

**QAS INSPECTION**  
**PAPERS PUBLISHED BY PG STUDENTS**

<b>2025</b>	
1	Public Awareness and Perceptions of Medicolegal Autopsies in Kerala
2	A cross-sectional study on knowledge, attitude, and level of preparedness of medical interns in a teaching hospital from India on antibiotic use and antimicrobial resistance
<b>2024</b>	
3	Correlation Between Hba1c and Time in Range in Type 2 Diabetes Patients with Normal Hba1c, Attending A Tertiary Care Medical College Hospital in South India
4	Exploring the research landscape: a study of newly enrolled medical postgraduate student's understanding and attitudes toward research
5	Targeting the Gut Microbiome for Atopic Dermatitis: A Comprehensive Review of Mechanisms and Therapeutic Approaches
6	Perinatal Outcome of Twin Pregnancies in Relation to Chronicity at a Tertiary Care Centre in Central Kerala, India: A Prospective Cohort Study
7	Immunoglobulin G4-related Disease: A Series of Four Cases
8	Association between Cord Blood Haematocrit and Neonatal Outcome among Neonates of Diabetic Mothers: A Cohort Study
9	A rare case report on subcutaneous dirofilariasis in Kerala, South India
10	Colloid-crystalloid preloading vs Crystalloid Only preloading: A Randomized Control Trial for Preventing Hypotension After Spinal Anaesthesia
11	Pulmonary Function test and Exercise Capacity in COPD Smokers vs. Healthy Smokers.
12	A study of cardiovascular autonomic functions and vo max in 2 young offsprings of type 2 diabetic parents
13	Knowledge Gaps in the Treatment of Atopic Dermatitis
14	Beyond the Surface: Exploring the Mind-Skin Dynamics of Psychodermatology
15	Comparative Analysis of Phenylephrine Infusion, Bolus Usage, and Atropine Administration in Colloid vs. crystalloid Preloaded Groups in preventing hypotension after Spinal Anaesthesia: A randomized controlled trial
16	To Study the Clinical Factors Predicting the Presence of Esophageal Varices in CLD patients Admitted to A Tertiary Care Medical College Hospital in South India



<b>2023</b>	
17	Safety and efficacy of the trans obturator tape for stress urinary incontinence
18	Incidence of Nocturnal Hypoglycaemia in Type II Diabetes Patients with Normal Hba1c, Attending A Tertiary Care Medical College Hospital in South India
19	Non-invasive assessment of volume status of children with edema due to steroid sensitive nephrotic syndrome using urinary indices and inferior venacava ultrasonography
20	A Comparative Study of Duration of Analgesia with Ropivacaine Against Ropivacaine Plus Dexmedetomidine given by Subarachnoid Block in Patients who undergo Total Abdominal Hysterectomy.
21	Breast Arterial Calcification in Screening Mammograms and its Correlation with Carotid Intima Media Thickness: A Cross-sectional Study
22	Correlation between Myo steatosis and Liver Fibrosis among Patients with Non-Alcoholic Fatty Liver Disease: A Cross-sectional Study
23	Fasting and post prandial functioning of the kidney measured by serum creatinine and creatinine clearance data distribution in healthy individuals above forty years
24	A Comparative Study of Blood Loss Estimation in Normal Delivery by Visual Estimation Vs Gravimetric Method
25	Use of Mean Platelet Volume as a Predictor of Bleeding Risk in Thrombocytopenia
<b>2022</b>	
26	The Role of Health Education on Larval Indices and Fever Cases from Rural Area of Thrissur District, Kerala: A Quasi Randomized Control Study.
27	The role of D-NLR, RDW and PLR in predicting clinical severity in covid 19 infection: a single-centre, retrospective observational study in a tertiary care medical hospital in central Kerala
28	Patterns of late gadolinium enhancement in injured myocardial tissue – A descriptive single centre study
29	Reference Interval, Biological Variations and Distribution of Creatinine Level in Fasting Urine: A Cross-sectional Study
30	Effect of Second-hand smoke exposure on Pulmonary Function Test and predictors of abnormal PFT in children attending a tertiary care centre in a semiurban area in South India



**QAS INSPECTION**  
**PAPERS PUBLISHED BY UG STUDENTS**

<b>2024</b>	
1	Correlation Between Hba1c and Time in Range in Type 2 Diabetes Patients with Normal Hba1c, Attending A Tertiary Care Medical College Hospital in South India
2	A Study of Intussusception in Children Admitted in A Medical College Hospital in Central Kerala



AIMS PUBLICATION REPORT 2022-2025 (16/12/2025)

	No. of Scopus indexed articles	No. of Peer-reviewed articles	Total
2025	42	9	51
2024	25	50	75
2023	18	43	61
2022	20	37	57
Total	105	139	244

Betsy



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PAPERS PUBLISHED IN 2025

1	Electrochemical oxidation and biological degradation of azo dyes: Mechanistic insights and efficacy in contaminant removal from industrial effluents
2	Response surface methodology in postharvest and food technology research: A bibliometric assessment
3	A critical review on innovative targets for signal disruption in <i>Enterococcus faecalis</i> infection management
4	<i>Enterobacter hormaechei</i> mediated biodegradation of PET: a sustainable approach to plastic waste
5	Global Research Trends on Nano plastics in Food: A Bibliometric Analysis of Human Health Concerns
6	Carbon dots as nano-pioneers: A critical review on advances in fabrication and antibacterial mechanism
7	The Impact of Antibiofilm Strategies in Controlling Microbial Colonization
8	Attitude of first-year undergraduate medical students towards the medical profession: a cross-sectional study at the start of the orientation program
9	Impact of Gut Microbiota and Probiotics on Rheumatoid Arthritis: A Potential Treatment Challenge
10	Microbiota–gut–brain axis and probiotics: potential therapeutic strategies for treating Alzheimer’s disease
11	<i>Morchella esculenta</i> polysaccharides: a functional food with potential immunomodulatory properties
12	Analysis of Carbapenemase and Extended-spectrum Beta-lactamases-producing Cephalosporin-resistant Strain of <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i> among Children in a Tertiary Care Centre, South India
13	Effectiveness of stand-alone anti-adult mosquito control strategies against Aedes-borne diseases: scoping review with meta-analysis
14	“Differentiated care is not a matter of feasibility but a necessity”- service providers’ perception on initiating a comprehensive tuberculosis care package (CCp-K) to reduce deaths in Kerala, India
15	Work Ability Index and its Correlates among Police Officers in a District of South Kerala
16	Facilitators for establishing a home-based medicine reverse logistic system in low- and middle-income countries – a scoping review
17	Investigation of an outbreak in a resource limited setting - <i>Burkholderia cepacia</i> blood stream infection in an oncology unit
18	A Cohort Study on the Early De-Escalation of Empirical Meropenem in Febrile Neutropenia with a High Prevalence of MDR Infections



19	Addressing practical challenges with bispecific antibody therapy in multiple myeloma
20	Prevalence of recurrent urinary tract infections and its associated factors in female staff of reproductive age group in a medical college in central Kerala: a cross-sectional study
21	Modelling the Corrosion Inhibition Efficiency of Garcinia Cambogia Extract on Mild Steel in Acid Media Using ANN and RSM Approaches
22	Sinonasal Small Cell Neuroendocrine Carcinoma Invading to Skull Base in a Young Female
23	Validation of Peripheral Perfusion Index as a non-invasive Screening Tool in Predicting Adverse Neonatal Outcome
24	Molecular and genomic characterization of <i>Leptospira</i> isolates in humans and its relation to disease severity
25	Central Nervous System Manifestations of Graft-Versus-Host Disease
26	Comparative Accuracy of Critical Care Pain Observation Tool (CPOT), Behavioural Pain Scale (BPS), and Non-verbal Pain Scale (NVPS) for Pain Assessment in Mechanically Ventilated Intensive Care Unit Patients: A Prospective Observational Study
27	Managing Professional Stress is Every Doctor's Business
28	Rare Neuromelioidosis Case that Required Long Intensive Phase Therapy
29	Nasal Methicillin Resistant <i>Staphylococcus Aureus</i> Colonisation and the Incidence of Invasive Staphylococcal Infection in Patients Undergoing Haemodialysis
30	Rheumatic manifestations of HIV/AIDS
31	Prospective evaluation of small bowel dose and acute gastrointestinal toxicity during pelvic radiotherapy for gynaecologic malignancies
32	Kidney Injury Molecule-1 as a Urinary Biomarker for Aminoglycoside Induced Acute Kidney Injury, among Non-Critically Ill Children: Authors' Reply
33	<i>Vermamoeba vermiformis</i> causing primary amoebic meningoencephalitis – A diagnostic challenge
34	Trichodaganomania: A Curious Habit
35	The Varying Faces of MOGAD: A Case Series
36	A case series of proximal femur tumour excisions done through a medial approach
37	Immunomodulatory and anti cytokine therapeutic potential of three Indian spices constituents and its hyaluronic acid conjugates for prevention and post COVID-19 complications: a computational modelling approach
38	Melioidosis, the great masquerade: From lung to joints: A case report
39	Epidemiological, and management challenges in tuberculosis with chronic kidney disease



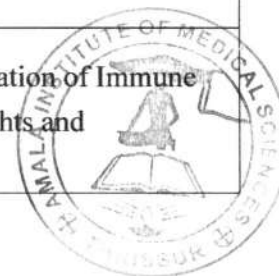
40	Repurposing Nano-Dimensions of a Small Phyto molecule, Rhein, Into Nano-Rhein to Unveil Its Efficacy on Hypercalciuria-Induced Nephropathies on a SERS-Based Calcification Profiling Platform
41	Unveiling the potential of lichen compounds hyaluronic acid conjugates for cervical cancer treatment: a comprehensive in silico analysis
42	A comparative observational study on the effect of two different doses of fentanyl on the effect site concentration of propofol during induction of anaesthesia using clinical assessment score and bispectral index
43	Public Awareness and Perceptions of Medicolegal Autopsies in Kerala
44	A cross-sectional study on knowledge, attitude, and level of preparedness of medical interns in a teaching hospital from India on antibiotic use and antimicrobial resistance
45	Markers of Inflammation and Bone Turnover in Type 2 Diabetic Patients at Risk of Charcot Arthropathy
46	Clinical and serological profiles of 802 Allergic Broncho Pulmonary Aspergillosis (ABPA) patients across 23 centres in India
47	HRCT and Chest X-ray findings in 802 Allergic Broncho Pulmonary Aspergillosis (ABPA) patients across 23 centres in India
48	DeSTILD: Development of a Screening Tool for Interstitial Lung Disease
49	Targeting the Tumor Microenvironment in Lung Cancer with a Focus on Immune Evasion, Hypoxia, and Treatment Resistance
50	When the Skin Speaks: Dermatological Clues in Multiple Myeloma
51	Role of C-reactive Protein, D-dimer, and Ferritin in Predicting the Clinical Outcomes of COVID-19 Patients: A Retrospective Study

#### PAPERS PUBLISHED IN 2024

Sl. No.	Title of the article
52	A Recent Update on the Role of Estrogen and Progesterone in Alzheimer's Disease



53	What our children lost and gained at the time of school closure during the Covid-19 pandemic: a study on psychological distress, behavioural concerns and protective factors of resilience among preschool children in Kerala, India
54	Utilizing nerve conduction studies to identify very early Guillain–Barré syndrome and distinguish it from mimics in emergency settings
55	Impact of the COVID-19 pandemic on treatment of patients with acute myeloid leukaemia in India
56	The effectiveness of synchronous online clinics and conventional clinics among medical students: Assessing the influence of e-learning
57	Bioactive extract of <i>Morchella esculenta</i> ameliorates cyclophosphamide-induced mitochondrial dysfunction and cardiotoxicity by modulating KEAP1/NRF2 and pro-inflammatory genes expression
58	Current Status on Management of Primary Plasma Cell Leukaemia
59	Factors Influencing the Well-being of Nurses in Selected Oncology Departments of Tertiary Hospitals in Kerala, India: A Qualitative Study
60	Novel drug delivery materials: Chitosan polymers conjugated with <i>Spondias pinnata</i> phytochemicals for enhanced anti-microbial and anti-cancer properties
61	Kidney Injury Molecule-1 as a Urinary Biomarker for Aminoglycoside Induced Acute Kidney Injury, among Non-Critically Ill Children
62	Adolescent and Young Adults with Gastric Cancer (AYA-GC)-The Dilemma of an Under-Represented Group: A Multi-Institutional Analysis from the Indian Subcontinent
63	Real-World Data on Treatment Outcome of ALK-Positive Non-Small Cell Lung Cancer from an Indian Multicentric Cancer Registry
64	Foramen Magnum – A Study on Its Morphometry Among the South Indian Population
65	A Multicentre Study on the Challenges and Real-World Utilization of Immune Checkpoint Inhibitors in Resource-Constrained Settings: Insights and Implications from India



66	Hepatoprotective effect of <i>Ganoderma lucidum</i> (Curt.:Fr.) P. Karst
67	Comparative Study of Endonasal Endoscopic Dacryocystorhinostomy with or without Preservation of Nasal Mucosal Flap
68	Natural evolution of idiopathic carpal tunnel syndrome with respect to wrist and hand anthropometry: A prospective cohort study
69	Can Lichen Planus be a Forerunner of Paraneoplastic Pemphigus?
70	Prevalence and Antibigram of <i>Escherichia coli</i> Isolated from Children Under Five Years of Age Presented with Acute Diarrhoea: Cross Sectional Study from a Tertiary Care Centre in South India
71	Impact of International Medical Graduates on the UK Healthcare System: Current Contributions and Future Challenges
72	Molecular Characteristics of Cephalosporin Resistant <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i> Isolated from Children in a Tertiary Care Centre of Central Kerala, India
73	Outcome of early emergency intubation and early emergency dialysis in deliberate self-harm with formic acid in a tertiary care center in South India: A retrospective cohort study
74	Real-World Experiences of Next-Generation Sequencing in Oncology: From an Indian Multicenter Registry and Collaborative Centers
75	Profile of Childhood Cancers from Hospital-Based Cancer Registries in India, 2012–19
76	Clinicopathologic Profile and Treatment Outcomes of Colorectal Cancer in Young Adults: A Multicentre Study from India
77	Perinatal Outcome of Twin Pregnancies in Relation to Chronicity at a Tertiary Care Centre in Central Kerala, India: A Prospective Cohort Study
78	Anatomy of original research article and reporting checklists
79	A Study of Intussusception in Children Admitted in A Medical College Hospital In Central Kerala



80	A multicentre Study on the Challenges and Real-World Utilization of Immune Checkpoint Inhibitors in Resource-Constrained Settings: Insights and Implications from India
81	Quadratus lumborum block versus transversus abdominis plane block for post-operative analgesia in lower abdominal surgeries
82	Title, abstract, keywords, and authorship criteria
83	Knowledge, attitude, practices, and perceived barriers towards research among undergraduate medical students in a teaching hospital: a cross-sectional study
84	Pulmonary Function test and Exercise Capacity in COPD Smokers vs. Healthy Smokers.
85	Colonoscopy Participation Rate and its Determinants among First-Degree Relatives of Colorectal Cancer Patients: A Cross-sectional Study
86	How to write an introduction and literature review for your research?
87	Youngest Encounter with Gorlin–Goltz Syndrome: Navigating Early Diagnosis and Management
88	A rare case report on subcutaneous dirofilariasis in Kerala, South India
89	A study of cardiovascular autonomic functions and vo max in 2 young offsprings of type 2 diabetic parents
90	Adolescent and Young Adults with Gastric Cancer (AYA GC) The Dilemma of an Under -Represented Group: A Multi-Institutional Analysis from the Indian Subcontinent
91	5-year analysis of methicillin resistant, vancomycin intermediate and vancomycin resistant staphylococcus aureus- from a tertiary care hospital in northern India
92	Incidence of Clostridium difficile in Patients with Antibiotic Associated Diarrhoea
93	Myriad findings of multisystem radiological-manifestations in a case of Erdheim–Chester disease



94	Complications of laser in situ keratomileusis (LASIK)
95	Curated article summaries- outcomes and clinical features predictive of fungal endophthalmitis & risk of renal damage associated with intravitreal anti-vegf therapy for diabetic macular edema in routine clinical practice
96	From practice to publication: Let the wheels turn
97	Real-World Experiences of Next-Generation Sequencing in Oncology: From an Indian Multicentre Registry and Collaborative Centres
98	Laboratory Diagnosis of Herpes Simplex Virus in Mucocutaneous Lesions by Light Microscopy, ELISA and PCR: A Cross-sectional Study from a Tertiary Care Hospital
99	Difficult Terrains of Research Publications Faced by Researchers: A Cross-Sectional Study
100	Effect of apremilast on cardiovascular risk in psoriasis patients in comparison with methotrexate
101	Beyond skincare routines: Follow your gut to healthy skin – A review of the interplay between gut microbiome and skin
102	Study on Screen Time and its Association with Behaviour in Children of Age Group 8-15 Years
103	Correlation Between HbA1c and Time in Range in Type 2 Diabetes Patients with Normal HbA1c, Attending A Tertiary Care Medical College Hospital in South India
104	Association between Cord Blood Haematocrit and Neonatal Outcome among Neonates of Diabetic Mothers: A Cohort Study
105	An Unusual Presentation of a Bleeding Vallecular Cyst in a Newborn
106	Predictive factors for hypocalcaemia in post-thyroidectomy patients: A prospective cohort study
107	To Study the Clinical Factors Predicting the Presence of Oesophageal Varices In CLD patients Admitted To A Tertiary Care Medical College Hospital In South India



