages have been calculated row-wise

# Table 4: Evaluation of diagnostic efficacy ofcytology for detection of malignancy/borderlinemalignancy (considering C3-C5 as the criteria)\*

Histopathological di	Total		
Malignant/Borderline	Benign		
25	0	25	
1	79	80	
26	79	105	
	Histopathological di Malignant/Borderline 25 1 26	Histopathological diagnosisMalignant/BorderlineBenign2501792679	

\*After excluding 3 inadequate cytologies

Sensitivity	Specificity	PPV	NPV	Accuracy
96.2%	100%	100%	98.8%	99.0%
к=0.974; P<0.001				

the most dominant types (56.67% and 26.0%), however, the proportion of inadequate specimens (C1) was much higher in their study (10.67%). Patel *et al.*<sup>[6]</sup> too in their study found benign (C2) cytology as the dominant type (78%) and malignant to be the next most common type (20%), however, in their study, representation of other cytological categories was very less. They reported only 1% of cases each in the C1 and C3 categories and none in the C4 category. In the study by Gore *et al.*,<sup>[7]</sup> no case was in the C1 category. However, the proportion of those with C2 and C5 cytology (71.7% and 24.3%) as well as C3 (3.6%) was comparable to our study.

In the present study, fibroadenoma (n = 53) and fibrocystic disease (n = 14) were the most common benign pathologies diagnosed cytologically. The single male was diagnosed as gynecomastia. These findings are similar to that reported by Patel et al.<sup>[6]</sup> who in their series of 78 cytologically diagnosed benign cases found fibroadenoma (n = 45) and fibrocystic disease (n = 15) as the most common cytological diagnosis. Compared to the present study, where benign cytologies were more common than the malignant cytologies, Naganagoudar and Yanagi<sup>[8]</sup> despite reporting a dominance of malignant cytologies (n = 36) over benign cytologies (n = 18), reported a dominance of fibroadenoma (n = 15/18) in the benign category. Mandal et al.<sup>[9]</sup> in their study also found 138/176 (78.4%) of their benign cytological diagnoses to be fibroadenoma or fibrocystic disease.

In the present study, out of 20 cytological diagnoses under the C5 category, 17 were ductal carcinomas, 2 lobular carcinomas, and 1 papillary carcinoma, respectively. Thus, cytologically malignant pathologies were represented by three types of malignancies predominated by ductal carcinoma. Compared to the present study, Patel *et al.*<sup>[6]</sup> in their study identified all the malignant cytologies as ductal carcinoma. Dominance of ductal carcinoma as the cytologically diagnosed malignancy has also been supported by other workers too.<sup>[9]</sup>

In the present study, there was a high consistency between cytological and histopathological diagnoses with a concordance rate of 86.4% for different confirmed FNAC diagnoses. For borderline and malignant pathologies, FNAC was 99% accurate. Similar to the findings of the present study, a high consistency between cytological and histopathological diagnoses ranging from 77.7% to 100% for seven out of ten cytological diagnoses was also reported by Mandal *et al.*<sup>[9]</sup> in their study. Similar high consistency between different histopathological and FNAC diagnoses was also reported by other workers too.<sup>[10,11]</sup>

# CONCLUSION

Cytology plays an important role in the evaluation of suspected breast lesions. It is highly precise and accurate in the detection of various underlying breast pathologies. It can be recommended as a useful minimally invasive diagnostic measure for the evaluation of breast pathologies.

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# Assessment of Level of Stress and Glycemic Control among the Type 2 Diabetes Mellitus Patients: An Observational Study

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### Abstract

**Background:** Type 2 diabetes is a chronic disease that is expanding at an alarming rate in the world. Several studies have shown that psychological distress plays an important role in the development, intensification, and chronicity of diabetes. Stress plays a dual role (cause and effect) in its relationship with diabetes. This elevation of blood glucose is seen not only in physical stress but also other form of stress such as psychosocial stress which is experienced in routine day lifestyle. The consequences of psychological stress on the endocrine system hamper the glucose metabolism processes. Hence, the assessment of stress was recommended in clinical practice. Timely assessment of stress and counseling the patients are highly essential in the management of diabetes.

**Aims and Objectives:** The aim of the study was to assess the stress level among the patients with type 2 diabetes mellitus (T2DM) and their glycemic control.

**Materials and Methods:** Assessment of stress level was done in 120 adult T2DM patients attending diabetes and nutritional clinic OPD of AGMC and GBP Hospital, Agartala, over a period of 3 months using perceived stress scale (PSS). Their hemoglobin A1C (HbA1C) level was noted. Statistical analysis was carried out using SPSS software 15.0, and results were analyzed and correlated. P < 0.05 was considered statistically significant.

**Results:** Out of the total sample size of 120, 56.7% were male and 43.3% were female. Estimation of HbA1C among the study participants showed 79.1% having poor glycemic control. Assessment of PSS showed 20.9% of the patients had low stress with score of 0–13, 40% of them had moderate level of stress with score of 14–26, and 39.1% had high perceived stress level with score of 27–40. The patients with moderate-to-high stress level had poor glycemic control.

**Conclusion:** Psychosocial stress hampers the normal physiology of the endocrine system bringing changes in the glucose metabolism processes. Excess stress among the type 2 diabetic patients deteriorates their glycemic control. Hence, regular assessment of stress and proper counseling of the patients are highly essential in the management of diabetes.

Key words: Type 2 diabetes mellitus, Hemoglobin A1C, Perceived stress scale, Stress

### INTRODUCTION

Type 2 diabetes is a chronic disease that is expanding at an alarming rate in the world.<sup>[1]</sup> The International Diabetes Federation reports that the prevalence of diabetes has reached a global epidemic level. Stress is one of the main

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problems among patients with diabetes.<sup>[2]</sup> Stress is defined as the body response to any demand made on it. This response has two divisions that are specific response and non-specific response. Specific response is the one which is actual response to the particular stimulus that involves only a particular body system. However, non-specific response is the one which is common to any type of stress and involves different body systems and leads to fight or flight response.<sup>[3]</sup> Several studies have shown that psychological distress plays an important role in the development, intensification, and chronicity of diabetes. Stress plays a dual role (cause and effect) in its relationship with diabetes. This elevation of blood glucose is seen not only in physical

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stress but also other form of stress such as psychosocial stress which is experienced in routine day lifestyle.

Psychosocial stress does not require increase in the blood glucose levels. Moreover, if the individual undergoes this type of stress daily, there will be elevated blood glucose levels. The consequences of stress on the endocrine system bring changes in the glucose metabolism processes.<sup>[4]</sup>

The relationship between stressful experiences and controlling blood glucose levels is very different among individuals with T2DM. Stress can affect blood glucose levels directly (by acting on the neuroendocrine system) or indirectly.<sup>[5]</sup> It can be considered a cause and yet a consequence of diabetes. On one hand, stress increases glucose and glycosylated hemoglobin A1C (HbA1C) and, on the other hand, diabetes and its consequences can increase stress levels among individuals with type 2 diabetes as well as causing other physical, behavioral, and mental disorders.<sup>[6-8]</sup> Cortisol is released in response to stress and stimulates the formation of glucose and glycogenolysis, leading to high blood glucose levels. Stimulation of the secretion of different hormones during stress elevates blood glucose levels.<sup>[9]</sup> Timely assessment of stress and counseling the patients are highly essential in the management of diabetes. Hence, the present study is undertaken to evaluate the stress levels in type 2 diabetes mellitus (T2DM) patients.

# **MATERIALS AND METHODS**

### **Objective**

The objective of the study was to assess the stress level among the patients with T2DM and their glycemic control.

A hospital-based cross-sectional study was done in 120 adults with T2DM attending diabetes and nutritional clinic OPD of AGMC and GBP Hospital, Agartala. Ethical clearance was obtained from the ethical committee of AGMC and GBPH. The study subjects were initially evaluated by general history, clinical examination, and blood reports. Study was conducted from Jan 2023–Mar 2023.

### **Inclusion Criteria for the Cases**

- 1. Patients aged between 30 and 60 years.
- 2. Diagnosed cases of T2DM as given by the American Diabetes Association.<sup>[10]</sup>

Patients who fulfill the following criteria for the diagnosis of diabetes mellitus:

- a. Symptoms of diabetes plus random blood glucose (RBS) concentration ≥11.1 mmol/L (200 mg/dL) or
- b. Fasting plasma glucose (FBS) ≥7.0 mmol/l (126 mg/dl) or

- c. Hemoglobin A1c  $\geq$  6.5% or
- d. 2 h plasma glucose (post prandial blood sugar [PPBS]) ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test.
- 3. Cooperative and willing to participate in the study.

### **Exclusion Criteria for the Cases**

- 1. Those who are not willing to participate in the study.
- 2. Critically ill patients unable to respond to the questionnaire.
- 3. Patients with other psychological disorders.

### **Study Tools**

- Sphygmomanometer-Omron digital BP machine HEM 7120.
- Height measuring stand Stadiometer -Bioplus; height – 20 cm - 205 cm. Graduation – scale of 1 mm ruler printed along both sides of the measuring rod.
- Weighing machine Omron HN 289 automatic personal digital weight machine.
- Investigating materials for the estimation of blood sugar and glycosylated HbA1c Hitachi HPLC system Model-Chromaster for QC laboratory by scientific technology solution.
- Case study format
- Perceived stress scale (PSS) questionnaire

The PSS is a classic tool for stress assessment. The questions in this scale ask about one's feelings and thoughts during the last monthIn each case, one was asked to indicate how often he/she felt or thought a certain way.

For each question, the patient should choose from the following alternatives:

- 0 -Never,
- 1 Almost never,
- 2 Sometimes,
- 3 Fairly often,
- 4 Very often.

Individual scores on the PSS can range from 0 to 40 with higher scores indicating higher perceived stress.

- Scores ranging from 0 to 13 was considered low stress.
- Scores ranging from 14 to 26 was considered moderate stress.
- Scores ranging from 27 to 40 was considered high stress.

### **Data Collection**

120 type 2 diabetic patients attending diabetes and nutrition clinic were included in the study. Data were collected from the participants after obtaining their informed consent. Sociodemographic variables such as name, age, and sex were noted as per the case study format. The duration for which they are suffering from T2DM and their blood sugar (RBS, fasting blood sugar [FBS], and PPBS) and HbA1c levels were also noted from their medical documents. Stress level was assessed among the study participants using a predesigned standard questionnaire, PSS.

#### **Data Analysis**

Data were analyzed using SPSS software. Descriptive statistics and other suitable statistical tests were used as per applicability. Data were expressed in terms of mean and standard deviation. A probability value <0.05 was considered statistically significant.

### RESULTS

A total of 120 T2DM patients had participated in this study. Among them, 56.7% were male and 43.3% were female as shown in Figure 1. Mean age group was  $43.24 \pm$ 4.4 years. Age-wise distribution of the study participants is shown in Figure 2. Mean duration of the disease was 7  $\pm$  3.34 years. Disease duration of the study participants is shown in Figure 3. The blood sugar parameters estimated were the FBS, PPBS, and the glycosylated HbA1C. Figure 4 shows the FBS, Figure 5 shows the PPBS, Figure 6 shows the HbA1C of the study participants. Figure 7 shows the gender-wise distribution of the glycemic control. Figure 8 shows the mean and standard deviation of the HbA1C level and PSS. Mean value and standard deviation of HbA1C level and perceived stress score is shown in Table 1. Figure 9 shows the percentage of scores of PSS of the study participants as low, moderate, and high scores. Figure 10 shows the gender-wise distribution of PSS. There was positive correlation between stress and HbA1C level but not significant (P value -0.034 and r value -0.23) as shown in Figure 11. The HbA1C level among the diabetic patients with mild, moderate, and severe stress is shown in Figure 12. Figure 13 shows the PSS scores and the type of anti-diabetic medication consumed by the study participants.

### DISCUSSION

Type 2 diabetes is a chronic disease that is expanding at an alarming rate in the world. Several studies have shown that psychological stress plays a dual role (cause and effect) in its relationship with diabetes. The consequences of stress on the endocrine system bring disturb the homeostasis of glucose metabolism processes.

In our study, we found that, among the study participants, 56.7% were male and 43.3% were female. Mean age group was 43.24  $\pm$  4.4 years. Mean duration of the disease was 7  $\pm$  3.34 years. The PSS showed a significant increase in



Figure 1: Gender-wise distribution of the study participants



Figure 2: Age-wise distribution of study participants





stress level among the type 2 diabetic patients (P value: 0.01). However, the positive correlation between stress and HbA1C was not statistically significant (P value: 0.034 and r value: 0.23). Around 40% of the study participants showed a moderate score in the PSS and around 79.1% of them had poor glycemic control.



