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CONTENTS

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Editorial

Contributions to medical literature by Indus Hospital Health Network through Research

Shaukat Ali Jawaid

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Ever since the establishment of Indus Hospital Health Network (IHHN) by Dr. Abdul Bari and his colleagues, they have made a commendable progress and practically demonstrated that provision of free tertiary care is possible with the help of philanthropists and donors. It only becomes possible once an institution has earned credibility and the donors are confident that their contributions are being used judiciously for the purpose they are made.

Starting with a major hospital at Karachi, IHHN has now expanded its network in the country and this institution has emerged as an important non-governmental player in health sector. It offers treatment facilities in almost every discipline of medicine with a multidisciplinary team approach with exceptional results. Apart from providing healthcare, it also realized the importance of documentation and publication for which they established a Research Department. Hospitals in Pakistan are considered as goldmine of data offering innumerable opportunities for research but most of them lack proper record keeping hence the data needed for research publications is not easy to find. However, IHHN knowing its importance managed to install the Health Information Management System which makes their researcher's job easy. Since the researchers are also lucky to get help, guidance and assistance from the Research Department, IHHN faculty members and postgraduate trainees have managed to complete numerous research project thus showcasing their research work at international conferences which IHHN holds regularly and much of this research work is also published.

We in Pakistan Journal of Medical Sciences published a special issue at the time of their last conference ICON 2021. This year too, we were approached and after initial discussions on working modalities, the project was started in March 2021. As agreed IHHN provided us manuscript after peer review by two reviewers which were then finally reviewed and edited by our editorial team before they were accepted for publication in this "Only Online Edition". The workshop that we organized at Indus Hospital on Medical Writing and Peer Review during 2020 was very helpful and the experience which the IHHN Research Department gained while working with us last year proved very helpful with the result that this time it was mostly a smooth sailing.

This special issue covers some very important subjects. Faiza Ahmed and colleagues in their write up has highlighted the knowledge and perceptions of sepsis among doctors. Sepsis, they have concluded remains a challenge to treat, it is often misdiagnosed. Early diagnosis and prompt management is the key to improving the outcome.[1]

Asthma severity and hospital admissions measured by PRAM score have been discussed by Kazi et al. Their conclusions are that this score is the best predictor for the need for hospitalization for these patients suffering from asthma. They have suggested that this should be put to use in clinical practice in paediatric emergency

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departments. They suggest better facilitation of intensive therapy of patients at triage which will decrease the need for hospitalization.[2]

Obstructive lung disease is an important NCD. According to Saima Saeed and colleagues the OLD programme at IHHN uses capacity building, gold standard diagnostic and management strategies in primary care. This enables early diagnosis of suspected patients which improves the morbidity and mortality. [3]

Drug resistant tuberculosis remains yet another important problem in Paksitan. Nazia Khursheed and colleagues have identified in their study a number of such cases. They have advocated development of new strategies to reduce the spread of this disease.[4]

Safety and efficacy of Remdesivir on mortality and length of stay in hospitalized Covid19 patients has been studied by Quratulain Shaikh et al., in this prospective cohort study which enrolled two hundred sixty eight patients. The findings of this study showed that there was no difference in in-hospital mortality while length of stay was longer in these patents. In addition more patients had severe ARDS in the RDV group.[5]

Ensuring privacy and confidentiality while examining a patient is extremely important but unfortunately practically it is not possible in overcrowded Out Patients Departments of public hospitals. Syed Ghuzzanfar Saleem et al studied the patient's perceptions on this issue who visited the emergency department of Indus Hospital Adult Emergency Department. They found out that despite overcrowded and busy environment patients generally felt that privacy and confidentiality were maintained which must be very satisfying for the hospital administration.[6]

There are numerous other studies covered in this special issue which shed light on many important subjects which the researchers have discussed which make an important reading.

We are delighted to be a part of this project and by offering highly concessional publication charges despite the massive devaluation of the currency, we have contributed our share to promote and project the image of this remarkable institution of which the country should be proud of. In future too, we will be delighted to help, assist and cooperate with IHHN to showcase its research work thereby making significant contribution to the world medical literature from Pakistan. We are extremely grateful to the management of IHHN for providing us this opportunity and the two Guest Editors Dr. Farhana Amanullah and Dr. Naila Baig Ansari for their hard work in compiling, this special supplement.

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Note from Guest Editors

ICON 2022 Supplement

Farhana Amanullah[1], Naila Baig-Ansari[2]

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COVID-19 pandemic has taken a distinct toll on routine health service provision, taking away precious lives, resources and health staff focus that none of us have ever witnessed before. During these testing times, the Indus Hospital & Health Network quickly adapted itself to ensure our services were available and the demands of COVID-19 treatment, both in the hospital as well as the community, were met. While IHHN rapidly partnered with stakeholders and participated in much needed clinical research including international drug and vaccine trials, the spirit of action and self was exhibited by all our staff, whether frontline, ancillary or support with the same zeal and courage. And thus, it was only befitting that our ICON 2022 theme would be called "Beyond the Call of Duty", especially dedicated to the spirit of intense courage and personal sacrifice that our health staff displayed throughout the difficult COVID-19 waves.

Our journal supplement also carries this theme, as it highlights work that clinicians and researchers from over 22 specialties have produced above and beyond their routine work in this all-consuming pandemic. We have deliberately opted for only an online version of this supplement as a direct tribute to the global medical community's swift adaptation to virtual conferences and online meetings as well as a reflection of Indus' paperless hospital concept. Writing an academic article requires collaboration, expertise and time. It is commendable that those who submitted their articles managed to carry out their clinical duties as well as coordinate their academic work during the pandemic's multiple waves. Our publication committee received 32 submissions that underwent double blind peer review. Fourteen original articles, three case reports, one correspondence and one review article were accepted for publication. The articles were diverse and not necessarily focused towards COVID-19. In fact, only four articles are related to the pandemic even though a lot more COVID-19 related research took place at IHHN.

We understand that when international collaborations take place or there is unique research from Pakistan, authors prefer submitting to international indexed journals over local ones. This phenomenon will change when more and more Pakistani journals are indexed and the turnover time for publication is reduced. As such, we are especially thankful to all the authors for their faith in submitting an article to this conference supplement to showcase IHHN's research capabilities. We are also grateful to our publication committee for their detailed reviews and feedback for improving manuscripts and for collaborating with other reviewers. Our excellent publication coordinator ensured efficient correspondence between reviewers and authors, as well as with the Pakistan Journal of Medical Sciences' publication team, to ensure the production of this special ICON edition.

It is our hope that this supplement will continue to encourage and inspire Indus' clinicians to work towards and contribute to future editions.

1. Farhana Amanullah
2. Naila Baig-Ansari
Guest Editors,
ICON 2022 Supplement.

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Original Article

The Obstructive Lung Diseases Program: Integrated obstructive lung disease services within primary care in Pakistan

Saima Saeed[1], Madiha Siddiqui[2], Rahma Altaf[3]

ABSTRACT

Objective: To assess the learning impact of e-curriculums on healthcare professionals (HCPs). The second objective was to report the screening, detection and clinical features of patients with obstructive lung diseases (OLD) through an integrated care program at The Indus Hospital & Health Network (IHHN), Karachi, Pakistan.

Methods: A retrospective, observational study was conducted in the Family Medicine outpatient department from January 2019 till July 2021. HCPs were trained on the diagnosis and management of OLD through e-learning. Patients were screened clinically for OLD and had spirometry performed if suspect. Baseline characteristics, patient-reported outcome measures (PROMs), spirometry and treatment modalities were collected. Univariate analysis was done on Excel and paired t-testing was performed on Stata 16.

Results: Online training on clinical aspects of OLD was completed by 33 HCPs, amongst whom 77.9% demonstrated improved post-test evaluations of 26.8% (p=0.000). Of 1896 patients screened, 60.8% were diagnosed as OLD. Asthmatics accounted for 66.5% (60.9% females, median age 39 years). In 84.5% of patients who completed PROMs, poor control of symptoms was reported. Inhaler technique was taught in 66.5%. Breathless patients, with a high modified Medical Research Council score (mMRC ≥ 2, n=234), were referred for pulmonary rehabilitation in 92% of cases. Tobacco cessation advice was delivered to 61.1% of all current users (n=229).

Conclusion: The OLD program uses capacity building, gold standard diagnostics and updated management strategies in primary care, allowing earlier diagnosis of suspected patients and implementation of evidence-based interventions, aiming to improve their morbidity and mortality.

KEYWORDS: Obstructive lung disease, E-curriculums, Integrated care program, Spirometry.

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INTRODUCTION

Non-communicable diseases (NCD) are gaining recognition globally, and are a major public health challenge. In a ten-year review, the World Health Organization (WHO) declared chronic respiratory diseases (CRD), affecting the lungs and airways, one of the four most detrimental NCDs.[1] These include Obstructive Lung Diseases (OLD), namely Chronic Obstructive Pulmonary Disease (COPD) and asthma, prevalent worldwide.[2] Generally, clinical presentation is with breathlessness, cough, and wheeze. Breathlessness is scored using four-point,

modified Medical Research Council (mMRC) score which increases with intensity of dyspnea. Cumulative exposure to tobacco and biomass can contribute to both the pathogenesis (especially of COPD) and acceleration of disease. Spirometry is the diagnostic test of choice and is performed to detect airflow obstruction. Patient-reported outcome measures include Asthma Control Test (ACT) and COPD Assessment Test (CAT), documenting symptom control. Treatment focuses on inhaled bronchodilators and steroid therapy, which may be difficult for patients to use correctly. Inadequate therapy and poor technique may lead to disease flare ups ("exacerbations") requiring emergency care. Optimizing treatment type and technique, and interventions such as tobacco cessation advice, prophylactic vaccination against pneumococcus and influenza, risk factor avoidance and pulmonary rehabilitation (PR) are highlighted in international guidelines for the management of asthma (GINA)[3] and COPD (GOLD).[4] These evidence-based strategies are designed to address the morbidity and mortality of these CRDs.

In low-middle-income countries (LMICs), the prevalence of COPD and asthma cannot be fully understood due to underdiagnosis,[5] yet a recent systemic review showed over 80% of deaths were attributed to them[6]. In South Asia, these diseases accounted for 8% of all Disability–Adjusted Life Years.[7] The need for increasing general awareness about COPD and access to diagnostics has been highlighted in LMICs.[8] Careful estimates of the prevalence of COPD and asthma in Pakistan are 2.1% and 4.3% respectively.[9] With 61.4% of the Pakistani population residing in rural areas, the lack of strong primary care healthcare systems leads to reduced accessibility to health facilities for vulnerable populations.[10] The most recent local paper dates back to 2011 where adherence to asthma guidelines was suboptimal amongst Karachi general practitioners.[11] Additionally, 20% of Pakistani adults smoke tobacco[12] and there is increased tobacco consumption amongst the youth.[13] Indoor and outdoor biomass exposure such as wood burning stoves leads to airflow limitation and development of comorbid conditions like lung cancer.[14] Spirometry, inhaler technique review, patient counselling and PR programs are also not widely available.[15]

Only 20% of the estimated asthma and COPD cases are currently being identified and diagnosed in primary care in Pakistan.[15] This issue may be addressed using an integrated, multidisciplinary approach as seen in integrated practice units (IPU) and integrated care programs (ICP). IPUs provide comprehensive services for a medical condition using a multidisciplinary approach. An ICP offers seamless care across multiple health and non-health sectors to optimize patient-centric outcomes. Indus Hospital and Health Network (IHHN) has an expanding primary care program with 25 primary care facilities and 12 standalone clinics nationwide.[16] Opportunities thus exist for targeted capacity building and the integration of lung health services at the patients first port of call, coordinating and unifying the approach to these common CRDs.

METHODS

Training: An e-learning platform, Canvas, was used to train relevant healthcare professionals (HCP) in four modules: spirometry, COPD, asthma and inhalers. Bespoke modules were developed based on internationally accepted guidelines.

Each module consisted of a (1) thirty-minute pre-course assessment, (2) overview, (3) main objectives, (4) marking criteria, (5) course content and (6) thirty-minute post-course assessment. Illustrations, algorithms and quizzes were added to enhance the course content.

Both pre- and post-course assessments involved ten questions in a case-based format. Marking criteria stipulated scores greater than 70% as passing and eligible for completion certificates while lower scores are offered a re-attempt option to be completed within the same week.

The module learning cycle had a four-week format:

- **Week zero:** Pre-course assessment,
- **Week one and two:** HCPs read through course content,
- **Week three:** Post-course assessment,
- **Week four**: Pre- and post-course assessment results compiled and distributed; re-attempts offered where necessary.

Learning was supported by online and selected in-person interactive sessions where needed. Nurses further shadowed Consultant Pulmonologists in outpatients to become Specialist Lung Health nurses.

Study Design: A retrospective, observational study was conducted at the Family Medicine outpatient department at The Indus Hospital – Korangi campus from January 2019 to July 2021. Patients with breathlessness, wheeze, cough and other clinical features suggestive of OLD were referred for evaluation. Characteristics including

demographics, occupation, comorbidities, biomass exposure and tobacco status were captured. Spirometric data with reversibility was used to diagnose asthma and COPD and to assess severity of obstruction using Forced Expiratory Volume in first second (FEV1) values. Patient-reported outcome measurements were used to assess control of disease, CAT ≥ 10 and ACT ≤ 19 showing poor control (Table-I). Numbers of annual exacerbations of disease and mMRC were also recorded. These variables were used to derive the GOLD staging in COPD. Management strategies were identified using frequency of medications, inhaler technique, tobacco cessation advice and percentage of PR referrals.

Analysis: An electronic data collection tool, REDCap, was used for data collection. Excel was used for univariate analysis. Quantitative data was expressed as percentage and median (interquartile range (IQR)) where appropriate. Stata 16 was used for statistical testing (paired t-test) with significance set at $p < 0.01$. Ethical approval was obtained from the Institutional Review Board IRD_IRB_2020_05_013 and IRD_IRB_2021_05_021.

Table-I: Asthma Control and COPD Assessment Tests.

	Asthma Control Test (ACT): Each question is scored from 1 to 5 points, where 1 is the worst score (most frequent)
Q1	Activity level affected at work, school or home
Q2	Shortness of breath
Q3	Sleep quality
Q4	Reliever medication frequency
Q5	Asthma control perception
	COPD Assessment Test (CAT): Each question is scored out from 0 to 4 points, where 5 is the worst score (always present/ impaired)
Q1	Cough
Q2	Phlegm
Q3	Chest tightness
Q4	Shortness of breath
Q5	Activity level
Q6	Ease of leaving home
Q7	Sleep quality
Q8	Energy level

RESULTS

Training: A total of 33 HCPs (30 primary care physicians and three nurses) enrolled in the online training modules (Fig.1). Each physician took the inhalers, COPD and asthma course and three nurses took spirometry courses. When comparing cumulative pre- and post-course assessment scores, 77.9% showed an improvement in knowledge scores by 26.8% (99% CI; 0.99-2.36; p=0.000).