108	Exploring the research landscape: a study of newly enrolled medical postgraduate student's understanding and attitudes toward research
109	Immunoglobulin G4-related Disease: A Series of Four Cases
110	Clinical Presentations of Melioidosis and Antibiogram of Burkholderia pseudomallei: An 8-year Study in a Tertiary Care Centre, South India
111	Nanobots in Cancer Treatment – Framing Lung Cancer
112	Role of Arterial Lactate and Lactate Clearance in Risk Stratification of Patients with Upper Gastrointestinal Bleeding Presenting to the Emergency Department for use at Primary Health Care Level
113	Targeting the Gut Microbiome for Atopic Dermatitis: A Comprehensive Review of Mechanisms and Therapeutic Approaches
114	Breeding preferences of Aedes mosquitoes during monsoon in a Gram Panchayat of Thrissur district, Kerala-India
115	Live continuing medical education programs in the era of virtual learning: Strategies for success
116	Colloid-crystalloid preloading vs Crystalloid Only preloading: A Randomized Control Trial for Preventing Hypotension After Spinal Anaesthesia
117	Knowledge Gaps in the Treatment of Atopic Dermatitis
118	Beyond the Surface: Exploring the Mind-Skin Dynamics of Psychodermatology
119	Impact of covid-19 on heart rate variability and pulmonary function tests parameters among patients with chronic lung diseases - a cross-sectional study
120	Revolutionizing oral cancer screening: unleashing the synergy of liquid-based cytology, the bethesda system, and cell block innovation with hpv detection
121	Comparative Analysis of Phenylephrine Infusion, Bolus Usage, and Atropine Administration in Colloid vs. crystalloid Preloaded Groups in preventing hypotension after Spinal Anaesthesia: A randomized controlled trial
122	Sex Differences in Mortality Rate Among Chronic Obstructive Pulmonary Disease Patients with Covid - 19 In South Indian Population



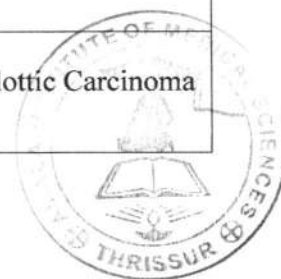
123	Incidence, Antibiogram, and Comorbid Conditions of Nontyphoidal Salmonella Infections Before and After the COVID-19 Outbreak: A Retrospective, Cross-sectional Study
124	Free-living amoebic encephalitis – Case series
125	The “Brave New World” of biosimilars: Look before you leap!
126	Comparison of Demographic, Lifestyle, and Anthropometric Characteristics between COPD Smokers and Healthy Smokers

#### PAPERS PUBLISHED IN 2023

Sl. No.	Title of the article
127	Adherence of Candida Species Isolated from Patients with Head and Neck Cancer Presented for Radiation Therapy and its Correlation with Hemogram
128	Feasibility study of total marrow lymphoid irradiation with volumetric modulated arc therapy: clinical implementation in a tertiary care centre
129	Chronic exposure of industrial grade calcium carbide and ethylene glycol exert genotoxic effect in Wistar albino rats
130	Complementary administration of curcumin in PCOS: a systematic review
131	Patient-reported Outcome of Mild Coronavirus Disease 2019 Infection in Patients diagnosed from a Tertiary Care Centre in Kerala: A 1-year Follow-up Study
132	Impact of COVID-19 on Rheumatic Diseases in India: Determinants of Mortality and Adverse Outcome: A Retrospective, Cross-Sectional Cohort Study
133	Authors’ reply
134	A Rare Surgical Cause of Chronic Diarrhoea and Malabsorption
135	Dermatologic care of the lesbian, gay, bisexual and transgender community of India



136	Radiotherapy for successful symptom control in recurrent refractory endometriosis: A case report
137	Triorchidism: A Differential Diagnosis of Inguinal Swelling in a 28-Year-Old Male
138	Comparison of two ultrasound-guided techniques for radial arterial cannulation in adults - Observational cross-sectional study
139	Comparison of hand hygiene compliance among healthcare workers in Intensive care units and wards of COVID-19: A large scale multicentric study in India
140	Development and Growth of the Spine and Lungs
141	ROS1-positive lung cancer: Facts to be remembered
142	Granulomatous infection of parotid gland and its subcutaneous tissue by Mycobacterium abscessus subspecies massiliense in a 3-year-old child
143	Tuberculosis and childhood cancer – A review of literature
144	Anticancer Activity of the Bioactive Extract of the Morel Mushroom ( <i>Morchella elata</i> , Ascomycetes) from Kashmir Himalaya (India) and Identification of Major Bioactive Compounds
145	Genomic analysis unveils genome degradation events and gene flux in the emergence and persistence of <i>S. Para typhi A</i> lineages
146	Papulopustular periorbital demodicosis: A diagnosis often overlooked
147	Fasting plasma adiponectin levels in young non diabetic individuals with and without family history of diabetes mellitus
148	Methicillin resistant staphylococcus aureus in various clinical specimens- prevalence and antibiogram from a multi-speciality hospital in punjab
149	Prevalence and Factors Associated with Medication Nonadherence in Patients with Major Psychiatric Disorders in Southern India
150	Invasive Aspergillosis and Candidiasis in a Patient with Supraglottic Carcinoma undergoing Chemoradiotherapy: A Case Report



151	A Comparative Study of Blood Loss Estimation in Normal Delivery by Visual Estimation Vs Gravimetric Method
152	onsite virtual classroom for undergraduate medical education
153	Prevalence and major contributing factors predicting the 10-year risk for cardiovascular disease in post-menopausal women based on the Framingham Risk Score
154	A Comparative Study of Conventional Cold Dissection and Coblation Method of Tonsillectomy
155	COVID-19 among health-care providers during the first and second wave of infection in India: A systematic review
156	Non-invasive assessment of volume status of children with edema due to steroid sensitive nephrotic syndrome using urinary indices and inferior venacava ultrasonography
157	Fasting and post prandial functioning of the kidney measured by serum creatinine and creatinine clearance data distribution in healthy individuals above forty years
158	Red Cell Parameters and their Correlation with Level of Glycaemic Control among Patients Undergoing Treatment for Diabetes at a Tertiary Care Centre
159	Use of Mean Platelet Volume as a Predictor of Bleeding Risk in Thrombocytopenia
160	Proportion of Sarcopenia in Cirrhotic Patients of Age More than 18 Years Admitted with Complications at a Tertiary Care Centre in Thrissur District
161	A Study to Assess the Proportion of Hypocortisolaemia among Patients Admitted in Medical Intensive Care Unit in a Tertiary Care Hospital in Central Kerala
162	Menstrual practices, fertility intentions and decision-making regarding family planning by women belonging to various indigenous groups of Wayanad- A qualitative study
163	A study on the prevalence of nomophobia and its associated factors among the medical students of a medical college in central Kerala
164	Prevalence of depression in persons with schizophrenia – a cross-sectional study from a tertiary psychiatric hospital



165	Comparison of ondansetron and metoclopramide in the prevention of postoperative nausea and vomiting in general anaesthesia – a prospective cohort study
166	A Study on Prevalence of Post- Covid Symptoms and Impact of Vaccination among patients attending a tertiary care centre in Kerala.
167	Relationship of fasting plasma adiponectin with fasting plasma insulin in young non diabetic individuals
168	Analysis of various airway evaluation tests to prognosticate difficult endotracheal intubation
169	A Study on Sexual and Reproductive Health Communication Between Adolescents and Parents Among High School Students in Thrissur District, Kerala
170	Incidence of Nocturnal Hypoglycaemia in Type II Diabetes Patients with Normal HbA1c, Attending A Tertiary Care Medical College Hospital in South India
171	Antibacterial Activity of Silver, Gold and Amoxicillin Silver Nanoparticles against Methicillin Resistant Staphylococcus aureus - an invitro Study
172	Peritumoral and Intratumoral Distribution of Langerhans Cell in Oral Squamous Cell Carcinoma and its Association with Known Prognostic Factors
173	Comparison Between Two Different Doses of Intravenous Ketamine for Prevention of Post Operative Shivering in Patients Undergoing Surgeries Under Subarachnoid Block
174	COVID-Somnia: A Multicentric Study on Sleep Disturbances During the COVID-19 Pandemic with Spatial Mapping of Hotspots
175	Trend of mosquito larval indices over a year in a rural area of Thrissur district, Kerala
176	Occupational Hazards Under a Warmer Planet: A Cross-Sectional Study on Occupational Dermatitis, Musculoskeletal Disorders, and Heat Strain Score Index among Construction Workers at Kottayam, Kerala
177	A Comparative Study of Duration of Analgesia with Ropivacaine Against Ropivacaine Plus Dexmedetomidine given by Subarachnoid Block in Patients who undergo Total Abdominal Hysterectomy.
178	Mechanisms of Azole Resistance in Candida- A Narrative Review



179	Correlation between Myosteatorsis and Liver Fibrosis among Patients with Non-Alcoholic Fatty Liver Disease: A Cross-sectional Study
180	Campylobacter Infection Associated Intestinal Perforation: A Case Report
181	Safety and efficacy of the trans obturator tape for stress urinary incontinence
182	A Study on Subsite-specific Prevalence of Candidiasis in Head and Neck Cancer Patients and its Antifungal Susceptibility Pattern: A Cross-sectional Study
183	Prevalence of stress, anxiety, depression and its associated factors among undergraduate medical students of Thrissur district during COVID-19 pandemic: a cross-sectional study
184	Breast Arterial Calcification in Screening Mammograms and its Correlation with Carotid Intima Media Thickness: A Cross-sectional Study
185	Extracellular Enzymatic Activity of Candida Species Isolated from Patients with Head and Neck Cancer Undergoing Radiation Therapy and its Correlation with Mucositis: A Cross-sectional Study
186	Pulmonary Morbidity of Workers and Local Residents of a Spinning Mill in Kerala: A Comparative Study
187	A Rare Case of Isolated Hindgut Malrotation with Internal Hernia and Coexisting Enteric Duplication Cyst

#### PAPERS PUBLISHED IN 2022

188	Fine Governance of Difficult Tracheostomy in Difficult Airway with Stridor and Respiratory Distress
189	Formative acceptance of ingestible biosensors to measure adherence to TB medications
190	Patient age and donor HLA matching can stratify allogeneic hematopoietic cell transplantation patients into prognostic groups
191	Commentary: Correlation analysis of serum vitamin D levels and post-operative cognitive disorder in elderly patients with gastrointestinal tumor
192	Relationship of irradiated bone marrow volume and neutropenia in patients undergoing concurrent chemoradiation therapy for cervical cancer



193	Intrauterine onset of multisystem inflammatory syndrome in a neonate temporally associated with maternal COVID-19
194	Left or right is right? Ectopic gallbladder
195	COVID-19 vaccine hesitancy among medical students: A systematic review
196	Marked New Bone Formation on Treatment of Multiple Myeloma
197	Chronic exposure of industrial grade calcium carbide and ethylene glycol alter histological architecture of systemic organs by disrupting redox balance in rat
198	Bacteriological and antibiotic profile of infection among infants in the post-neonatal period at a tertiary care hospital in South India
199	Association of proton-pump inhibitor use with adverse health outcomes: A systematic umbrella review of meta-analyses of cohort studies and randomised controlled trials
200	Scrotal Centesis: Due to Anasarca in an End-stage Pancreatic Cancer Patient
201	Efficiency of 90-Min Extended EMLA-Induced Stimulated Skin-Wrinkling Test in the Diagnosis of Carpal Tunnel Syndrome
202	Sleep disorders in elderly population suffering from TB and respiratory diseases
203	Cerebroplacental ratio as a predictor of perinatal outcomes in intrauterine growth restriction
204	Effectiveness of cervical encerclage and its perinatal outcome-A cohort study
205	No Family Should Suffer from Cervical Cancer Twice--The Palliative Care Role in HPV Prevention
206	Outcomes of community acquired pneumonia in a tertiary hospital
207	Morel mushroom, Morchella from Kashmir Himalaya: a potential source of therapeutically useful bioactive that possess free radical scavenging, anti-inflammatory, and arthritic edema-inhibiting activities
208	Wet museum enhances the teaching and learning ability of gross & clinical anatomy
209	A study to compare thyroid profile between premenopausal and postmenopausal women
210	Vitamin D Status and its Correlation with Disease Severity among Patients Presented with Major Depressive Disorders in a Tertiary Health Care Hospital in South India
211	Reference Interval, Biological Variations and Distribution of Creatinine Level in Fasting Urine: A Cross-sectional Study
212	Immune-enhancing agents in autoimmune skin diseases – A review
213	Assessment of effectiveness of fetal medicine foundation calculator in predicting risk for preterm preeclampsia using first trimester mean uterine artery pulsatility index and maternal factors in Indian population



214	No-touch management in tick infestation of periocular skin
215	Bioactive extract of mycelia biomass of <i>Ganoderma lucidum</i> protects doxorubicin induced cardiomyopathy
216	Unusual Sites of Rcc Metastasis-Case Series
217	Atypical presentation of multiple sclerosis – A few points to ponder
218	Role of serum uromodulin estimation to assess functioning renal cell mass in early stages of diabetic kidney disease and chronic kidney disease stage 3-5
219	Surgical site infection in obg - pre and post covid -19 pandemic a comparative study
220	Anti synthetase Syndrome: A Rare Cause of Rapidly Progressive Interstitial Lung Disease Increasingly Common in Post-COVID Era
221	Fungal sternal wound infection following coronary artery bypass graft surgery – A rare case of surgical site infection
222	Patterns of Medication Use and Their Determinants in Pregnancy among Women Admitted to the Obstetrics Wards of a Tertiary Care Hospital: A Cross-Sectional Study: Patterns of Medication Use and Their Determinants in Pregnancy
223	Association of socio-demographic profile with types of tuberculosis among patients attending a rural DOTS centre in central Kerala, South India
224	Diagnostic utility of cancer ratio in differentiating malignant from non-malignant pleural effusions in a tertiary care centre in central Kerala
225	A study of the hearing status in the contralateral healthy ear of patients with chronic otitis media following mastoidectomy surgery in a tertiary care hospital, Kerala, India
226	A Study on Mosquito Density and Trend of Larval Indices from a Hospital Campus of Rural Area, Thrissur District Kerala.
227	Analysis of Internal Controls in the matrix of HCV RT-PCR assays showed analytical and pre-analytical influences independent of template concentrations
228	Delta variant SARS-CoV-2 infections in paediatric cases during the second wave in India
229	Changes in anatomy education - an overview of the impact of social media on modern medical education
230	Barriers and facilitators of noncommunicable disease (NCD) prevention in Kerala: A qualitative study
231	The Role of Health Education on Larval Indices and Fever Cases from Rural Area of Thrissur District, Kerala: A Quasi Randomized Control Study.
232	Correlation between red cell distribution width (RDW), and other clinical parameters in a cohort of COPD patients
233	A study to assess the Aedes mosquito diversity and the different mosquito genera in a rural area in Thrissur, Kerala



234	Assessment of weaning outcome in chronic obstructive pulmonary disease patients on mechanical ventilation in a tertiary care centre
235	A study on the diagnostic value of Epworth sleep scale in left ventricular failure patients with obstructive sleep apnoea as compared to polysomnogram
236	Patterns of late gadolinium enhancement in injured myocardial tissue – A descriptive single centre study
237	Breastfeeding Promotion by Breastfeeding Promotion Group, Kerala University of Health Sciences, Kerala, India
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243	Progression patterns of normal-tension glaucoma groups classified by hierarchical cluster analysis
244	An analysis of genetic mutations in lung adenocarcinoma and their relationships to demographic patterns and histopathological features.

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## Letter of Acceptance

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Dear Author(s),

Suhail P, Abhishek V, Ajay Mohan, Rahba Madhathodiyil, Amal Joseph, A P Lakshmi, Edwin J George, \*Merly MV

\*Corresponding Author: Dr. Merly MV

Title: *A STUDY TO ASSESS THE RELATIONSHIP BETWEEN CARDIAC DYSAUTONOMIA AND GLYCEMIC CONTROL IN PATIENTS ATTENDING A TERTIARY CARE MEDICAL COLLEGE HOSPITAL IN SOUTH INDIA*

I would like to inform you that the 1<sup>st</sup> round evaluation of your manuscript has been completed. Based on the reviewer's recommendations, I am delighted to inform you that your manuscript has been initially accepted. The article as well as has been processed utilizing the peer-review process, and has been **accepted for publication**. The article will be published in **Volume 14 Issue 5 (May) 2025** of International Journal of Life Sciences Biotechnology and Pharma Research (IJLBPR). Thank you very much for submitting your article to "International Journal of Life Sciences Biotechnology and Pharma Research"

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# The Clinical and Metabolic Derangements after Using 0.9% Normal Saline as Maintenance Intravenous Fluid in Children

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## Abstract

**Background:** Isotonic fluids like 0.9% normal saline (NS) are recommended for maintenance intravenous fluid (mIVF) therapy in children. However, concerns exist regarding hyperchloremia and its associated complications, particularly in younger children. **Objective:** The objective of the study was to evaluate the clinical and metabolic effects of 0.9% NS as mIVF in noncritically ill pediatric patients. **Materials and Methods:** This longitudinal study included 80 children aged 1 month to 13 years admitted to a tertiary care center, who received 0.9% NS as mIVF for at least 50% of a 24-h period. Baseline and 48-h clinical and biochemical parameters were recorded and compared. **Results:** After 48 h, there was a significant decrease in heart rate, respiratory rate, blood urea, and serum creatinine, and a significant increase in blood pressure, serum sodium, potassium, and chloride ( $P < 0.05$ ). Hyperchloremia was observed in 7.5% of children, all aged  $< 5$  years. **Conclusion:** 0.9% NS may lead to significant clinical and metabolic changes, particularly hyperchloremia in younger children.