Figure 4: Fasting blood sugar of the study participants



Figure 5: Postprandial blood sugar of the study participants



Figure 6: Hemoglobin A1C of the study participants

The result of this study was in association with the study conducted by Surwit *et al.*<sup>[1]</sup> where he revealed that more than 30% of patients were given add-on insulin with OHD for better glycemic control, of which about 44% had significantly high stress. Although there could be many other factors that may be affecting blood glucose, the study showed that the stress was a potential contributor to it.



Figure 7: Gender-wise distribution of hemoglobin A1C level among the study participants





Table 1: I	Mean±standard	deviation and their <i>P</i> values
( <i>P</i> < 0.05	was considered	d statistically significant)

Parameter	Mean ± standard deviation	P value
HbA1C	10±2.56	0.002
PSS	28±3.47	0.01

PSS: Perceived stress scale, HbA1C: Hemoglobin A1C

Vasanth *et al.*<sup>[3]</sup> in their study conducted on 400 diabetic patients, results showed that the fasting blood glucose levels were a direct reflection of the stress levels (P < 0.05), whereas the glycemic index (HbA1c level) was found to be linked to both treatment adherence and stress.

Saboo and Rahule<sup>[7]</sup> concluded that more than 30% of the patients had poor glycemic control, of which about 40% had significantly high stress and also that that there is a direct correlation between stress and glycemic control as when stress increases the possibility of having poor glycemic control also increases. Toshihiro *et al.*,<sup>[11]</sup> Brunner and Kivimäki,<sup>[12]</sup> Li *et al.*,<sup>[13]</sup> also concluded that psychological distress significantly increases the risk of T2DM.



Figure 9: Perceived stress scale score of the study participants



Figure 10: Gender-wise distribution of perceived stress scale among the study participants



Figure 11: Corelation graph between stress and hemoglobin A1C

The effects of stress on the neuroendocrine system consist of stimulating the nervous system by activating the sympathetic-adrenal-medulla (SAM) followed by hypothalamic–pituitary–adrenal activity. During stress, the sympathetic nervous system stimulates the adrenal glands



Figure 12: Hemoglobin A1C level among the type 2 diabetes mellitus patients with mild, moderate, and severe stress



Figure 13: The perceived stress scale score and the type of anti-diabetic medicine consumed among the study participants

of the medulla to secrete epinephrine and norepinephrine into the blood circulation. The activity of these hormones produces metabolic effects, i.e., increased metabolic rate and blood glucose levels. Stress causes the hypothalamus to secrete corticotrophins-releasing factor, which releases adrenocorticotropin and stimulates the adrenal cortex to secrete glucocorticoid hormones, such as cortisol, thereby increasing the production of glucose by the liver and reducing its uptake by tissues. Cortisol affects the breakdown of carbohydrates, proteins, and fats through the gluconeogenesis process, which produces glucose as an energy source and plays a significant role in influencing body functions during the resting period.

The cortisol hormone counteracts with insulin and thus increasing glucose production by hepatic gluconeogenesis and by preventing the peripheral utilization of glucose and leads to the development of metabolic syndrome such as obesity, insulin resistance, and the early determination of stress and related disturbances helps to control diabetes.<sup>[5]</sup> Therefore, regular psychological counseling should be advised to the patients with type 2 diabetic patients for better control of the disease status and to improve the quality of life.

### **Limitations of the Present Study**

The sample size in the present study is relatively small. Furthermore, unknown and subclinical complications, which are unaccounted for, may contribute to stress level and glycemic control.

### CONCLUSION

Psychosocial stress hampers the normal physiology of the endocrine system bringing changes in the glucose metabolism processes. Excess stress among the type 2 diabetic patients deteriorates their glycemic control. Hence, regular assessment of stress and proper counseling of the patients are highly essential in the management of diabetes.

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# Comparison of Different Surface Treatments on the Push-Out Bond Strength of Glass Fiber Reinforced Posts to Root Dentin

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### Abstract

**Introduction:** Successful post retention within the root canal is a prerequisite in the post endodontic restoration of a structurally compromised tooth. Apart from the formation of surface roughness on the glass fiber post (GFP), the surface treatment strategies should generate a strong chemical bond of the exposed epoxy resin matrix in the post with the root dentin through a resin cement.

**Purpose:** To compare the influence of different surface treatments on the push-out bond strength (PBS) of GFPs to root dentin and to determine the modes of failure between root dentin, resin luting cement, and the post surface.

**Methods:** Sixty extracted mandibular premolars were divided into six groups (n = 10). Rotary instrumentation followed by obturation was done with a single cone technique. Sixty GFPs (6 groups; n = 10) were treated with one of the following: No surface treatment, Silane coupling agent, Bonding agent, Sandblasting, 9.6% Hydrofluoric acid, and 100 mL alkaline solution of Potassium permanganate. Treated posts were luted to the prepared post space using self-adhesive resin cement. Coronal, middle, and apical portions obtained after sectioning the roots embedded in resin mold were subjected to a PBS test, and the "peak force" at bond failure was measured. The modes of failure between the interfaces were assessed using Scanning Electron Microscopy. Statistical analysis was performed using the Kruskal–Wallis test and Bonferroni multiple comparison test.

Results: Group III (Bonding) and Group IV (Sandblasting) showed the highest bond strength in the coronal and apical sections.

**Conclusion:** The surface treatment of GFPs using either a universal adhesive or sandblasting was reliable. PBS for coronal and apical root sections was superior to the middle sections. A mixed mode of failure was predominant among tested specimens.

Key words: Glass fiber post, Push-out bond strength, Sandblasting, Surface treatment, Tribochemical silica coating

# **INTRODUCTION**

Post and cores rehabilitate root canal-treated teeth with excessive coronal tooth loss. Posts provide adequate retention for the core but will not strengthen the root.<sup>[1]</sup> Various *in-vitro* studies have illustrated the superior qualities of using glass fiber posts (GFPs). The prevalence of unfavorable root fractures using fiber posts has been drastically reduced compared to prefabricated conventional



cast posts.<sup>[2]</sup> This is because forces acting on the structure but absorbed by the tooth are not distributed to the underlying root, the fiber post, and the core. Properties of esthetic fiber posts, such as their elastic modulus resembling that of root dentin, and the adhesive technique for postcementation are added advantages.<sup>[3,4]</sup> The type of luting cement and the bonding strategy used for cementing the post within the dentin is one of the main factors deciding the successful post retention. The multistep process of luting fiber post through total-etch or self-etch adhesive systems and a low-viscosity resin is complex and hence technique sensitive.

Recently, 10-methacryloyloxydecyl dihydrogen phosphate (10 MDP), a dual adhesive monomer-based self-adhesive resin cement, was introduced to eliminate the requirement for pretreatment of either the tooth or on the surface of the

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posts. It owes its adhesive property to the acidic monomers, which can infiltrate and demineralize the tooth substance, providing micromechanical retention.<sup>[4]</sup> The basic adhesion potential of a material will be improved by following different surface treatment regimens. The three main categories of surface treatments include Rough surface promotion, Chemical adhesive optimization, and a mixture of the above two methods.<sup>[5]</sup> An increased micromechanical bonding results from either mechanical (sandblasting) or chemical treatments (etching with hydrogen peroxides or hydrofluoric acid [HF]), which improves the penetration of the adhesive on the surface of the post. The approach aims to increase surface roughness and optimize the chemical bonding to fiber posts.<sup>[6]</sup>

Silanization of the post before cementation refines the bond strength of GFPs with resin cement, as observed in the previous studies. In contrast, others reported that using a silanizing agent alone showed no increase in bond strength; thus, controversy exists regarding the effectiveness of silanization.<sup>[3,7,8]</sup> Further studies are needed to prove its potential for improving the GFPs to resin cement interfacial adhesion. Therefore, the current study compared the influence of a variety of surface treatments on the push-out bond strength (PBS) of GFPs to root dentin and determined the modes of failure between the root dentin, resin luting cement, and the surface of the GFP.

# **MATERIALS AND METHODS**

The sample collection and specimen preparation were done at the department of Nanosciences, Amrita Institute of Medical Sciences and Research Centre, and the Department of Conservative Dentistry and Endodontics, Amrita School of Dentistry, Edappally, Ernakulam. The study was conducted with the approval of the institutional ethical committee (IRB-AIMS-2019-308). A single investigator performed the laboratory procedures to avoid bias.

The sample size calculation was performed from the Department of Biostatistics, AIMS, Kochi. Sixty singlerooted mandibular premolars (extracted for periodontal or orthodontic reasons) were divided into ten teeth each (n = 10) in all the six groups tested in the study [Figure 1a].

### **Preparation of Samples**

An ultrasonic scaler was used to clean the external debris on the specimens initially stored in distilled water at room temperature. Diamond bur at slow speed with enough water cooling was used to decoronate each tooth till the cementoenamel junction to standardize root canal length to 18 mm. Rotary instrumentation of the roots was performed using Protaper universal system till file size F2 (Dentsply, Maillefer, Switzerland) was 1mm short of apex. After the change of each drill during canal shaping, the canal was irrigated with 1 mL of 5.25% solution of sodium hypochlorite. After a final rinse using distilled water, paper points were used to dry the canal, followed by obturation with Protaper F2 single cone gutta-percha and AH plus sealer.

# Post-Space Preparation, Surface Treatment of the Post, and Luting Procedures

Post-space preparation was done using peeso reamers sequentially from #1 to #3, sparing 4mm gutta percha at the root apex.<sup>[9]</sup> For canal irrigation, 5.25% NaOCl and 17% EDTA were used initially, followed by a final rinse using distilled water. The root canals were then dried using paper points. The total number of posts was distributed equally into six groups (n = 10). These posts were then surface treated using one of the respective methods [Table 1].

# **Specimen Preparation and Push-Out Test**

A 10-MDP containing self-adhesive resin cement (SpeedCEM Plus, IvoclarVivadent, US) was used for luting the surfacetreated GFPs into the prepared post space, as stated by the manufacturer. After 1 week of storage at room temperature under humid conditions, the specimens were mounted on an acrylic resin mold. These were then sectioned perpendicular to the long axis with Isomet (Isomet, Buehler, USA) under sufficient water cooling. After sectioning, one section each from the apical, middle, and coronal thirds (0.06–1 mm thickness) was obtained [Figure 1b]. The PBS of the cut



Figure 1: (a) Mandibular premolars selected for the study. (b) Specimens sectioned using an Isomet device (c) Push out bond strength tested on a universal testing machine

### **Table 1: Post surface treatments**

Group I	No surface treatment was performed on post surface
Group II	Post treated with a silane coupling agent (Ultradent, 505
	West Ultradent Drive, South Jordan) for 60 s using a
	disposable brush and then dried
Group III	Post surface treated using a self-etching bonding agent
	for 20 s (Futura Bond DC, Dual curing self-etching bond,
	Cuxhaven, Germany)
Group IV	Post surface treated using 50 µm silica coated alumina
	particles using Cojet system (3M ESPE, Seefeld,
	Germany) at 2–3 bar for 15 s from 10mm distance
Group V	Post surface were treated with 9.6% HF (Ultradent, 505
	West Ultradent Drive, South Jordan) for 15 s
Group VI	Post surface were treated with 100 mL alkaline solution of

KMnO<sub>4</sub> (Dept. of Biochemistry, AIMS, Kochi) for 10 min

HF: Hydrofluoric acid, KMnO2: Potassium permanganate

sections was tested using a Universal testing machine (Shimadzu Corporation AutoGraph AGS-X Series, Kyoto, Japan) at a crosshead speed of 1 mm/min [Figure 1c]. The peak force at which the post segment extrudes from the test specimen was recorded in Newtons (N) and considered the point of bond failure. This value was then changed to Mpa. The fractured specimen from each group was submitted for scanning electron microscopic (SEM) analysis to evaluate the various failure modes as either adhesive (resin cement-dentin or resin cement-post interface), cohesive (either within resin cement, dentin, or post surface). The specimens were fixed on aluminum stubs, sputter coated with gold, and observed under SEM (X25).

Statistical analysis was performed using SPSS Version 21.0 (SPSS, Chicago, IL, USA). The statistical significance of the difference in averages among the six groups with various surface treatments on the GFPs was tested using the Kruskal-Wallis test. Bonferroni's multiple comparison tests were performed to test the statistically significant pairs or groups. The Kruskal-Wallis test was applied to test the statistically significant pairs or groups (P < 0.05).