Baseline characteristics: Since 2019, a total of 1896 patients were screened on first visit. Of these, 60.8% were diagnosed as OLD on both spirometric and/or clinical grounds. Asthma (66.5%, n=767) was more common in females (60.8%) with a median (IQR) age of 39 (28-50) years and COPD (33.5%, n=387) in males (79.1%) with a median (IQR) age of 60 (50-67) years (Fig.2). By occupation, most patients (n=96) worked in textile (12.5%), construction (8.3%) and transportation (6.3%). Comorbidities were present in 26.3% with hypertension (17.4%), diabetes (10.2%) and ischemic heart disease (1.6%) being common. Comorbidities were more prevalent in asthmatic patients (55.9%). A history of burnt biomass exposure (wooden stoves, 14.2% and fumes, 5%) was seen in asthma (24.9%) and COPD

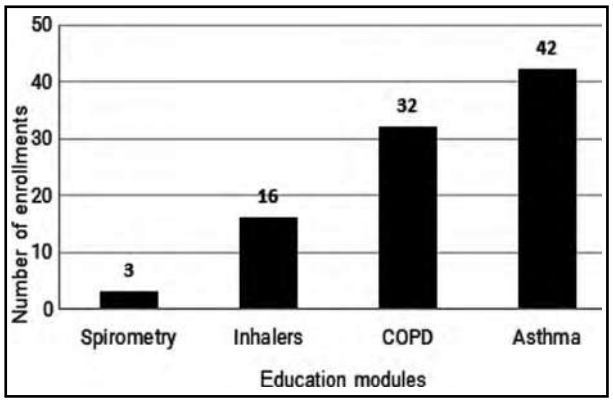

Fig.1: Total number of enrollments per module.

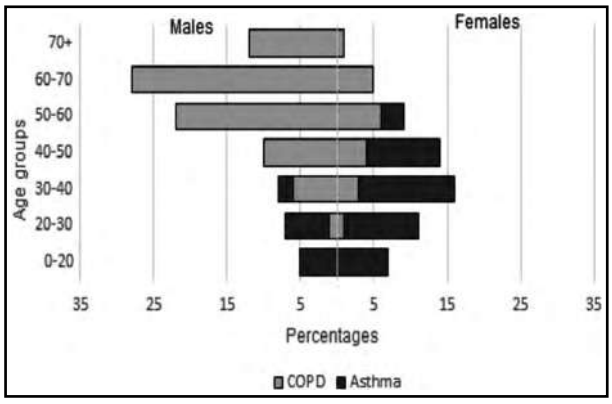

Fig.2: Population pyramid for obstructive lung diseases.

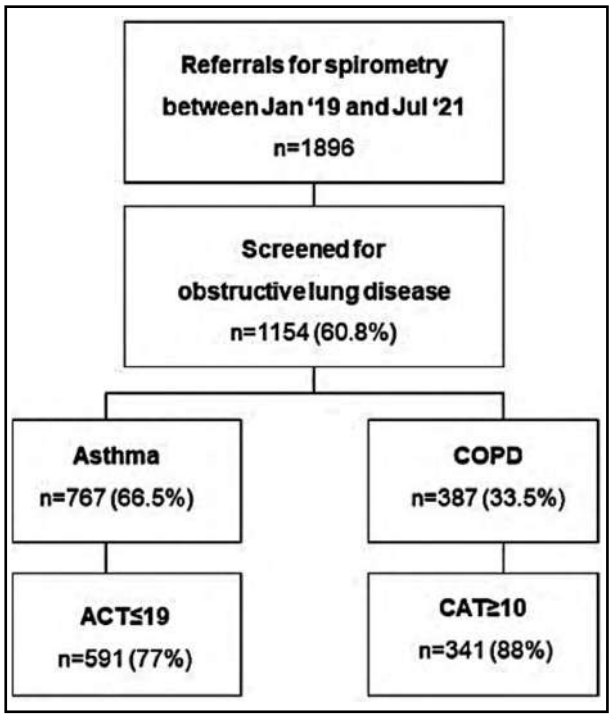

Fig.3: Obstructive lung disease and severity

(29.2%) with median (IQR) exposure of 15 (10-25) years. Tobacco use was identified in 479 patients whilst 50.9% were current users. Of these, 34% were smokers and 16.9% consumed smokeless tobacco. Smoking history was reported in 22% of asthmatics.

Diagnostics and PROMs: Baseline spirometry was offered to all suspected OLD cases (n=1154). A diagnosis of OLD was based on spirometry in 845 cases (73.2%) whilst clinical diagnosis alone accounted for 309 (26.8%). Airflow obstruction ranged from severe to very severe intensity in 42.6% of COPD and 32.5% of asthma cases. Using mMRC, 45.2% of OLD patients scored two or above. CAT scores in COPD showed 88% had poor symptom control whilst ACT scores demonstrated uncontrolled asthmatic disease in 77% (Fig.3).

Staging for COPD patients showed 11.6% at GOLD stage A (less risk, less symptoms), 31.3% stage B (less risk, more symptoms), 1.3% stage C (high risk, less symptoms) and 55.8% at stage D (high risk, more symptoms). Two or more exacerbations requiring increased therapy (oral steroids and/or antibiotics or increased reliever medication) were seen in 42% of OLD patients.

Management: Of 1129 OLD patients, 54% had inhaled therapy prescribed. This included combined inhaled corticosteroid and long-acting beta 2-agonists (ICS/LABA, 39.3%), short-acting beta2-agonists (SABA, 28.2%) and long-acting antimuscarinics (10.2%). Montelukast (31.4%) was prescribed as an add-on oral therapy. Inhaler technique was taught in 66.5%. Those with mMRC score of two and above (n=234) were referred for PR in 96.2% of cases. Advice on tobacco cessation was delivered to 61.1% of all current users (n=229).

DISCUSSION

Integration of the OLD program into Family Medicine through training and formal diagnostics showed that (1) e-curriculums enable improved HCP knowledge of OLD, (2) asthma was more common than COPD, was associated with more co-morbidities and was predominant in females. In this population, a high prevalence of biomass exposure and both smoking and smokeless tobacco use was noted in both asthma and COPD. Spirometry revealed advanced disease in over half the patients with OLD.

The OLD program is an integrated care program where CRDs, namely asthma and COPD, are diagnosed and managed in primary care and to our knowledge is the first of its kind in Pakistan. Implementation strategies for interventions in lung health in LMICs have been suggested by Brakema and colleagues.[6] They collated and interpreted implementation challenges to provide a broad toolkit for LMIC. Similar strategies are emphasized in the WHO package of essential noncommunicable disease interventions for primary care, aiming to bridge the gaps in universal health coverage for those impacted with NCDs.[17] In line with this, we aimed to identify and address local challenges in integration, by gaining stakeholder and resource support. Primary care facilities at IHHN were conducive to program integration with HCP training, thereby providing an ideal platform for further OLD implementation.

Through our e-learning platform, HCPs were introduced to updated, evidence-based learning material covering all aspects of OLD in a flexible and accessible manner. In Pakistan, a precedent for e-learning was reported by The Aga Khan University. Their massive open online course on Drug Discovery was well received by participants.[18] Several postgraduate online courses in India and other LMICs were reported by Gupta and colleagues.[19] Meanwhile, in Latin America, a tobacco cessation module was successfully completed by hospital-based HCPs online and the value of sharing resources amongst culturally similar countries emphasized.[20] All highlighted

the need for strong organizational and resource support for success in e-learning. The value of digital medical education is being emphasized both in LMICs[21] and worldwide.[22]

In our experience, limitations to training were seen as HCP turnover interrupted the e-curriculum format and created lag time. Internet access was variable. Training time was often compromised by other clinical activity during the work day, delaying completion. Importantly, whilst pre- and post-test evaluations demonstrate improved learning, we cannot conclude a clear link with improved diagnosis of OLD within the constraints of this work. This is similar to the e-learning strategy reported in the UK, teaching fundamentals of prescription writing and causes of prescription errors. Whilst pre and post course assessments done on general practitioners and pharmacists demonstrated scores increased by 17.4%, the impact on patient outcomes could not be established.[23]

Our data collection methods were online and easily accessible. This information can be interrogated to provide important epidemiological data on these poorly documented NCDs. Notably the population selected for confirmation of OLD were likely suspects of disease, so true incidence and prevalence figures cannot be reliably interpretated. Patients with OLD are more likely to abuse tobacco, we identified 34% were smokers of our patient, higher than the national average.[12] The strength of the program is the high detection of OLD based on clinical screening. As the program gains traction, a database of clinical findings, diagnostics and management strategies can be reported. The method of data collection also aides monitoring and evaluation, simplifying performance of clinical audit and ensuring clinical governance. Similar to e-learning, limitations involve consistent internet access and time for training and data entry.

Amongst patients who were screened for OLD, 16.2% were unable to perform spirometry in their first visit. Technicians performing spirometry have an important role in appropriate coaching but factors such as worsened breathlessness, coughing or communication issues can still limit outcomes. Where spirometry provides a gold standard for diagnosis, its absence relies on clinical judgement and we noted 26.8% of diagnosed OLD patients had no spirometry performed. Meanwhile, despite careful HCP training, we found inadequate inhaler therapy prescription in some patients. Our program could not evaluate the causes of this, which may include unaffordability, lack of compliance or need for remedial training of HCPs. Advice on tobacco cessation was missing in 59% eligible cases, possibly demonstrating a gap in training.

Spirometry completely halted in April 2020 in view of the COVID pandemic, as it is an aerosol generating procedure likely to spread disease. This limitation inevitably impacted program performance and data collection. Since August 2020, services were restarted with careful verbal screening by technical staff who were otherwise in full personal protective equipment and were relocated to ventilated areas. A pragmatic approach to continue services, as done worldwide, was therefore adapted.

The programmatic requirements of extensive data collection and highly trained resources for each patient may serve as a limitation by proving expensive and difficult to further integrate. However, the program provides an evidence-based package, impacting both the patient and their health ecosystem. Patients may have improved self-awareness and slower decline in lung function. Meanwhile, the health system may have a reduced burden of emergency visits and hospitalizations. A complete cost-benefit analysis is warranted to evaluate this further. Other potential areas of development include development of home-based support both in the medical and non-medical sectors, completing the cycle and becoming truly integrated practice units and integrated care programs.

CONCLUSION

The Obstructive Lung Disease program has shown itself to be a useful primer for establishing a sustainable and scalable integrated care program within primary care. It has used innovative training models, dealt with implementation challenges and provided learning opportunities on how to develop further. Providing evidence-based care for common NCDs begins to address the Sustainable Development Goals (good health and well-being and quality education in LMICs) within Pakistan. Further expansion is planned to protect the health of our communities.

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Authors' Contribution:

SS: Conception and design, program development, drafting the manuscript, revision for accuracy an is responsible for integrity of the study.
MS: Educational module development, data interpretation, manuscript drafting, revision for accuracy.
RA: Design of data collection tools and acquisition of data, computations and analysis, manuscript drafting, revision for accuracy.

Open Access

Original Article

Wound closure after total knee replacement: Comparison between staples and sutures

Mansoor Ali Khan[1], M. Waseem Memon[2], Amin Chinoy[3], Salman Javed[4], Rahil Barkat[5], Ahsun Jiwani[6]

ABSTRACT

Background and Objective: Total Knee Arthroplasty is a commonly performed procedure for arthritic knees. Preventing complications is of utmost importance for good functional outcomes and preventing morbidity. Wound closure after the procedure is as important as the replacement aspect of surgery.The objective of this study was to provide subjective and objective evidence of better closure technique and material; we conducted the study so that the outcome of TKA can be further improved

Methods: We conducted a randomized trial at The Indus Hospital, Karachi, from December 2018 to June 2020. All patients from age 40 to 70 years who underwent total knee arthroplasty were included in the study. The wound of one knee was closed with Polypropylene (Prolene) sutures, and the other with staples. The wound was assessed independently by two assessors using Hollander's score; lower score means a worse outcome. All data was entered and analyzed using STATA version 16.

Results: Thirty patients who underwent bilateral total knee replacement were included in the analysis, among which 71.8% were female. The average age of participants was 57.3 (± 7.5) years. The mean incision length on the right knee was 17.6 ± 1.1 cm, while on the left the incision length was 18.3 ± 1.2 cm. Overall, the mean Hollander score was significantly different among participants in the sutures and staples group in both the right (p-value=0.001) and left knees (p-value=0.001). The score was significantly higher in knees closed with sutures as compared to staples. Also, the mean Hollander score is significantly higher in females than males in both the right knee (B=0.56, p-value=0.049) and the left knee (B=0.38, p-value=0.044).

Conclusion: The study has shown that Hollander's score was significantly higher in knees closed with sutures as compared to the patients in whom staples were used for wound closure.

KEYWORDS: Staples, Sutures, Total Knee Replacement.

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INTRODUCTION

Total knee arthroplasty (TKA) is one of the most commonly performed procedures as a definitive treatment for arthritis.[1] Even though outcomes of TKA have improved considerably in recent years, few complications are still common. There are several complications of TKA which include bleeding, thromboembolism, neural deficit, vascular injury, deep joint infection, implant loosening, patellofemoral dislocation, tibiofemoral dislocation, and reoperation.[2,3]

The post-operative outcomes are regulated by the following factors: preoperative education, an understanding of rehabilitation procedures, maintenaning operative protocols, and postoperative wound care. Wound closure and its management is one of the most important aspect of surgical procedures. Poor technique or inappropriate wound closure can lead to surgical site infections, which can be devastating following TKA. It sabotages patients' recovery and significantly elevates the morbidity rate which may ultimately lead to treatment failure.[4-6] Various wound closure techniques and materials are used for skin closure, such as sutures, staples, adhesive compounds, etc.[7]

The use of sutures for wound closure is an important part of a surgical procedure. Sutures helps to control bleeding, provides better approximation, and are a time-effective.[8] However, for closing deeper layer, braided sutures are considered to have fewer postoperative complications.[9] Recently, skin closure using staples has been considered a preferred choice. This is because they provide the fastest closure with a lower incidence of infection.

Although few studies have been published showing the superiority of one method/material over the other, it is mostly the surgeon's preference which closure method and material are used. An important aspect of wound closure is that the wound should be closed tension-free with watertight everted skin-edges, which ultimately is very important for wound healing.[10] We, therefore, aimed to provide subjective and objective evidence of better closure technique and material; we conducted the study so that the outcome of TKA be further improved.

METHODS

A randomized controlled trial was conducted at the Orthopedics Department of The Indus Hospital, Karachi, from December 2018 to June 2020. We recruited 30 patients undergoing bilateral TKA. Patients aged between 40-70 years undergoing primary TKA for osteoarthritis, rheumatoid arthritis, or post-traumatic arthritis were included. Patients having previous skin, neuromuscular, or connective tissue disorder, and those taking steroids or with a BMI >30 were excluded. All the patients were recruited at the Orthopedics outpatient clinic after assessing their eligibility criteria. Informed consent was obtained following the guidelines of the Institutional Review Board after obtaining an IRB approval for the study (Ref. No. IRD_IRB_2018_06_006; dated Dec. 12, 2019).