**Keywords:** Children, intravenous fluid therapy, isotonic solution, metabolic changes

## Résumé

**Contexte:** Les solutions isotoniques comme le sérum physiologique à 0,9 % (NS) sont recommandées pour la thérapie liquidienne intraveineuse d'entretien (mIVF) chez les enfants. Cependant, des préoccupations subsistent concernant l'hyperchlorémie et ses complications associées, en particulier chez les jeunes enfants. **Objectif:** L'objectif de cette étude était d'évaluer les effets cliniques et métaboliques du sérum physiologique à 0,9 % utilisé comme perfusion intraveineuse d'entretien (mIVF) chez des patients pédiatriques non critiques. **Matériels et Méthodes:** Cette étude longitudinale a inclus 80 enfants âgés de 1 mois à 13 ans admis dans un centre de soins tertiaires, ayant reçu du sérum physiologique à 0,9 % comme mIVF pendant au moins 50 % d'une période de 24 heures. Les paramètres cliniques et biochimiques de base et à 48 heures ont été enregistrés et comparés. **Résultats:** Après 48 heures, on a observé une diminution significative de la fréquence cardiaque, de la fréquence respiratoire, de l'urée sanguine et de la créatinine sérique, ainsi qu'une augmentation significative de la pression artérielle, du sodium, du potassium et du chlore sériques ( $P < 0,05$ ). Une hyperchlorémie a été observée chez 7,5 % des enfants, tous âgés de moins de 5 ans. **Conclusion:** Le sérum physiologique à 0,9 % peut entraîner des modifications cliniques et métaboliques significatives, notamment une hyperchlorémie chez les jeunes enfants.

**Mots-clés:** Enfants, thérapie par perfusion intraveineuse, solution isotonique, modifications métaboliques

## INTRODUCTION

Hypotonic solutions were widely accepted as the maintenance intravenous fluid (mIVF) of choice during the last 50 years, until more recent evidence demonstrated a clear association between the use of hypotonic fluids and iatrogenic hyponatremia-related morbidity and mortality.<sup>[1-4]</sup> Consequently, isotonic solutions are now recommended by a number of practice guidelines

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as a safer and more appropriate empiric mIVF of choice in children.<sup>[5-13]</sup>

Although hospital acquired hyponatremia may be reduced by isotonic fluids,<sup>[14,15]</sup> there is a growing concern about iatrogenic hyperchloremia. There is emerging evidence in both adult and pediatric populations that hyperchloremia is increasingly common following use of isotonic solutions as mIVF and may be associated with adverse outcomes. Hyperchloremia has been reportedly associated with acute kidney injury, coagulopathy, gastrointestinal dysfunction, and even increased mortality in critically ill adults and children.<sup>[16-20]</sup> There is a scarcity of literature that has looked into this issue, especially in young children. Literature regarding the addition of maintenance potassium chloride to the intravenous infusion of 0.9% normal saline (NS) is also scarce. In this study, our objective was to determine the clinical and metabolic derangements after using 0.9% NS as an isotonic mIVF in pediatric patients.

## MATERIALS AND METHODS

This longitudinal study was undertaken at a semi-urban tertiary care hospital for a period of 18 months. The study was approved by the institutional ethics committee, and informed consent from parents was taken before enrollment. Consecutive noncritically ill children between age groups 1 month to 13 years admitted to the pediatric ward whose treatment necessitated the use of 0.9% NS as mIVF and who had at least 50% of their calculated maintenance fluid for 24 h as IVF, were include in the study. The total amount of total daily fluid (oral + intravenous) administered was based on Holliday Segar formula, based on body weight.

Exclusion criteria were children with acute diarrheal disease with dehydration, nephrotic syndrome, on various drugs such as furosemide, hydrochlorothiazide, vasopressin or desmopressin, congestive cardiac failure, diabetes mellitus, acute or chronic liver failure, abnormal baseline serum sodium or metabolic acidosis (as per standard lab values), and those children whose treatment necessitated a shift to Pediatric Intensive Care Unit (PICU). The study used to calculate sample size was Malviya *et al.*<sup>[21]</sup> Assuming a power of 80% and 5% significance level, the sample size was calculated as 80. To allow for a potential recruitment failure rate, 560 children were assessed for eligibility for enrollment in the study. A pro forma containing socio-demographic variables, relevant history, and examination findings was filled. Baseline clinical variables like blood pressure (BP), heart rate (HR), and respiratory rate (RR) were noted, and blood was collected for metabolic variables such as serum sodium, potassium, chloride, blood urea, serum creatinine, and venous blood gas (VBG). Serum electrolytes were analyzed with direct potentiometry and VBG by blood gas analyzer. Children received 0.9% NS with potassium chloride (KCL) at the standard infusion rate for weight (20 meq of potassium/L). Repeat blood samples were taken 48 h after the intravenous infusion. Baseline BP, HR, RR, serum sodium, chloride and bicarbonate, blood urea, creatinine, pH,

and lactate levels and changes in these variables 48 h after starting mIVF were documented. Standard normal lab values and those for hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypochloremia, hyperchloremia, acidosis, and alkalosis were defined. The range for each parameter was calculated as between  $\pm 2$  standard deviation (SD) from the mean baseline value. The value which fell beyond this range at 48 h after mIVF was considered abnormal.

The anonymity of the patient was maintained, privacy was ensured, and confidentiality of data was assured. An informed written consent, in a language that is familiar to them, was procured from the parents of the participants of the study. The study was commenced following approval from the Institutional Ethics Committee.

## Statistical analysis

Categorical and quantitative variables were expressed as frequency (percentage) and mean  $\pm$  SD, respectively, the normality of distributed data was tested using histogram and parametric test done. The paired *t*-test was used to compare paired samples for the continuous variables. Statistical analyses were performed using a statistical software package SPSS Statistics Version 23 (IBM Corp., Armonk, NY, USA). For all statistical interpretations,  $P < 0.05$  was considered the threshold for statistical significance.

## RESULTS

A total of 560 patients were assessed for eligibility in the study, of whom 408 were not eligible as they did not receive IVF (flow chart study plan). A total of 152 children fitting the inclusion criteria were enrolled in the study. Out of these, 72 were excluded based on exclusion criteria. A total of 80 children were finally included in the study [Figure 1]. The baseline clinical characteristics with the mean and SD for the clinical and metabolic variables are presented in Table 1. The etiological diagnosis of the study subjects included in the study is presented in Table 2. The proportion of patients with abnormal values was seen more in the <5-year age group compared to older children (5–13 years of age). The abnormal values with the highest proportion were for serum potassium,

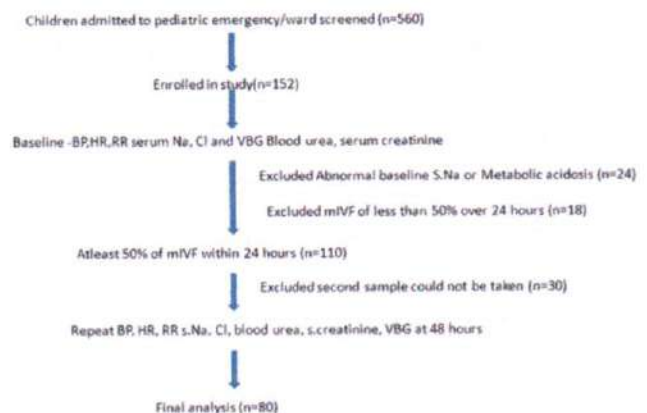


Figure 1: Flow chart of the study plan

**Table 1: Baseline clinical characteristics**

Characteristic	n=80, n (%)
Age	
1 month–5 years	54 (67.5)
5 years–13 years	26 (32.5)
Sex	
Male	40 (50)
Female	40 (50)
Clinical and metabolic parameters (mean±SD)	
HR/min	118.2±25.9
RR/min	41.6±14.51
Systolic BP (mmHg)	93.80±7.792
Diastolic BP (mmHg)	55.05±7.073
Sodium (mEq/L)	137.3±2.69
Potassium (mEq/L)	4.169±0.590
Chloride (mEq/L)	103.2±2.707
Urea (mg/dL)	19.65±7.718
Creatinine (mg/dL)	0.351±0.118
PH	7.374±0.047
Bicarbonate (mEq/L)	21.29±3.745
PCO <sub>2</sub> (mmHg)	38.16±7.747
Lactate (mmol/L)	1.664±0.630

SD=Standard deviation, BP=Blood pressure, HR=Heart rate, RR=Respiratory rate

**Table 2: Etiological diagnosis of the study subjects**

Diagnosis	n (%)
Pneumonia/LRTI	37 (46.25)
Viral fever	11 (13.75)
Upper respiratory infection	9 (11.25)
HFMD/oral ulcers	8 (10.00)
Acute wheeze	5 (6.25)
Acute bronchiolitis	5 (6.25)
Dengue fever	2 (2.50)
Migraine	1 (1.25)
UTI	1 (1.25)
Meningitis	1 (1.25)

LRTI=Lower respiratory tract infection, HFMD=Hand, foot and mouth disease, UTI=Urinary tract infection

followed by diastolic BP (DBP), serum chloride, and serum sodium as presented in Table 3. The clinical and metabolic parameters after 48 h of mIVF showed a statistically significant difference from the baseline value so far as HR, RR, systolic BP (SBP), DBP, serum sodium, potassium, chloride, creatinine, and blood urea were concerned as detailed in Table 4. After 48 h of 0.9% NS as mIVF in noncritically ill pediatric patients; there was a statistically significant ( $P < 0.05$ ) decrease in HR, RR, blood urea, and serum creatinine values from baseline. There was also a statistically significant ( $P < 0.05$ ) increase in SBP and DBP, serum sodium, serum potassium, and serum chloride values from the baseline. Serum chloride in 6 (7.5%) study subjects was in the hyperchloremia range [Table 5]. None of the other values fell into the hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypochloremia, acidosis, and alkalosis range.

## DISCUSSION

The study included children between 1 month to 13 years with an equal number of males and females. 47.5% (38 out of 80) participants were between 1 month and 5 years old, with more females than males in this age group. Pneumonia was the most common diagnosis (46.25%), followed by viral fever (13.75%) and upper respiratory tract infection (11.25%) [Table 4].

This study found a statistically significant change in HR and RR after 48 h of 0.9% IVF therapy. The HR decreased significantly from  $118.2 \pm 25.95$  before IVF to  $105.5 \pm 16.82$  after IVF. Similarly, the RR decreased significantly from  $41.63 \pm 14.51$  before IVF to  $33.94 \pm 8.47$  after IVF. However, neither the HR nor the RR showed a change  $>2$  SD from baseline.

In this study 8.75% of patients, there is elevation in SBP  $>2$  SD, and 3.75% patients, there is an increase in DBP  $>2$  SD. Increase in the SBP is more pronounced in females than in males and is nearly the same in both age groups under 5 years and over 5 years. Increase in the DBP is higher in females and  $>5$  years old compared to  $<5$  years. Both increases in SBP and DBP are statistically significant. SBP significantly increases after IVF administration ( $96.78 \pm 7.59$ ) compared to before IVF administration ( $93.80 \pm 7.79$ ). DBP also significantly increases after IVF administration ( $57.70 \pm 6.14$ ) compared to before ( $55.05 \pm 7.07$ ). Earlier research has revealed variable effects on BP, with some studies not reporting an increase in BP like Malviya *et al.*<sup>[21]</sup> When compared to isotonic fluids, Choong *et al.* found that 1.54% of children receiving hypotonic fluids developed new-onset hypertension.<sup>[22]</sup>

In this study, 6.2% of patients exhibited a  $>2$  SD increase in serum sodium levels after 48 h of mIVF, mostly in males under 5 years old. Sodium levels increased after IVF administration ( $139.0 \pm 2.15$ ) compared to before ( $137.3 \pm 2.68$ ), which was statistically significant. There were no occurrences of notable hypo- or hypernatremia in this study. In the study by Malviya *et al.*, the increase in serum sodium from baseline to 48 h ( $P = 0.017$ ) was significant like in our study.<sup>[21]</sup> Choong *et al.*<sup>[22]</sup> and Kannan *et al.*<sup>[18]</sup> studies have revealed a negligible risk of hypernatremia and a decreased risk of hyponatremia after 0.9% NS as isotonic mIVF. Studies of Sen *et al.*<sup>[23]</sup> noted significant changes in serum sodium after isotonic saline administration, particularly in critically ill patients. In the majority of research, isotonic and hypotonic fluids have been compared.<sup>[8–13]</sup> Saba *et al.* randomized 16 children to receive 0.9% NS and 21 children to receive 0.45% NS as maintenance IVFs, monitoring the alteration in serum sodium as the main outcome. Serum sodium was assessed at baseline and 12 h later. Results indicated an increase in serum sodium in 0.9% NS group compared to the 0.45% NS group. The difference between the two groups was not found to be statistically significant.<sup>[24]</sup> In a related study, Bagri *et al.*<sup>[25]</sup> discovered that children receiving 0.9% NS had higher serum sodium levels at 24 h compared to those receiving 0.45% NS ( $P < 0.01$ ). But at 48 h, there was no significant difference in serum sodium between the two groups, nor were there any cases



**Table 3: Clinical and metabolic parameters values in abnormal range (>2 SD) after 48 h**

Clinical and metabolic parameters	Mean ± 2 SD (range)	Abnormal values, n (%)	Age 1 month–5 years, n (%)	Age 5–13 years, n (%)	Direction of change
HR/min	66.3–170.1	-	-	-	
RR/min	12.58–70.6	-	-	-	
Systolic BP (mmHg)	78.2–109.4	7 (8.75)	4 (57.14)	3 (42.86)	Increase
Diastolic BP (mmHg)	40.9–69.2	3 (3.75)	1 (33.3)	2 (66.6)	Increase
Sodium (mEq/L)	131.9–142.7	5 (6.2)	4 (80)	1 (20)	Increase
Potassium (mEq/L)	3.58–4.76	19 (23.7)	16 (84.0)	3 (15.8)	Increase
Chloride (mEq/L)	97.78–108.61	6 (7.5)	6 (100)	-	Increase
Urea (mg/dL)	4.21–35.08	1 (1.25)	1 (100)	-	Decrease
Creatinine (mg/dL)	0.115–0.587	1 (1.25)	-	1 (100)	Decrease
PH	7.28–7.468	-	-	-	-
Bicarbonate (mEq/L)	13.8–28.78	3 (3.75)	2 (66.6)	1 (33.3)	Decrease
PCO <sub>2</sub> (mmHg)	23.21–53.11	3 (3.75)	1 (33.3)	2 (66.6)	Decrease
Lactate (mmol/L)	0.404–2.924	4 (5)	3 (75)	1 (25)	Increase

SD=Standard deviation, BP=Blood pressure, HR=Heart rate, RR=Respiratory rate

**Table 4: P value of clinical and metabolic parameters values baseline and after 48 h**

Clinical and metabolic parameters	Baseline, mean ± SD	After 48 h, mean ± SD	P
HR/min	118.2±25.95	105.5±16.82	0.000
RR/min	41.6±14.51	33.94±8.475	0.000
Systolic BP (mmHg)	93.80±7.792	96.78±7.594	0.000
Diastolic BP (mmHg)	55.05±7.073	57.7±6.147	0.000
Sodium (mEq/L)	137.3±2.689	139±2.152	0.000
Potassium (mEq/L)	4.169±0.590	4.31±0.537	0.046
Chloride (mEq/L)	103.2±2.707	104.1±3.532	0.017
Urea (mg/dL)	19.65±7.718	16.43±6.838	0.000
Creatinine (mg/dL)	0.351±0.118	0.30±0.110	0.001
PH	7.374±0.047	7.283±0.825	0.333
Bicarbonate (mEq/L)	21.29±3.745	22.12±4.122	0.116
PCO <sub>2</sub> (mmHg)	38.16±7.474	38.53±7.647	0.732
Lactate (mmol/L)	1.664±0.630	1.661±0.881	0.981

SD=Standard deviation, BP=Blood pressure, HR=Heart rate, RR=Respiratory rate

**Table 5: Incidence of hyperchloremia at 48 h**

Serum chloride (mEq/L)	108–109	≥110	Total (n=5), n (%)
n=80	2	4	6 (7.5)

of symptomatic hypo- or hypernatremia. Likewise, Kumar *et al.*<sup>[26]</sup> documented notable alterations in serum sodium levels at 12 and 24 h compared to baseline in the group receiving isotonic solution (12 h:  $P=0.005$ ; 24 h:  $P<0.001$ ). However, there were no occurrences of notable hypo- or hypernatremia, like in our study.