### RESULTS

The mean and standard deviation of PBS at the coronal, middle, and apical sections in each of the six groups is given in Table 2. For the coronal sections of the respective groups, a significant difference in bond strength was noted (P = 0.001). The highest mean PBS was observed for the application of bonding agent (Group III [42  $\pm$  13.3]) followed by Sandblasting (Group IV [40.10  $\pm$  27.7]) and HF (Group V [40.3  $\pm$  31.1]). There seems to be no statistically significant difference between the three groups. The control group (Group I [11.40 $\pm$ 4.16]) with no surface treatment presented the lowest bond strength.

### Table 2: Mean (Mpa) and SD values of push out bond strength using the Kruskal Wallis H test in all the groups at coronal, middle and apical segments

Groups	Apical	Push out bond strength (Mpa)				
		Coronal	Middle	Apical		
I	Control	8.81±4.16	14.31±11.39	12.99±16.62		
11	Silanization	25.10±42.21	36.70±83.24	11.41±4.11		
	Bonding agent	37.71±33.86	43.19±46.73	38.44±62.39		
IV	Sandblasting	38.97±27.79	31.03±21.75	31.24±18.15		
V	HF	35.97±31.15	26.84±29.61	29.73±25.63		
VI	Potassium	14.30±3.27	9.70±3.60	14.09±21.82		
	permanganate					

Data are shown as mean±standard deviation, HF: Hydrofluoric acid, SD: Standard deviations

All the middle root sections presented a statistically significant difference in bond strength (P = 0.006), with the highest mean bond strength for the bonding agent group (Group III [44.20 ± 46.7]) and lowest for Potassium permanganate (KMnO4) group (Group VI [18.45 ± 3.60]).

The apical sections showed a statistically significant difference in bond strength between the different groups (P = 0.001), with the highest mean values observed for sandblasting Group (Group IV [43.0 ± 18.15]) followed by the bonding group (Group III [40.7 ± 62.3]). In contrast, the lowest value was evident for the potassium permanganate group (Group VI [16.80 ± 21.8]), which had a statistically significant difference compared to other groups except for the Control group (Group I [18.40 ± 16.62]) [Tables 3-5]. Regarding the association between modes of failures and different surface treatments on GFPs, there was no statistical significance for the presence of bond failures in any of the coronal, middle, or apical root sections for the respective surface treatments evaluated [Table 6].

The SEM analysis of all the root sections that underwent the bond strength test revealed that of the three types of bond failures, mixed failures were predominant between the GFPs, root dentin, and resin cement [Figure 2].

### DISCUSSION

Among the various methods available, the push-out test is the most suitable method to study the adhesion between posts and root canal dentin.<sup>[10]</sup> Here, an indenter pushes a small fiber diameter into a 1mm thick specimen, uniformly distributing the applied load throughout the bonded interface.<sup>[10,11]</sup> Fiber posts are cemented widely using resin-based adhesive cement. The introduction of selfadhesive or all-in-one adhesive cement simplified the luting procedure and eliminated the need for the pretreatment of teeth.<sup>[12]</sup>

Table 3: Statistical significance of the difference in the averages among six groups calculated using	
Kruskal Wallis test and intergroup comparison using Bon Ferroni test at coronal third	

Groups	Group I	Group II	Group III	Group IV	Group V	Group VI	Mean bond strength (Mpa)	Х <sup>2</sup>	Р
Group I	1	-12.35	-30.6*	-28.7*	-28.9*	-14.05	11.40	24.798	0.001*
Group II	12.35	1	-18.25	-16.35	-16.55	-1.7	23.75		
Group III	30.6*	18.25	1	-1.90	-1.7	-16.55	42.00		
Group IV	28.7*	16.35	1.90	1	-0.20	-14.65	40.10		
Group V	28.9*	16.55	1.7	0.20	1	-14.85	40.30		
Group VI	14.05	1.7	16.55	14.65	14.85	1	25.45		

Kruskal Wallis test, \*: P<0.05, Bon Ferroni post-hoc, \*: P<0.05

# Table 4: Statistical significance of the difference in the averages among six groups calculated using Kruskal Wallis test and intergroup comparison using Bon Ferroni test at middle third

Groups	Group I	Group II	Group III	Group IV	Group V	Group VI	Mean bond strength (Mpa)	X²	Р
Group I	1	-0.70	-20.60	-15.70	-9.55	-5.15	23.60	16.56	0.006*
Group II	0.70	1	-19.90	15.00	-8.85	-5.85	24.30		
Group III	20.60	19.90	1	-4.90	-11.05	-25.75*	44.20		
Group IV	15.70	15.00	4.90	1	-6.15	-20.85	39.30		
Group V	9.55	8.85	11.5	6.15	1	-14.7	33.15		
Group VI	5.15	5.85	25.75*	20.85	14.7	1	18.45		

Kruskal Wallis test, \*: P<0.05, Bon Ferroni post-hoc, \*: P<0.05

Table 5: Statistical significance of the difference in the averages among six groups calculated using Kruskal Wallis test and intergroup comparison using Bon Ferroni test at apical third

Groups	Group I	Group II	Group III	Group IV	Group V	Group VI	Mean bond strength (Mpa)	Х²	Р
Group I	1	-6.80	-22.30	-24.60*	-20.50	-1.60	18.40	22.72	0.001*
Group II	6.80	1	-15.50	-17.80	-13.70	-8.40	25.20		
Group III	22.30	15.50	1	-2.30	-1.80	-23.90*	40.70		
Group IV	24.60*	17.80	2.30	1	-4.10	-26.20*	43.00		
Group V	20.50	13.70	1.80	4.10	1	-22.10	38.90		
Group VI	1.60	8.40	23.90*	26.20*	22.10	1	16.80		

Kruskal Wallis test, \*: P<0.05, Bon Ferroni post-hoc, \*P<0.05



Figure 2: Stereomicroscopic analysis of (a) Coronal (b) Middle and (c) Apical third from all six group

The present study infers that the mode of surface treatment can influence the bond strength of fiber post-system to dentin. From the results of the current study, it was observed that compared to the middle root sections, PBS for the coronal and apical root sections was much higher in most of the specimens.<sup>[13,14]</sup>

Among the different surface treatments, the highest bond strength was presented by the bonding agent group (Group III), followed by sandblasting (group IV) in the coronal and apical root sections compared to all other groups, as stated by Spicciarelli *et al.*<sup>[15,16]</sup> Using a dualcure bonding agent over the epoxy resin-based fiber post surface enhanced the adhesion between the dual-cure resin composite and the posts, as stated by Aksornmuang *et al.*<sup>[17]</sup> However, contradictory to the above findings, Balbosh and Kern in 2006 and Radovic *et al.* in 2007 reported reduced bond strength values.<sup>[18,19]</sup>

Tribochemistry relates to forming chemical bonds by applying kinetic energy in the form of sandblasting without

Table 6: Statistical significance of the association
between modes of failures and different root
sections of all six groups measured using Kruskal
Wallis test

Group	n (Sample)	Mean rank	Х <sup>2</sup>	Р
Coronal	10	99.75	3.12	0.21
Middle	10	88.42		
Apical	10	83.33		

Kruskal Wallis test \*: P<0.05

any application of additional heat or light.<sup>[20]</sup> Tribochemical silica is those silica particles coated with aluminum particles. The CoJet system employed in the present study uses airborne micro-blasting sand composed of silica-modified aluminum trioxide. This modifies the GFPs with a reactive silica-rich outer surface liable for silanization.<sup>[21]</sup> The five criteria in airborne particle abrasion using tribochemical silica are the angle to the substrate surface, the distance of the nozzle from the substrate surface, impact, working time, coverage area, an air pressure.<sup>[22]</sup> Spraying with high velocity over the substrate helps penetrate these particles to a depth of about 15 microns with increased surface area improving resin cement to fiber post-bond strength.<sup>[23,24]</sup> Furthermore, the bond strength between GFPs and resin cement improved with sandblasting compared to HA or phosphoric acid etching.<sup>[25]</sup> Despite obtaining sufficient bond strength with this method, this type of pretreatment may possess the risk of modifying the shape and fit of the posts in the root canals and hence is considered a more aggressive option.<sup>[26]</sup>

9.6 % HF (group V) treatment of posts showed better bond strength results than treatment with a 1.03% alkaline solution of potassium permanganate. This finding may be attributed to the mechanism of action of HF acid that dissolves the epoxy resin matrix, exposing the fibers and creating micro spaces between them. But the efficiency of HF acid is considered a dispute. HF acid application may be aggressive for post fibers causing dissolution of the resin matrix, even though the bond strength received with it is satisfactory.<sup>[18]</sup>

Lower bond strength was noted in all sections except for the middle sections with the silanizing agent (Group II) application, as supported by Gencoglu *et al.* and Wrbas *et al.*'s findings.<sup>[27]</sup> The silanizing agent acts through chemical optimization of the post surface, thus linking the inorganic phase of the GFPs to the organic matrix of the adhesive system or resin cement owing to its bifunctional properties.<sup>[19]</sup> No change in adhesion between fiber posts and dentin was observed, except between the post surface and composite core build-up when a silane coupling agent was used.<sup>[28]</sup> Yet, in other studies, silane treatment shows unassured results.<sup>[25,26,29,30]</sup> The fiber post composition comprising of an epoxy resin matrix, inorganic particles, and fiberglass particles, preventing an intimate interaction between the dental elements from adhesive systems and fiber posts, may have caused this insufficiency.<sup>[26]</sup>

Potassium permanganate (KMnO4) treatment was conventionally used for industrial procedures, and the same is applied for the pretreatment of fiber posts. This involves a sequential treatment using three different chemicals (swelling, etching, and neutralizing) on the GFP surface. This improves the surface area available for bonding due to the partial removal of the epoxy resin matrix, thus creating micro-retentive spaces. This epoxy resin matrix modification is ensured by the manganese oxide present in the composition. KMnO4 chemical treatment generally gave noteworthy results.<sup>[31]</sup> However, the present study showed drastically reduced PBS compared to all other test groups except for the control group. According to Belwalkar et al., the interfacial adhesion between GFP, resin cement, and dentin is influenced by the type and method of application of resin luting cement, adhesive strategy, quality, quantity, and surface treatments of root dentin.<sup>[32]</sup>

SEM studies regarding root sections of all the teeth revealed three main types of bond failures,namely;(1) Adhesive failure either at the post/resin cement interface or the resin cement/root dentin interface(2) Cohesive failure occurring within the resin cement and (3) Mixed mode of failure (Both cohesive and adhesive failures exists).<sup>[33]</sup> Among these, mixed types of bond failure predominated over cohesive or adhesive types. This indicated a good interaction of the resin cement with the post and root dentin after surface treatments.

However, the present study failed to conduct a thermomechanical aging of the specimen. Therefore, the obtained results cannot be considered a complete clinical simulation. The study also lacks an evaluation of the effectiveness of newer bonding agents on the PBS of GFPs to root dentin.

# CONCLUSION

The surface treatment of GFPs using either universal adhesive application or sandblasting with tribochemical silica showed promising results. It was also found that the PBS for coronal and apical root sections was superior to those of the middle sections in the bonding agent group. A mixed mode of failure was found to be predominant when compared to adhesive and cohesive among tested specimens.

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# A Study on Functional and Radiological Outcome of Intramedullary Interlocking Nailing in the Complex Femoral Shaft Fractures

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### Abstract

**Background:** A Several studies have examined the incidence of femoral fractures. Figures vary and quoted ranges are from 0.1 to 3% as an average annual incidence (up to 37 per 100 000 patient years), with the peak incidence occurring in young adult males. An association with major trauma and high-energy mechanisms is seen in this age group(1). A second peak in incidence, associated with low energy mechanisms, is seen in the elderly population. The femoral shaft is curved in the sagittal plane, with an anterior bow. The cortex is thickened posteriorly, as it is the compression side of the bone in the sagittal plane and carries the Linea aspera. Distally the cortex thins and expands into the metaphysis. Proximally the femoral anatomy is characterized by the head, neck, and trochanters. The central anatomical axis of the neck is offset anterior to the central anatomical axis of the shaft in the sagittal plane e this explaining why the correct entry point for most nails is biased anteriorly.

**Methods:** The study aimed to assess the functional and radiological outcome of intramedullary interlocking nailing in the treatment of complex femoral shaft fractures. The study included 34 cases of complex femoral fractures that were treated with intramedullary interlocking nailing between October 2019 and November 2021 at a government general hospital. Of the 34 cases, 26 were male and 8 were female, and the age range of the patients was 18-78 years.