Baseline data regarding the patient's age, gender, height, weight, ASA grade, comorbidities, primary diagnosis, incision length (measured by standardized sterile measuring scale), and duration of surgery were recorded. If a wound was found to be infected or had discharge, a wound culture and sensitivity test were done. All patients participating in the trial followed a standardized care pathway for surgical wounds. The surgeries were performed by one of the senior surgeons of the orthopedics department. The patients were daily followed until discharge. A detailed wound assessment of all the participants was performed on 3rd, 7th, 15th, 30th, and one year, postoperatively by an independent senior surgeon from the orthopedics department.

Blinding and Randomization: This trial was an open-label trial. The patients, surgeon, and the study team couldn't be blinded to the study intervention due to the different nature of visible sutures used on the skin. Randomization was done, and envelopes were prepared using SNOSE protocol, i.e., they were sequentially numbered, opaque sealed envelopes.[11] Before opening the envelope, the primary investigator wrote the patient's medical record number, date and signed the envelope. The envelope contained carbon paper which transferred the handwritten data on the allocation paper inside. The patients were randomized into two intervention groups. In the interventional ARM-1, the wound closure of the right knee was done using staples, and the wound closure of the left knee was done with polypropylene (prolene) sutures. In the interventional ARM-2, the wound closure of the right knee with prolene sutures and wound closure of the left knee was done with staples.

Study products were prolene sutures and staples. Prolene sutures are non-absorbable, sterile surgical sutures composed of an isotactic crystalline stereoisomer of polypropylene. After completion of the procedure, deep tissues were closed with a subcuticular prolene suture. Specialized staples are used in surgery in place of sutures to close skin wounds. After completion of the procedure, deep tissues were closed with absorbable braided sutures, and then the skin was closed using staples.

Data were analyzed using STATA Version 16.0. For continuous variables, mean and standard deviation were calculated, and for categorical variables, frequencies and percentages were determined. Mean Hollander score was computed at 3rd, 7th, 15th,

30th, and 1-year follow-up along with its standard deviation. Mixed model linear regression was used to determine the impact of sutures and staples on wound healing after total knee replacement. A separate analysis was done for the right knee and left knee to understand whether the impact of two groups on wound healing is constant on each knee or not. To assess the significance, the cut-off of the p-value was kept at 0.05.

RESULTS

Thirty patients who underwent bilateral total knee replacement were included in the analysis. The characteristics of study participants is shown in Table-I. The majority of participants were females, i.e., 71.8%. The average age of participants is 57.3 (± 7.5) years. The numbers of knees closed by staples were the same as the numbers of knees closed by using sutures, i.e., 30 in each group. Twenty-seven patients were obese (90%). Eleven patients (52.4%) had diabetes, while Twenty-three patients (85.2%) had hypertension. The mean incision length on the right knee is 17.6 ± 1.1 cm, while the mean incision on the left length is 18.3 ± 1.2 cm.

The mean Hollander scores of patients at different time intervals and effect of suture and staples on both right and left knee are presented in Table-II. On the right knee, the mean Hollander score was highest after one year of surgery, i.e., 4.06 followed by the 30th postoperative day (4.8±1.1). On the left knee, the mean Hollander score on the 3rd postoperative day was 3.2 (±1.3). On the 7th postoperative day, the mean score was 3.6 (±1.3). The mean Hollander score was highest after one year of surgery, i.e., 3.9 ±0.6.Overall, the mean Hollander score was significantly different among participants in the sutures and staple group in both right knees (p-value=0.001) and left knee (p-value=0.001). . In the right and left knee, the overall difference of mean Hollander score between the two groups is 2.6 and 1.96, respectively. Gender was significantly associated with the mean Hollander score. The mean Hollander score was significantly higher in females than males in both right knee (B=0.56, p-value=0.049) and left knee (B=0.38, p-value=0.044).

DISCUSSION

Total knee replacement has evolved over time with respect to surgical techniques[12] Soft tissue handling is of equal importance in its success as is the proper implant placement. Early rehabilitation post-surgery is dependent on optimal wound healing. Hence wound closure material and technique carry great importance.

Studies have shown that wound closure at flexed position can allow more flexion and better rehabilitation.[13] Although the closure position is surgeon-dependent, but is of paramount

Table-I: Demographical information of Patients n=30.

Age	
Mean ± SD (Years)	57.3 ± 7.5
Gender	
Male	10 (33.3%)
Female	20 (66.7%)
ASA Level	
I	06 (20%)
II	21 (70%)
III	03 (10%)
Hypertension (n=27)	
Yes	23 (85.2%)
No	04 (14.8%)
Diabetes (n=21)	
Yes	11 (52.4%)
No	10 (47.6%)
Albumin Level	
Mean ± SD	3.9 ± 0.33
Body Mass Index (BMI)	
Normal	01 (3.3%)
Overweight	02 (6.6%)
Obese	27 (90%)
Open Surgical Procedure on the Same Site	
Yes	02 (6.7%)
No	28 (93.3%)
Infection in any other body part	
No	30 (100%)
Incision Length on Right Knee	
Mean ± SD	17.6 ± 1.1
Min-Max	16-20
Incision Length on Left Knee	
Mean ± SD	18.3 ± 1.2
Hollander Scores	
Right Knee	
3rd post-op day	4.5 ±1.3
7th post-op day	4.5 ±1.3
15th post-op day	4.6 ±1.2
30th post-op day	4.8 ±1.1
1 year follow-up	4.9 ±0.6
Left Knee	
3rd post-op day	3.2 ±1.3
7th post-op day	3.6 ±1.3
15th post-op day	3.8 ±1.2
30th post-op day	3.9 ±1.1
1 year follow-up	3.9 ±0.6

Table-II: Effect of Study groups on Hollander Score (Right Knee and Left Knee).

	Right Knee		*Left Knee*	
Variable	*B (95% CI)*	*p-value*	*B (95% CI)*	*p-value*
Treatment				
Staples	*Reference*			
Sutures	2.26 (1.31-2.90)	0.001*	1.96 (1.43-2.50)	0.001*
Time				
Day 3	*Reference*			
Day 7	0.30 (-0.07-0.69)	0.119	0.28 (-0.05-0.61)	0.1
Day 15	0.52 (0.13-0.90)	0.001*	0.46 (0.13-0.80)	0.006*
Day 30	0.81 (0.42-1.19)	0.001*	0.65 (0.32-0.98)	0.001*
Day 365	1.81 (1.38-2.24)	0.001*	1.5 (1.15-1.84)	0.001*
Gender				
Male	*Reference*			
Female	0.57 (0.002-1.13)	0.049*	0.61 (0.008-1.19)	0.045*

* Significant at p-value<0.05.

importance. Similarly, the material used for closure also dictates the outcomes; the functional outcome aong with the cosmesis.

In our study, we aimed to determine the best outcome of the material for skin closure after total knee replacement. Since, significant knee flexion and extension rehabilitation therapies starts after surgery, would healing has significant value. For this purpose, the same patient underwent different closures in different knees, which helped us to exclude the patient-related factors. We used the Hollander Wound evalution scale, which is a validated scale and has been previously used in the assessment of wounds in other surgeries. Wound-related complications in our study were considerably less than previously reported.[14-16]

Yuenyongviwat et al. had reported no overall difference between the two groups (suture versus staples).[6] However, Yuenyongviwat et al. used sutures and staples in the same knee (upper wound closed with staples and lower have by sutures), hence had a higher rate of infection then our study. In our study, sutures were found to have better results over staples as the Hollander score for females and those closed with sutures was reported to be higher.[6] Khan et al. used skin staples, subcuticular sutures, and 2-octyl cyanoacrylate for closure of wounds in hip and knee replacements and found no difference in outcome.[17] Our study reported different outcome than both Yuenyongviwat et al and Khan et al. however, they had followed the patient for six weeks while we have reported our final outcomes after one year follow up.

Hlubek et al. had different ourcomes from our study and preferred staples over sutures however, they reported higher and severe infection rate with staples.[14] Kerbs et al. reported no difference in the two methodes of skin closure.[9] The majority of previous authors had compared suturing time and pain in removal with more interest than the overall functional and cosmetic aspects.[17-19] We did not take into account the suturing time as this could have affected outcomes. Newman et al. reported a 9% complication rate with sutures, which included superficial and deep infections. This proved to be different from our findings as no significant infection was reported in both groups. However, their findings in terms of cosmesis were similar with staples and sutures.[20]

Hollander scoring also pointed towards the overall satisfaction with respect to cosmesis. In the randomized trial by Clayer et al. on hip surgeries, the better cosmesis was noted with sutures which were similar to our study findings, but in knee joint compared to hip the incisions vary in size and direction and the amount of stress on the wound during moving is different.[21] Similarly, Singh et al. found similar results to us, indicating significantly less wound discharge and erythema with the use of sutures.[15]

The wound was also assessed independently by the assessors at the same time, which added more reliability to our results. Our follow-up was of one year, which was the strength of our study. The reason of better outcomes with continuous running sutures is also explained by a study by Wyles et al.[21] which reported running sutures maintained better perfusion to the skin, hence leads to better healing and cosmesis.

Limitation of the study: Our study had a small sample size, and although nor the patient or the assessor was blinded, using different techniques of closure on the same patient helped us remove all patient-related factors. We had the closures done in a similar way by the same surgeon, which removed any bias. We did not take into account the position of wound closure, which according to the literature might also affect the outcomes. We also did not consider the removal of suture kind staples technique as that can also cause pain and morbidity to the patient. We recommend a trial with a larger sample size to determine the best method of closure so the patient outcomes could further be improved.

CONCLUSION

The study has shown that Hollander's score was significantly higher in knees in which sutures were used as compared to the patients in which staples were used for wound closure. Skin staples had an advantage over prolene sutures in terms of operative time, but on the other hand, they are more difficult to remove than prolene stitches.

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MAK: Conceived and designed the study.
MWM: Data collection and manuscript writing and responsible for the integrity the manuscript.
MAC: Editing and critical review of the manuscript.
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Original Article

To determine the association between asthma severity and hospital admission measured by Pediatric Respiratory Assessment Measure (PRAM) score at Indus Hospital and Health Network, Karachi, Pakistan, 2020-2021

Unaisa Kazi[1], Saira Gul Rukh[2], Suha Zawawi[3], Saba Laila[4], Mohammad Fareeduddin[5], Syed Ghazanfar Saleem[6]

ABSTRACT

Objectives: To determine the association between asthma severity and the likelihood of hospitalization by using Pediatric Respiratory Assessment Measure (PRAM) score for pediatric patients who present to the emergency department (ED) with mild, moderate or severe asthma exacerbations and those who received standard intensive asthma therapy.

Methods: This was a retrospective study conducted in children aged between 2 to 14 years. The data was entered and analysed using Statistical Package for the Social Sciences (SPSS) version 21. To be included in the study, the children must have received "intensive asthma therapy" defined as administration of systemic corticosteroids with three albuterol treatments and ipratropium.

Results: A total of 437 patients were enrolled in the study out of which 250 were male and 187 were female. The mean age was 6.1 ± 3.4 years with a minimum age of two and a maximum age of 14 years. The 4-hour PRAM score (AUC = 0.88) overall significantly improved the predictive value of admission (p value <0.001) as compared to the PRAM score calculated at triage (AUC = 0.81).

Conclusion: The 4-hour PRAM score is the best predictor for the need of hospitalization. It is suggested that these results are applied clinically in the pediatric ED to improve patient flow and to better facilitate intensive therapy of patients at triage to decrease the need for hospitalization.

KEYWORDS: Asthma, Paediatric Respiratory Assessment Measure.

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INTRODUCTION

Asthma is a chronic respiratory disease that affects people of all ages and is characterized by episodic and reversible attacks of wheezing, chest tightness, shortness of breath, and coughing.[1] Estimations show that approximately 30% of asthma-related emergency visits in the pediatric age group result in hospitalization.[2] In Pakistan, the prevalence of asthma among children ranges from 15 to 20% in different areas of the country.[3,4] Many authentic scoring systems such as, the Paediatric Respiratory Assessment Measure (PRAM) score, Respiratory Rate-Accessory Muscle Use-Decrease breath sounds (RAD) score and Paediatric Asthma Severity score are in use for classifying the severity of asthma, and guiding

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treatment.[5,6] For PRAM scoring, mechanisms of wheezing, entry of air, scalene muscle contraction, suprasternal retraction and oxygen saturation are all incorporated into a score that is used for children aged between 2 to 17 years that present with acute exacerbation of asthma. The PRAM scoring system has shown to be a quick assessment and differentiating tool with high reliability.[7] Although authorised scorings that guide evidence-based management are present, there still remains substantial underuse of the proven treatments of asthma.[8] Besides the emotional burden on patients and families, paediatric asthma also carries a huge financial burden; up to 45% of asthma health care expenses are related to visits to the emergency department (ED) and inpatient hospital care.[9] Research shows that up to 30% of children who present with severe asthma in the ED are ultimately hospital admissible.[10]

According to research, the use of 'intensive asthma therapy' comprising systemic corticosteroids with three albulterol treatments and ipratropium 1 hour after triage reduces the duration of ED stay and hospital admission.[11] Literature shows that standardizing care for asthma patients during early course in the ED helps in optimizing patient care.[9] Early identification of the asthma severity using the PRAM score has the ability to enhance the ED patient flow. Previous literature shows us that there have been efforts to determine the role of PRAM at different hours but there still happens to be a gap in knowledge as most studies do not include PRAM scoring in accordance with administration of standardized evidence-based asthma treatment with complete adherence. Data shows that patients presenting to the ED with mild asthma exacerbations were at low risk of admission.[12] It has been proven that after initiation of evidence-based treatment, the PRAM scoring is preferable to estimate the likelihood of hospitalization compared with intensive management in the ED. This ability would assist with better management of patient flow in the ED and may also encourage the physicians to administer more aggressive patients earlier in the high-risk population presenting with higher PRAM scores. The main goal of our study was to determine when the PRAM score best predicts the need for patient hospitalization.

METHODS

A retrospective cohort study was conducted including male and female children between two to 14 years of age that presented to the Emergency Department at The Indus Hospital and Health Network (IHHN) with mild, moderate or severe asthma between October 2018 and March 2019. Two hundred and twenty-seven children were selected using non-probability convenient sampling with a 95% confidence interval and significance level of $p<0.05$. The data was entered and analysed using Statistical Package for the Social Sciences (SPSS) version 21. Cleaning and coding of data was done prior to analysis. Mean ± standard deviation (STD) was computed for normally distributed continuous variables, while for skewed data, median with interquartile range was observed along with mean ± STD. Normality of data was checked by Shapiro Wilk's test, histogram and quantile-quantile (Q-Q) plot. On the other hand, frequency with percentage was calculated for categorical variables. To assess the predictive ability of PRAM score for admission, Receiver operator characteristic (ROC) curve were constructed and area under the curve (AUC) was obtained along with best cut-off values for sensitivity and specificity of the PRAM score. This study was approved by IRB and the number is IRD_IRB_2019_09_004.