In this study, 17.5% of children had a >2 SD increase in serum potassium levels after 48 h of IVF infusion. Potassium levels increased after IVF administration ( $4.31 \pm 0.53$ ) compared to before ( $4.169 \pm 0.590$ ), which is statistically significant. Most of these children were under 5 years old, with a majority under 1 year and a predominance of males but there were no cases

of hyperkalemia. A possible reason for this increase could be the addition of KCL to the maintenance IVF at our hospital. No other study has analyzed the changes in potassium. We postulated that the increase could be secondary to extracellular shifting of potassium as a result of hyperchloremia.

In the present study, 7.5% of patients had a >2 SD increase in chloride after 48 h of IVF administration ( $104.1 \pm 3.53$ ) compared to before ( $103.2 \pm 2.70$ ), which is statistically significant and comparable to the study by Malviya *et al.*<sup>[21]</sup> All of these patients in our study were children under 5 years old, with most being males, and 4 (5%) had serum chloride  $\geq 110$  meq/L and 6 had serum chloride  $\geq 108$  meq/L. Previous reports have documented significant hyperchloremia following 0.9% NS in adults,<sup>[17-20,23]</sup> but there are limited data about pediatric cases. Lima *et al.*<sup>[27]</sup> conducted a comparison between 0.9% NS and balanced crystalloid in 49 pediatric patients undergoing neurosurgery. There was a marked increase in serum chloride levels compared to the initial measurement in the 0.9% saline group ( $P<0.01$ ). Furthermore, the occurrence of hyperchloremic metabolic acidosis was more prevalent in the saline-treated group following surgery ( $P=0.02$ ). Bulfon *et al.*<sup>[28]</sup> conducted a retrospective study with 543 PICU patients who received minimum 50% of total maintenance fluid intravenously, as 0.9% NS, during the first 24 h. It found that the occurrence of hyperchloremia was 94.9%, and the incidence of hyperchloremic metabolic acidosis was 38.9% at 72 h of admission. Evidence suggests that using 0.9% NS for resuscitation increases the likelihood of hyperchloremia and hyperchloremic metabolic acidosis, which supports the use of balanced solutions in the adult population.<sup>[17,19,20,29]</sup> Earlier research has shown notable mortality and morbidity associated with hyperchloremia, mainly because of its impact on kidneys.<sup>[17-20,23,27-30]</sup> Hyperchloremia might impair the reabsorption of chloride in PCT, enhancing chloride transport to the distal nephron. This leads to a negative feedback mechanism causing vasoconstriction of afferent renal vessels, which reduces renal perfusion and can result in kidney injury and failure.<sup>[30]</sup>



Blood urea levels decreased after IVF administration ( $16.43 \pm 6.83$ ) compared to before IVF ( $19.65 \pm 7.71$ ). Similarly, serum creatinine levels decreased after IVF administration ( $0.30 \pm 0.11$ ) compared to before IVF ( $0.35 \pm 0.11$ ). The change in both urea and creatinine levels was statistically significant.

The change in VBG pH after IVF administration was not statistically significant. The pH after IVF administration ( $7.28 \pm 0.82$ ) was almost the same as before IVF administration ( $7.37 \pm 0.04$ ). The bicarbonate level was nearly unchanged after IVF administration ( $22.12 \pm 4.122$ ) compared to before ( $21.29 \pm 3.745$ ). Similarly, carbon dioxide levels also showed minimal change after IVF administration ( $38.53 \pm 7.647$ ) compared to before ( $38.16 \pm 7.47$ ). In other words, there was no statistically significant difference in  $\text{HCO}_3$  and  $\text{CO}_2$  in VBG after IVF administration. There was no statistically significant change in lactate levels after IVF administration ( $1.66 \pm 0.88$ ) compared to before ( $1.66 \pm 0.63$ ).

One of the limitations of the study was the study design; a randomized controlled trial would have had more significance. Furthermore, there is the risk of unaccounted confounding associated with the observational design of the study. While we powered our study adequately, we acknowledge the potential for imprecision given the relatively small number of patients. We did not address the quantitative relevance of fluids administered as drug diluents and to guarantee catheter patency, the so-called fluid creep. There was an unexpectedly low volume of crystalloids, as mIVF is usually deescalated to oral as soon as child improves. However, we ensured that a minimum of 50% of mIVF was given to all study subjects. Finally, our findings are limited to one center and hence may not be generalizable. The strengths of the study were that there were well-defined inclusion and exclusion criteria which were strictly adhered [Figure 1]. There was a uniform fluid strategy based on weight, and none of the children received fluid bolus as part of fluid resuscitation. We did a sequential evaluation of the variables, which may provide more relevant information than an isolated measurement.

Based on results, hyperchloremia could be a major electrolyte abnormality following 0.9% NS as mIVF in noncritically ill patients. In addition, 0.9%NS as mIVF does lead to statistically significant alterations in clinical parameters and certain metabolic parameters like serum sodium, chloride, potassium, urea, and creatinine. Hyperchloremia was seen in younger children. While providing a high level of evidence, this study does not give a definitive answer. The most appropriate mIVF type in children is still debatable. Although the most recommended and widely used isotonic mIVF fluid has been 0.9% NS, increased incidence of adverse effects like hyperchloremic metabolic acidosis cannot be ignored more so in centers with a large number of patients requiring mIVF with resource limited settings of patient monitoring.

## CONCLUSION

Use of 0.9% normal saline can lead to notable clinical and metabolic disturbances, with younger children being particularly prone to developing hyperchloremia.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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## A Study Of Intussusception In Children Admitted In A Medical College Hospital In Central Kerala

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### Abstract

#### Introduction:

Intussusception is one of the most commonly seen emergencies in pediatric surgical speciality and also in the routine clinical practise of a paediatrician. The classical symptoms of intussusception (INTUSN) in a child is the presence of intermittent abdominal pain, vomiting, and a particular type of red "currant jelly" coloured stools. The incidence of INTUSN has a varied course and usually starts in a very young age group and may continue to early childhood. Amala Institute of Medical Sciences is a medical college located in the central part of Kerala State and caters to a large population from surrounding districts. The medical college has a tertiary level care Paediatric department and the Paediatric surgery department is efficient in treating any paediatric surgical emergencies. The paediatric department receives many children with various surgical emergencies and INTUSN is common. The prompt diagnosis of INTUSN can prevent the various morbidity and mortality associated with it.

#### Aim:

To study the clinical presentation of children at the time of admission, clinical course in the hospital and treatment modalities in children admitted with INTUSN. Also to study the gender difference, age of admission, seasonal variation, association with weaning habits and also specific reference to abnormalities in laboratory parameters in children admitted with INTUSN.

#### Materials and methods:

The present medical college based descriptive study was conducted including a total of 63 children who attended the outpatient, inpatient and casualty-emergency departments in Amala Institute of Medical sciences, Thrissur, Kerala, India for a period of one year from June 2018 to 2019. The total duration of the study was for one year study period.

**Results:** The present study revealed a male preponderance of children with INTUSN in 38 boys (60.3%). Age group wise 3(4.76 %) were below the age group of 6 months. 24 (38.09%) were between 1 to 2 years. The majority of children (56%) with INTUSN were from the rural population. The majority of admissions were in the months of April to July (54%). 68% of children presented within 24 hours from the onset of symptoms to the hospital. 96.82% presented with abdominal pain, followed by incessant crying and irritability (93.65%), vomiting and blood in stools in 90.47% and 77.78% respectively. Children with mass per abdomen (59%) with 23% having abdominal distension. There was a past history of INTUSN in 5 (79.35%) children in the age group less than 4 years. Majority had ileo colic type of INTUSN 58(92.06%). Hydrostatic reduction was done for 90.47% children.

**Conclusions:** A smart clinical judgement, proper abdominal examination and a simple per rectal examination if possible can diagnose INTUSN in most of the situations. Ultrasonography can pick up the INTUSN in the hands of an experienced radiologist and hydrostatic reduction is the commonest modality in the treatment. Majority of the children were discharged on the fourth day 38(60.31%) There was no mortality in the present study.

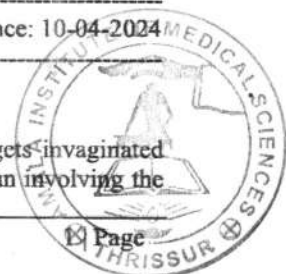
**Keywords:** Intussusception, Mass per abdomen, Blood in stools, Intestinal obstruction, Hydrostatic reduction

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### I. Introduction

The term "intussusception"(INTUSN) is defined when one portion of the intestine gets invaginated with another part of the intestine adjacent to this part. Small bowel INTUSN are commoner than involving the

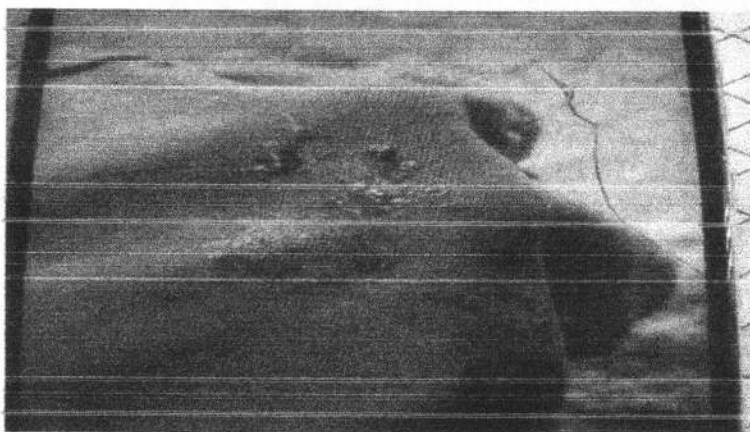


large bowel<sup>2</sup>. There are data showing a peak age of 4 to 9 months age for INTUSN to develop and is seen when complementary feeding is initiated in these babies<sup>3</sup>. INTUSN has a preponderance in male sex(3:1)<sup>1-3</sup>.

Mostly children are susceptible to develop an INTUSN and in most cases the etiology is unknown. But many causes are known in the adult population and in older children. The reasons could be a lymphoid hyperplasia in the intestines especially in younger children and babies. Intestinal polyps, bowel adhesions after surgery or infections of the gastro intestinal tract, tumors of the intestine, Meckel's diverticulum and endometriosis<sup>4</sup> in the adult and adolescents. Other malignant tumors could be ganglioneuroma and hamartomas characteristically seen in Peutz-Jeghers syndrome, an autosomal dominant syndrome. INTUSN is also seen in association with mesenteric or duplication cysts, a subset of patients with vasculitis such as Henoch Schonlein Purpura and disorders of the coagulation cascade can develop sub mucosal hematomas and can result in INTUSN<sup>5</sup>. In all these conditions there is a lead point in the intestine to cause an INTUSN.

The viral and bacterial infections are known to be associated with INTUSN. Many studies have shed light into these findings after a adenoviral infection in children. Human herpesvirus 6 is also known to cause INTUSN. Salmonella species, Escherichia coli organisms, Shigella species or Campylobacter jejuni are some of the bacterial infections causing the gastro intestinal manifestations and associated with INTUSN<sup>6,7,8</sup>. Administration of Rota viral vaccine has been observed to cause INTUSN<sup>9</sup>.

The intestine in an INTUSN has two important parts, namely the proximal part known as intussusceptum (that part of the intestine that prolapses) and the second distal part the intussuscipiens (the part that is in the distal part receiving the intestine). All this happens because of the vigorous peristaltic action of the intestine and in about 10% of the cases of INTUSN there is an anatomic part known as the lead point as a result of which this occurs. It is interesting to find that the stool is described as red currant jelly (Figure.1) as there is ischemia in the intestine and there is damage and oedema of the intestinal mucosa causing sloughing of blood and mucous into the intestine<sup>10</sup>.

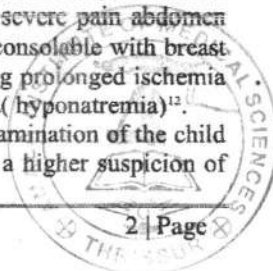


**Fig 1: Characteristic Red "currant jelly" stool in a case of Intussusception in a 1 year old child in the present study.**

Literature review and teachings from textbook of Surgery mentions that the order of INTUSN is Ileocolic – Most common type(77%), Ileo-ileo-colic, Ileoileal –(12% and 4% respectively) Colocolic (2%). The cases of multiple(1%) and retrograde(0.2%) INTUSN are rare, but seen<sup>11</sup>.

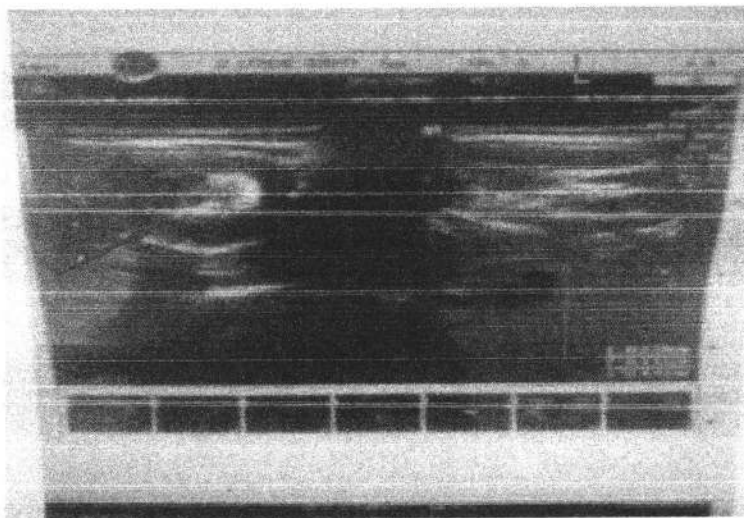
The notable triad of INTUSN a undergraduate or any postgraduate in Surgery should note is the symptomatic triad of red currant jelly stools, pain abdomen and increased vomiting episodes. The vomiting can be bilious or clear initially. And the characteristic feature of blood in stools is seen only 33% of the patients. The baby becomes very irritable during the progression of the trapping of the intestine and severe pain abdomen causes the baby to flex the lower limbs to abdomen and associated incessant crying not consolable with breast feeding or medicines. There has been reports of gangrene of the part of intestine following prolonged ischemia and baby can have fever, sepsis and encephalopathy like status following dyselectrolytemia (hyponatremia)<sup>12</sup>.

The diagnosis of INTUSN is made possible by experience and proper clinical examination of the child and palpation of the abdomen. Always any child presenting with blood in stools carries a higher suspicion of



this emergency surgical condition. INTUSN can be confirmed by following methods: 1) On examination of abdomen, there is a mass palpable in more than 85% cases of INTUSN and there is a typical sausage-shaped mass in the right hypochondrium. The recommendation is to palpate the mass when the baby is quiet in between the spasms of the intestine. This results in the emptiness of the right lower part of the abdomen and standard textbooks of surgery refer it as a "Sign of dance" of the intestine i.e. the emptiness in the right lower quadrant during palpation. 2) A per rectal examination carefully can help the surgeon to feel the intussusceptum and while removing the finger one can also appreciate the red currant jelly stool tickling out of the rectum<sup>10-12</sup>. 3) Imaging studies are the need of the hour, especially the ultrasonography (USG) of the abdomen. Abdominal X-rays with air enema, Barium or contrast enema, assessment of the intestine, Computer Tomography examination of the intestines are the various modalities used<sup>13</sup>.

Many radiology textbooks mention different signs in USG of the INTUSN: 1) the target sign which gives appearance of a round soft tissue mass that contains a radiolucent ring of mesenteric fat within the INTUSN, usually at the head of the INTUSN (**Figure .2**)



**Fig 2: Acute Ileocolic intussusception in a 10 month old baby – Right side-Bowel within bowel loop-Target sign in intussusception on ultra sound and second on left side-Pseudokidney sign in the longitudinal axis.**

2) bull's eye sign results as a result of coiling of the proximal part of the intestine within the distal part, 3) pseudo kidney sign which is the similarity of the mass to a kidney in the longitudinal axis 4) The doughnut sign is appreciated by USG as concentric bands arranged as alternating echogenic and hypoechoic areas, mucosa and muscularis layer of the intestines constitute the echogenic area and submucosa of intestine marks the hypoechoic bands 5) Another sign of INTUSN is the crescent in a doughnut sign which refers to the transverse USG appearance of a crescent only on one side of the bowel and is formed by mesentery which is pulled into the INTUSN. Barium enema or with contrast can reveal following signs 1) meniscus sign is designated for a crescent of air inside the lumen of the colon and is outlining the apex of INTUSN 2) coiled spring sign is formed when the Barium passes through the mucosal folds produces a coiled-spring like appearance 3) claw sign (pincer defect or shouldering defect) is due to a convex filling defect caused by the apex of the intussusceptum. Barium enema is the gold standard for diagnosis and also has therapeutic potential for reducing the INTUSN<sup>12,13</sup>.