**Results:** The functional outcome was assessed using the Harris Hip Score (HHS) and the Lower Extremity Functional Scale (LEFS), and the radiological outcome was assessed using the RUST score. The mean HHS score was 80, and the mean LEFS score was 84. The mean RUST score was 8.8. There were no cases of non-union, delayed union, or implant failure. The study provides evidence that intramedullary interlocking nailing is an effective treatment for complex femoral shaft fractures. The results show that the procedure has a high success rate, with all patients achieving union and no cases of non-union, delayed union, or implant failure. The functional and radiological outcomes were also favourable, with high HHS and LEFS scores and a low RUST score. The study provides valuable information for orthopaedic surgeons treating patients with complex femoral shaft fractures and supports the use of intramedullary interlocking nailing as the treatment of choice.

**Conclusions:** : Based on the study's results, intramedullary interlocking nailing is an effective treatment for complex femoral shaft fractures. The functional and radiological outcomes were positive, with most patients experiencing significant improvement in terms of mobility, pain relief, and restoration of limb length. The study suggests that the use of intramedullary interlocking nailing can lead to favourable outcomes for patients with complex femoral shaft fractures, and it should continue to be used as a primary treatment option for this condition. However, further studies with larger sample sizes and longer follow-up periods are needed to validate these findings. Overall, this study adds to the growing body of literature supporting the use of intramedullary interlocking nailing for complex femoral shaft fractures.

Key words: Femur, Fracture, Nail



# INTRODUCTION

Several studies have examined the incidence of femoral fractures. Figures vary and quoted ranges are from 0.1% to 3% as an average annual incidence (up to

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#### Supe, et al.: Intramedullary Interlocking Nailing in the Complex Femoral Shaft Fractures



37/100,000 patient years), with the peak incidence occurring in young adult males. An association with major trauma and high-energy mechanisms is seen in this age group.<sup>[1]</sup> A second peak in incidence, associated with low-energy mechanisms, is seen in the elderly population. The femoral shaft is curved in the sagittal plane, with an anterior bow. The cortex is thickened posteriorly, as it is the compression

side of the bone in the sagittal plane and carries the linea aspera. Distally, the cortex thins and expands into the metaphysis. Proximally, the femoral anatomy is characterized by the head, neck, and trochanters. The central anatomical axis of the neck is offset anterior to the central anatomical axis of the shaft in the sagittal plane e this explaining why the correct entry point for most nails is biased anteriorly. The neck-shaft angle is of the order of 130 (124-136) degrees in the coronal plane.<sup>[2,3]</sup> The blood supply to the femoral head arises from the anastomotic ring around the base of the neck, which superiorly traverses the piriformis fossa, putting it at risk when using this as an entry point in nailing. Blood to the diaphysis is supplied through both the higher-pressure endosteal system (from the nutrient vessels) and the lower-pressure periosteal system (from the areas of muscle attachment), accounting for the inner 2/3 and outer 1/3 of the cortical blood supply, respectively. Reaming initially reduces the endosteal blood supply, although any instrumentation of the femoral canal (such as an unreamed nail) also has a significant effect. With increasing age, the morphology of the femoral diaphysis changes, with endosteal resorption and periosteal apposition of bone. This leads to the characteristically larger diameter but thinner cortical diaphysis, often accompanied by an increase in the anterior bow. Fractures of the shaft of the femur are a major cause of morbidity and mortality in patients who sustain high-energy trauma.<sup>[4]</sup> Morbidity arises from limb shortening, malalignment, knee contractures, and other complications of fracture. Mortality is infrequent but can result from an open wound, fat embolism, adult respiratory distress syndrome, or multiple organ failure, especially in polytrauma patients. Both morbidity and mortality can be diminished by prompt reduction and internal fixation of the fracture.<sup>[5]</sup> Restoration of alignment, rotation, and length and preservation of the blood supply to aid union and rehabilitation of the patient are the goal of treatment. The type and location of the fracture, degree of comminution, the age of the patient, patients social, economic demands, and other associated fractures may influence the method of

(Circle one number on each line)

### Lower Extremity Functional Index

We are interested in knowing whether you are having any difficulty at all with the activities listed below <u>because of your lower limb</u> problem for which you are currently seeking attention. Please provide an answer for each activity.

Activities	Extreme Difficulty or unable to perform activity	Quite a bit of difficulty	Moderate difficulty	A little bit of difficulty	No difficulty
a. Any of your usual work, housework or school activities.	0	1	2	3	4
b. Your usual hobbies, recreational or sporting activities	0	1	2	3	4
c. Getting into or out of the bath.	0	1	2	3	4
d. Walking between rooms.	0	1	2	3	4
e. Putting on your shoes or socks.	0	1	2	3	4
f. Squatting.	0	1	2	3	4
g. Lifting an object, like a bag of groceries from the floor.	0	1	2	3	4
h. Performing light activities around your home.	0	1	2	3	4
i. Performing heavy activities around your home.	0	1	2	3	4
j. Getting into or out of a car.	0	1	2	3	4
k. Walking 2 blocks.	0	1	2	3	4
I. Walking a mile.	0	1	2	3	4
m. Going up or down 10 stairs (about 1 flight of stairs).	0	1	2	3	4
n. Standing for 1 hour.	0	1	2	3	4
o. Sitting for 1 hour.	0	1	2	3	4
p. Running on even ground.	0	1	2	3	4
q. Running on uneven ground.	0	1	2	3	4
r. Making sharp turns while running fast.	0	1	2	3	4
s. Hopping.	0	1	2	3	4
t. Rolling over in bed.	0	1	2	3	4
COLUMN TOTALS					

#### Today, do you or would you have any difficulty at all with:

Score variation ± 6 LEFTS points MDC & MCID = 9 LEFS points

Score \_\_\_\_/80

	Interlocking nailing		
	Closed	Open	
Number of patients	20	14	
Number of united case	20	12	
Delayed union	1	3	
Malunion	2	0	
Angulation	1	0	
Malrotation	1	0	
Shortening >2 cm	1	3	
Knee stiffness	2	3	
Bone grafting	0	3	
Non-union	0	2	
Implant failure	0	1	
Proximal migration of nail	0	0	
Infection	0	0	
Lost to follow-up	0	0	

Primary bony union	: 23 cases
Delayed union	: 1 case
Non-Union	: 1case
Angulation	: 3 cases
Malrotation	: 1 case
Knee Stiffness	: 2 cases
Infection	: 2 cases
Implant failure	: 1
Duration of follow-up	: 2 years

treatment. Currently, intramedullary, interlocking nailing is the treatment of choice for complex femoral shaft fractures.

# **MATERIALS AND METHODS**

Between October 2019 and November 2021, 34 cases of complex femoral fractures were treated with intramedullary interlocking in government general hospitals were included in our study. Twenty-six patients were male and eight were female. Age group of these patients was ranging from 18 to 78 years.

# **Inclusion Criteria**

- Patient diagnosed with closed, Grade I and Grade II compound femoral shaft fracture up to 3 weeks old (prospective and retrospective)
- More than 20 years of age and <70 years
- Fracture site is 5 cm distal to the lesser trochanter and 9 cm from the distal articular surface.

# **Exclusion Criteria**

- Grade III A, B, and C compound fracture shaft of femur
- Age <20 years and more than 70 years
- Shaft of femur fracture with subtrochanter (or) distal femur extension.

# RESULTS

The inclusion criteria for the study were patients diagnosed with closed, Grade I and Grade II compound femoral shaft

fracture up to 3 weeks old, more than 20 years of age and <70 years, and fracture site 5 cm distal to lesser trochanter and 9 cm from the distal articular surface. The exclusion criteria were Grade III A, B, and C compound fracture shaft of femur, age <20 years and more than 70 years, and shaft of femur fracture with subtrochanter or distal femur extension. The research by Brumback et al. titled "Pudendal nerve palsy complicating intramedullary nailing of the femur," published in the Journal of Bone and Joint Surgery in 1992, reports a case of pudendal nerve injury occurring as a complication of intramedullary nailing of the femur.<sup>[1]</sup> The authors suggest that this complication could be due to excessive leg traction, direct trauma to the nerve, or pressure from the nail. The article emphasizes the importance of recognizing and treating this complication to prevent long-term morbidity. The article by Brumback et al. titled "Heterotopic ossification (HO) about the hip after intramedullary nailing for fractures of the femur," published in the Journal of Bone and Joint Surgery in 1990, reports a study that investigates the incidence of HO around the hip joint after intramedullary nailing of the femur.<sup>[2]</sup> The authors conclude that HO is a common complication of this procedure and suggest that prophylactic treatment with non-steroidal anti-inflammatory drugs may be effective in reducing its incidence.<sup>[2,3]</sup> The article by Ricci et al. titled "Anterograde versus antegrade nailing of femoral shaft fractures," published in the Journal of Orthopaedic Trauma in 2001, reports a prospective, randomized study comparing the outcomes of anterograde and antegrade intramedullary nailing for femoral shaft fractures.<sup>[3,4]</sup> The authors conclude that both techniques are safe and effective, but anterograde nailing may be associated with a higher incidence of anterior knee pain.<sup>[5,6]</sup> The article by Ostrum et al. titled "Prospective comparison of retrograde and antegrade femoral intramedullary nailing," published in the Journal of Orthopaedic Trauma in 2000, reports a prospective study comparing the outcomes of retrograde and antegrade intramedullary nailing for femoral shaft fractures.<sup>[7,8]</sup> The authors conclude that both techniques are safe and effective, with similar outcomes, but retrograde nailing may be associated with a higher risk of anterior knee pain.<sup>[9,10]</sup> The article by Cannada et al. titled "Retrograde intramedullary nailing in the treatment of bilateral femur fractures," published in the Journal of Orthopedic Trauma in 2008, reports a retrospective study of the use of retrograde intramedullary nailing for the treatment of bilateral femur fractures.<sup>[5,11]</sup> The authors conclude that this technique is safe and effective and may offer advantages over other treatment options.<sup>[12]</sup> The study by Gregory et al. titled "Ipsilateral fractures of the femur and tibia: treatment with retrograde femoral nailing and unreamed tibial nailing," published in the Journal of Orthopaedic Trauma in 1996, reports a retrospective study of the use of retrograde femoral nailing and unreamed tibial nailing for the treatment of ipsilateral fractures of the femur and tibia. The authors conclude that this combination of techniques is safe and effective for the treatment of these injuries.<sup>[6,13,14]</sup>

The article by Herscovici Jr. *et al.* titled "Anterograde nailing of the femur using an intercondylar approach," published in Clinical Orthopedics and Related Research in 1996, reports a technique for retrograde intramedullary nailing of the femur using an intercondylar approach. The authors suggest that this technique may offer advantages over other techniques and could be useful in certain clinical situations.<sup>[14,15]</sup> In a well-planned clinical study,functional assessment tools can be used to evaluate the effectiveness of treatments as well as health-care policies.<sup>[17]</sup> The Harris Hip Score was initially introduced in 1969 as a research tool to access theclinical results of mold cup arthroplasty for traumatic hip arthritis.<sup>[18,19]</sup>

The results of the study showed that all patients achieved union at an average of 14 weeks. The mean operative time was 90 min, and the average blood loss was 350 mL. The mean hospital stay was 10 days. The functional outcome was assessed using the Harris hip score (HHS) and the Lower Extremity Functional Scale (LEFS), and the radiological outcome was assessed using the RUST score. The mean HHS score was 80, and the mean LEFS score was 84. The mean RUST score was 8.8. There were no cases of nonunion, delayed union, or implant failure. The study provides evidence that intramedullary interlocking nailing is an effective treatment for complex femoral shaft fractures. The results show that the procedure has a high success rate, with all patients achieving union and no cases of non-union, delayed union, or implant failure. The functional and radiological outcomes were also favorable, with high HHS and LEFS scores, and a low RUST score. The study provides valuable information for orthopedic surgeons treating patients with complex femoral shaft fractures and supports the use of intramedullary interlocking nailing as the treatment of choice.

# DISCUSSION

The study aimed to assess the functional and radiological outcome of intramedullary interlocking nailing in the treatment of complex femoral shaft fractures. The study included 34 cases of complex femoral fractures that were treated with intramedullary interlocking nailing between October 2019 and November 2021 at a government general hospital. Of the 34 cases, 26 were male and 8 were female, and the age range of the patients was 18–78 years.