Sample Selection:

Inclusion Criteria:

- Children of both genders between two and 14 years of age
- Children presenting with acute asthma exacerbations (defined as triage PRAM score ≥ 4, but < 11)
- Patients with a prior diagnosis of asthma or those who have had three or more episodes of wheezing responsive to beta-2 agonists

Exclusion Criteria:

- Children with PRAM scores <4 (mild exacerbation) or >11
- Hypersensitivity to dexamethasone or oral corticosteroids
- Chronic respiratory conditions such as broncho-pulmonary dysplasia or cystic fibrosis, cardiac, metabolic, or immunologic disease
- History of adrenal suppression
- Patients with a coexisting acute illness such as pneumonia, pertussis, or croup
- Use of oral corticosteroid in the past 14 days
- Exposure to varicella in the previous three weeks in a susceptible child

Using the IHHN Health Management Information System (HMIS), patients were stratified into mild, moderate and severe groups based on the PRAM score on arrival and after four hours of presentation.

Data Collection: The data collected during the study includes 1) the PRAM score assessed by physicians on duty at approximately 0, one and four hours or until admission or discharge (depending on the nature of ED care), 2) time of administration of oral steroid; 3) time of inhaled beta-2 agonist, inhaled anticholinergic, and other medications; 4) time of discharge from ED; 5) time taken for the physician to admit the patient; 6) time of admission to inpatient unit; and 8) duration of inpatient stay.

Data Analysis: Data was analysed using SPSS version 2.0. and the results were presented as frequency and percentages for qualitative variables and means ± SD for quantitative variables. Chi square test was used to assess the association and a p-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 437 patients were enrolled; 250 (57.2%) were male, while 187 (42.8%) were female. The mean age was 6.1 ± 3.4 years with a minimum age of two and a maximum age of 14 years. Overall, 288 (65.9%) of the children had inspiratory and expiratory wheeze on auscultation. Air entry was normal in a total of 334 (76.4%) patients. Table-I.

Table-I: Baseline demographic and clinical parameters of asthmatic children n=437.

		n (%) / Mean STD & Median, IQR
Gender	Male	250(57.2)
	Female	187(42.8)
Age in years		6.1 ± 3.4 & 5, 5.5
Length of stay		8.3 ± 9.3 & 4, 12
Pram score		4.6 ± 2.5 & 5, 5
Wheeze	Inspiratory and expiratory	288(65.9)
	Expiratory	124(28.4)
	Absent	21(4.8)
	Audible without Stethoscope	4(0.9)
Air entry	Normal	334(76.4)
	Decreased at basis	73(16.7)
	Widespread decreased	30(6.9)
Oxygen saturation	> 95%	247(56.5)
	92% - 95%	122(27.9)
	< 92%	68(15.6)

On calculating the PRAM score at arrival, we observed that 213 (48.7%) of the children had mild asthma, while moderate and severe asthma was present in 208 (47.6%) and 16 (3.7%) patients, respectively. Majority of the children needed nebulization 420 (96.1%) and steroids 294 (67.3%). On reassessment of the patients after one hour in the ED, an overall improvement in the severity was observed with just 2 (0.5%) of 16 patients with severe asthma at one hour Similarly, 114 out of 208 children who had initially presented with moderate asthma improved after being treated in the ED. On assessing the PRAM score at four hours, we observed that out of 94 children with moderate asthma, only 59 (13.9%) children were left with moderate disease while 303 (69.3%) were discharged after treatment within four hours. 62 (14.2%) patients were referred out to other health facilities, 65 (14.9%) were admitted in our hospital out of which 53 (81.5%) were admitted in the paeds high dependency unit. Table-II.

The ROC curve for PRAM on arrival to the ED i.e., 0 time showed an AUC of 0.81 (95% CI 0.76

Table-II: Assessment and management of patients with help of PRAM score n (%).

PRAM score at arrival of patients	Mild (1-4)	213(48.7)
	Moderate (5-8)	208(47.6)
	Severe (9-15)	16(3.7)
PRAM score at 1st hour	Mild (1-4)	341(78)
	Moderate (5-8)	94(21.5)
	Severe (9-15)	2(0.5)
PRAM score at 4 hour	Mild (1-4)	171(39.1)
	Moderate (5-8)	59(13.5)
Nebulization		420(96.1)
Use of Steroids		294(67.3)
Use of MgSO4		137(31.4)
Triage	P1	13(3)
	P2	337(77.1)
	P3	82(18.8)
	P4	5(1.1)
Plan for patient	Admission	65(14.9)
	Discharge	303(69.3)
	LAMA	7(1.6)
	Refer out	62(14.2)
Admitting place	General ward	4(6.2)
	PHDU	53(81.5)
	PICU	5(7.7)

Table-III (a): Sensitivity and specificity of PRAM score at arrival.

Positive if Greater Than or Equal To[a]	*Sensitivity*	*Specificity*
-1.0	1.0	1.0
0.5	100.0	3.6
1.5	100.0	16.9
2.5	100.0	32.0
3.5	95.8	41.5
4.5	88.7	55.2
5.5	73.2	68.3
6.5	60.6	80.6
7.5	42.3	90.2
8.5	25.4	98.4
9.5	4.2	99.5
10.5	1.4	100.0
12.0	0.0	100.0

Table-III (b): Sensitivity and specificity of PRAM score at one hour.

Positive if Greater Than or Equal To[a]	*Sensitivity*	*Specificity*
-1.0	1.0	1.0
0.5	100.0	37.3
1.5	100.0	51.3
2.5	100.0	65.6
3.5	93.0	60.8
4.5	81.7	79.0
5.5	54.9	91.9
6.5	35.2	97.8
7.5	11.3	100.0
8.5	4.2	100.0
9.5	1.4	100.0
11.0	0.0	100.0

– 0.86), depicting that the PRAM scoring system has good capability in predicting the admission probability of asthmatic patients. At 0 hour, at the cut-off of 5.5, the PRAM score showed a sensitivity of 73.2% to predict true admission and a specificity of 68.3% to detect true cases with no need of admission. These findings are highlighted in Fig.1 and Table-III(a).

When we recalculated the PRAM score at one hour, we observed that there was an improvement in the predicted capacity of PRAM score as AUC was increased up to 0.88 (95% CI 0.85-0.92) with the statistically significant p value of <0.001. In the same way sensitivity and specificity were also increased from 73.2% to 81.7% and 68.3% to 79% respectively at the cut-off level of 4.5. Fig.2 and Table-IIIb.

DISCUSSION

Asthma is a heterogenic condition that is underdiagnosed and undertreated despite that the skills needed to diagnose it are readily attainable and effective treatments are available.13 Chronic lower airway inflammation is known to be more common in individuals that

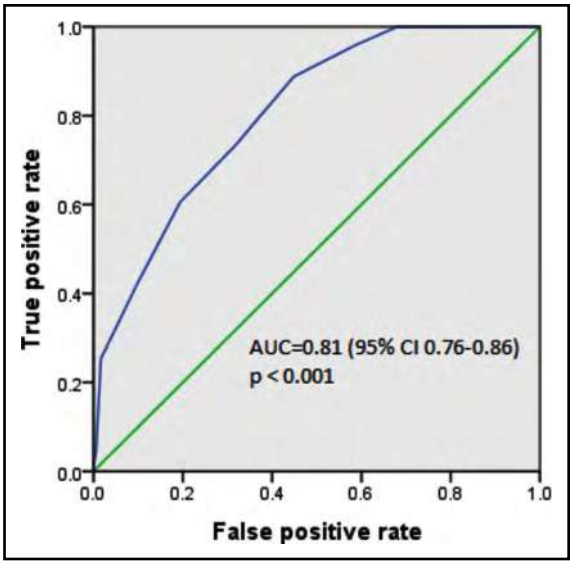

Fig.1: ROS Curve.

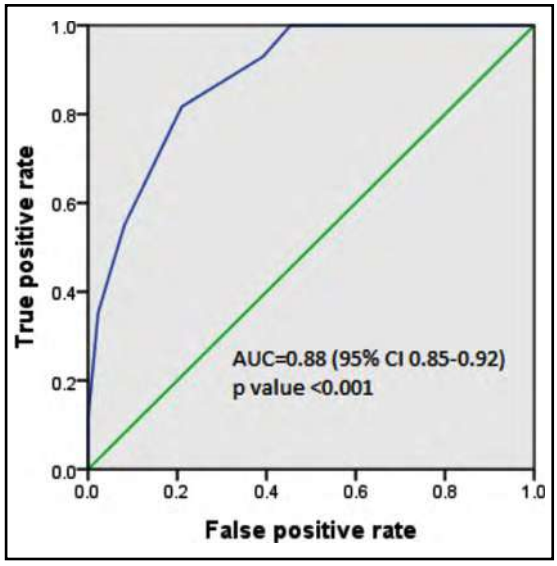

Fig.2: ROS Curve.

also have inflammatory disorders of the upper airway.13 A retrospective observational cohort study was carried out in the pediatric emergency department of the Indus Hospital and Health Network (IHHN) on PRAM scoring and its predictive capacity at different hours for the need of hospitalization.

The patients were received at triage for assessment of vitals followed by transfer to the pediatric ED for assessment. PRAM scoring was done at the first encounter of the patients with physicians in the ED after triage and was labelled as "0 hour" followed by administration of standard evidence-based asthma treatment. To our knowledge, there is one such study that includes patients receiving standardized asthma therapy.[14] The null hypothesis of the study was defined as no association between asthma severity and the possibility of hospital admission for pediatric patients through the ER which was rejected as a statistically significant difference was observed. In a low-resource setting, upon reassessing the patients at the 1st hour after administering treatment, a remarkable increase was reported in the predictive capacity of PRAM scoring with increased sensitivity and specificity in comparison to the PRAM score calculated at "0 hour".

According to literature, besides PRAM, a number of clinical scores have been studied such as, the Pediatric Asthma Severity Score (PASS), the Clinical Asthma Score (CAS), the Asthma Severity Scare (ASS) and the Pulmonary score with the Pulmonary Index (PI). The Pulmonary score with PI is the score most widely used in asthma clinical trials.[15] A study conducted in the ED of the Aga Khan University Hospital, Karachi investigated the outcomes of children aged between one month to 16 years using the Clinical Respiratory Score (CRS) and concluded that patients with higher scores were more likely to be admitted to the pediatric critical care unit.[16] As compared to the PRAM score, CRS takes into account the mental status and appearance of the child and does not require expert training to use.

Another prospective study studied the comparison between Wood's and PRAM score to determine which was a better predictor of severity of childhood asthma exacerbations and the results showed that both scores were promising in predicting the outcome and severity in children.[17]

It is therefore suggested that the PRAM score should be used in the assessment of asthma severity in the pediatric population and should be recalculated at hour one after administering treatment. By using this assessment tool, physicians may be able to predict hospitalizations better and admit sicker patients with higher scores earlier, freeing beds in the ED and assisting in improving patient flow. Implications of this study's findings have the potential to improve the emergency department's throughput, reliability and quality of patient care for children with asthma.

Strengths and Limitations: This was a retrospective study that collected data from the Health Management Information System (HMIS) and the extraction of such data is dependent on the level and accuracy of documentation in the medical record. Due to patient improvement by the 1st hour, it was possible to determine the disposition of the patient which led to a lot of the participants being discharged before the mark of the 4th hour. Moreover, the study only included children from one center in Karachi which is a limited cohort of the general pediatric population of Pakistan. The scoring and decision of disposition of the patient was dependent upon the clinical judgment of the treating physician. Lastly, Children of ages < 2 and > 14 years were not included in the study and the PRAM scores for all hours were not available. However, the study consisted of a large sample size with an almost equal distribution of genders and a variety of age groups were still included.

CONCLUSION

It is concluded that the use of PRAM at hour-1, measured after the initiation of evidence-based therapy, is the best predictor of hospitalization. It should therefore be adopted in routine use of pediatric asthmatic patients. The PRAM scoring system has shown credibility in improving the Emergency Department patient flow and managing patients who have not received maximum intensive therapy in order to initiate more aggressive methods and prevent hospitalization.

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Author Contribution:

UK: Substantial contribution towards the concept and design of the study, initial write up, revised it critically for important intellectual content.
SGR: Data collection, literature search, contributed the initial write-up.
SZ: Substantially contributed towards data cleaning, analysis, interpretation and result section write up.
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Original Article

Patient perception regarding privacy and confidentiality: A study from the emergency department of a tertiary care hospital in Karachi, Pakistan

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ABSTRACT

Background and Objective: Maintaining privacy and ensuring confidentiality with patients is paramount to developing an effective patient-provider relationship. This is often challenging in over-crowded Emergency Departments (EDs). This survey was designed to explore patients' perceptions on maintenance of privacy and confidentiality and their subsequent interactions with providers in a busy tertiary care hospital in Karachi.

Methods: Trained nursing staff conducted structured interviews with 571 patients who presented to The Indus Hospital (TIH) ED from January to December 2020. All patients were 14 years of age or older, could speak and understand Urdu, and provide informed consent. Patients were asked about their perceptions of privacy and confidentiality in the ED and whether this affected their interactions with providers.

Results: Respondents were primarily men (64%) under the age of 45 (62%) presenting for the first time (49%). The majority of patients felt that privacy and confidentiality were maintained, however 10% of patients reported that they had rejected examination due to privacy concerns and 15% of patients reported that they had changed or omitted information provided to a provider due to confidentiality concerns. There was correlation between privacy and confidentiality concerns and patient-provider interactions ($p<0.0001$).

Conclusions: Despite the often over-crowded and busy environment of the ED, patients generally felt that privacy and confidentiality were maintained. Given the correlation between perception and behavior and the importance of an effective patient-provider relationship, particularly in the acute setting when morbidity and mortality is high, initiatives that focus on maintaining privacy and confidentiality should be pursued.

KEYWORDS: Emergency Department, Privacy, Confidentiality, Survey, Patient perception, Patient-provider interactions.

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INTRODUCTION

The concept of privacy emphasizes the individuality of a person and concerns a human being's decision to deny or grant access to self and individual behaviors, opinions, and attitudes; to personal or identifying information; and to private property or territory. More broadly, privacy includes physical seclusion, protection of personal information, protection of identity, and the ability to make choices without interference. In short, it is

the right of an individual to selective expression of themselves, to sharing information about themselves, and to making decisions that affect them personally without interference.[1]

Confidentiality refers to protection of personal information. In medicine, confidentiality acknowledges respect for privacy, decreases vulnerability, and ensures trust – all of which are imperative for obtaining an accurate history and exam, and, ultimately, diagnosis.[2,3]

Physical and environmental limitations as well as high patient volumes make the protection of patient privacy and confidentiality challenging in the Emergency Department (ED) setting.[2] The spaces for patients can be undersized; patients may be placed in close proximity to each other, family members, health care providers, and staff when volume is high; there may not be solid or enclosed spaces; and health care providers are often moving quickly between spaces.[2,3] For example, with ED overcrowding, patients are often placed in or near hallways, exacerbating the challenges of protecting privacy and ensuring confidentiality.[4] Furthermore, patients in the ED often have sensitive issues related to their disease and livelihood, such as substance use disorders, intimate partner violence, concerns about sexual and reproductive health, and psychiatric conditions. Additionally, the privacy and confidentiality of severely ill or injured patients is often not a focus during acute resuscitation, and patients in this state may also not be capable of advocating for themselves.[5,6] As a result, the responsibility lies with ED providers to be sensitive to issues concerning privacy and confidentiality in order to establish an effective patient-physician relationship, to foster an environment where patients can disclose sensitive and essential information, and be able to detect and manage acute illness and injury that might otherwise result in high morbidity or mortality.[7-10] Furthermore, privacy and confidentiality are one of the core indicators of patients' satisfaction and quality care.[11]

The Indus Hospital (TIH) Korangi campus is a 300-bed tertiary care hospital in one of the lowest resourced areas of Karachi, one of the largest cities in the world. TIH is one of the main hospitals of the Indus Hospital and Health Network (IHHN), a private health network that provides care free of cost through a network of public outreach programs, clinics, physical rehabilitation centers, blood centers, and hospitals throughout all of the administrative units of Pakistan. To date, there is no information about patients' perspectives of the protection of their privacy and confidentiality as it relates to their interaction with providers and overall satisfaction with care at TIH. This study investigates patients' perceptions of maintenance of privacy and protection of confidentiality as well as potential correlations with alterations in patient-provider interactions during their ED visit.