The treatment of INTUSN is by hydrostatic reduction under USG. Air enema is used and this reduces the need for immediate surgery. Hydrostatic reduction of INTUSN has a success rate of over 83%. Usually the paediatric surgeon waits for 12 hours and repeat the USG to look for any recurrence. There is a chance for recurrence of INTUSN in about 10 % of children [ 14]. During surgery the trapped part of the intestine is squeezed out and if complications such as intestinal perforation or gangrene has occurred then resection surgery/laparoscopy surgery was done along with administration of appropriate antibiotic treatment<sup>14</sup>.

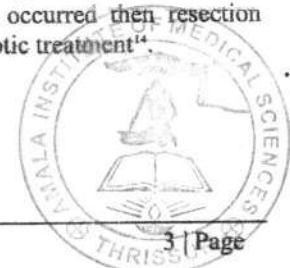
## **II. Materials And Methods**

**Study design:** Hospital based Descriptive study

**Type of study:** Observational study

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**Study duration:** 1 year, June 2018 to June 2019

**Study area/location:** Department of Paediatrics in collaboration with Department of Paediatric surgery, Amala Institute of Medical Sciences, Thrissur, Kerala.

**Study population:** 63 children who attended the outpatient, inpatient of the Department of Paediatrics and casualty-emergency, Amala Institute of Medical Sciences, Thrissur, Kerala. were included in the study.

**Sampling procedure:** Convenient sampling was used to select the participants for the study among the study population who suitably fulfill the selection criteria. Written informed consent was obtained from all the participants.

**Inclusion criteria:** All children aged below 12 years and diagnosed having INTUSN by clinical examination and then confirmation by radiological diagnosis of INTUSN attending the outpatient, inpatient and casualty-emergency departments of our medical college hospital were included in the study.

**Exclusion criteria:** Children who were above 12 years of age and having diagnosis other than intussusception were excluded from this study.

**Study tools:**

A standard proforma was used to collect data for the study. Parents of these children were explained about the study on INTUSN and the written consent was taken before including in the study.

**Data collection:** The cases were analysed with special reference to INTUSN. A standard proforma was prepared to collect the information. A standard proforma included age, sex of the children, types of symptoms on admission, clinical course and treatment given. Also a proper history of gender, weaning habits, immunisation schedule, time of admission of these children with INTUSN, socio-economic status of the family (according to the modified Kuppuswamy scale), duration of stay and the treatment outcome were analysed. Relevant investigations including complete Hemogram, serum electrolytes with ESR, USG Abdomen which were done in all these cases with INTUSN were analysed. So a total of 63 children were studied for INTUSN.

**Statistical Analysis**

The collected data was analysed using institutional Statistical Package for Social Sciences (SPSS) 2023 software. Clinical variables were studied and their frequency distribution and percentage analysis was done, then represented as pie chart and bar diagram.

**III. Results**

All cases were seen by the Paediatric surgeon and also discussed in detail about the type of INTUSN and any complications.

The present study revealed a male preponderance of children with INTUSN in 38 boys (60.3%) and 25 were female children (39.68%).

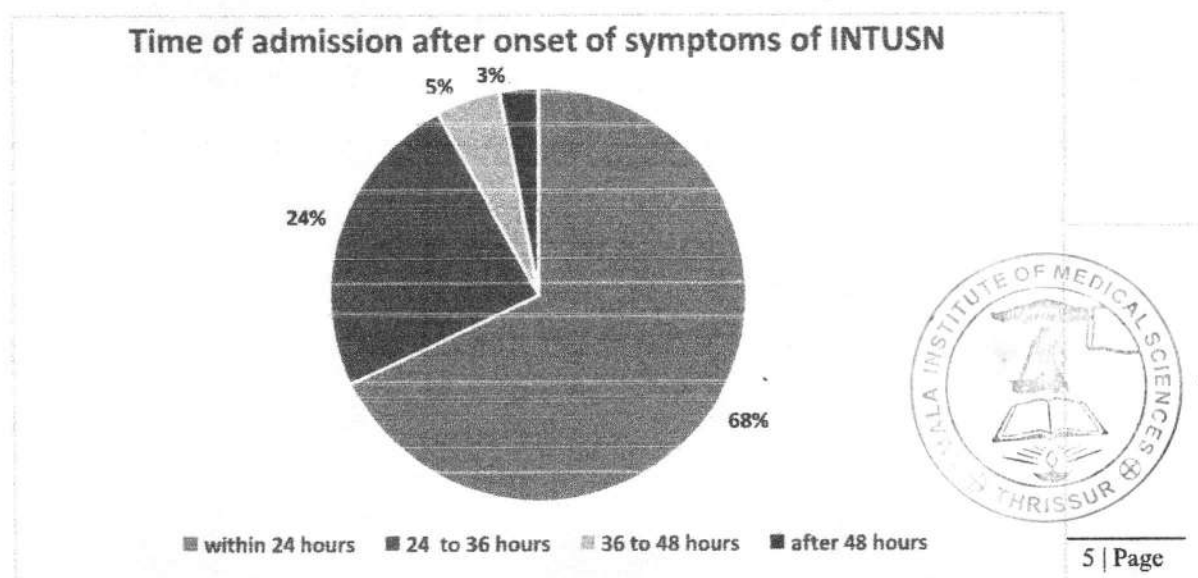
Age group wise, 3 (4.76%) were below the age group of 6 months, 23 (36.50%) were between 6 months to 1 year old children, 24 (38.09%) were between 1 to 2 years, 4 (6.34%) - between 2 to 3 years, 2 (3.17%) were between 3 to 4 years. In the age group 4 to 5 years, 5 to 6 years, 6 to 7 years, 7 to 8 years, 8 to 9 years, 9 to 10 years, 10 to 11 years, 11 to 12 years one child each i.e. (1.58%) of the total study population (Table .1).



Age of child	Frequency	Percent	Male	Female
< 6 months	3	4.76	2	1
6 months to 1 year	23	36.50	16	7
1 to 2 years	24	38.09	15	9
2 to 3 years	4	6.34	2	2
3 to 4 years	2	3.17	-	2
4 to 5 years	1	1.58	1	-
5 to 6 years	1	1.58	-	1
6 to 7 years	1	1.58	-	1
8 to 9 years	1	1.58	1	-
9 to 10 years	1	1.58	-	1
10 to 11 years	1	1.58	1	-
11 to 12 years	1	1.58	-	1
Total	63	100.00	38(60.31%)	25(39.68%)

**Table No 1: Distribution of study population according to age and sex**

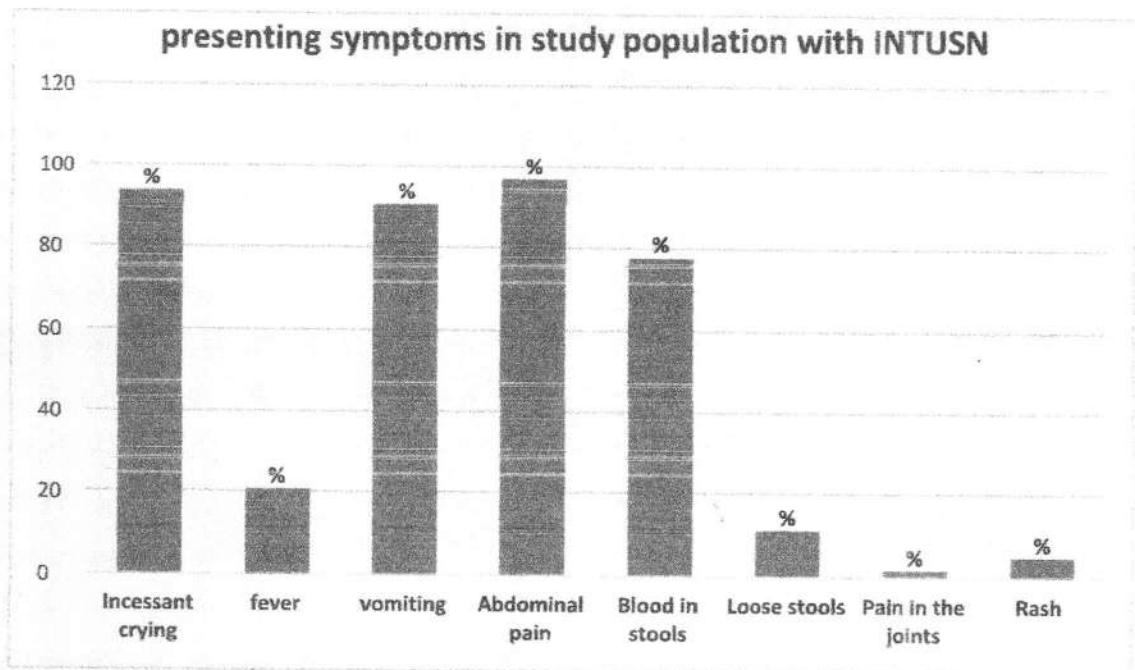
The majority of children(56%) admitted with INTUSN were from the rural population from in and around Thrissur district. More than 60% belonged to the class 3 according to the Modified Kuppusswamy scale. The majority of admissions were in the months of April to July (54%). Regarding the data on time of admissions from the onset of symptoms the children, presented within 24 hours to the hospital (68%), between the first and second day in 24% and the remaining 5 % were brought to hospital in the third and fourth days and 3 % after that period (Figure. 3).



**Fig 3: Pie diagram showing category of children based on time of admission after onset of symptoms of INTUSN**

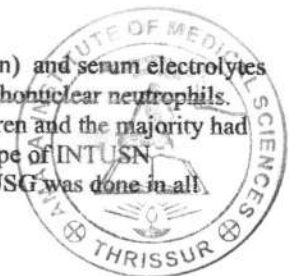
Majority of the babies had exclusive breast feeding (53%), but complementary feeding was found to be started early in the rest of the study population(47%).Bottle feeding was started with supplementary feeding in 28% of these children.Interestingly the population from the urban population (86%) were found to introduce bottle feeding and early complementary feeding in these babies.

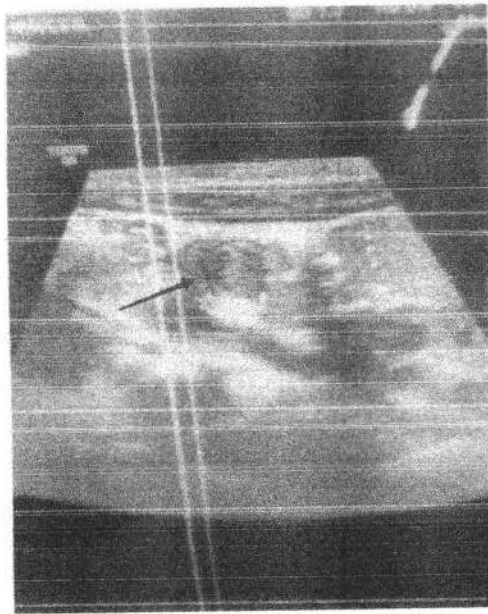
Analysis of the presenting complaints in these babies were seen as following :majority of the children presented with abdominal pain(96.82%),followed by incessant crying and irritability (93.65%),vomiting and blood in stools in 90.47% and 77.78% respectively,fever was present in 20.63% and loose stools in 11.11%. Pain in joints (1.57%) and rash in 4.76% children.A child had pain in joints and rash over the extremities with pain abdomen and was diagnosed to have Henoch Schonlein purpura (HSP).A maculopapular rash was present in 2 children who had a viral fever.3 children had acute diarrhoeal diseases and USG was done following fever and vomiting revealed transient INTUSN. A subset of children had the evident mass per abdomen (59%) with 23% having abdominal distension. 7.9 % children presented with an acute viral infection with mild cough and running nose. About 74 % were dehydrated following vomiting and 11 % following loose stools (Figure 4). There was a past history of INTUSN in 5 (79.35%) children in the age group less than 4 years.



**Fig.4 Presenting symptoms in present study as percentage**

A routine Hemogram ,ESR( Erythrocyte sedimentation rate) , CRP ( C Reactive protein) and serum electrolytes was done for all children.The majority had normal to mild leucocytosis with polymorphonuclear neutrophils. About 5 children had hyponatremia. In the present study a USG was done for all children and the majority had ileo colic type of INTUSN 58(92.06%). The remaining five children had ileo -ileal type of INTUSN (7.93%).Chest xrays and barium enema was not done in any of the children.A repeat USG was done in all children after 12 to 24 hours(**figure 5**).





**Fig 5: A short intussusception ileo –ileal (in the centre) in a 1 year old child**

All the children were admitted in the paediatric surgery ward. All children were monitored for signs of dehydration, shock, peritonitis and long segment INTUSN crossing from the right hypochondrium to left side by USG. If the child was dehydrated with dyselectrolytemia appropriate fluid correction was given. The hydrostatic reduction was done for all children without any of the above mentioned complications by the paediatric surgeon under USG. Fortunately in the present study only 3 children required open reduction following surgery. 2 children had spontaneous reduction of INTUSN after treating for diarrhoea. One 12 year old child was better after receiving treatment for vasculitis condition –HSP. The other remaining children hydrostatic reduction was done (90.47%) (Table .2).

Type of INTUSN	Frequency
Ileo colic	58(92.06%)
Ileo ileal	5(7.93%)
Type of treatment	Frequency
Hydrostatic reduction	57(90.47%)
Surgery	3(4.76%)
Spontaneous reduction	2(3.17%)
Reduction with treatment for HSP	1(1.58%)

**Table 2: Table depicting type of INTUSN and treatment modality given**



The child was sedated and a foleys rubber tube 16 F was inserted per rectum under USG. The pre warmed Saline solution was pushed into the colon through the rubber tubing by connecting the IV set .The hydrostatic pressure created reduced the INTUSN.

The children admitted with INTUSN was treated according to standard guidelines and sent home by the fourth day after admission. There was no mortality in the present study. Majority of the children were discharged on the fourth day 38(60.31%) . 22 (34.92%) children were discharged on day 3 after admission. The 2 children with diarrhoea and one child with HSP after their illness was treated.

#### IV. Discussion

Intussusception is a condition which requires adequate clinical suspicion and appropriate examination of the presenting child is vital in its management. Literature review has shed light on the various aspects of INTUSN especially the male dominance<sup>15</sup>. Male preponderance of children with INTUSN was seen in other studies as well, in our study it was 60.3% and female 39.68%. Weihmiller et al in their study found 67% were males<sup>16</sup>. Bajaj et al and Khan et al also in their historic studies found the male predominance (61% and 64%) respectively<sup>16,17</sup>. Kumar et al found a male predominance 63% in their study<sup>18</sup>.

Age group wise ,there are studies showing that neonatal INTUSN are rare<sup>15,19</sup>. In our study 4.76 % were below the age group of 6 months. 36.50 % (6 months to one year), 38.1%(1 to 2 year). Other studies are showing this trend in the prevalence of INTUSN, Justice FA et al found INTUSN to be increased in children below 2 years [12], krishnakumar et al INTUSN more seen less than 3 years<sup>19</sup>.

56% children admitted with INTUSN were from the rural population from in and around Thrissur district. More than 60% belonged to the class 3 according to the Modified Kuppuswamy scale. Majority of the babies had exclusive breast feeding (53%), but complementary feeding was found to be started early (47%). There is a hypothesis that early introduction of complimentary feeds and the lack of adequate breast feeding can jeopardise the maternal immunity required for the babies and can result in INTUSN<sup>20</sup>. The practise of exclusive breast feeding (EBF) and the effective implementation of the various strategies promoting EBF has shown a protective effect in smaller babies .The swelling of the Payers patches and the resultant lymphoid hyperplasia by introduction of early nutrition can result in INTUSN<sup>21,15,20</sup>. The distribution of cases of INTUSN was done in various parts of the globe<sup>15</sup>, but no seasonal predilection was noted except in a study [25]. The majority of admissions were in the months of April to July (54%) in our study.

A meta analysis done by a group of researchers Yee X et al <sup>21</sup> analysed the various symptoms of these babies on admission and it was same as in our study. The presenting complaints in our study were abdominal pain(96.82%), incessant crying and irritability (93.65%). Vomiting was seen more in a study <sup>22</sup> and abdominal pain predominant 78.08% in another study<sup>16</sup>.

There are many conditions causing INTUSN in adults and in children as mentioned in the subheading "Introduction". So a thorough knowledge of the various differential diagnosis is important in the diagnosis of any child with blood in stools and its appropriate treatment. Literature review shows that the pediatric INTUSN accounts for only 10 % cases with a definite cause and is usually idiopathic<sup>24</sup>. Some authors found a seasonal variation of the INTUSN that co existed with acute viral gastro enteritis resulting in hypertrophy of Payers patches<sup>25</sup>. A syndrome called Waugh syndrome was noted in literature search cases with malrotation as a result of prolapse of the ileo colic region into the ascending colon. This condition is very important as there is non reduction methods of management of INTUSN <sup>26</sup>.