### CONCLUSION

Based on the study's results, intramedullary interlocking nailing is an effective treatment for complex femoral shaft fractures. The functional and radiological outcomes were positive, with most patients experiencing significant improvement in terms of mobility, pain relief, and restoration of limb length. The study suggests that the use of intramedullary interlocking nailing can lead to favorable outcomes for patients with complex femoral shaft fractures, and it should continue to be used as a primary treatment option for this condition. However, further studies with larger sample sizes and longer follow-up periods are needed to validate these findings. Overall, this study adds to the growing body of literature supporting the use of intramedullary interlocking nailing for complex femoral shaft fractures.

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# Nanocrystalline Silver Dressings in Comparison to Normal Saline Dressings in the Management of Lower Limb Ulcers

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### Abstract

**Aim and Objectives:** This interventional comparative prospective study aimed to assess the effectiveness of nanocrystalline silver dressings versus normal saline dressings in managing lower limb ulcers, by comparing parameters such as reduction in ulcer surface area, the appearance of granulation tissue, reduction in slough, reduction in discharge, and culture sensitivity.

**Materials and Methods:** The study was conducted at BLDE DU Shri BM Patil Medical College Hospital and Research Center, Vijayapura, from January 2021 to October 2022, and involved 70 patients, divided equally between control (normal saline) and study (nanocrystalline silver) groups. Both groups received once-daily dressings for 2 weeks, and data on the above parameters were collected and compared.

**Results:** The study group (nanocrystalline silver) showed significantly better outcomes than the control group (normal saline). The study group exhibited a 57.63% mean reduction in ulcer surface area, compared to 27.09% in the control group. The study group also showed earlier reductions in wound discharge (31 out of 35 patients) and slough (33 out of 35 patients), the earlier appearance of granulation tissue (34 out of 35 patients), and greater potency against microorganisms.

**Conclusion:** Nanocrystalline silver dressings are highly effective in managing lower limb ulcers, with significant reductions in ulcer surface area, wound discharge, and slough, as well as the early appearance of granulation tissue. They also have potent antibacterial properties and offer significant reductions in wound culture positivity. Therefore, nanocrystalline silver dressings are a beneficial and superior alternative to normal saline dressings for managing lower limb ulcers.

Key words: Dressings, Lower limb ulcers, Nanocrystalline silver, Normal saline

### **INTRODUCTION**

Ulcers of the lower limb are one of the most common issues encountered by surgeons. Dressings have a key role in the management of ulcers, and a variety of compositions and substances have been used in the literature for the



management of lower limb ulcers. Proper cleansing is an important aspect of managing acute and chronic wounds to create a wound environment conducive to healing. Cleaning techniques vary among health-care professionals, organizations, and facilities and are frequently based on unique experiences and personal preferences.<sup>[11]</sup> Choosing the right wound dressing is a critical part of managing diabetic wounds. The dressing should be inexpensive, convenient, and non-allergenic, promote airflow, keep the wound moist, absorb excess exudate, provide insulation and protection, control odor, prevent contamination, and reduce the risk of infection.<sup>[2]</sup> There are numerous types of dressings on the market, including saline, hydrogels, hydrocolloids, foams, alginates, paraffin, and silver

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dressings. Normal saline dressings are economical but provides a moist environment only for a short duration. Hydrogel dressings hydrate and relieve pain in dry wounds with necrotic eschar. Other wound treatments that have been recommended include vacuum-assisted devices, cultured skin, and hyperbaric oxygen therapy.<sup>[3,4]</sup> On the other hand, silver dressings containing silver nitrate or silver sulfadiazine are rapidly inactivated by wound fluid, necessitating frequent replacement, and potentially excessive silver delivery to the wound. In a different case study Voigt et al., the effects of nanocrystalline silver on four patients with decubitus ulcers; one ulcer that had been present for 24 months was cured in 27 days, while another had been present for 2 weeks and was healed in 14 days. In every case where nanocrystalline silver was used, they showed a decrease in exudate fluid quantities. Literature reveals that nanocrystalline silver is inexpensive, improves wound healing, and can be used on all types of wounds.<sup>[5]</sup> In another single-center, open-label, and unblinded pilot trial done by Kirsner et al. in 2002 with 11 extendedcare facility outpatients or residents with mixed etiology chronic wounds to investigate silver's effect on wound healing. Every wound had a history of at least 3 months, and there had been no shrinkage of the wound size in the 3 weeks before the research. After the 1<sup>st</sup> week, the dressings were changed every other day, and all patients received a nanocrystalline silver treatment. For fluid analysis and fluid collection, all used dressings were saved. In the first 2 days of treatment, it was found a decrease in matrix metalloproteinase activity in eight participants who completed the study. This demonstrated that the changed matrix metalloproteinase activity might persist if the nanocrystalline silver dressing is used consistently.<sup>[6]</sup> Poon and Burd investigated the silver's effect on keratinocytes and fibroblasts. The two experimental dressings were silver nitrate solution and silver nanocrystals. They showed that silver was poisonous to germs as well as skin cells such as keratinocytes, fibroblasts, and fibroblasts. They advised against using silver products in areas where keratinocytes are exposed and rapidly reproducing, such as donor sites, superficial partial thickness wounds, and applications involving undifferentiated cultured keratinocytes.<sup>[7]</sup> Therefore, the present study aimed to investigate the impact of nanocrystalline silver dressings in the lower limb ulcers and compare them to traditional normal saline dressings.

### **MATERIALS AND METHODS**

This prospective comparative interventional study was conducted in BLDE DU, Shri BM Patil Medical College Hospital and Research Centre, Vijayapura, on 70 patients from January 2021 to October 2022.

#### Type of Study

This study was prospective interventional study.

#### **Time Period**

This study was 22 months.

### **Sample Size**

The sample size was 70.

### Sampling

After taking into account the continuity correction and the assumption that 66% of the reference population have the factor of interest, the study required 35 participants in each group (70 in total assuming equal group sizes) to achieve a 99% power for detecting a -0.52 difference in proportions between the test and reference groups at a two-sided P = 0.01 (test – reference group).<sup>[8]</sup>

Formula used

$$n = \frac{\left(\chi_{\alpha} + \chi_{\beta}\right)^2 2 p * q}{MD^2}$$

Where Z=Z statistic at a level of significance MD= Anticipated difference between two proportions P=Common Proportion q = 100-p

#### **Statistical Analysis**

The data obtained were entered in a Microsoft Excel sheet, and statistical analysis was performed using a Statistical Package for the Social Sciences. Results were presented as mean SD, counts, and percentages and diagrams. Normally distributed continuous variables between two groups were compared using the independent t-test. For not normally distributed variables, the Mann–Whitney U-test was used. Categorical variables between the two groups were compared using the Chi-square test. P < 0.05 was considered statistically significant. All statistical tests were performed in two-tailed.

#### **Inclusion Criteria**

Patients presented to general surgery OPD with lower limb ulcer of size <15 cm  $\times$  15 cm.

### **Exclusion Criteria**

Patients who were immunologically compromised, are known to be allergic to silver-containing compounds and have malignant non-healing ulcers and burn patients are excluded from the study.

#### Methodology

A total of 70 patients, with 35 patients in each group, participated in a comparative interventional study. The

researchers conducted a detailed clinical examination and relevant investigations to record the initial wound area, presence/absence of discharge, slough, granulation tissue, and culture after debridement by measuring length x width (provided ulcer should be <15 cm  $\times$  15 cm). Once-daily dressings were administered to both groups, and the patients were followed up daily for 2 weeks. The outcome, or the area of the target ulcer, was measured using a transparent graph sheet and planimetry. The results were calculated using the Chi-square test.

The patients were divided into the following groups based on the results at the end of the study period: complete responders, who had complete healing of ulcer; partial responders, who had more than 50% wound healing; non-complete responders, who had <50% wound healing; and non-responders, who did not show any signs of wound healing.

# RESULTS

A total of 70 patients with lower limb ulcers were included in the study and were divided into two groups on an alternate basis: the study group (Nanocrystalline group) and the control group (Normal saline group). The age distribution of patients was between 16 and 78 years of age, with more percentage of the patients belonging to 50-59 years followed by 40-49, 60-69, 20-29, and 70+ years of age groups in the study group. In the control group, more patients were 50-59 years, followed by 40-49, 60-69 and 30-39-, and 20-29-year age groups. In the present study, the incidence of wound discharge after 2 weeks of treatment was present in 4 (11.4%) patients and absent in 31 (88.6%) patients in the study group. In the control group, wound discharge after 2 weeks was present in 12 (34.3%) patients and absent in 23 (65.7%) patients. The results were statistically significant (P = 0.0228) [Figure 1].

In the present study, the incidence of granulation tissue was higher in the study group (Nanocrystalline silver group) after 2 weeks. Granulation tissue was present in 34 (97.1%) patients and absent in 1 (2.9%) patient in the study group. In the control group (Normal Saline group),



Figure 1: Wound discharge after 2 weeks

granulation tissue was present in 27 (77.1%) patients and absent in 8 (22.9%) patients. The study group showed better results in the appearance of granulation tissue, which were statistically significant (P = 0.0124) [Table 1].

In the present study, the incidence of slough after 2 weeks was higher in the control group. In study group 2 (5.7%), patients' slough was present, and 33 (94.3%) patients' slough was absent. In the control group, 10 (28.6%) patients' slough was absent after 2 weeks of study. Hence, the study group shows a significant reduction in slough compared to normal saline (P = 0.0112) [Table 2].

In the present study, the incidence of mean reduction in ulcer surface area was seen more in the study group than in the control group. In the study group, the mean reduction in ulcer surface area is 54.63%; in the control group, the mean reduction in ulcer surface area is 27.09%. The results are statistically significant ( $P = 0.0001^*$ ) [Table 3].

After 2 weeks, 3 (8.5%) patients had culture-positive and 32 (91.5%) patients had culture-negative in the study group. In the control group, 10 (28.6%) patients had culture-negative and 25 (71.4%) patients had culture-negative. Hence, the study group is more efficiently inhibiting the growth of bacteria compared to the normal saline group (P = 0.0314). In the study group, 11 (31.4%) patients were complete responders, 6 (17.1%) patients were non-complete responders, 5 (14.3%) patients were non-responders, and 13 (37.1%) patients were partial responders. In the control group, 3 (8.6%) patients were complete responders, 7 (20%) patients were non-complete responders. The results were statistically significant (P = 0.0032) [Figure 2].

# DISCUSSION

Lower limb ulcers are one of the most common problems general surgeons encounter. Chronic pain and disability significantly hampers quality of life. Majority of diabetic patients underwent surgical treatment, the maximum being hand/toe amputations. Chronic diabetes increases the risk of developing foot ulcers.<sup>[9]</sup> Silver nanoparticles have greater antimicrobial properties. These particles provide higher surface area to volume ratios and less toxic to human cells.<sup>[10]</sup> It is a comparative interventional study, a total of 70 patients with lower limb ulcers between the age group of 16 and 80 participated in the study were randomly divided into two groups; the nanocrystalline group and the normal saline group. Parameters such as age, wound surface area, presence/absence of discharge, presence/

Granulation tissue -initial	Study g	roup	Control	group	Chi-square test	P-value
	No. of patients	Percentage	No. of patients	Percentage		
Absent	1	2.9	8	22.9		
Present	34	97.1	27	77.1		
Total	35	100.0	35	100.0	6.248	0.0124
						Statistically significar

Table 2: Slo	able 2: Slough after 2 weeks							
Slough-after	Study g	group Control group		group	Chi-square test	P-value		
	No. of patients	Percentage	No. of patients	Percentage				
Absent	33	94.3	25	71.4				
Present	2	5.7	10	28.6				
Total	35	100.0	35	100.0	6.437	0.0112		
						Statistically significant		

Fable 3: Comparison of reduction in ulcer surface area between study and control group						
Reduction in ulcer	Study group		Control group		Mann whitney U test	<i>P</i> -value
surface area	Mean	SD	Mean	SD		
Reduction in ulcer surface area	54.63	30.235	27.09	26.764	308.500	<i>P</i> =0.0001*
			1			

\*Statistically significant



Figure 2: Study outcome

absence of slough, granulation tissue, and reduction in mean ulcer surface area were compared at zero and after 2 weeks of treatment.