METHODS

A prospective convenience sample of patients at TIH, a single tertiary care level center in Karachi, Pakistan, was surveyed. Ten nursing staff working on different shifts received standardized training from study leadership on conducting the structured interview, and they conducted interviews for approximately two hours daily during the study period of January to December 2020. Patients above 14 years of age who were able to understand and speak Urdu, with a triage coding of P3 or P4 (Manchester Triage System), and who presented to the Adult ED were included.[12] Patients with a triage level of P1, P2, or P5; patients brought dead/expired while in the ED; patients with altered mental status; patients unable to understand or speak Urdu, and patients who did not provide consent were excluded. Verbal consent was obtained from study participants. The study was approved by the IRB (IRD_IRB_2019_09_015).

Data was analyzed using Microsoft Excel (Microsoft 365, Redmond, Washington) and Stata (StataCorp, release 17.0 BE, College Station, Texas). Spearman's rank correlation was used to investigate for a potential correlation between the patient's perceptions and the impact on patient-provider interactions, and the Wilcoxon rank-sum test was used to identify differences in responses between demographic groups.

RESULTS

Overall, 571 interviews meeting the pre-specified inclusion criteria were conducted. The average age of participants was 41 years (range 14-85), with 366 male patients, 204 female patients, and one transgender patient. Demographic information of the respondents is summarized in Table-I. Primary presenting chief concerns are summarized by general categories in Table-II.

We first evaluated patient's perceptions of confidentiality overall. 54% of patients "Agreed" or "Strongly Agreed" that the confidentiality of their medical information was properly maintained (Fig.1A), and 55% "Agreed" or "Strongly Agreed" that patient information was not kept open in front of other patients.

Table-I: Demographic information of respondents.

Variable	*Detail: n (%)*
Age	14-25: 113 (20%) 26-35: 122 (21%) 36-45: 120 (21%) 46-55: 104 (18%) 56-65: 72 (13%) 65+: 40 (7%)
Gender	Women: 204 (36%) Men: 366 (64%) Transgender: 1 (<1%)
Primary Language	Urdu: 270 (47%) Punjabi: 88 (15%) Pashto: 58 (10%) Sindhi: 54 (9%) Other: 90 (16%) Not Specified: 11 (2%)
Education	None: 282 (50%) Formal: 288 (50%); mean 10 years (range: 1-25) Not Specified: 1 (<1%)
Triage Category	P3: 512 (90%) P4: 59 (10%)
Time of Presentation	Morning (6AM to 11:59AM): 242 (42%) Afternoon (12PM to 5:59PM): 205 (36%) Evening (6PM to 11:59PM): 92 (16%) Night (12AM to 5:59AM): 32 (6%)
ED LOS	≤6 hours: 309 (54%) >6 to 12 hours: 218 (38%) >12 hours: 44 (8%)
Frequency of ED Presentation	First presentation: 279 (49%) Once a year: 80 (14%) Once a month to once every 6 months: 122 (21%) Once a month: 90 (16%)

ED – Emergency Department; LOS – Length of Stay.

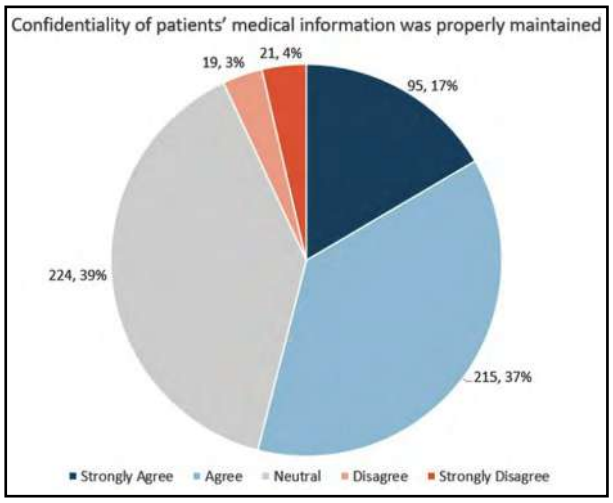

Fig.1A: Patient perception of maintenance of confidentiality of medical information.

Table-II: Primary chief concerns of the respondents.

Presenting Symptom	*Percent*
Gastrointestinal Symptoms	30%
Genitourinary Symptoms	12%
Trauma	12%
Chest Pain/Cardiac Symptoms	10%
Musculoskeletal Symptoms	10%
Fever	7%
Respiratory Symptoms	6%
Headache/Neurologic Symptoms	3%
Other	10%

We next evaluated whether patients felt privacy was maintained during their clinical evaluation. 76% "Strongly Agreed" that they were given enough privacy when discussing their medical conditions (Fig.1B), and 79% "Agreed" or "Strongly Agreed" that other patients could not hear their conversations with health care providers. Additionally, 83% "Agreed" or "Strongly Agreed" that their personal information could not be heard by other people, while 79% "Agreed" or "Strongly Agreed" that they had not heard the conversations of others. Furthermore, 70% of patients "Strongly Agreed" that there was a screen or curtain around the bed to ensure privacy, 80% of patients "Disagreed" or "Strongly Disagreed" that unauthorized persons had been able to see them while they were receiving assistance and that people not attending to them

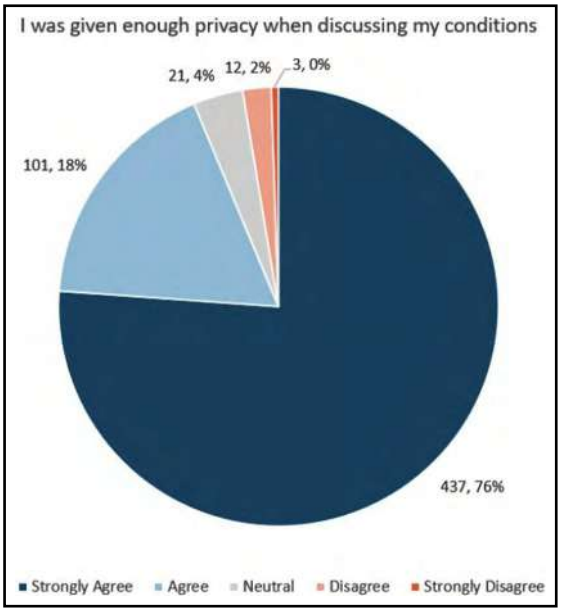

Fig.1B: Patient's perception of privacy with speaking about their concerns.

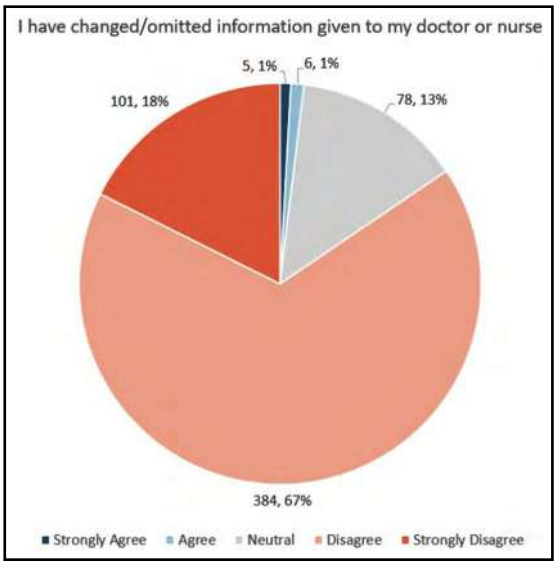

Fig.2A: Patient-provider interactions regarding communication as a result of perceived lack of maintenance of privacy and/or confidentiality.

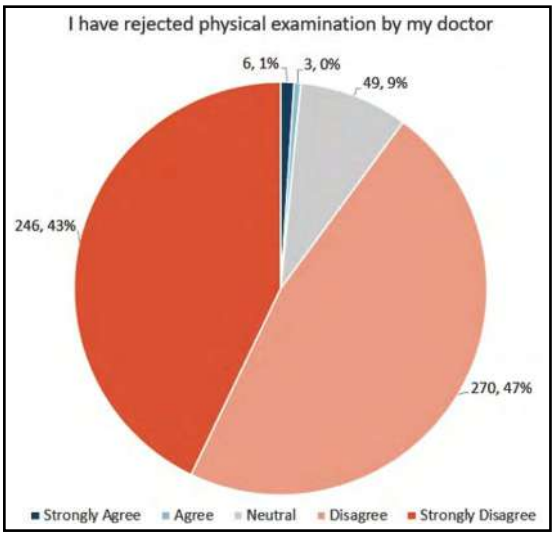

Fig.2B: Patient-provider interactions regarding physical examination as a result of perceived lack of maintenance of privacy and/or confidentiality.

had been able to see intimate parts of their body while receiving attention. Finally, 85% of patients "Disagreed" or "Strongly Disagreed" that they had been able to see other patients while they were being examined.

Finally, we evaluated the effects of concerns about privacy and/or confidentiality on the patient-provider interaction. About 85% of patients "Disagreed" or "Strongly Disagreed" that they had changed or omitted information given to health care providers because they felt it could be heard (Fig.2A), and 90% of patients "Disagreed" or "Strongly Disagreed" that they had rejected physical examination because they thought they could be seen by unauthorized persons (Fig.2B). Conversely, 15% of patients were "Neutral", "Agreed", or "Strongly Agreed" that they had changed or omitted information, and 10% were "Neutral", "Agreed", or "Strongly Agreed" that they had rejected physical examination by a doctor because of privacy concerns. There was a correlation between patient concerns about protection of privacy and/or confidentiality and a negative impact on the patient-provider interaction (Spearman's rho 0.3121, $p<0.0001$).

Finally, there were significant differences noted on some of the responses to some of the questions both on perception (e.g. "confidentiality of patient's medical information was properly maintained"; $z = 1.977$, $p = 0.05$) and interaction with staff (e.g. "I have rejected physical examination by my doctor because I had feeling the process could be seen by unauthorized persons"; $z = -3.456$, $p=0.0005$), with more women agreeing/strongly agreeing with the former statement and fewer women strongly disagreeing with the latter statement.

DISCUSSION

Privacy and confidentiality are cornerstones of an effective patient-provider relationship built on trust, particularly in an acute setting when morbidity and mortality risks are high. Overall, in this study, patients agreed that their privacy and confidentiality were maintained in a busy, tertiary center level ED in Karachi. The survey did also reveal, however, that patient perceptions may impact patient-physician interactions. This is consistent with prior work also demonstrating the correlation between perception of privacy and its effects on care.[13-15]

More broadly, this work is the first step in identifying and addressing patient concerns about privacy in the ED as well as further investigation of potential differences in concerns among different patient populations (e.g., between men and women). Understanding patient concerns and recognizing the impact they have on patient care is fundamental to improving patient experience and patient outcomes, and targeted interventions to increase the protection of privacy and confidentiality have been shown to be effective in the ED setting.[16,17]

Limitations of the study: It include potential selection bias for more satisfied patients given the reliance on convenience sampling. Additionally,

response bias is a potential confounding factor, particularly as interviewers were nursing staff and not research assistants or other staff removed from patient care. Although all respondents could speak and understand Urdu, it was only the primary language in 47% of respondents, so language barriers may have complicated the assessments. Finally, interviewer bias is also a factor, although this was minimized by consistent training of interviewers.

Despite these limitations, this survey highlights a large sample population from a diverse and busy ED in Karachi. We demonstrate that, while patients report satisfaction with privacy and confidentiality in the ED in general, their concerns do affect the patient-provider relationship and clinical care; therefore, targeted interventions to address confidentiality may help not only improve patient satisfaction, but also outcomes.

CONCLUSION

Despite the over-crowded and busy environment of the ED, patients generally felt that privacy and confidentiality was maintained. Given the correlation between perception and behavior, and the importance of an effective patient-provider relationship, particularly in the acute setting when morbidity and mortality is high, initiatives that focus on maintaining privacy and confidentiality should be pursued.

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Authors' Contribution:

SGS, SA, NG, QM, MIJ, and TA conceived, designed, and did data collection.
NG, DS, and MR did data analysis.
MR did manuscript writing.
SGS, SA, NG, QM, MIJ, TA, DS, and MR reviewed the manuscript.
SGS, SA, and MR did final review and approval of the manuscript.

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Original Article

Clinical spectrum and outcomes of patients with different resistance patterns of *Salmonella enterica*

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ABSTRACT

Background and Objective: Unceasing rise in cases of enteric fever, in particular extensively drug resistant (XDR) strain of *Salmonella enterica*, has led to a growing threat, leaving only carbapenems and azithromycin as the precious option. In this regard, we determined the burden and clinical course of XDR salmonella in comparison to multidrug-resistant (MDR) and drug sensitive (DS) strains.

Methods: A retrospective chart review of 1515 *Salmonella Typhi* (*S.typhi)* culture positive patients was conducted at Indus Hospital and Health Network, Karachi from July 2017 to December 2018.

Results: During our study, we observed children at the age of 5-6 years and adults at the age of 20-22 years were the chief targets of *S.typhi*. Further, we witnessed a rapid shift of drug resistance from MDR to XDR over the one year of study. Almost all patients presented with fever. However other signs and symptoms like malaise, body aches, anorexia, diarrhea, vomiting and abdominal pain were more common in XDR Typhoid patients. Further, the need of hospitalization, total hospital stay and mortality was also greater for XDR typhoid patients.

Conclusion: There is a crucial requirement for consolidated steps to curtail the spread of XDR *Salmonella tyhi* disease as its management is challenging, and it is associated with increased morbidity and mortality.

KEYWORDS: XDR, MDR, Drug sensitive, S.*typhi*, Clinical course.