USG is the main modality to diagnose INTUSN. If we note the history of INTUSN it was in 1674 first mentioned by Barbette of Amsterdam. But the advent of USG in 1977 revolutionised its diagnosis. There are many signs seen in USG of the INTUSN as mentioned in the subheading "Introduction". USG has a high sensitivity of 98% to 100% in diagnosing the commonest type namely the ileo colic INTUSN. The diagnosis of small bowel INTUSN by USG is challenging even for a experienced radiologist. Apart from the mentioned signs a multi-layered "onion skin" round mass on a transverse scan is described. In children any modality of treatment of INTUSN depends on the type of INTUSN. Ileocolic INTUSN requires hydrostatic reduction by USG. Fluoroscopic reduction is not utilised now as USG has advantage over it as there is no radiation. A small bowel INTUSN will have spontaneous reduction. But if persistent and long segment INTUSN will require surgical intervention. In contrast to ileocolic INTUSN , in small bowel INTUSNs there is a lead point <sup>23</sup> and is invariably associated with pathological lead points . Selcan Et al presented a case of idiopathic ileocolic INTUSN in a 4 year old child without a lead point in a 4-year-old child<sup>27</sup> . Literature review mentions that in 2% to 12% children lead points are there and as age advances it is seen to increase and ultimately a surgery is required<sup>28,29</sup>.

#### V. Conclusion:

An intervention including early detection, thorough clinical observation and judicious management of INTUSN and its possible complications as per recent guidelines would surely reduce the mortality and morbidity among these babies and children admitted with INTUSN. One should know the excellent prognosis if

acting fast with hydrostatic reduction ,but if child presents with long segment prolapse with ischemia and necrosis ,the mortality increases requiring definitely surgical intervention. So a thorough knowledge of all the aspects of INTUSN is pertinent in its management.

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## A cross-sectional study on knowledge, attitude, and level of preparedness of medical interns in a teaching hospital from India on antibiotic use and antimicrobial resistance

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### ABSTRACT

**Background:** The topic of antibiotic prescription and antimicrobial resistance is an integral part of the Indian medical undergraduate curriculum; however, the newly passed-out medical interns find it difficult to prescribe the appropriate antibiotics when they practice. The impact of teaching about antimicrobial resistance and antibiotic use in medical colleges still remains uncertain.

**Aim:** This study aims to assess the knowledge, attitude, and level of preparedness regarding antibiotic use and antimicrobial resistance among medical interns from a teaching hospital in Kerala, India.

**Methods:** This questionnaire-based study evaluated the knowledge, attitude, and level of preparedness among medical interns toward antibiotic use and antimicrobial resistance. The assessment included 20 knowledge questions (max score: 26), five attitude questions (max score: 5), and eight preparedness questions (max score: 8). A passing score of 60% was set for each category, with scores below this threshold considered as poor performance. Participants included medical interns from the 2018 batch, who were nearing the end of their internship, and those from the 2019 batch, who had just started their 1-year internship. This study was done from June to October 2024.

**Results:** The study involved 85 medical interns (43 from the 2018 batch and 42 from the 2019 batch). It was observed that 98.8% ( $n = 84$ ) interns displayed good general knowledge about antibiotics, but with regard to specific topics, only 44.7% ( $n = 38$ ) interns showed good knowledge about antibiotic resistance and only 47.1% ( $n = 40$ ) interns showed good knowledge about clinical scenarios. The overall knowledge score showed that 70.6% ( $n = 60$ ) of interns have good knowledge regarding antibiotic use. With regards to overall attitude, 94.1% ( $n = 80$ ) of the interns displayed a good attitude. In terms of preparedness, 55.3% ( $n = 47$ ) of interns displayed a good level of preparedness to use and prescribe antibiotics. Both batches showed similar knowledge (69.8% for 2018 and 71.4% for 2019) and attitude scores (90.7% and 97.6%). With regard to the level of preparedness, the 2018 batch showed a statistically significant good level of preparedness in using and prescribing antibiotics compared to the 2019 batch (74.4% and 35.7%,  $p$ -value = 0.0001).

**Conclusion:** The study shows that the medical interns have a good theoretical knowledge and understanding of antibiotics, but the study also emphasizes the importance of training interns with regard to attitude and practice toward antibiotic use and antimicrobial resistance. This study also reveals the importance of bedside teaching and 1-year internship in improving the level of preparedness toward antibiotic use among medical interns.


**Keywords:** Knowledge, attitude, level of preparedness, antimicrobial resistance, medical interns.

### Introduction

According to the World Health Organisation, AMR contributes to at least 700,000 deaths globally (Dadgostar 2019; Murray *et al.*, 2022; Naghavi *et al.*, 2024). AMR resources analysis revealed that AMR could lead to an economic loss of trillions by 2050 through causes such as healthcare, productivity and trade, and food security. AMR complicates the effectiveness of managing day-to-day infections with diseases such as pneumonia, UTI, and sepsis (Inoue 2019; Grant and Saux 2021; Abbott *et al.*, 2023; Ferdinand *et al.*, 2023; Tamma *et al.*,

2024). According to the Centre for Disease Dynamics, Economics & Policy estimate for 2015, AMR will cause 2 million deaths per year by 2050 to India besides sepsis killing over 50,000 newborns in the same year (Dixit *et al.*, 2019; Kalra *et al.*, 2022; Ahmed *et al.*, 2024). India is ranked highly in the global list of resistance to antimicrobial agents that are used in both human and food animals (Taneja and Sharma 2019; Bhatia 2024; Rana *et al.*, 2024). India is ranked highly in the global list of resistance to antimicrobial agents that are used in both human and food animals and as per Kerala Government's

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strategic plan for fighting AMR called Kerala Antibiotic Resistance Strategic Action Plan (Nambiar 2020; Barik et al., 2023), Kerala will be the first state to have AMR committees in all 191 block panchayats to build up AMR literacy in grassroots. The standardization and the guidelines of the working of the block-level AMR committees are published by the Kerala government and all the hospitals will become 'antibiotic smart' (Mathew et al., 2024; Raju et al., 2024).

In Indian medical schools, even though there are multiple teaching sessions on antibiotic prescription and resistance as part of the phase II competency-based medical education curriculum, the attitude and practice toward antibiotic use and resistance seem poor and require significant improvement, which was described in the cross-sectional study conducted by Gupta et al. (2019) that included 103 medical colleges distributed across 22 states of India, in which the majority of the data came from the central and northern states of India (Gupta et al., 2019) with very limited information from the southern states such as Kerala. Hence, our study from Kerala, India would be of great relevance. The objectives of this study are to evaluate the knowledge, attitude, and level of preparedness about antibiotic use and antimicrobial resistance among medical interns doing their 1-year compulsory rotatory internship after completing their undergraduate education, which is a prerequisite to become a registered medical practitioner in India.

#### Methods

A cross-sectional study was conducted among medical interns to evaluate knowledge, attitude, and level of preparedness about antibiotic use and antimicrobial resistance using an online questionnaire given as a Google Form, which was developed by Lubwama et al. (2021) The Google Form was set up in a way that only one response was allowed from a particular email to ensure that multiple attempts were not made by the participants. This instrument has 20 questions about knowledge with a total score of 26; five questions on attitude with a total score of 5 and eight questions about level of preparedness, which has a total score of 8. The passing criterion was set at 60% for each parameter, i.e., knowledge, attitude, and level of preparedness. With scores below 60%, the candidate was deemed to have poor score and score equal to and above 60% was considered as good score within each parameter. At the time of recruitment for this study, we had two batches of interns (2018 batch and 2019 batch) 100 in each batch doing the internship in our medical school. The 2018 batch was about to complete their 1-year compulsory internship within a month, and contrary to this, the 2019 batch just joined the internship in less than a month. Therefore, the 2018 batch has had extensive bedside training in various clinical departments of about 10-11 months and the 2019 batch was new to this internship with very limited training. This study was done from June 2024 to October 2024. We followed a universal

sampling, as we wanted to include all the interns who were willing to participate in this study as we had only a total of 200 interns from both batches. This study was conducted in a tertiary care teaching hospital and was approved by the Institutional Ethics Committee with the approval number: 20/EC/24/AIMS-24 dated 07.05.2024.

#### Statistical analysis

The analysis was done using IBM SPSS version 23 (Armonk, NY: IBM Corp). Mean  $\pm$ SD (standard deviation) was calculated for age and frequency taken for age, gender, and year of enrolment. Knowledge, attitude, and preparedness scores were analyzed as descriptive statistics and the comparison between the 2018 and 2019 batches was analyzed using Fisher's exact test for knowledge and attitude, while the chi-square test was considered for comparing preparedness to find the association between batch (or internship training) and preparedness. A  $p$ -value  $< 0.05$  was considered significant.

#### Results

A total of 85 interns ( $n = 43$ ) from the 2018 batch and ( $n = 42$ ) from the 2019 batch participated in this study out of a total of 200 interns who were doing internship at the time of this study. The total age group of participants ranged between 23 and 26 years, of which 75.3% ( $n = 64$ ) were females and 24.7% ( $n = 21$ ) were males. The results about knowledge of antibiotics, resistance, clinical scenarios, and overall knowledge score are depicted in Figure 1. It was observed that 98.8% ( $n = 84$ ) interns displayed good general knowledge about antibiotics, but with regard to specific topics, only 44.7% ( $n = 38$ ) interns showed good knowledge about antibiotic resistance and only 47.1% ( $n = 40$ ) interns showed good knowledge about clinical scenarios. It is a cause of concern to see that 55.3% ( $n = 47$ ) and 52.9% ( $n = 45$ ) interns displayed poor knowledge about antibiotic resistance and in clinical scenarios, respectively. The overall knowledge score showed that 70.6% ( $n = 60$ ) of interns have good knowledge and 29.4% ( $n = 25$ ) of interns have poor knowledge regarding antibiotic use. The results on attitude and perception on antibiotic use are depicted in Figure 2. With regard to overall attitude, 94.1% ( $n = 80$ ) of interns displayed a good attitude, while 5.9% ( $n = 5$ ) of interns displayed poor attitude. However, with regard to specific attitude about over-the-counter use of antibiotics without prescription and use of leftover antibiotics, 43.5% ( $n = 37$ ) and 37.6% ( $n = 32$ ) of interns, respectively, showed poor attitude. With regard to the level of preparedness, as shown in Table 1, only 55.3% ( $n = 47$ ) of interns displayed a good level of preparedness, while 44.7% ( $n = 38$ ) displayed a poor level of preparedness to use and prescribe antibiotics. Our results as shown in Table 2 indicate that both the batches (2018 and 2019) displayed similar scores with regard to knowledge (69.8% and 71.4%, respectively) and attitude (90.7% and 97.6%, respectively), as shown in Table 3.



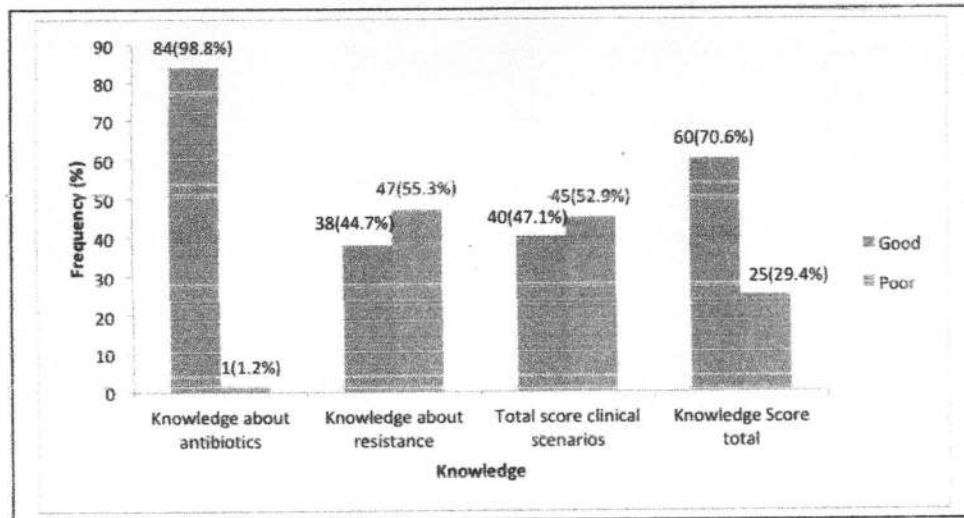


Fig. 1. Knowledge about antibiotics, resistance, total score in clinical scenarios, and total score among medical interns.

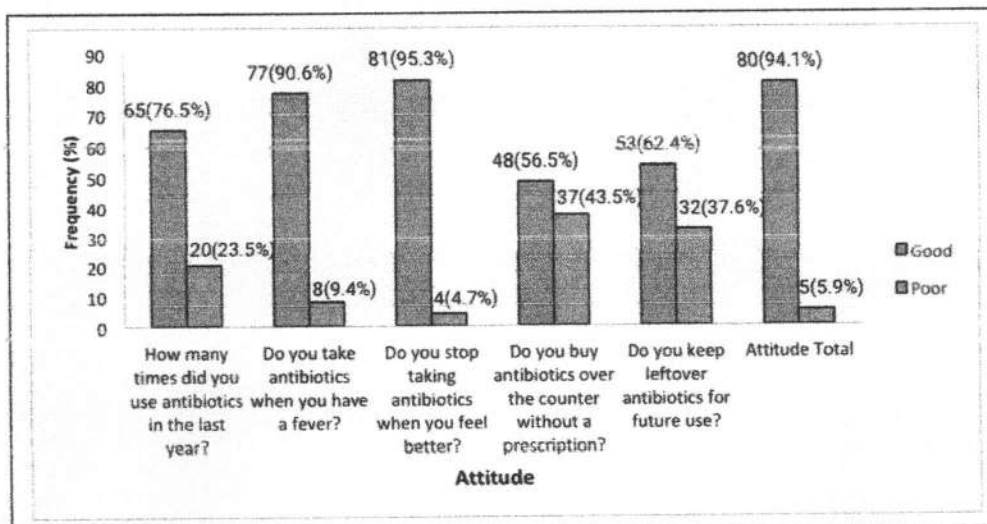


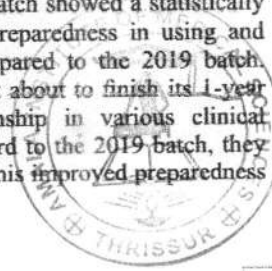
Fig. 2. Attitude and perception of antibiotic use among medical interns.

However, with regard to the level of preparedness, as shown in Table 4, the 2018 batch showed a statistically significant good level of preparedness in using and prescribing antibiotics compared to the 2019 batch (74.4% and 35.7%,  $p$ -value = 0.0001).

#### Discussion

The results from our study show that even though the overall knowledge and general knowledge about antibiotics is good among interns, when it comes to knowledge about antibiotic resistance and various clinical scenarios, the knowledge is poor among the majority. Both batches (2018 and 2019) displayed similar knowledge and attitude about antibiotics, resistance,

and use in clinical scenarios overall. However, it is a cause of concern to see that there are interns who still practice over-the-counter use of antibiotics without a prescription and keep leftover antibiotics for future use. This shows that more training is required about antibiotic resistance and attitude toward antibiotic prescription among interns. With regard to the level of preparedness, the 2018 batch showed a statistically significant good level of preparedness in using and prescribing antibiotics compared to the 2019 batch. The 2018 batch was almost about to finish its 1-year compulsory rotatory internship in various clinical departments, but, with regard to the 2019 batch, they just joined the internship. This improved preparedness



**Table 1.** Level of preparedness about antibiotic use among medical interns.

	Prepared		Not prepared	
	N	%	N	%
Know whether to give an antibiotic or not?	61	71.8	24	28.2
Know when to start antimicrobial therapy?	62	72.9	23	27.1
Know how to select the best antibiotic?	27	31.8	58	68.2
Know the dosage of antibiotic to give?	48	56.5	37	43.5
Know when to switch from an intravenous antibiotic to oral regimen?	43	50.6	42	49.4
Know the correct and relevant specimen to collect for an infection?	66	77.6	19	22.4
Distinguish between normal flora and a true pathogen from a microbiology report?	49	57.6	36	42.4
Understand resistance mechanisms based on a microbiology report?	55	64.7	30	35.3
Total	47	55.3	38	44.7

**Table 2.** Comparison between 2018 and 2019 batch medical interns about knowledge on antibiotics, resistance, and clinical scenarios.

Knowledge		Year of enrolment		Total	p-value (chi-square)
		2018	2019		
About antibiotics	Good	42 (97.7%)	42 (100%)	84	0.241*
	Poor	1 (2.3%)	0 (0%)	1	
Resistance	Good	20 (46.5%)	18 (42.9%)	38	0.735
	Poor	23 (53.5%)	24 (57.1%)	47	
Clinical scenarios	Good	20 (46.5%)	20 (47.6%)	40	0.919
	Poor	23 (53.5%)	22 (52.4%)	45	
Total	Good	30 (69.8%)	30 (71.4%)	60	0.867
	Poor	13 (30.2%)	12 (28.6%)	25	

\* Fisher's exact test.

**Table 3.** Comparison between 2018 and 2019 batch medical interns about attitude toward antibiotic use.

Attitude	Year of enrolment		Total
	2018	2019	
Good	39 (90.7%)	41 (97.6%)	80
Poor	4 (9.3%)	1 (2.4%)	5
Total	43	42	85

Fisher's exact p-value = 0.161.