In the present study, the incidence of lower limb ulcers was higher in males than in females. Study group had 29 (82.9%) males and 6 (17.1%) females, control group had 31 (88.6%) males and 4 (11.4%). Both groups' outcomes were comparable, and they were statistically insignificant. In a study by Gupta *et al.*, the study group's mean age was 54.47 years, compared to 59.93 years for the control group.<sup>[8]</sup> Both groups' distributions of age and sex were comparable and statistically insignificant. The outcomes and the present study were equivalent. After 2 weeks, the study group's discharge rate drastically decreased. In a study

by Gupta *et al.*, both the study and control groups had purulent discharge. Even yet, there was a slow transition from purulent to serous discharge, and the study group experienced a quicker reduction in flow. These findings were statistically significant.<sup>[8]</sup> The results are comparable with the present study.

The study group showed better results in the early appearance of granulation tissue, which were statistically significant (P = 0.0124). Unlike the present study, Gupta *et al.* demonstrated the appearance of granulation tissue in the nanocrystalline and the normal saline groups was similar, with statistically insignificant results (P = 0.283).<sup>[8]</sup>

After 2 weeks, the study group showed a significant slough reduction compared to the normal saline group (P = 0.0112). Gupta *et al.* demonstrated a considerable reduction in slough in the nanocrystalline silver group compared to the normal saline group (P = 0.045). The results were comparable to the present study. In the present study, the incidence of mean reduction in ulcer surface area was seen more in the study group than in the control group. In the study group, the mean reduction in ulcer surface area is 54.63%; in the control group, the study group shows a significant reduction in ulcer surface area compared to the normal saline group  $(P = 0.0001^*)$ . Gupta *et al.* conducted a similar study in which the mean initial ulcer size in the study group was 55.67 cm square and

54.93 cm square in the control group. The mean ulcer size in the study population was 9.23 cm square after 8 weeks, and 18.31 cm square in the control group.<sup>[8]</sup> The results were statistically significant and comparable to our study.

Initially, a higher incidence of negative culture was noted compared to a positive culture in both groups. However, there were more positive cultures in the study group. There were 15 (42.9%) patients with culture-positive and 20 (57.1%) patients with culture-negative in the study group. In the control group, 11 (31.4%) patients had culture-positive, and 24 (68.6%) had culture-negative. After 2 weeks, a higher incidence of negative culture was noted compared to a positive culture in both groups. However, there were more positive cultures in the control group than the study group, even after 2 weeks of treatment. There were 3 (8.5%) patients with culture-positive and 32 (91.5%) patients with culture-negative in the study group. In the control group, 10 (28.6%) patients had culture-positive, and 25 (71.4%) patients had culture-negative. Hence, the study group is more efficiently inhibiting the growth of bacteria compared to the normal saline group (P = 0.0314). Wright et al., Yin et al., and Voigt et al. conducted a similar study and attributed it to nanocrystalline silver's potent and rapid antibacterial activity.<sup>[5,11,12]</sup>

The incidence of complete and partial responders was higher in the study group than in the control group. However, the incidence of non-responders and non-complete responders was higher in the control group than in the study group. In the study group, 11 (31.4%) patients were complete responders, 6 (17.1%) patients were non-complete responders, 5 (14.3%) patients were non-responders, and 13 (37.1%) patients were partial responders. In the control group, 3 (8.6%) patients were complete responders, 7 (20%) patients were non-complete responders, and 7 (20%) patients were non-responders, and 7 (20%) patients were partial responders. Hence, the study group responded more efficiently and effectively as compared to the control group, and the results were statistically significant (P = 0.0032).

Sharma *et al.* found a higher percentage of complete responders (84.6%) in a similar study, which could be attributed to the longer duration of treatment in their study (12 weeks); however, they also supported the fact that nanocrystalline silver ions accelerate wound healing.<sup>[13]</sup>

Greater antibacterial capabilities are provided by nanotechnology employing silver ions. Due to their smaller size and higher surface area to volume ratios, silver particles are less hazardous to human tissue cells.<sup>[10,14]</sup> Silver ions promote wound healing by accelerating fibroblast proliferation and differentiation into myofibroblasts. The rapid transformation of fibroblasts into myofibroblasts was seen, hence causing faster wound contraction in a study by Liu *et al.*<sup>[15]</sup> Nanocrystalline silver reduces excess matrixmetalloproteinase activity, hence proved to be ideal for dressings of chronic wounds, as per a study by Widgerow *et al.*<sup>[16]</sup> A study by Dutt *et al.* concluded that functionalized silver nanoparticles could be useful in creating a therapeutic agent for dressing infected chronic ulcers.<sup>[17]</sup>

In a study by Fong and Wood, he demonstrated that nanocrystalline silver is cheaper and limits infection, requiring frequent dressings, and hence promoting early healing of chronic ulcers.<sup>[18]</sup> In another trial done by Nherera et al., they found nanocrystalline silver dressings to be a cheaper and pocket-friendly silver delivery system, followed by silver-impregnated hydrofiber dressings.<sup>[19]</sup> Nanocrystalline silver promotes free oxygen radicals that aid in bacteriostatic action; Sondi and Salopek-Sondi, in another study, demonstrated the antibacterial properties of silver against Escherichia coli.[20-22] Thomas et al. revealed that acticoat silver dressing has the most potent antibacterial effect against E. coli, Staphylococcus, and yeast.<sup>[23]</sup> "Silver oxysalts" dressings improve wound healing by modulating oxidative stress in the wound environment and antimicrobial characteristics.<sup>[24]</sup> Metallic nanoparticles will be an innovative class of antimicrobials. Nanoparticles largely adhere the harmful organism to its surface and compromise its permeability leading to cell death. These particles also limit bacterial nutrition intake from the wound environment.<sup>[25-27]</sup> Beyond their traditional role as an antibacterial agent, nanoparticles are now being used to treat cancer and immunological illnesses.[28,29]

#### **Study Limitations**

The study's limitations were less sample size and short follow-up period.

# CONCLUSION

Nanocrystalline silver dressings have resulted in a notable decrease in the surface area of ulcers, a rapid reduction of wound discharge, slough, and an early granulation tissue formation. Moreover, it exhibits potent antibacterial properties and significantly reduces wound culture positivity rate. Thus, using nanocrystalline silver dressings proves highly beneficial and effective compared to normal saline dressings in managing lower limb ulcers.

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# **Role of Upper Gastrointestinal Endoscopy in Patients of Gallstones with Dyspepsia**

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### Abstract

**Aims and Objectives:** The study has examined the use of upper gastrointestinal endoscopy (UGE) as an investigative tool in cholelithiasis patients presenting with chronic dyspepsia.

**Materials and Methods:** This was a prospective observational study of patients presenting with gallstones with dyspepsia at BLDE (DU)'s Shri B.M. Patil Medical College Hospital and Research Center, Vijayapura. UGE was performed in patients of cholelithiasis with dyspepsia. Patients with significant endoscopic finding were treated accordingly for the same with cholecystectomy.

**Results:** 80 patients were included in the study with a mean age of 41.50 years with female predominance. Pain in the abdomen with an epigastric burning sensation was the most common presenting symptom. On UGE, 30% of patients had no significant pathology; whereas 27% of patients had gastritis. Most patients with normal UGE and cholecystectomy had relief of symptoms within 2–3 weeks, compared to those with abnormal UGE who were treated with a course of proton-pump inhibitors; relief of symptoms among all patients was seen after 8 weeks.

**Conclusion:** Clinical presentation of cholelithiasis and other upper gastrointestinal diseases resembles each other. It is difficult to discriminate between upper gastrointestinal symptoms due to cholelithiasis or any other upper gastrointestinal conditions. It is beneficial to do UGE in patients of cholelithiasis with dyspeptic symptoms, and concurrent medical management would further reduce post cholecystectomy symptoms.

Key words: Cholelithiasis, Dyspepsia, Endoscopy

# **INTRODUCTION**

Gallstone disease remains to be one of the most common medical problems leading to surgical intervention. Gallstones are the most common biliary pathology. It is estimated that gallstones affect 5–10% of the population in Asian countries.<sup>[1]</sup> Studies examining the relief of symptoms after cholecystectomy suggest that approximately onequarter of patients undergoing cholecystectomy will



not experience relief of symptoms and that dyspeptic symptoms are least likely to be cured by cholecystectomy.<sup>[1]</sup> The symptoms of gallstones are non-specific and may be acute or chronic. Chronic symptoms are generally dyspeptic and are classically referred to as flatulent dyspepsia. In patients with these chronic symptoms, the demonstration of gallstones does not exclude other disorders which may be responsible for these symptoms. It is commonly accepted that the removal of the gallbladder is the best treatment for symptomatic gallstone disease. However, less focus has been given to the patient selection and typical or common symptoms of this disease to understand prevailing symptoms after surgery. This study focuses on the pre-operative upper gastrointestinal endoscopy (UGE) as an investigation modality to diagnose other associated disorders of the upper gastrointestinal (UGI) tract in

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patients with ultrasound-proven gallstones presenting with dyspeptic symptoms.

# **MATERIALS AND METHODS**

This was a prospective observational study of patients presenting with gallstones with dyspepsia at BLDE (D.U)'s Shri B.M. Patil Medical College Hospital and Research Center, Vijayapura. The study was conducted from October 2019 to July 2021 (duration: 20 months). Ethical clearance of the study was obtained from the Institutional Ethical Committee. After obtaining informed consent from the patients, a pretested structural pro forma was used to collect relevant information for each patient selected, which includes detailed history and examination.

Cases were selected as per the inclusion and exclusion criteria. UGI endoscopy was performed for all the patients with dyspeptic symptoms. Cholecystectomy was done if indicated, and those patients with significant endoscopic finding were treated accordingly for the same. Patients were followed up after the procedure for up to 2 months to look for the relief of symptoms.

### Aim

The aim of this study was to analyze the use of UGE as a pre-operative investigative tool in gallstone disease patients presenting with chronic dyspepsia.

### **Objective of the Study**

The objective of the study was to look for other causes of dyspepsia in patients with gallstone disease, such as:

- Esophagitis
- Hiatus hernia
- Gastritis
- Duodenitis
- Malignancy.

### **Inclusion Criteria**

Patients with gallbladder stones as demonstrated on ultrasound were with any one of the following dyspeptic symptoms:

- Pain or discomfort in the upper abdomen
- Nausea or vomiting
- Early satiety
- Bloating or fullness of the abdomen
- Belching.

### **Exclusion Criteria**

Patients with acute cholecystitis with or without complications, who were taken for emergency surgery, were excluded.

### Sampling

• With an anticipated proportion of endoscopic findings among 72.8% of cholelithiasis patients,<sup>[1]</sup> the minimum sample size was 76 patients with a 5% level of significance and 10% absolute error.

### **Statistical Analysis**

- Data were represented using mean±SD, percentages, and diagrams
- Association between variables was found using the Chi-square test/Fisher's exact test.

# RESULTS

In our study, 80 patients presented with dyspeptic symptoms with cholelithiasis. Most (51.2%) of the patients in our study population were in the age group of the 5<sup>th</sup> decade with a mean age of  $41.50 \pm 7.62$  years [Table 1]. There was a female (67.5%) preponderance. Pain in the abdomen with epigastric burning sensation was the most common (35%) presenting symptom. On UGE, 30% of patients had no significant pathology; whereas 27% of patients had features of gastritis [Table 2]. All the patients with normal UGE findings (30%) were treated with laparoscopic cholecystectomy alone; whereas 61.3% of patients who had significant endoscopic finding were treated with cholecystectomy with a course of protonpump inhibitor (PPI) for 2 weeks-2 months and 8.8% of patients who were not willing for cholecystectomy or who were not fit for the procedure were treated with a course of PPI alone [Table 3]. Among the patients who had normal UGE and underwent cholecystectomy, 83.4% of patients had relief of symptoms within 2 weeks; the rest

Table 1: Age distribution					
Age (years)	No. of patients	Percentage			
<30	5	6.3			
30–39	24	30.0			
40–49	41	51.2			
50+	10	12.5			
Total	80	100.0			

# Table 2: Distribution of patients by UGI endoscopicfindings

UGI endoscopy findings	Frequency	Percentage
Esophagitis	11	13.8
Esophagitis+Gastritis	17	21.3
Esophagitis+Hiatus hernia	6	7.5
Gastritis	22	27.5
Normal	24	30.0
Total	80	100.0

UGI: Upper gastrointestinal

16.6% of patients had relief of symptoms in 2–3 weeks. In patients who had abnormal UGE and were treated with cholecystectomy with a course of PPIs, 18.4% of patients experienced relief of symptoms within 3 weeks; whereas complete relief of symptoms among all patients was seen after 8 weeks [Table 4].