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INTRODUCTION

Enteric fever is an acute systemic illness, caused by a gram negative bacterium, *Salmonella enterica, Serovar typhi* (*S. typhi*) or Paratyphi.[1] The disease is characterized mainly by the presence of persistent fever and can include other symptoms such as, malaise, headache, anorexia, constipation, diarrhea and non-productive cough.[2] Presently, enteric fever is a global health issue; annual estimated burden of disease is 11-21 million cases worldwide, resulting in 200, 000 deaths.[3] The burden of enteric fever is the highest in the Asian region , with 93% of the global cases being reported here.[4] In Pakistan, the incidence of enteric fever is estimated to be 413 / 100 000 person-years among children between two to four years of age and 573 / 100 000 person-years among children between 5 to 15 years of age.[5]

First line treatment for typhoid includes ampicillin, trimethoprim-sulfamethoxazole (TMP-SMZ), and chloramphenicol.[6] In recent years, emergence of strains of *S. typhi* resistant to antibiotics commonly used for treatment has been a major concern. These multi-drug resistant (MDR) strains are no longer susceptible to orally administered first line antibiotics previously used for treatment.[7] Moreover, resistance to fluoroquinolones, which were used to treat MDR cases, has also been reported frequently.[8] This leaves the option of using ceftriaxone, a third-generation cephalosporin, and azithromycin, a macrolide, for treatment against these resistant strains.[6] Rampant use of Ceftriaxone will add to the Multi drug resistant organisms including Salmonella. In MDR Salmonella, as long as it's sensitive it is a good parenteral option with a convenient once a day dose. Moreover with clinical improvement it can be switched to oral option. Azithromycin is the only oral option left against MDR salmonella, the loss of which will mean broad spectrum carbapenems with no oral options.

A three year review of antimicrobial resistance of typhi and paratyphi in Pakistan was conducted from 2009-11; this showed resistance to fluoroquinolones increasing from 84.7% to 91.7%, along with two cases of cephalosporin resistance.[9] In November 2016, an outbreak of ceftriaxone-resistant *S. typhi* was detected in Hyderabad, Sindh,[10] later spreading to Karachi. This was the largest outbreak of ceftriaxone-resistant *S. typhi* that has been reported globally.[8] This leaves very limited options for the treatment of new cases of enteric fever; carbapenems, azithromycin and tigecycline. Unfortunately, cases of azithromycin resistance are now being reported in South-east Asia as well.[11]

Given the burden of disease, which may be underreported due to lack of proper facilities of microbiological diagnosis, case fatality rate of enteric fever is expected to be higher and further rise. The clinical paradigms of patients diagnosed with XDR strain of enteric fever are slowly surfacing, with greater complications, and protracted clinical course and mortalities. With the paucity of appropriate diagnostic tools and limited antibiotics, clinicians will soon be at a loss on how to successfully treat this disease.

This study was conducted to determine the clinical course of XDR salmonella, comparing the severity of the strain to the MDR and drug-sensitive strains in both adult and pediatric population in a tertiary care setting. The study further evaluates the burden of the XDR salmonella strain in all cases of enteric fever, along with the complications, treatment course and clinical outcomes.

METHODS

A retrospective chart review was conducted of patients diagnosed with enteric fever at Indus Hospital and Health Network from 1st July, 2017 to 31st December, 2018. All patients, both adult and pediatric, with culture-proven enteric fever were included in the study. The data was extracted through the Health Management Informatics System (HMIS). IRB approval was obtained and the approval number is: IRD_IRB_2018_08_009 on 29th August 2018.

Blood cultures were performed using 5 ml of blood, drawn under aseptic measures, and collected in BacT/Aert culture bottles, which were then sent to the microbiology laboratory for analysis. Antibiotic susceptibility for antibiotics was tested using Disc Diffusion Method. Clinical and Laboratory Standards Institute (CLSI) guideline was followed to interpret the susceptibility pattern.

A pre-designed questionnaire was used to record detailed information about patient demographics, signs and symptoms, clinical course, treatment, complications, and final outcomes. Laboratory parameters were also recorded to determine the severity and course of the disease; these included complete blood count (CBC), liver function test (LFTs), serum electrolytes, Urea and Creatinine.

RESULTS

The study enrolled 1515 culture-proven enteric fever patients (Male: 890; Female: 625) (Table-I). The ratio of children was much higher than adults (88 % children up to 15 years age). The age groups most affected by *S.typhi* infection in our study include children 5-6 year age and adults 20-22 year age. (Table-I). In terms of drug resistance, we have observed three different strains of Salmonella with alarming numbers of resistant strains i.e. 50.5 % of XDR, 46.6 % of MDR and only 2.9 % of drug sensitive strains (Table-I). The patient inflow was much higher in the period of May to November, more specifically in July, which represented the peak season of bacterial illness. Over the one year, there was a rapid shift of predominant *S.typhi* strain from MDR to XDR

Table-I: Characteristics of enrolled patients.

Category	*Characteristics*	*XDR*		*MDR*		*Drug sensitive*	
		Adult	*Paeds*	*Adult*	*Paeds*	*Adult*	*Paeds*
Demographics	Age, Median, Years	22	5	21	6	20	5
	Male	51	391	50	374	10	14
	Female	35	288	27	255	3	17
Severity	Fever, Median (Range), Days	15 (1-90)	7.5 (1-150)	14.5 (1-180)	7 (1-210)	15 (3-90)	7 (1-90)
	Hospitalization, Median (Range), Days	8 (2-20)	6 (1-19)	5 (2-14)	4 (1-14)	4 (2-6)	4.5 (2-11)
Therapy	Single drug	30	245	31	307	7	11
	Multiple Drug	23	201	13	87	1	7
Outcomes	Known (Cured-Death)	40 (40-0)	270 (266-4)	29 (29-0)	162 (161-1)	2 (1-1)	13 (13-0)
	Lost to follow or LAMA	37	358	44	454	11	18
	Referred due to unavailability of bed	9	51	4	13	0	0

i.e. 78.4% MDR patients were registered in 2017 as compared to 38.6% in 2018, while XDR cases increased from 16.4% in 2017 to 59.1% in 2018 leading to a further decline in drug sensitive cases from 5.2% to 2.3% respectively (Fig.1).

The total number of patients who needed admission was 288 (19 %), while remaining patients were treated in outpatient (OPD) or daycare departments. Amongst patients requiring hospitalization, 211 were admitted at the hospital, whereas 77 were referred due to unavailability of space. A huge number of patients (922 patients, 60.85 %) were lost to follow or left against medical advice during our study, hence their outcomes were unknown. Almost all patients (admissions & OPD) presented with fever along with other sign and symptoms. Among adults and children, fever lasted for approximately fifteen days and seven days respectively (Range: 1-210 days) with no significant difference between drug sensitive and resistant *S.typhi* species. Other frequently noticed symptoms were malaise, body aches, anorexia, diarrhea, vomiting and abdominal pain. During the study, it was observed that patients with above symptoms were most likely to have XDR typhoid. Taking malaise, body aches and

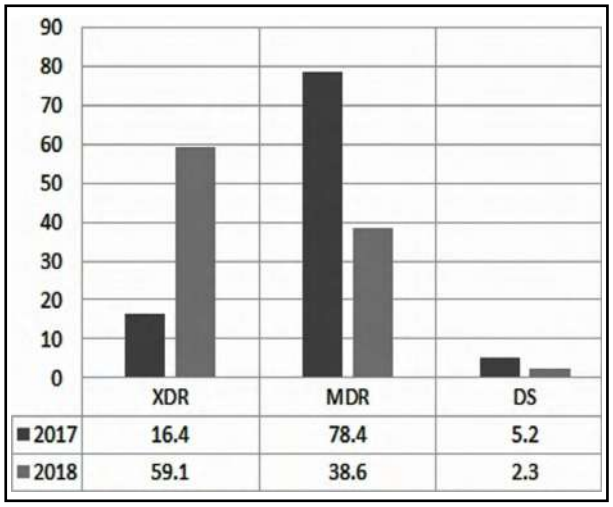

Fig.1: Yearly distribution of Drug resistance typhoid.

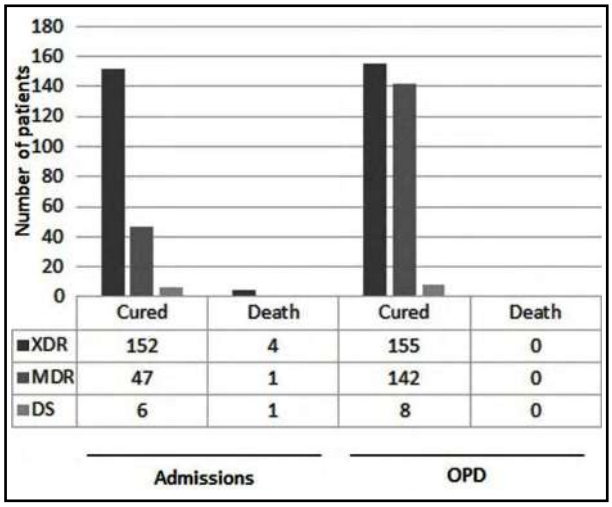

Fig.2: Known outcomes of enrolled patients.

Table-II: Commonly reported complications in enrolled patients.

Complication	*XDR*	*MDR*	*DS*
Jaundice	24	9	2
Acute abdomen	83	27	1
PR bleeding	9	5	1
Metastatic abscess	2	1	0
CNS manifestations	13	3	0
Cholecystitis	6	0	1
Septic arthritis	2	0	0
Death	4	1	1

diarrhea as reference, 23.66%, 10.84% and 26.53% of XDR typhoid patients reported these symptoms while only 3.54%, 8.25% and 19.54% of MDR typhoid patients and 6.81%, 9.09% and 9.09% of DS typhoid patients reported these symptoms respectively. In addition, the severity of disease was portrayed by days of hospitalization and mortality. The need for hospitalization was greater among XDR patients in comparison to MDR and DS. Out of 211 hospitalized patients, 156 (73.93 %) were diagnosed as XDR while 48 were MDR and seven belonged to DS (Fig.2). Furthermore, XDR patients were hospitalized for longer duration (eight days for adults and six days for children) than MDR and DS (4-5 days in both children and adults). In addition, mortality rate was also higher among XDR typhoid patients compared to those with MDR and DS typhoid. (Four, one and one respectively). One possible reason for increased hospitalization need and higher mortality in XDR patients was the complication rate. Abdominal pain and jaundice were the common manifestations of infection, followed by CNS manifestations, PR bleeding, cholecystitis and other (Table-II).

With lowered antibiotic sensitivity and minimal drug options for XDR salmonella, treatment has been very challenging. In our study, either azithromycin or meropenem was used as monotherapy or in combination in XDR patients while cephalosporins were used in MDR patients. In total, monotherapy was given more frequently (65.52% patients) in comparison to a combination of drugs. However, considering only cured patients, combination therapy was preferred over monotherapy in XDR patients (62.8%) while vice versa in MDR patients (40.9%).

DISCUSSION

This study witnessed a rapid shift of drug resistance from MDR to XDR over the one year of study. Further, we observed that the need of hospitalization, total hospital stay and mortality was greater for XDR typhoid patients. The disease burden of Enteric fever is highest in Asia and Africa. Although the environmental drivers for the seasonality of the disease are not well understood, however it has been assumed that it is related to monsoon and flooding in low income countries with poor infrastructure. The peak season for typhoid was seen in July in our study, while the numbers remained high from May through November, this correlated well with the seasonal pattern of the disease documented for the region of Asia.[12] In 2016, an extremely resistant strain of salmonella was documented for the first time in Pakistan.[9] This was depicted in our study with the gradual shift of resistance pattern from MDR to XDR over one year eventually accounting for more than 50% of the cases of *Salmonella typhi*.

Conventionally, enteric fever has been a mild disease treated in the outpatient department, but now with increasing antibiotic resistance, the need for hospitalization has increased due to prolonged, severe disease, complications and the need for parenteral antibiotics. In a prospective surveillance for enteric fever done in three Asian countries, Pakistan, Bangladesh and Nepal, 32% patients were hospitalized.[13] The hospitalization rate in our study was 13.92% (excluding the 5% additional patients who were unable to get inpatient accommodation due to space constraints). Of these 73.93% patients had XDR salmonella infection. The growing resistance

to antibiotics has shown adverse implications in enteric fever. In a systematic review evaluating clinical characteristics of enteric patients, those with MDR salmonella had delayed presentation to the hospital, with a more complicated course compared to the drug sensitive arm.[14] Complications are noted in 10-15 % of hospitalized patients, the most commonly reported being GI bleed, intestinal perforation, altered mental status, arthritis and jaundice.[15] Similarly in our study, duration of hospitalization, was prolonged in the XDR salmonella patients leading to higher number of complications subsequently, compared to MDR and DS. The reason for admission in 10% of the patients was some sort of complication while the remainder required parenteral antibiotics. The most common complications in our patients in chronological order were acute abdomen, jaundice, CNS manifestations, PR bleeding, cholecystitis, metastatic abscesses and septic arthritis. Seeding of salmonella was seen in the form of tuboovarian abscess, gallbladder empyema and abscess in the elbow in our study. This tendency of salmonella to seed in other locations has also been documented in other case reports.[16-18] Most of these complications in our patient pool however were more common in patients with XDR salmonella. Salmonella is known to be commoner is pediatric age group. Children tend to exhibit fewer symptoms as may not be able to express, yet when they do manifest symptoms they are shorter and sicker compared to adults who tolerate longer and seek medical advice a little delayed compared to pediatric age group, as observed in our study. Treatment has been very challenging with increasing resistance and no definitive guidelines, especially for the relatively new XDR salmonella. There has been strong evidence of activity of azithromycin[19] against MDR salmonella however not much evidence for the use of carbapenems. Carbapanems are used as last resort antibiotics for multidrug resistance gram negative bacteria. In a study evaluating treatment strategies in XDR salmonella patients, in Pakistan during the period of 2017-2018, azithromycin and meropenem monotherapy was given in 27% and 25% patient respectively, while 48% received a combination of both.[20] There was similar time to fever defervescence in all three groups, however the cost in the azithromycin group was substantially lower. In our study, 37.2% patients of XDR with known outcomes were cured on monotherapy i.e. either azithromycin or meropenem, while 62.8% (n=182) were cured with combination drug therapy. In MDR 59.1% (n=91) were cured on monotherapy, while 40.9% (n=63) were cured on multidrug therapy. Monotherapy in MDR was mainly cephalosporins.

The case fatality rate previously concurred was 1%,[4] however in a recent meta-analysis, done in 2018, it was estimated to be 2.45% overall and 4.45% for those hospitalized.[21] In this meta-analysis, there was considerable heterogeneity in CFR between studies, which could not be explained despite evaluating for World bank income level, different serovars, HIV status etc. In fact, this heterogeneity was even seen in studies from the same country, In our study, six hospitalized patients expired. Four of these being of pediatric group infected with XDR salmonella. This is in concordance with the known fact that children are less immune-competent as compared to adults and may have more complicated bacterial infections. The case fatality rate for our hospitalized patients was hence 0.4%. However, as a major proportion of the patients were loss to follow or referred due to non-availability of beds, the overall mortality may be an underestimate. These observations are of major concern especially in low income countries with a lack of robust health care system.

CONCLUSION

Growing antibiotic resistance in *Salmonella enterica* has made it a complicated disease to treat. This may be of grave consequence especially in low middle income countries where access to health care facilities and expensive antibiotics is not available to many. Steps should be taken to improve antibiotic prescribing practices and provide unified guidelines for management of extremely drug resistant *Salmonella enterica*.

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Authors Contribution:

FH, SS & SS: Conceived, designed and supervised the study.
FH & MI: Did manuscript writing & editing.
MI, NG & MM: Did data collection & statistical analysis.
FH: Did review, analysis and final approval of manuscript.