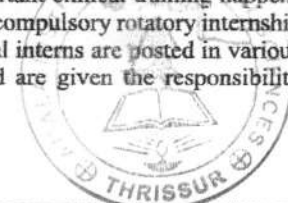
to use antibiotics among the 2018 batch can be attributed to the hands-on training they received during their internship, which was lacking in 2019 as they just joined internship. Our assumption why the 2018 batch showed improved preparedness compared to the 2019 batch is that our medical students in India during their training from first year to final year, the bedside clinical teaching mainly focuses on history taking and physical

**Table 4.** Comparison between 2018 and 2019 batch medical interns about level of preparedness on antibiotic use.

Preparedness	Year of enrolment		Total
	2018	2019	
Prepared	32 (74.4%)	15 (35.7%)	47
Not prepared	11 (25.6%)	27 (64.3%)	38
Total	43	42	85

Chi-square test p-value = 0.0001.

examination of the patient. There is not much focus on the day-to-day medical management of the patients and the undergraduate students are also not part of the daily clinical rounds and follow-up of the patients. Such practical and important clinical training happens at the time of the 1-year compulsory rotatory internship during which the medical interns are posted in various clinical departments and are given the responsibility



of medical management of out-patients and in-patients under the supervision of a faculty, who trains them on how to treat and follow-up the patients until discharge from the hospital, and it is during this time that the medical interns actually go through the case sheets and understand more about the various commonly used drugs in clinical practice and how it benefits the patients. They also get trained practically about the rational and judicious use of antibiotics during this internship. This highlights the importance of bedside training received during internship and how much the students can learn by being actively involved in direct patient care under proper supervision.

In a 2021 study by Lubwama *et al.* (2021) in East Africa, the age group found was 25.5 years, our study where the mean age among the medical interns of the study was 24.24 (SD = 0.840) years. Our study had 75.3% ( $n = 64$ ) and 24.7% ( $n = 21$ ) females and males. In the East Africa study, the total knowledge good score ranged between 55% and 67%, which was less than our study that displayed a total knowledge good score of 70%. Our interns displayed much more overall knowledge about antibiotics. In the East Africa study (2021), the mean good scores for general knowledge about antibiotics, knowledge about antibiotic resistance, and knowledge about antibiotic use in clinical scenarios were 95%, 54%, and 46%, respectively, which was like our study (98.8%, 47.7%, and 47.1%, respectively). In the same study with regard to general attitude toward over-the-counter use of antibiotics, 61% of medical students showed poor attitude, while in our study, it was only 43.5%, which was showing poor attitude. Our study showed that the proportion of interns showing poor attitude was lesser compared to other studies, but still, 43% is a good number and it is a cause of concern, because these interns are future primary care physicians of our country. In the East Africa study (2021), with regard to the level of preparedness, 70.1% of final-year students perceived themselves to be prepared to use antibiotics appropriately while working at the district hospital, while in our study, only 55.3% perceived themselves to be prepared (Lubwama *et al.*, 2021). In another study conducted in UAE (2019) by Jairoun *et al.* (2019) the average knowledge and attitude good score was 59% and 76% (Jairoun *et al.*, 2019), while in our study, the average knowledge and attitude good score was 70.6% ( $n = 60$ ) and 94.1% ( $n = 80$ ), respectively. Our study showed that our interns have better knowledge and attitude toward antibiotic use. In another Chinese study (2018) conducted by Hu *et al.* (2018) 64% of medical students kept leftover antibiotics for future use. On the other hand, our result displayed only 37.6% ( $n = 32$ ) of medical interns kept leftover antibiotics for future use, which was far better than the Chinese study (Hu *et al.*, 2018). In a Columbian study (2018) conducted by Higuaita-Gutiérrez *et al.* (2020) the overall knowledge and attitude score was more than 80% compared to our study, which reported

70.6% ( $n = 60$ ) and 94.1% ( $n = 80$ ), respectively. It also showed that antibiotic consumption in the last year was 49.1%, while our study showed that 76.5% ( $n = 65$ ) consumed antibiotics up to 3 times in a year. It was also observed that 80.3% of the antibiotics sold were without prescription, while our study displayed 43.5% ( $n = 37$ ) (Higuaita-Gutiérrez *et al.*, 2020). Even though our study demonstrated better practice on using antibiotics and using it with a prescription, still 43.5% using antibiotics without prescription is a concern as these practices can have a major impact in the future and even small mistakes with regard to antibiotics cannot be accepted. In a study conducted in 2019, in India by Gupta *et al.* (2019) the level of knowledge about antibiotics was quite high (91.8%) like our study that displayed 98.8% ( $n = 84$ ). With regard to attitude, almost 66% kept leftover antibiotics for future use and around half bought antibiotics without prescription, while our study showed only 37.6% ( $n = 32$ ) and 43.5% ( $n = 37$ ) (Gupta *et al.*, 2019).

This study has some limitations as we considered only interns from a single center, so we were forced to do a universal sampling without a sample size calculation as we had a small size of interns in our center. In the future, we recommend more similar studies, which are conducted as multicentre studies involving medical colleges across states and nation.

### Conclusion

This study shows that more emphasis should be given to training interns with regard to attitude and practice toward antibiotic use and antimicrobial resistance. Another aspect that this study shows is that bedside teaching and clinical training improve the preparedness toward antibiotic use among medical interns and prepare them for future as they become primary care physicians.

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### Conflict of interest

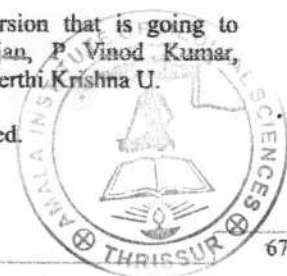
None.

### Authors' contributions

1. Concept and design of the study or acquisition, analysis, and interpretation of data: Kunjumary Scariah, Keerthi Krishna U, Boney Rajan, and P Vinod Kumar.
2. Drafting and revising the manuscript for important intellectual content: P Vinod Kumar and Boney Rajan.
3. Final approval for the version that is going to be published: Boney Rajan, P Vinod Kumar, Kunjumary Scariah, and Keerthi Krishna U.

### Data availability

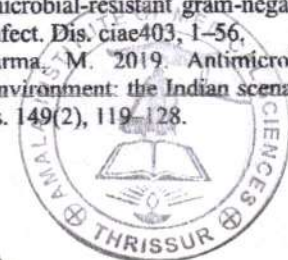
Data will be provided if required.



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Betsy



## Original Research Article

# Immunoprofiling in poorly differentiated non-small cell lung cancer, analysis of data in a tertiary care center

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### ABSTRACT

**Background:** Lung cancer is a leading cause of cancer-related deaths worldwide, including India, where it accounts for 5.9% of cancer cases and 8.1% of cancer-related mortality. Differentiating between major histologic subtypes of non-small cell lung carcinoma (NSCLC)-adenocarcinoma (ACA) and squamous cell carcinoma (SCC) is crucial due to significant differences in treatment response. Our study addresses the IHC profile of NSCLC in a tertiary care centre in South India. We have also deliberated whether a 2 panel IHC markers would be sufficient for the final diagnosis in a resource poor setting as compared to the traditional 4 IHC panel.

**Methods:** A hospital-based cross-sectional study (2018-2022) analysed 319 histologically confirmed poorly differentiated NSCLC cases. IHC markers (TTF-1, Napsin A, p63 and p40) were used for subtyping per WHO classification. Staining patterns were semi-quantitatively scored against controls. Sensitivity, specificity, PPV, NPV, and overall accuracy were calculated. Data analysis was performed using SPSS v23.

**Results:** Of the 319 cases, ACA was the most common (65.2%), followed by SCC (31.03%). Males accounted for 81.2% of cases, with the peak incidence in the 62-66 age group. For ACA, TTF-1 had higher sensitivity (97.17%) compared to Napsin A (83.49%), while Napsin A showed better specificity (96.04%). For SCC, p63 demonstrated higher sensitivity (93.07%) than p40 (78.22%), while p40 had better specificity (89.62%).

**Conclusions:** The study highlights the need for tailoring the IHC panel to suit the histopathological specimen in order to clinch the final diagnosis. In finance effectiveness, two marker panel can also be used.

**Keywords:** Immunohistochemistry, p63, TTF-1, Napsin-A, Squamous cell carcinoma, Adenocarcinoma

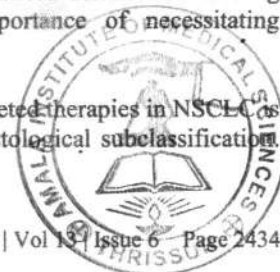
### INTRODUCTION

In India, lung cancer ranks among the prominent cancer sites, comprising 5.9% of total cancer cases and 8.1% of all cancer related deaths. Kerala exhibits a concerning surge in lung cancers in both males and females with lung cancer ranking in the top 5 cancers in both sexes (male-20.8% and female-4%).<sup>1</sup>

Recent strides in NSCLC treatment and molecular diagnosis underscore the necessity to differentiate between major histologic subtypes-ACA and SCC. Disparities in

their response to chemotherapy highlight the importance of accurate subtyping. Notably, certain drugs, such as bevacizumab, pose risks for SCC patients due to fatal hemorrhage observed in these patients.<sup>2</sup> Gefitinib and erlotinib demonstrate greater effectiveness in treating ACA compared to SCC in NSCLC.<sup>3</sup> Conversely, Pemetrexed, an antifolate agent, exhibits enhanced efficacy in non-SCC cases.<sup>4</sup> These distinctions in drug response underscore the importance of necessitating tailored treatment strategies.

The clinical application of targeted therapies in NSCLC is heavily reliant on accurate histological subclassification.



This is especially crucial for patients with advanced-stage disease (stage III and IV) and metastatic NSCLC, where surgical resection is often not an option. About 70% of lung cancer cases are diagnosed when the disease has already reached an advanced stage and is deemed unresectable.<sup>5</sup> In these cases, Tru-cut needle biopsy is commonly utilized to obtain tumor tissue for diagnostic purposes, including histologic and molecular testing. Most NSCLC cases can be subclassified through histomorphologic examination using hematoxylin and eosin stained slides, which remains a fundamental approach in clinical practice.<sup>6,7</sup> However there remains a subset of carcinomas which are poorly differentiated and which require IHC for their final diagnosis.

Retrospective studies done in USA showed that a 2-marker panel of TTF-1/p63 is sufficient for subtyping the majority of ACA and SCC, and addition of Napsin A is useful in only subset of cases. Whereas performing expanded 4-marker panel (TTF-1, Napsin A, p63, p40) upfront is time-efficient option for specimens with sufficient cellularity.<sup>8</sup>

Recent studies have explored the potential of combining multiple IHC markers to improve the subclassification of NSCLC. These investigations have shown promising results, particularly with dual markers. For instance, a combination of TTF-1 and Napsin A demonstrated 74% sensitivity and 87-96% specificity in identifying lung ACA using fine-needle aspiration material. Similarly, the dual marker of p63 and CK5 achieved 100% sensitivity and specificity for identifying lung SCC with FNA samples. Additionally, lung tumor tissue microarray data revealed that a combination of TTF1 and p40 provided 93% sensitivity and 92% specificity for diagnosing SCC. These findings suggest that dual or triple IHC markers can offer comparable sensitivity and specificity to individual markers while also minimizing the amount of tumor tissue required for accurate histological subclassification.<sup>9-12</sup>

Research encompassing a broad age range and a substantial patient cohort, particularly focused on small biopsy specimens, is limited in India.<sup>13</sup> Consequently, our study aims to fill this gap by investigating the immunoprofiling of poorly differentiated lung carcinoma using markers such as TTF1, Napsin, P63, and P40.

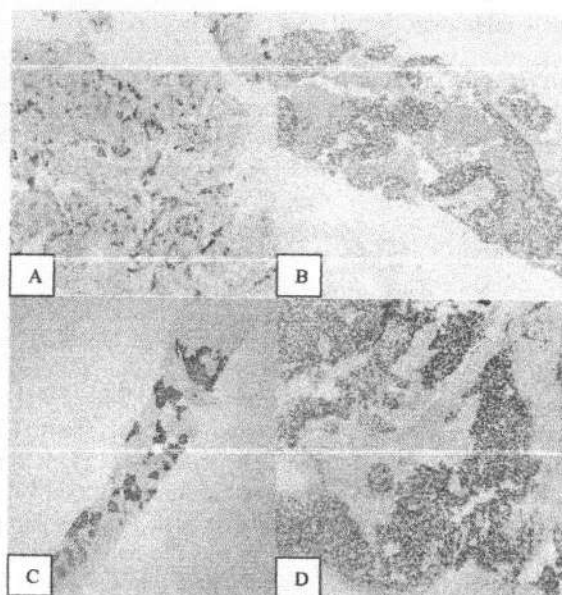
Our objective is to evaluate the practicality of IHC markers in subtyping poorly differentiated NSCLCs based on biopsy specimens. This comprehensive approach seeks to enhance our understanding of the IHC characteristics of poorly differentiated NSCLCs, particularly in the context of diverse patient demographics and the challenges posed by small biopsy samples in the Indian population.

## METHODS

The research adopted a hospital-based cross-sectional design conducted over a 4-year period (2020-2024) at Amala Institute of medical sciences, Kerala, India,



focusing on 319 histologically confirmed cases of lung carcinomas. The sample size was calculated using statistical methods ( $n = Z^2 \cdot \alpha / 2pq / d^2$ ).<sup>14</sup> The study exclusively involved small biopsy specimens from patients with poorly differentiated NSCLCs, subjected to immunohistochemical analysis using four markers: TTF-1, Napsin, p63, and p40. Exclusions comprised biopsy specimens for non-malignant lung pathology, large resection specimens, and lung biopsies with prior neoadjuvant chemotherapy or radiotherapy. The formalin-fixed endobronchial biopsy from all cases underwent processing and paraffin embedding. Multiple 3-5 mm sections were stained with hematoxylin and eosin (H and E), and subtyping of lung carcinomas was performed based on WHO classification of lung tumors.<sup>15</sup> Immunohistochemical examination employed a soluble complex method. Four-micrometer-thick sections were prepared on poly lysine-coated slides, subjected to overnight incubation at 37°C and one hour at 60°C, followed by dewaxing in xylene. Hydration, antigen retrieval, and staining procedures ensued.



**Figure 1 (A-D): A-Napsin A staining of lung biopsy specimens diagnosed as ACA. B-TTF-1 staining of lung biopsy specimens diagnosed as ACA. C-p-63 staining of lung biopsy specimens diagnosed as SCC. D-p-40 staining of lung biopsy specimens diagnosed as SCC.**

A-Granular cytoplasmic staining of lung biopsy specimens that were diagnosed as ACA. Rabbit monoclonal antibody Napsin-A was used for immunohistochemical staining. B-Nuclear staining of lung biopsy specimens that were diagnosed as ACA. Rabbit monoclonal antibody TTF-1 was used for immunohistochemical staining. C-This figure shows the nuclear staining of tumor cells in lung biopsy specimens that were diagnosed as SCC. Rabbit monoclonal antibody p-63 was used for immunohistochemical staining. D-Nuclear staining of squamous cells in lung biopsy specimens that were diagnosed as SCC. Rabbit monoclonal antibody p-40 was used for immunohistochemical staining.

The employed antibodies for immunohistochemistry were as follows: Rabbit monoclonal antibody p40, mouse monoclonal antibody p63, rabbit monoclonal antibody TTF-1 and rabbit monoclonal antibody Napsin-A.

Cytoplasmic staining indicated positivity for Napsin-A, while nuclear staining indicated positivity for TTF-1, p40, and p63. (Figure 1 A-D) Immunoreactivity was semi-quantitatively scored based on the percentage of reactive tumor cells, with pneumocytes and bronchial basal cells serving as internal controls.

Subsequent analysis, conducted using SPSS version 23, focused on immunoprofiling and its correlation with various subtypes of poorly differentiated NSCLC in terms of sensitivity and specificity. This approach aimed to identify an effective and efficient panel of two immunohistochemistry markers out of four (TTF1, Napsin-A, p63 and p40) in aiding the categorization of poorly differentiated NSCLCs.

**RESULTS**

The 319 cases of poorly differentiated NSCLC were diagnosed during the 4-year period from 2020 to 2024. Of these, ACA accounts for 65.2% (208 cases) followed by SCC 31.03% (99 cases), adenosquamous 1.2% (4 cases), not otherwise specified 0.6% (2 cases) (Figure 2).

Out of 319 cases of NSCLC 267 (83.6%) occurred in males and 52 (16.4%) in females. Incidence of NSCLC peaked among patients aged 55-69 years (Figure 3 and Table 1).

**Table 1: Age at the time of diagnosis and sex of the patient during the 4-year study period in patients with poorly differentiated NSCLC, (n)=319.**

Lung cancer cases	2019	2020	2021	2022	Total	Percent (%)
<b>Age group (in years)</b>						
0-54	13	27	19	7	66	21
55-69	28	46	53	35	162	51
≥70	18	35	20	18	91	28
<b>Sex</b>						
Male	52	89	76	50	267	83.60
Female	7	20	16	10	52	16.40

**Table 2: Statistical parameters of immunohistochemical markers Napsin-A and TTF-1.**

Statistical parameter	TTF-1	NAPSIN-A
<b>Sensitivity</b>	97.17%	83.49%
<b>Specificity</b>	92.08%	96.04%
<b>Positive likelihood ratio</b>	12.27	21.08
<b>Negative likelihood ratio</b>	0.03	0.17
<b>Positive predictive value</b>	96.26%	97.79%
<b>Negative predictive value</b>	93.94%	73.48%
<b>Accuracy</b>	95.53%	87.54%

Napsin-A and TTF-1 used for staining lung biopsy specimens diagnosed as ACA via histopathological parameters. SPSS version 23 was used for statistical analysis.