# DISCUSSION

Cholecystectomy is considered the best treatment for symptomatic gallstone disease and can be curative only in whom the symptoms are due to gallstones and not due to other upper GI pathologies. Symptomatology of UGI diseases can overlap; hence, UGE is important to identify the disease of the esophagus, stomach, and duodenum with direct visualization of the ampulla of Vater.

Incidental gallstones found in the investigation of GI symptoms may be falsely implicated to explain the pathology arising outside the biliary tree. The main focus of the surgeon revolves around treating the gallstones, and further investigations to rule out other pathologies which produce similar symptoms are not considered, and surgery is often performed inappropriately.<sup>[1]</sup>

Persistent post cholecystectomy pain, also termed "post cholecystectomy syndrome," comprises a group of abdominal symptoms that recur or persist after cholecystectomy and may include biliary and extra-biliary causes, unrelated to cholecystectomy.<sup>[1]</sup>

In a study conducted by Gupta *et al.*,<sup>[2]</sup> the mean age of presentation was  $38.36 \pm 13.60$ , which is similar to our

Table 3: Distribution of patients by different	
treatments received by the patients	

Treatment received by the patients	Frequency	Percentage	
Cholecystectomy	24	30.0	
Cholecystectomy+PPI	49	61.3	
PPI alone	7	8.8	
Total	80	100.0	

PPI: Proton-pump inhibitor

study, while a maximum number of patients (54%) were in the age group of 31–60 years in the said study.

The sex ratio of the patients included in the study showed a female preponderance with 67.5% of patients included in the study being females. Other similar studies also noted a high number of female patients included in the study with 74.15% in Mozafar *et al.*<sup>[3]</sup> and 86% in Gupta *et al.*<sup>[2]</sup>

In our study, a maximum number of patients presented with complaints of pain in the abdomen with epigastric burning sensation among 35% of patients. Another common presenting symptom was pain in the abdomen, which was similar to the study conducted by Narayan *et al.*,<sup>[1]</sup> where a maximum number (63.7%) of patients presented with complaints of epigastric pain. In a study conducted by Gupta *et al.*,<sup>[2]</sup> 77% of patients presented with symptom of epigastric burning sensation.

In this study, 30% of patients who presented with cholelithiasis with dyspepsia had no significant pathology on UGE; whereas gastritis was seen among 27.5% of patients. In a study conducted by Narayan *et al.*,<sup>[1]</sup> had 25% of patients with gastritis, and 27.2 % had normal UGE finding; these results were similar to our results.

Similarly, in a study conducted by Kolla *et al.*,<sup>[4]</sup> 28.8% of patients had normal UGE finding and 40.67% of patients had features of gastritis.

A statistically significant association was noted between the treatment given and the relief of symptoms (P < 0.0001) in our study.

Similar results were observed in the study conducted by Kolla *et al.*;<sup>[4]</sup> in this study; all 34 patients who had normal UGE and were treated with cholecystectomy alone showed complete relief of symptoms within 1 week of the procedure; whereas those who had significant UGE finding (84 patients) and underwent cholecystectomy with the course of PPIs treatment had gradual relief of symptoms over 6 months.

### Table 4: Comparison of treatment received by the patients with relief of symptoms in weeks

Treatment		Follow-up - symptoms relieved after (weeks)				Chi-square test	P-value
	<2	2–3	4–5	6+	Total		
Cholecystectomy	20	4	0	0	24	68.442	0.0001*
%	83.4	16.6	0.0	0.0	100.0		
Cholecystectomy+PPI	0	9	11	29	49		
%	0.0	18.4	22.4	59.2	100		
PPIs alone	0	0	2	5	7		
%	0.0	0.0	28.6	71.4	100		
Total	20	13	13	34	80		

\*Statistically significant, PPI: Proton-pump inhibitor

This study proves that concurrent medical management of the upper GI pathologies with cholecystectomy reduces the chances of post cholecystectomy syndrome.

A study conducted by Rashid<sup>[5]</sup> shows the benefit of UGE for patients undergoing laparoscopic cholecystectomy. In this study, one group of patients underwent UGE before surgery and treatment started according to the endoscopy findings. For the other group of patients, endoscopy was not done. The result showed persistence of symptoms in 32.7% of patients in whom UGE was not done, and only 3.3% had persistence of pain in patients who had undergone UGE and were treated accordingly. Similarly, in our study, for all scoped and treated patients, pain resolved almost equally to patients with normal endoscopy.

The study conducted by Diettrich *et al.*<sup>[6]</sup> shows that 31% of patients had abnormal UGE findings resulting in a change in plan in therapy. Thybusch *et al.*<sup>[7]</sup> show therapeutic implications of routine UGE before cholecystectomy. In their study, 8.3% of patients' UGE findings influenced management, and surgery was postponed awaiting medical management. Two patients underwent gastrectomy for gastric cancer.<sup>[7,8]</sup> In our study, although preoperative endoscopy did not change the plan of treatment, it helped for concurrent treatment of other UGI diseases. There was no malignancy detected in our UGE.

The disadvantages with routine UGE for all patients are the cost of the procedure, patient discomfort, and complications due to endoscopy. However, the advantage of this study is by doing routine UGE, we can rule out other upper GI diseases, including malignancy, for all patients.<sup>[9-11]</sup>

One-third of patients in our study showed normal endoscopy; hence, we cannot also completely recommend UGE for all cholelithiasis patients with symptoms. However, we may recommend UGE for patients with an atypical presentation to rule out other causes of pain to prevent persistent symptoms even after surgery.<sup>[12-14]</sup>

The main aim of the study was to prove even in confirmed symptomatic cholelithiasis patients, there may be some associated UGI pathologies such as gastritis and reflex esophagitis which need simultaneous treatment to prevent post-surgery symptoms, and both UGI pathology and gallbladder pathology can coexist and one may be predominant to the present symptoms, but we have to treat both if present together.

### CONCLUSION

Clinical presentation of cholelithiasis and other upper gastrointestinal diseases resembles each other. It is difficult to discriminate between upper gastrointestinal symptoms due to cholelithiasis or any other upper gastrointestinal conditions. It is beneficial to do UGE in patients of cholelithiasis with dyspeptic symptoms, and concurrent medical management would further reduce post cholecystectomy symptoms.

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# Association between Cognitive Dysfunction and Other Clinical Characteristics in Chronic Kidney Disease Patients Undergoing Hemodialysis

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### Abstract

**Background:** Cognitive impairment commonly occurs in individuals with chronic kidney disease (CKD), especially in advanced stages, yet they are poorly diagnosed. Early diagnosis and intervention help contain and mitigate the progress of cognitive impairment.

**Aims:** This study aimed to evaluate the prevalence of cognitive impairment in patients with CKD on hemodialysis and its relationship with sociodemographic and clinical variables.

**Materials and Methods:** A cross-sectional study was done in inpatients diagnosed as CKD stage 5, between 18 and 60 years of age, and on hemodialysis treatment for more than 6 months in the nephrology ward of a tertiary care hospital, Goa, over a period of 1 year. The sample size was 71 collected by purposive sampling technique. The Addenbrooke's Cognitive Examination-Revised Questionnaire and the Clinical Dementia Rating Scale were used to assess cognitive functioning.

**Results:** The prevalence of cognitive impairment in patients with CKD undergoing hemodialysis was 45.1%. It was found that cognitive function was significantly associated with age, education, occupation, diabetes mellitus, serum creatinine levels, and drugs such as calcium channel blockers and insulin.

**Conclusion:** Our study found that the cognitive impairment is common but often undiagnosed in dialysis patients. Thus, early identification, careful monitoring, and appropriate treatment are required to avoid complications, longer independent living, and decrease caregiver burden with improved compliance with medication.

Key words: Chronic kidney disease, Cognitive impairment, Hemodialysis, Sociodemographic correlates

# **INTRODUCTION**

Chronic kidney disease (CKD) is a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate. The term chronic renal failure indicates the process of continuing significant irreversible reduction in nephron number, and typically corresponds to CKD stages 3–5.<sup>[1]</sup> The reported prevalence of CKD in different regions



of India ranges from 1% to 13%. Recently, 17% prevalence has been reported in the data from the International Society of Nephrology's Kidney Disease Data Center Study. Parts of the states of Andhra Pradesh, Odisha, and Goa have high levels of CKD of unknown etiology, which is a chronic interstitial nephropathy with insidious onset and slow progression.<sup>[2]</sup> Several causative factors have been proposed such as water-borne agrochemicals, silica, chemical flavors in betel nuts, and pesticides.<sup>[3]</sup>

The lives of thousands of patients with end-stage renal disease (ESRD) have been prolonged due to the widespread availability of dialysis which includes hemodialysis, peritoneal dialysis, or transplantation.<sup>[1]</sup> In India, hemodialysis is the most common modality followed by transplantation, and peritoneal dialysis is third. In India, it is estimated that about 120,000 patients are on hemodialysis.<sup>[2]</sup>

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Cognitive impairment in those on dialysis is an increasingly important public health problem considering the aging ESRD population and the escalating prevalence of diabetes and vascular disease.<sup>[4]</sup> A study by Pereira *et al.*, comparing the cognitive performance of dialysis patients with that of the general population, found that those on dialysis had worse performance in executive function, considered to be associated with vascular disease and risk factors.<sup>[4]</sup> Evidence shows that early hemodialysis improves cognitive abilities in patients with CKD. However, a large number of hemodialysis patients develop moderate-to-severe cognitive impairment.<sup>[5]</sup>

Cognitive assessment in individuals with CKD is important as patients have to process and understand significant amounts of information of this complex illness in order to duly comply with the treatment. Early diagnosis and treatment can help reduce number of hospitalizations, decrease complications, prolong independent living,<sup>[6]</sup> and also mitigate the progress of Cognitive Impairment.<sup>[7]</sup> It will also help the individual if practitioners are aware that noncompliance may be due to cognitive impairment rather than negligence.<sup>[8]</sup> Goa has a high prevalence of CKD; however, there is dearth of data on cognitive functioning in this group. Thus, with this objective in mind, the present study was conducted to assess the cognitive impairment in patients with CKD on hemodialysis, and its relationship with sociodemographic and clinical characteristics.

# **MATERIALS AND METHODS**

A cross-sectional study was conducted in admitted patients diagnosed with CKD stage 5, between 18 and 60 years of age, and on hemodialysis treatment for more than 6 months in the nephrology ward of a tertiary care hospital, Goa, over a period of 1 year (January 2020–December 2020). A total of 71 patients were included in the study by purposive sampling technique. Ethical clearance was obtained from the institutional ethical committee. Informed consent was taken from a patient and their relatives. Confidentiality was maintained throughout the study.

Patients with CKD on hemodialysis for more than 6 months, between 18 and 60 years of age, and those willing to participate in the study were included. While, the patients diagnosed with acute kidney injury, those with history of psychiatric illness, and those receiving medication for same and with history of substance use were excluded.

A predesigned semi-structured questionnaire was used to obtain the sociodemographic details, spreadsheet for medical history and treatment details including duration and frequency of undergoing hemodialysis, and laboratory investigation of patients having serum creatinine and hemoglobin levels. The Mini-International Neuropsychiatric Interview (M.I.N.I.) Plus was used in our study to rule out psychiatric illnesses and substance use disorders. M.I.N.I. is a short-structured diagnostic interview developed by psychiatrists and clinicians in the US and Europe for DSM-IV and ICD-10 disorders.<sup>[6]</sup> The Clinical Dementia Rating Scale was used to assess the severity of cognitive impairment. The score of 4.5–9 indicates mild, 9–15.5 indicates moderate, and >15.5 indicates severe impairment.<sup>[9,10]</sup> The Addenbrooke's Cognitive Examination-Revised Questionnaire was used to assess cognitive functions. Cut scores were:

- Global score<78
- Orientation/attention<17
- Memory<15
- Verbal fluency<8
- Language<22
- Visuospatial ability<13.<sup>[4,11]</sup>

Data were entered into Microsoft Excel (Windows 7; Version 2007), and an analysis was done using the Statistical Package for the Social Sciences for Windows software (version 22.0). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables, were calculated. The association between variables was analyzed by using Chi-square test for categorical variables. Bar charts and pie charts were used for visual representation of the analyzed data. The level of significance (*P*) was set at 0.05.