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Original Article

Chemotherapy induced histopathological changes in retinoblastoma, assessment of high risk predictive factors & its correlation with comorbid conditions

Nausheen Yaqoob[1], Salima Mansoor[2], Nida Zia[3], Kanwal Aftab[4], Bushra Kaleem[5], Saba Jamal[6]

ABSTRACT

Background & Objectives: Retinoblastoma is a malignant intraocular tumor and its treatment requires a multidisciplinary approach. Chemotherapy is an important modality in treatment of retinoblastoma. The purpose of this study was to assess the histopathological changes in retinoblastomas treated with chemotherapy along with correlation of comorbid conditions with high risk histopathological factors (HRF).

Methods: All post-chemotherapy enucleated eye specimens received in the pathology department between 2017 to 2021 were included in the study. Slides were retrieved and reviewed for chemotherapeutic effects, tumor regression, and for assessment of HRF. Patient demographic data, information regarding chemotherapy and co-morbid conditions were retrieved through the hospital database. Chi-square was used to analyze the relation between comorbid conditions and HRF.

Results: Chemotherapeutic effects were seen in all eyes with varying degrees of responses. Necrosis, calcification, and gliosis were the most common findings. The majority of eyes showed tumor occupying less than 50% of the eye whereas complete regression was noted in one eye only. Retinal detachment, glaucoma, and buphthalmos were the most common comorbid conditions at the time of diagnosis. Patients with glaucoma were more likely to have ciliary body invasion. Kaplan Meier analysis showed that patients with more than two HRF had decreased survival rates in comparison to those with one or no HRF.

Conclusion: Histopathological evaluation of chemotherapy-treated eyes shows varying degrees of response to chemotherapy. Post enucleation histopathological evaluation of the globe plays an important role in assessing disease activity and guiding further treatment to prevent metastasis.

KEYWORDS: Retinoblastoma, High Risk Histopathological Features, Chemotherapy, Survival.

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INTRODUCTION

Retinoblastoma is a malignant intraocular tumor of the retina occurring due to the exuberant proliferation of retinoblasts. It accounts for 3% of all pediatric tumors.[1] The average age at diagnosis is 18 months. Leukocoria (white reflex) is the most common symptom at presentation. Other findings include vision loss, cataract, vitreous and sub-retinal seedlings, strabismus, neovascularization of iris, glaucoma, vitreous

hemorrhage, and pseudohypopyon. Proptosis can occur in advanced cases.

In the 1960s, initial classification of retinoblastoma was introduced by Reese and Ellsworth to evaluate the success of radiotherapy. This classification assessed tumor size, location, and multifocality. Following the introduction of chemotherapy, this classification was no longer helpful in predicting response to chemotherapy. The Reese Ellsworth classification was replaced by the International Classification of Retinoblastoma (ICRB) in 2003. This classification predicts globe outcome after chemo reduction.[2,3] According to the ICRB classification, tumors are grouped from A to E, based on their size and the extent of tumor seeds in the subretinal space and vitreous cavity.

Several options are available for the treatment of retinoblastoma including enucleation, systemic chemotherapy, external beam radiation, and local treatment options like cryotherapy, transpupillary thermotherapy, and laser. The primary goal of treatment in unilateral retinoblastoma is patient survival and prevention of extraocular dissemination of tumor. Preservation of visual function and protection of the eye are secondary goals in unilateral retinoblastoma. Treatment of retinoblastoma is individualized based on several factors including the ICRB group, laterality of tumor, and vision potential.

Historically, external beam radiation therapy and enucleation were common modalities of treatment. Chemotherapy has recently become an important modality to avoid enucleation. Chemotherapy helps to reduce the size of the tumor (chemoreduction) thereby facilitating local treatment measures like cryotherapy, laser, etc. to control the tumor. It is also used as an adjuvant therapy to decrease the risk of metastasis following enucleation in high-risk patients. There are various routes of administering chemotherapy which include intravenous, intravitreal, intra-arterial, and subconjunctival. Vincristine, Etoposide, and Carboplatin are the standard agents for systemic chemotherapy because of good intraocular penetration.

With recent treatment modalities, it is possible to salvage eyes with group A, B, C, and some group D intraocular tumors, however group E and extraocular tumors require enucleation.[4,5] The treatment for extraocular disease includes chemotherapy followed by enucleation. Group A to C eyes can be salvaged in more than 90 percent of cases. Group D eyes have a lower chance of successful salvage and eyes can be salvaged in 47 percent of cases.[6]

Following enucleation, histopathological assessment of the globe is very important as the histopathology report helps ocular oncologists in deciding further course of treatment. There are few studies on the histopathological findings in retinoblastoma primarily treated with chemotherapy. Histopathological features that are considered as high risk include massive choroidal invasion, invasion of iris, ciliary body, sclera, optic nerve invasion posterior to lamina cribrosa and to cut end of the optic nerve. Some researchers also consider anterior chamber invasion as a high-risk factor but it is still debatable.[7] This study will focus on histopathological features in chemotherapy-treated eyes along with the correlation of ocular co-morbidities with high-risk histopathological factors.

METHODS

All patients with retinoblastoma who received chemotherapy only were selected for the study. Enucleated eye specimens received in the pathology department between September 1st, 2017 to February 28th, 2021 were retrieved for review.

Patient demographic data and information regarding chemotherapy regimen, number of chemotherapy cycles given, ICRB classification, and indication for enucleation were retrieved through Health Management Information System. The slides were reviewed for tumor regression and histopathological changes in the tumor. Status of retinoblastoma was noted as tumor occupying greater than 50% of the eye, less than 50% of the eye, less than 5% or completely regressed. Invasion of eye structures was noted including invasion of the anterior chamber of eye, iris, ciliary body, minimal (tumor <3mm in diameter) and massive (tumor >3mm in diameter) choroidal invasion, scleral/extrascleral invasion, and optic nerve invasion anterior to lamina cribrosa, at lamina cribrosa, posterior to lamina cribrosa and to the cut end of the optic nerve. Only anterior chamber invasion, massive choroidal invasion, scleral invasion, optic nerve invasion posterior to lamina cribrosa and to cut end of the optic nerve were considered as high-risk histopathological features. Other features like necrosis, calcifications, gliosis and retinal detachment were also reviewed. Necrosis and calcification were graded as extensive (>50%), moderate (25-50%), and minimal (<25%). Chi-

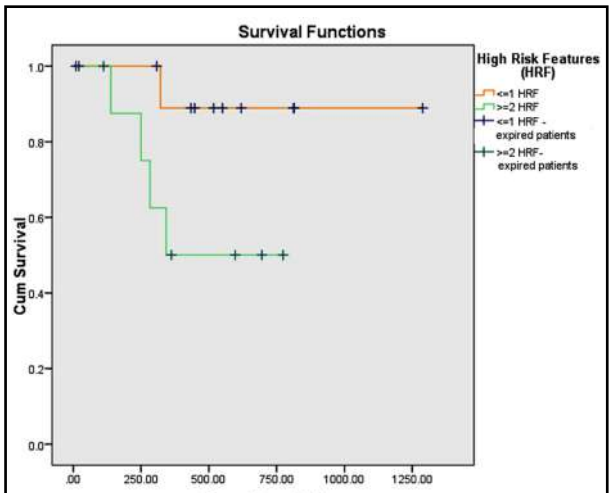
square test was used to analyze the association between comorbid conditions and invasive disease. KM analysis of study participants based on the number of high-risk factors was also done. ***Ethical Approval:*** An approval from the Review Board of Indus Hospital and Health Network was obtained for this study (IHHN_IRB_2021_03_006).

RESULTS

A total of 77 eyes were received in the histopathology department between September 1st, 2017 and February 28th, 2021. Out of these, 54 underwent primary enucleation whereas 21 received chemotherapy followed by enucleation. The median age of patients was 36 months (IQR: 24-48 months). The median time from diagnosis to enucleation was 2 months (IQR: 1 to 42 months). Demographic data, clinical and histopathological findings at the time of diagnosis are given in Table-I.

Of those who received chemotherapy, the majority of eyes were group E (10 eyes, 47.6 %) according to ICRB classification, six eyes (28.6 %) were group D and five (23.8%) had extraocular disease. Indication of enucleation was group E and extraocular disease in 15 eyes and treatment failure in six group D eyes. Nine patients had bilateral retinoblastoma and 12 patients had unilateral retinoblastoma. As per our institutional policy, bilateral retinoblastoma patients, with one advanced eye (Group E) were treated with two cycles of systemic chemotherapy for tumor reduction before enucleation. Group D patients were treated with chemotherapy initially followed by enucleation in case of progression or treatment failure. Most patients received intravenous chemotherapy with a three-drug regimen of Carboplatin (600mg/m^2 on Day 1), Etoposide (150mg/m^2 on Days 1 & 2), and Vincristine (1.5mg/m^2 on Day 1). Four patients received chemotherapy for extraocular Retinoblastoma which included Carboplatin (200mg/m^2 Days 1, 2 & 3), Etoposide (150mg/m^2 on Days 1, 2 & 3), Doxorubicin (50mg/m^2 on Day 1), and Cyclophosphamide (450mg/m^2 on Days 1, 2 & 3). The majority of patients received two cycles of chemotherapy prior to enucleation. Three patients also received intravitreal Melphalan.

Histopathologic evidence of chemotherapeutic effects was seen in all eyes showing varying degrees of necrosis and calcification. Histopathologic findings in eight (38%) eyes showed tumor regression to less than five percent. Complete regression of the tumor was seen in one eye. Rosettes were present in 33.3% eyes. In terms of HRFs involving the optic nerve,



HRF	Total number of patients, N	N of deaths, n	Overall Survival, %	Survival days, Median (IQR)	p-value
≤1.00	12	1	91.7	483.0 (311.5 – 764.0)	0.063*
≥2.00	9	4	55.6	343.0 (194.5 – 647.0)	

*Log-rank (Mantel-Cox) test.

Fig.1: Kaplan-Meier analysis of the study participants on the basis of number of HRFs

the tumor was still present up to the cut end in 19% patients while 42.9% were found to tumor free. The tumor was completely absent in 66.7% of patients with previously present choroidal invasion while massive invasion of the choroid was still present in 19% patients. Iris and ciliary body invasion was still observed in the post-chemotherapy period in 28.6% and 23.8% patients respectively.

A correlation was also done between co-morbid conditions and the presence of high-risk histopathological features shown in Table-II. The presence of glaucoma was found to be significantly associated with the presence of ciliary body invasion (p-value: 0.037). Fifteen patients were alive and five died as of April 2021. One patient was lost to follow up. Kaplan Meier analysis of study participants based on the number of high risk factors is displayed in Fig.1. Patients with two or more high risk factors had low survival rates compared to patients with one or no high risk factors, however, this was not statically significant.

DISCUSSION

The treatment of Retinoblastoma is complex and is in constant evolution. It requires a multidisciplinary approach with the involvement of pediatric oncologists, ophthalmologists, and radiation oncologists. The treatment varies worldwide but the primary goal remains the same

Table-I: Characteristics of study participants.

Variables	*N (%)*
DEMOGRAPHIC CHARACTERISTICS	
Age:	36 months
Median (IQR)	(24 – 48 months)
Gender:	
(M/F)	13 (61.9)/8 (38.1)
Time from diagnosis to enucleation, months:	
Median (IQR)	2 (1 – 42)
No. of patients received chemotherapy:	
CEV	17 (80.9)
EORB	1 (4.8)
CEV + EORB	3 (14.3)
Overall survival:	
N (%)	16 (76.2)
Days of survival:	
Median (IQR)	434 (266.5 - 658)
CLINICAL CHARACTERISTICS	
Clinical classification	
• Group D	6 (28.6)
• Group E	10 (47.6)
• Extraocular	5 (23.8)
Tumor stage:	
• pT0	1/21 (4.8)
• pT1	7/21 (33.3)
• pT2	4/21 (19.0))
• pT3	3/21 (14.2)
• pT4	5/21 (23.8)
Cannot be determined	1/21 (4.8)
Tumor grade:	
• G1	3/21 (14.3)
• G2	7/21 (33.3)
• G3	6/21 (28.6)
• G4	1/21 (4.8)
Cannot be determined	4/21 (19.0)
Vitreous seeds	
• Present	7/21 (33.3)
• Absent	14/21 (66.6)
Cataracts	
• Present	0/21 (0)
• Absent	21/21 (100)
Glaucoma	
• Present	4/21(19.0)
• Absent	17/21(80.9)
Retinal detachment	
• Present	7/21 (33.3)
• Absent	14/21 (66.6)
Pthisis bulbi	
• Present	0/21 (0)
• Absent	21/21 (100)
Iris neovascularization	
• Present	2/21 (9.5)
• Absent	19/21 (90.4)
Bupthalmos	
• Present	3/21 (14.2)
• Absent	18/21 (85.7)
Proptosis	
• Present	1/21 (4.7)
• Absent	20/21 (95.2)
Pseudohypopyon	
• Present	1/21 (4.7)
• Absent	20/21 (95.2)
HISTOLOGICAL FINDINGS	
Tumor status:	
• >50%	7/21 (33.3)
• <50%	3/21 (14.2)
• <5%	10/21 (47.6)
• Complete regression	1/21 (4.7)
Calcification	
• Extensive	7/21 (33.3)
• Moderate	2/21 (9.5)
• Minimal	12/21 (57.1)
Necrosis	
• Extensive	11/21 (52.3)
• Moderate	2/21 (9.5)
• Minimal	8/21 (38.0)
Gliosis	
• Present	8/21 (38.0)
• Absent	13/21 (61.9)
Rosettes	
• Present	7/21 (33.33)
• Absent	14/21 (66.66)
Optic nerve invasion	
• Pre-laminar	2/21 (9.5)
• Laminar	3/21 (14.3)
• Post-laminar	2/21 (9.5)
• To cut end of optic nerve	4/21 (19.0)
• Tumor free	9/21 (42.9)
• Cannot be determined	1/21 (4.8)
Choroid invasion	
• Minimal	2/21 (9.5)
• Massive	4/21 (19.0)
• Tumor free	14/21 (66.7)
• Cannot be determined	1/21 (4.8)
Scleral invasion	
• Present	3/21 (14.3)
• Absent	17/21 (80.9)
• Cannot be determined	1/21 (4.8)
Iris invasion	
• Present	6/21 (28.6)
• Absent	15/21 (71.4)
Ciliary body invasion	
• Present	5/21 (23.8)
• Absent	15/21 (71.4)
• Cannot be determined	1/21 (4.7)
Anterior chamber invasion	
• Present	6/21 (28.5)
• Absent	15/21 (71.4)

CEV-Carboplatin/Etoposide/Vincristine;
EORB-Extra-ocular retinoblastoma chemotherapy.

Table-II: Association between tumor invasion and various comorbidities.