Subtyping of NSCLC was based on the algorithm followed by the IATC/ATS/ERS international multidisciplinary team.

We started off, with the hypothesis that p63 and p40 are positive in cases of SCC s whereas TTF-1 and Napsin-A are positive in ACA.

Statistical analysis showed that: In the case of ACA (Table 2), TTF-1 is the more sensitive marker with a sensitivity of 97.17% as compared to Napsin-A (83.49%) and Napsin-A is the more specific marker with a specificity of 96.04% as compared to TTF-1 (92.08%).

In case of SCC (Table 3) p63 is the more sensitive marker with a sensitivity of 93.07% as compared to p40 (78.22%) and p40 is more specific marker with a specificity of 89.62% as compared to p63 (80%), (Figure 4).

Co-expression profiles of TTF-1 and Napsin showed double positivity in 168 cases (80.7%). Co-expression profiles of p63 and p40 showed double positivity in 74 cases (74.7%).

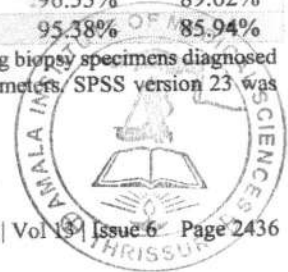
In the case of adenosquamous carcinoma both TTF-1 and p63 were seen to be positive in the 3 cases. One case of adenosquamous carcinoma showed positivity for Napsin-a TTF-1 and p63.

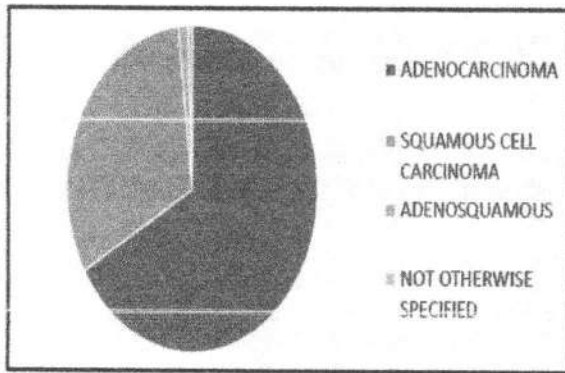
In the specimens of NSCLC NOS (not otherwise specified), a clear algorithm could not be decoded with positivity being highly variable in the 2 cases.

**Table 3: Statistical parameters of immunohistochemical markers P63 and P40.**

Statistical parameter	P63	P40
<b>Sensitivity</b>	93.07%	78.22%
<b>Specificity</b>	80.66%	89.62%
<b>Positive likelihood ratio</b>	26.86	7.54
<b>Negative likelihood ratio</b>	0.07	0.24
<b>Positive predictive value</b>	93.07%	78.22%
<b>Negative predictive value</b>	96.53%	89.62%
<b>Accuracy</b>	95.38%	85.94%

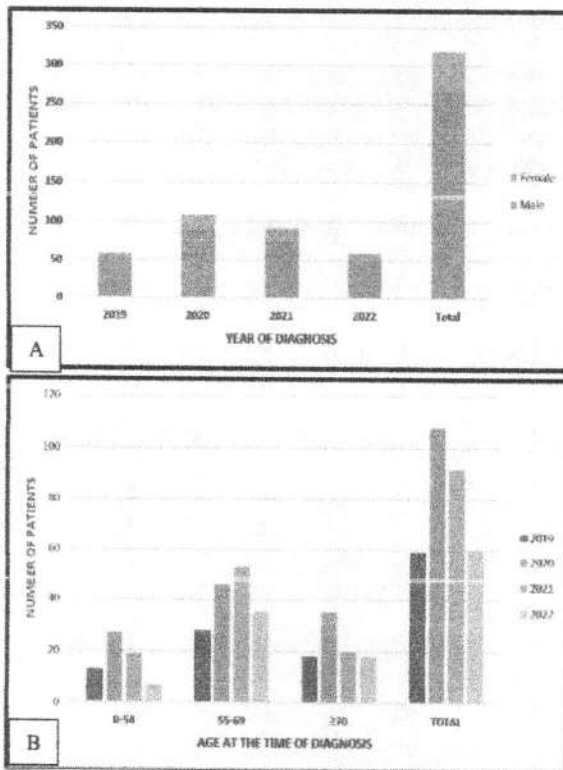
P-63 and p-40 used for staining lung biopsy specimens diagnosed as SCC via histopathological parameters. SPSS version 23 was used for statistical analysis.





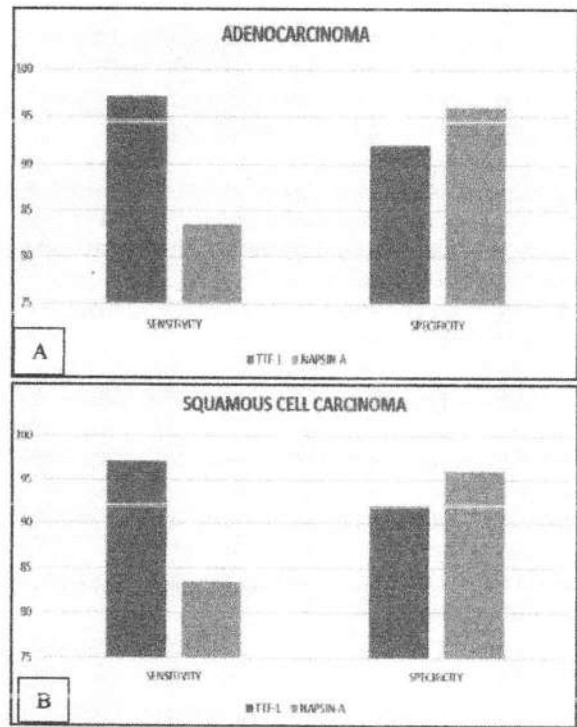
**Figure 2: Final diagnoses of the patients in the study group.**

This chart shows the relative prevalence of the different non-small cell lung cancer subtypes based on histopathology which was taken as our gold standard-ACA: (65.20%), SCC: (31.03%), adenosquamous: (1.20%), not otherwise specified: (0.60%)-(not otherwise specified refer to the samples which show an uncertain histopathology as a consequence of small sample sizes and highly heterogeneous tumors, which limit the consistency and accuracy of subtyping using bronchoscopic biopsies.



**Figure 3 (A and B): A-Gender distribution and year of diagnosis of patients with poorly differentiated NSCLC. B-Age at the time of diagnosis during the 4-year study period in patients with poorly differentiated NSCLC.**

A-The graph shows an 83.6% prevalence in males and 16.4% in females. B-The incidence of NSCLC peaked among patients aged 55 to 69 years.



**Figure 4 (A and B): Sensitivity and specificity of immunohistochemical markers Napsin-A and TTF-1. B- Sensitivity and specificity of immunohistochemical markers p-63 and p-40.**

Used for staining lung biopsy specimens diagnosed as ACA via histopathological parameters. SPSS version 23 was used for statistical analysis. In the case of ACA, TTF-1 is seen to be the more sensitive marker whereas Napsin-A is the more specific marker. Used for staining lung biopsy specimens diagnosed as SCC via histopathological parameters. SPSS version 23 was used for statistical analysis. In the case of SCC, p-63 is seen to be the more sensitive marker whereas p-40 is the more specific marker.

**DISCUSSION**

Lung cancer is the leading cause of adult cancer-related deaths in most countries, and non-small-cell carcinomas comprise about 80% of these cases.<sup>16</sup> The global lifetime risk of developing lung cancer is estimated to be 1 in 13 for men and 1 in 16 for women, with smokers facing a markedly higher risk compared to non-smokers. Despite significant advancements in therapeutic strategies over the past few decades, the prognosis for lung cancer patients remains dismal, with a 5-year overall survival rate stagnant at around 15%. This underscores the urgency for continued research and innovation in early detection, prevention, and treatment modalities to improve patient outcomes.<sup>15,17</sup>

This 4-year analysis represents one of the largest single-center studies in India, focusing on a substantial sample size of non-small cell lung cancer cases and uncovers several notable trends. The average age of our patients was 60 years, which is similar to that reported in previous studies conducted on Indian cohorts.<sup>18,19</sup> Our study showed



a peak in incidence among patients aged between 55-69 years. While the risk of developing lung cancer rises significantly after the age of 70, our study included fewer patients in this age group, likely due to mortality from other causes and comorbidities before a lung cancer diagnosis could be made.

Our study population showed a male predominance across the 4 years which is in accordance with Indian studies which reported similar findings.<sup>18,19</sup> No change in this trend was noted during the study period.

Of the 319 cases of poorly differentiated NSCLC ACA accounts for 65.2% followed by SCC 31.03%. This is similar to the studies of Thai et al and Travis et al which showed 50-60% of ACA cases and 20-30% of SCC cases in their respective study populations.<sup>20,21</sup>

Since the 2004 WHO classification, therapeutic advances for NSCLC have been closely linked to precise histologic classification. Morphologic diagnosis forms the basis of diagnosis of NSCLC and is further supplemented by a panel of immunohistochemical markers. Tumor cells in ACA are positive for TTF-1, Napsin and cytokeratin-7. SCCs are positive for p-63, cytokeratin-5/6 and NTRK-1 and NTRK-2.<sup>15</sup> These developments have underscored the importance of distinguishing between subtypes of NSCLC, as treatment responses vary significantly. For example, patients with ACA or NSCLC-NOS have shown greater responsiveness to pemetrexed compared to those with SCC.<sup>22</sup> Additionally, the use of bevacizumab in lung cancer treatment has raised concerns, as it has been associated with life-threatening hemorrhage in patients with SCC, leading to its contraindication in this subgroup.<sup>23</sup> These findings emphasize the critical role of accurate histologic classification in guiding treatment decisions and improving patient outcomes.

TTF-1 has long been the predominant IHC marker for identifying lung ACA, with a reported sensitivity of 75% to 80%. However, TTF-1 is not entirely specific to lung tissue, as it can also stain other tissues and tumors, including thyroid tissue, metastatic breast carcinoma, and neuroendocrine tumors like small cell lung carcinoma and carcinoid. TTF-1 is a nuclear protein, that regulates the transcription of lung-specific genes for surfactant and Clara cell secretory proteins. Additionally, TTF-1 expression decreases with tumor dedifferentiation, making poorly differentiated ACAs less likely to express this marker.<sup>24</sup>

Bishop et al observed that 69 of 95 (73%) ACA s to be positive for TTF-1, whereas Folpe et al and Kaufmann et al also observed TTF-1 expression in 90-100% of small cell lung carcinomas.<sup>24-26</sup> Studies by Balakrishnan et al also observed 100% sensitivity and specificity for TTF-1 in diagnosing ACA.<sup>14</sup>

Recently, Napsin-A has emerged as a novel marker for lung ACA, particularly for well to moderately

differentiated tumors. Napsin is also a promising marker and has been detected in the cytoplasm of type 2 pneumocytes and alveolar macrophages.<sup>27</sup> Studies have shown that Napsin-A performs comparably or even better than TTF-1 in determining lung origin in these cases. Napsin A has been evaluated on surgically resected lung cancers and has been found to be positive in a recent study in 79 of 95 (83%) of lung ACA s and negative in all 46 lung SCC in the study by Bishop et al.<sup>24</sup> Napsin A is moderately sensitive (79-85%) and highly specific (100%) for ACA.<sup>15</sup>

However, in our study, TTF-1 demonstrated a higher overall sensitivity (97.17%) compared to Napsin (83.49%). Napsin-A expression is also noted in the cytoplasm of normal lung cells and kidney cells, as well as in renal cell carcinomas, which must be considered when interpreting results.<sup>8,26,27</sup>

Our findings are consistent with previously reported studies, which demonstrate the usefulness of TTF-1+Napsin A dual color immunostaining in distinguishing lung AD C versus SCC.<sup>28,29</sup> Stoll et al have also reported that combined application of Napsin A and TTF-1 immunomarkers may be necessary to improve diagnostic accuracy in lung ACA.<sup>30</sup>

The human 'p63' gene, located on chromosome 3q27-29, produces two types of proteins through two promoters: the full-length TAp63, containing the N-terminal transactivation domain, and the truncated  $\Delta$ Np63, which lacks this domain. The  $\Delta$ Np63 isoform can be specifically identified by the p40 antibody, while the full-length TAp63 is detected using the p63 antibody (4A4). p63 is expressed in the normal respiratory epithelium of the central air conducting system and does not carry any prognostic implications in NSCLC patients.<sup>31</sup>

Recent studies have demonstrated that p40 exhibits exceptional performance in identifying SCC, with reported sensitivity and specificity of 100% and 98-100%, respectively. Antibody p40, identifies  $\Delta$ Np63, its use for distinction of lung SCC and ACA was only recently studied. p40 is consistently predominant isoform expressed in SCC.<sup>23</sup> Studies by Bishop et al and Nonaka showed that p40 has 100% sensitivity and specificity in lung SCC.<sup>25,33</sup> Another study by Tacha et al reported an 85% sensitivity and 98% specificity.<sup>34</sup>

The sensitivity of p-63 ranges from 75% to more than 95%, whereas the specificity for SCC is between 70% and 100%.<sup>15</sup> Immunostaining for p63 has been described as the single best marker to separate ACA from SCC, with a sensitivity of 84%, and specificity of 85% for SCC.<sup>35</sup>

In our study, p63 was observed to be the more sensitive marker, with a sensitivity of 93.07%, compared to p40's 78.22%. Conversely, p40 showed greater specificity at 89.62%, compared to p63, which had a specificity of 80%. These findings suggest that p63 and p40 offer

complementary roles in SCC diagnosis, with p63 providing higher sensitivity and p40 offering greater specificity.

The co-expression analysis of TTF-1 and Napsin-A revealed that both markers were positive in 168 cases (80.7%), highlighting their strong association with ACA phenotypes. In the study conducted by Fatima et al showed that dual TTF-1/Napsin A has a sensitivity of 74% and specificity of 87% for diagnosing ACA and, hence, is useful in differentiating ACA from SCC.<sup>9</sup>

Similarly, co-expression of p63 and p40 showed dual positivity in 74 cases (74.7%), affirming their relevance in SCC diagnosis. Notably, in the three cases of adenosquamous carcinoma, TTF-1 and p63 were both positive, indicating the mixed histologic nature of these tumors.

Analysis of co-expression profiles showed that co-expression of p63 and CK5/6 irrespective of TTF1 and co-expression of p63 and CK5/6 in TTF-1 negative tumor both were 100% sensitive and specific for SCC s in a similar study conducted in an Indian cohort.<sup>14</sup> Further it was also observed that TTF-1 positive and p63 negative co-expression profile showed 100% specificity in diagnosing ACAs.<sup>14</sup>

Interestingly, one case of adenosquamous carcinoma demonstrated triple positivity for Napsin A, TTF-1, and p63, further supporting the dual differentiation of these tumors. However, in the specimens of NSCLC-NOS, a consistent immunohistochemical algorithm could not be established due to the highly variable expression patterns observed in the two cases, underscoring the diagnostic challenges in this heterogeneous group.

This study provides valuable insights into the immunohistochemical characterization of poorly differentiated NSCLCs, yet several limitations must be acknowledged to contextualize the findings. The research was confined to a single tertiary care center, which may introduce institutional bias and restrict the broader applicability of the results. Inclusion of multiple centers with diverse patient populations would strengthen generalizability.

Molecular profiling was not incorporated into the study design. The addition of targeted mutation analysis, such as EGFR, ALK, or ROS1, could have enhanced diagnostic precision and aligned the findings with current trends in precision oncology. Another constraint lies in the lack of clinical follow-up. Without longitudinal data on treatment response or survival outcomes, the prognostic relevance of the immunohistochemical profiles remains uncertain. This limitation was further compounded by challenges during the COVID-19 pandemic, which likely introduced follow-up bias due to delayed investigations and missed visits, affecting long-term data collection.

The use of semi-quantitative scoring to assess immunoreactivity introduces potential interobserver variability. Employing digital image analysis or blinded assessments may improve reliability and reproducibility. While the study utilized a well-established panel of four markers-TTF-1, Napsin-A, p63, and p40-this focused approach may limit diagnostic accuracy in morphologically ambiguous cases. Expanding the panel to include additional markers such as CK5/6 or CK7 could enhance subtype differentiation. Overall, the study underscores the diagnostic utility of immunohistochemistry in poorly differentiated NSCLCs. Nonetheless, broader multicentric validation and integration with molecular and clinical data are essential for improving diagnostic fidelity and clinical applicability.

## CONCLUSION

A two-marker IHC panel consisting of TTF-1 and p63 shows 91.13% accuracy, 90.39% sensitivity, and 75.83% specificity, making it a cost-effective alternative in resource-limited settings. However, lower specificity suggests some cases may require additional markers such as Napsin A, p40 for definitive subtyping, ensuring greater diagnostic confidence where needed.

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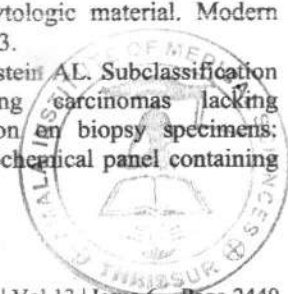
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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