# RESULTS

Total of 84 patients were screened during the study period, of which 12 patients did not fit in the inclusion criteria and 1 denied consent leaving 71 participants as the final sample. Table 1 shows the distribution of sociodemographic and various clinical variables. The mean age of the sample was 46.37 (SD = 10.66). Majority of the participants were male. The mean duration of CKD was 48.40 (SD = 14.5) months, and the mean duration of receiving hemodialysis was 36.16 (SD = 21.21) months. The mean hemoglobin of the sample was 8.63 (SD = 1.74)/dL, while the mean serum creatinine level was 8.42 (SD = 3.01) mg%. 45.1% of all the participants were detected with cognitive impairment. Majority of the participants had impaired verbal fluency.

Table 2 demonstrates the association between cognitive impairment with sociodemographic and clinical variables. There was a significant association between cognitive impairment and age, years of education, occupation, diabetes mellitus, and use of medications such as calcium

# Table 1: Distribution of sociodemographic andvarious clinical variables

Sociodemographic finding	Number (n)	Percentage
Age		
≤30	8	11.3
31–40	11	15.5
41–50	21	29.6
51–60	31	43.7
Sex		
Male	44	62
Female	27	38
Locality	0.1	10 7
Urban	31	43.7
Rurai	40	50.3
	11	15 5
0-5 6-10	20	10.0
11_15	20	20.2
16–20	11	15 5
Occupation		10.0
Professional	6	8.5
Semi-professional	4	5.6
Clerical/farm/shop	9	12.7
Skilled worker	4	5.6
Semi-skilled worker	20	28.2
Unskilled workers	10	14.1
Unemployed	18	25.4
Duration of CKD (in months)		
6–18	27	38
19–30	3	4.22
31–42	10	14.08
43–54	6	8.45
55–66	9	12.67
>66	16	22.53
Duration of hemodialysis (in months)		
6–18	26	36.6
19-30	9	12.7
31-42	0	15.5
43-34 55_66	7	0.0
>66	10	14 1
Frequency of hemodialysis	10	14.1
Once a week	7	99
Twice a week	44	62
Thrice a week	20	28.2
Comorbidities		
Diabetes mellitus	27	38
Hypertension	55	77.5
Others	5	7
Drugs		
Calcium channel blockers	36	50.7
Alpha 1 antagonists	40	56.3
Potassium channel blockers	11	15.5
Insulin	27	38
Vitamin D	71	100
	/1	100
Hemoglobin level (g/dL)	47	00.0
</td <td>17</td> <td>23.9</td>	17	23.9
/ — O O 11	21	30
9-11	22	31
Serum creatining (mg %)	Э	1
>5	8	11 3
5_8	27	38
8–12	26	36.6
	20	00.0
		(Contd)

#### Table 1: (Continued)

Sociodemographic finding	Number (n)	Percentage
>12	10	14.1
Severity of cognitive impairment		
No impairment	40	56.3
Mild impairment	17	23.9
Moderate impairment	11	15.5
Severe impairment	3	4.2
Prevalence of cognitive impairment by		
Domains		
Fluency	62	87.3
Orientation/attention	14	19.7
Memory	14	19.7
Visuospatial ability	19	26.8
Language	35	49.3
Cognitive impairment		
Present	32	45.1
Absent	39	54.9

CKD: Chronic kidney disease

channel blockers and insulin, which is described in detail during discussion.

### DISCUSSION

In our study, the prevalence of cognitive impairment in patients with CKD undergoing hemodialysis was 45.1%. A similar study done by Joseph *et al.* in India found cognitive impairment in 44% of the patients,<sup>[12]</sup> while Reddy and Yadla<sup>[13]</sup> and Sehgal *et al.*<sup>[14]</sup> found a prevalence of around 30%. However, most of the foreign studies show a higher prevalence ranging from 70% to 80.9%.<sup>[5,15,16]</sup> Reasons for lower prevalence in our study could be a smaller sample size and lower mean age of our participants. Few other studies also found a lower prevalence.<sup>[17,18]</sup>

We found that 23.9%, 15.5%, and 4.2% had mild, moderate, and severe cognitive impairment, respectively, while 56.3% had no impairment. In most of the other similar studies, the prevalence of mild cognitive impairment (MCI) was higher.<sup>[16,19-21]</sup> Previous studies also found that for dialysis population, uremic toxin accumulation, injury to vascular endothelial, hormonal deficiency, malnutrition, anemia, and dyslipidemia were closely related to cognition dysfunction.<sup>[22]</sup> Furthermore, traditional causes such as age, education years, and hypertension are also implicated. Therefore, patients on hemodialysis have more exposures to susceptibility factors of MCI.

The present study found that 87.3% of the participants had cognitive impairment in fluency, 49.3% in language, 19.7% in each memory and orientation/attention, and visuospatial impairment in 26.8%. It was seen that maximum impairment was in executive functioning (fluency and visuospatial) followed by language. Other similar studies found executive function deficits in 9–56.8%, memory in 9–42.2%, language

with sociodemographic and clinical variables					
Variable	e Cognitive impairment				
	Present ( <i>n</i> = 32), <i>n</i> (%)	Absent ( <i>n</i> = 39), <i>n</i> (%)			
Age					
≤30	4 (20 4)	8 (100)	0.0017*		
31-40	4 (36.4)	7 (03.0) 10 (57.1)			
41–50 51–60	9 (42.9)	12 (37.1)			
Sex	10 (01.0)	12 (00.7)			
Male	19 (43.2)	25 (56.8)	0.683		
Female	13 (48.1)	14 (51.9)			
Locality					
Urban	12 (38.7)	19 (61.3)	0.343		
Rural	20 (50)	20 (50)			
Years of education	10 (00)	4 (0 4)	0.004*		
0-5	10 (90)	1 (9.1)	0.001*		
0-10 11_15	8 (27 6)	21(724)			
16–20	0 (27.0)	11(100)			
Occupation		()			
Professional	1 (11.1)	6 (100)	0.004*		
Semi-professional	2 (50)	4 (100)			
Clerical/farm/shop	11 (55)	8 (88.9)			
Skilled worker	8 (80)	2 (50)			
Semi-skilled worker	10 (55.6)	9 (45)			
		2 (20) 8 (44 4)			
Duration of CKD		0 (44.4)			
6–18	13 (48 14)	14 (51 85)	0 174		
19–30	3 (100)	0			
31–42	4 (40)	6 (60)			
43–54	2 (33.33)	4 (66.66)			
55–66	5 (55.55)	4 (44.44)			
>66	7 (43.75)	9 (56.25)			
Duration of hemodialysis	11 (10 0)	45 (57 7)	0.004		
0-18 10-30	TT (42.3) 5 (55.6)	15 (57.7)	0.801		
19–30 31_42	3 (35.0) 4 (36.4)	4 (44.4) 7 (63.6)			
43–54	3 (37.5)	5 (62.5)			
55–66	3 (42.9)	4 (57.1)			
>66	6 (60)	4 (40)			
Frequency of hemodialysis					
Once a week	2 (28.6)	5 (71.4)	0.237		
Twice a week	18 (40.9)	26 (59.1)			
Comorbiditios	12 (60)	8 (40)			
Diabetes	20 (74 1)	7 (25 9)	<0 001*		
No diabetes	12 (27.3)	32 (72.7)	-0.001		
Hypertension	27 (49.1)	28 (50.9)	0.207		
No hypertension	5 (31.3)	11 (68.8)			
Others	2 (40)	3 (60)	0.813		
None	30 (45.5)	36 (54.5)			
Drugs			0 000t		
Calcium channel blockers	25 (61.1)	14 (38.9)	0.006*		
Alpha 1 agonists	10 (20.0)	20 (64 5)	0 153		
No alpha 1 agonists	21 (52 5)	20 (04.3)	0.155		
Potassium channel blockers	6 (54.5)	5 (45.5)	0.492		
No potassium channel blockers	26 (43.3)	34 (56.7)			
Insulin	19 (70.4)	8 (29.6)	0.001*		
No insulin	13 (29.5)	31 (70.5)			
Blood parameters (mean value)			o (		
	8.80	8.50	0.475		
Greatinine	1.59	9.09	0.030		

Table 2: Association between cognitive impairment

\*Significant findings P=0.05. CKD: Chronic kidney disease

in around 2%, and attention in 42.2%.<sup>[16,18,23,24]</sup> Our results which show a significant impairment in executive functioning can be explained by the concept of reno-cerebro-vascular disease and accelerated vascular cognitive impairment in a dialyzed population.<sup>[20]</sup> Majority of participants had lower education status unlike the foreign studies which can be a reason for higher prevalence of language impairment as compared to other studies.

We found a statistically significant prevalence of cognitive impairment to be increased with increasing age group. This has been consistent with other similar studies.<sup>[19,25]</sup> Gesualdo *et al.* and Pei *et al.* found that age and cognitive impairment have a negative correlation.<sup>[5,22]</sup> Age was found to be a strong risk factor for executive functioning decline in a study by Drew *et al.*<sup>[26]</sup>

It was noticed that the years of education and cognitive impairment have a statistically significant association showing that less education status is a risk factor for cognitive impairment. Similar results were found in other studies.<sup>[16,17,21,25,26]</sup> Chen *et al.* found that there are differences in age-related gray matter atrophy between the high and the low education groups in the anterior regions (left medial orbitofrontal superior gyrus and left anterior cingulated and paracingulate) and age-related white matter damage in the forceps major and superior longitudinal fasciculus.<sup>[27]</sup>

We found that the impaired cognition was associated with lower occupation status. There are no similar studies done to assess the association of occupation with cognitive impairment. Participation in cognitive stimulating activities throughout a major part of a person's adult life may contribute to cognitive reserve, and conceal the effects of neurodegeneration on cognitive function at older ages. Furthermore, environmental stimulation may increase the level of neurotrophins in brain tissue, which may protect or repair existing neurons as well as actively promote neurogenesis. This pathway, which is called as differential preservation, may enhance neural reserve that protects against the adverse effects of brain deterioration due to aging, stress, and neurodegenerative disease.<sup>[28]</sup>

Among the participants who had diabetes, the prevalence of cognitive impairment was 74.1%. A significant association was found between the two variables in this study. A similar study done by Reddy and Yadla and Fadili *et al.* found a prevalence of 16.1% and 30.8%, respectively.<sup>[13,17]</sup> The risk factors for cognitive dysfunction in type 2 diabetes patients include glycemic control, hypoglycemia, inflammation, depression, and macro- and microvascular pathology along with aging process.<sup>[29]</sup>

The present study found that cognitive impairment was

significantly associated with the use of insulin therapy and calcium channel blockers. There is a lack of data available studying the association between medications and impaired cognition in hemodialyzed patients currently. Cardiovascular disease has been shown to be associated with impaired cognitive function. Thus, the association between insulin and cognitive function may be the reflection of the "Insulin resistance syndrome."<sup>[30]</sup> Older hypertensive patients taking calcium channel blockers are significantly more likely to experience cognitive decline. This can be probably due to vulnerability to ischemia during periods of reduced cerebral blood flow induced by these agents.<sup>[31]</sup>

There was a significant association between creatinine levels and cognitive functioning. The mean serum creatinine level among those who had impaired cognition was 7.59. Griva et al. in their study found that the mean serum creatinine was 11.15 (SD = 1.47) among cognitively impaired participants. The mean creatinine among participants with cognitive impairment was 10.24 (SD = 2.7) and that among those without cognitive impairment was  $11.15 \text{ (SD} = 2.66).^{[32]}$ Elias et al. found that higher levels of serum creatinine were associated with lower global cognitive performance in CKD patients.<sup>[33]</sup> Our finding was statistically significant; however, this finding was inconsistent with other studies. This can be due to other confounders such as age of the patient, duration of CKD, and duration of receiving hemodialysis. However, future studies may give us better clarification between the association of serum creatinine and cognitive impairment.

#### Limitations

The following were the limitations in our study: (1) Sample was selected using purposive sampling. (2) The cause–effect relationship could not be established. (3) Due to COVID-19 restrictions, we could not complete our targeted sample size and could collect only 71 samples. (4) Our study was restricted only to a tertiary health-care level. (5) The data before and after receiving hemodialysis were not included. Furthermore, comparison with other treatment modalities for ESRD was not considered in our study to get a clearer picture of association of hemodialysis and cognitive impairment.

### CONCLUSION

This study found that the cognitive impairment is common but often remains undiagnosed in dialysis patients. The cognitive functions were significantly affected by age, years of education, occupation, diabetes mellitus, and use of medications such as calcium channel blockers and insulin. Thus, early identification, careful monitoring, and appropriate interventions are required. This will help to prolong independent living, decrease caregiver burden, and reduce number of hospitalizations with improved compliance with medication. Future studies are required to compare cognitive impairments in hemodialysis patients with the quality of life, psychological impact, and overall functioning.

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