	Optic nerve invasion			*Massive choroidal invasion*			*Minimal choroidal invasion*			*Iris invasion*			*Ciliary body invasion*			*Scleral invasion*		
	Yes	*No*	*p-value*	*Yes*	*No*	*p-value*	*Yes*	*No*	*p-value*	*Yes*	*No*	*p-value*	*Yes*	*No*	*p-value*	*Yes*	*No*	*p-value*
Time to enucleation																		
≤3 Months	8/14 (57.1)	6/14 (42.9)	0.574	3/14 (21.4)	11/14 (78.6)	0.657	2/14 (14.3)	12/14 (85.7)	1.000	5/14 (35.7)	9/14 (64.3)	0.613	4/13 (30.8)	9/13 (69.2)	1.000	2/14 (14.3)	12/14 (85.7)	1.000
> 3 Months	3/6 (50.0)	3/6 (50.0)		1/6 (16.7)	5/6 (83.3)		-	6/6 (100)		1/6 (16.7)	5/6 (83.3)		1/6 (16.7)	5/6 (83.3)		1/6 (16.7)	5/6 (83.3)	
Necrosis:																		
Extensive	4/8 (50.0)	4/8 (50.0)	1.000	2/8 (25.0)	6/8 (75.0)	1.000	1/8 (12.5)	7/8 (87.5)	1.000	3/8 (37.5)	5/8 (62.5)	0.631	3/8 (37.5)	5/8 (62.5)	0.347	1/8 (12.5)	7/8 (87.5)	1.000
Minimal/ Moderate	7/13 (53.8)	6/13 (46.2)		2/12 (16.7)	10/12 (83.3)		1/12 (8.3)	11/12 (91.7)		3/13 (23.1)	10/13 (76.9)		2/12 (16.7)	10/12 (83.3)		3/13 (23.1)	10/13 (76.9)	
Glaucoma:																		
Yes	2/4 (50.0)	2/4 (50.0)	1.000	1/4 (25.0)	3/4 (75.0)	1.000	-	3/3 (100)	1.000	3/4 (75.0)	1/4 (25.0)	0.061	3/4 (75.0)	1/4 (25.0)	0.037*	1/4 (25.0)	3/4 (75.0)	0.509
No	9/16 (56.3)	7/16 (43.8)		3/16 (18.8)	13/16 (81.3)		2/17 (11.8)	15/17 (88.2)		3/16 (18.8)	13/16 (81.3)		2/15 (13.3)	13/15 (86.7)		2/16 (12.5)	14/16 (87.5)	
Pseudohypopyon:																		
Yes	1/1 (100)	-	1.000	-	1/1 (100)	1.000	-	1/1 (100)	1.000	1/1 (100)	-	0.286	1/1 (100)	-	0.250	-	1/1 (100)	1.000
No	10/20 (50.0)	10/20 (50.0)		4/19 (21.1)	15/19 (78.9)		2/19 (10.5)	17/19 (89.5)		5/20 (25.0)	15/20 (75.0)		4/19 (21.1)	15/19 (78.9)		4/20 (20.0)	16/20 (80.0)	
Vitreous seeds:																		
Yes	4/7 (57.1)	3/7 (42.9)	1.000	-	6/6 (100)	0.267	2/6 (33.3)	4/6 (66.7)	0.079	2/7 (28.6)	4/14 (71.4)	1.000	1/6 (16.7)	5/6 (83.3)	1.000	1/7 (14.3)	6/7 (85.7)	1.000
No	7/14 (50.0)	7/14 (50.0)		4/14 (28.6)	10/14 (71.4)		-	14/14 (100)		4/14 (28.6)	10/14 (71.4)		4/14 (28.6)	10/14 (71.4)		3/14 (21.4)	11/14 (78.6)	
Retinal detachment:																		
Yes	4/7 (57.1)	3/7 (42.9)	1.000	-	7/7 (100)	0.249	2/7 (28.6)	5/7 (71.4)	0.111	2/7 (28.6)	5/7 (71.4)	1.000	2/7 (28.6)	5/7 (71.4)	1.000	-	7/7 (100)	0.255
No	7/14 (50.0)	7/14 (50.0)		4/13 (30.8)	9/13 (69.2)		-	13/13 (100)		4/14 (28.6)	10/14 (71.4)		3/13 (23.1)	10/13 (76.9)		4/14 (28.6)	10/14 (71.4)	
Iris neovascularization:																		
Yes	2/2 (100)	-	0.476	-	2/2 (100)	1.000	-	2/2 (100)	1.000	2/2 (100)	-	0.071	2/2 (100)	-	0.053	-	2/2 (100)	1.000
No	9/19 (47.7)	10/19 (52.6)		4/18 (22.2)	14/18 (77.8)		2/18 (11.1)	16/18 (88.9)		4/19 (21.1)	15/19 (78.9)		3/18 (16.7)	15/18 (83.3)		4/19 (21.1)	15/19 (78.9)	
Buphthalmos																		
Yes	1/2 (50.0)	1/2 (50.0)	1.000	2/3 (66.7)	1/3 (33.3)	0.088	-	4/4 (100)	1.000	2/3 (66.7)	1/3 (33.3)	0.202	2/3 (66.7)	3/16 (18.8)	0.155	1/3 (33.3)	2/3 (66.7)	0.404
No	10/18 (55.6)	8/18 (44.4)		2/17 (11.8)	15/17 (88.2)		2/16 (12.5)	14/16 (87.5)		4/17(23.5)	13/17 (76.5)		1/3 (33.3)	13/16 (81.3)		2/17 (11.8)	15/17 (88.2)	

i.e. to preserve life, prevent metastatic disease, and salvage the globe and vision whenever possible. Systemic chemotherapy is either given for chemo reduction (reduce tumor size via chemotherapy) or used as adjuvant therapy. Its effect is usually seen after two cycles of chemotherapy with an average reduction of 50% in tumor thickness.[8] Despite the development of more conservative approaches, approximately 20-30% of patients with bilateral retinoblastoma require enucleation.[9] The evaluation of the tumor status in the post-chemotherapy period is of immense importance as it helps in assessing the extent of viable tumor as well as the presence of HRFs. It further helps in predicting extraocular dissemination of tumor, the risk stratification of the patient and thus the need for neoadjuvant therapy to reduce the risk of metastasis. Current study evaluates the response to chemotherapy, and the presence of HRFs for future treatment strategy in retinoblastoma patients. Further the presence of co-morbidities was associated with the HRFs as certain features such as retinal detachment have resulted in optic nerve invasion of the tumor.

Histopathological evaluation of the eyes in this study showed that the tumor exhibited variable response to chemotherapy with complete regression of the tumor in one eye while no significant tumor regression (tumor occupying >50% of eye) was seen in 33.3% eyes as shown in Table-I. Enucleation is decided on the baseline grouping of the eye. Groups D and E are non-salvageable and thus have to be enucleated with no option of globe salvage. However, post-enucleation histopathology is important to further designate the management plan to decrease the metastatic potential, so as to improve the survival. According to a study by Carolyn P et al., the histopathological evaluation of nine eyes showed no residual tumor in one eye, calcified and necrotic tumor cells in two eyes, and non-calcified, non-necrotic tumor in six eyes.[4] Demirci et al. studied histopathological features in 10 eyes following chemo reduction. The study revealed regression of the main tumor in all eyes with complete regression in eight eyes and partial regression with viable retinoblastoma in two eyes.[5]

In our study, rosette formation was seen in 33.3% of cases. In a study by Stannard et al., the rosettes were commonly seen in patients with early stages of the disease and thus indicated a good prognosis.[10] Pseudorosettes characterized by tumor cells surrounding a central blood vessel were also noted in six cases. In our study, extensive necrosis was noted in 52.3% of eyes and extensive calcification was seen in 33.3% eyes. Extensively necrotic retinoblastoma is associated with high-risk histopathological findings like choroidal invasion and optic nerve invasion.[11] Thus, a thorough evaluation of the eye for the presence of high-risk features is needed in the presence of extensive necrosis. This is significant for eyes without pre-operative chemotherapy. However, its significance in post-chemotherapy-treated eyes has not been reported. In our study, no significant association of necrosis with high risk histopathological features was noted. Other findings seen on histopathological examination included gliosis, foamy histiocytes, hemosiderin-laden macrophages, fibrosis, foreign body type giant cells, and hemorrhage. In one eye, invasion of choroid, optic nerve, sclera and ciliary body could not be determined due to non-visualization of these structures as a result of extensive necrosis. Histologic grade could not be assessed in four eyes due to significant reduction in tumor.

Optic nerve invasion is seen in 25-45% of eyes that undergo primary enucleation.[9] In our study, optic nerve invasion was seen in 11 eyes (52.3%). According to Shield et al., invasion of optic nerve posterior to lamina cribrosa is associated with high metastatic risk especially if there is simultaneous choroidal invasion.[12] Choroidal invasion is seen in 12 – 42% of eyes but massive invasion is seen in less than 10 % of eyes.[13] In our study, massive choroidal invasion was seen in four eyes (19%).

We also correlated the presence of co-morbid conditions like glaucoma, buphthalmos, etc with high-risk histopathological features as shown in Table-II. Patients with glaucoma were more likely to have ciliary body invasion, which was statistically significant. A study by Balaguer et al reported that there is an association between comorbid conditions and invasive disease. The study reported that patients with retinal detachment and vitreous hemorrhage had more chances of optic nerve invasion.[9]

The overall survival rate in our study was 76.2 %. The survival rate of retinoblastoma in developed countries is between 95-98% which reduces to 50% worldwide. An Indian study conducted by Gupta et al. reported survival rate of 63%.[14]

Further studies on presence of high risk pathological features in retinoblastoma and their association with clinical predictors, chemotherapy induced changes and ocular co-morbidities are needed from developing countries which would impact on management strategies and improve survival outcomes.

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Authors' Contribution:

NY & NZ: Equal contribution towards the concept of the study and critical revision for important intellectual content;
SM: Drafted the work, revised it critically for important intellectual content;
KA, SJ: Revised it critically for important intellectual content;
BK: Substantially contributed towards data acquisition, analysis, and interpretation; drafted the work;
All authors approved the final version and also agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Original Article

High risk histopathological factors in retinoblastoma in upfront enucleated eyes: An experience from a tertiary care centre of Pakistan

Nausheen Yaqoob[1], Salima Mansoor[2], Kanwal Aftab[3], Bushra Kaleem[4], Ahmer Hamid[5], Saba Jamal[6]

ABSTRACT

Background & Objectives: The assessment of histopathological risk factors (HRFs) in retinoblastoma in upfront enucleated eyes is important in deciding treatment protocols. Limited data is available from the developing countries as very few studies were conducted on retinoblastoma. The study aims to report this data from Pakistan.

Methods: This cross-sectional study included treatment naïve retinoblastoma patients who underwent upfront enucleation between 2017 to 2021. Various tumor characteristics i.e. laterality, size, histologic grade, anaplasia grade, growth pattern, extent and length of optic nerve invasion, pathologic staging, tumor involvement of ocular structures were assessed. High-risk factors such as involvement of anterior chamber, choroidal, scleral, extrascleral, and optic nerve were also noted.

Results: A total number of 54 patients were enrolled, out of which 53.7% were females while remaining were males. Median age at presentation was 24 months. Unilateral tumor was seen in 92.6% cases. Most frequent histologic grade was G2 (64.7%) and moderate anaplasia was observed in 59.2% cases. Vitreous involvement was seen in (86.5%). Pathologic staging of most of the tumors was pT1 (39.2%). Assessment of high-risk factors revealed that optic nerve involvement (35.1%) was the most common finding with retrolaminar tumor invasion seen in 75% cases. Choroidal invasion (≤3mm) was seen in 55.6% of patients. Limited involvement of anterior chamber (3.8%), sclera (7.4%), and extrascleral (3.8%) tissue was also observed.

Conclusion: The presence of high risk histopathological factors in enucleated eyes diagnosed with retinoblastoma are known to have a profound impact on the risk stratification as well as decision of future treatment plan.

KEYWORDS: Retinoblastoma, Intraocular malignancy, High-risk features.

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INTRODUCTION

Retinoblastoma (Rb) is the most common primary intraocular malignancy of the neurosensory retina accounting for approximately 3% of childhood malignancies. Its incidence is between 1:17,000 - 1:20,000 live births and approximately 7000-8000 cases are reported per annum.[1] It exclusively affects infants and young children and shows no significant race or gender predilection. According to World Health Organization (WHO), 66% cases are detected

before 24 months whereas approximately 95% cases are seen before five years of age.[2] Local literature reports the incidence to be 4 and 2.4 in 100,000 children before age five and ten respectively.[3] In Asia-Pacific region, India reports highest number of Rb cases while Pakistan ranks sixth.[4]

Retinoblastoma is primarily a clinical diagnosis and histological evaluation of enucleated eyes for the presence of high risk factors is important in deciding further treatment including adjuvant chemotherapy. Histological presence of high risk factors (HRFs) can predict local recurrence ,distant metastases, tumor progression and overall prognosis. HRFs such as choroidal, scleral, extrascleral, and optic nerve invasion (posterior to lamina cribrosa or up to the cut end of the optic nerve) are predictors of metastases.[5]

Incidence of HRFs and systemic metastases is reported to be less in high income countries,[6-8] the reason being early presentation, diagnosis and treatment as compared to advanced-stage disease presentation in developing countries due to lack of education, low socioeconomic status and lack of access to health care facilities.[9]

Treatment of retinoblastoma depends on various factors including laterality and stage of disease. Chemotherapy along with local therapies like brachytherapy, cryotherapy and laser can be used to salvage eyes with early intraocular disease.[10] Despite of advancement seen in early diagnosis and treatment of retinoblastoma, it's management still remains a challenge in developing countries. This study assesses the frequency of HRFs in enucleated eyes which would be helpful in deciding future management of the patients.

METHODS

A cross-sectional observational analysis was performed on enucleated eye specimens of all patients who had a clinical diagnosis of intraocular retinoblastoma presenting to our institute between September 2017 and February 2021.

Ethical Approval: The study participants were enrolled after approval from the ethics review board of the institute (IHHN_IRB_2021_03_007) in accordance to the guidelines of Declaration of Helsinki and an exemption was provided due to retrospective nature of the study. Treatment naïve retinoblastoma patients <18 years and of either gender were included in the study.

Patient demographics included age and gender. Tumor characteristics included laterality, size of tumor, histologic grade, anaplasia grade, growth pattern (exophytic or endophytic), extent of optic nerve (ON) invasion, pathologic staging, tumor involvement of ocular structures, and additional findings (calcification, necrosis, inflammation, hemorrhage). Histologically, well differentiated tumors (G1) contained areas of retinocytoma (neuronal differentiation or fluerettes), moderately differentiated tumors were tumors with many Flexner-Wintersteiner or Homer-Wright rosettes (G2), or occasional Flexner-Wintersteiner or Homer-Wright rosettes (G3), while poorly differentiated (G4) tumors lacked any evidence of rosettes formation and/or extensive anaplasia (>50%). Endophytic growth pattern indicated growth from the inner retinal surface into the vitreous cavity while exophytic tumors grew primarily from the outer surface of the retina into the subretinal space toward the choroid. Combined growth pattern exhibited features of both endophytic and exophytic growth.

High-risk factors:

1. Anterior chamber invasion involving iris, ciliary body (Fig.1A)
2. Choroidal invasion (Fig.1B):

a. Massive: >3 mm in diameter and/or with the full thickness of choroidal involvement.

b. Minimal: ≤3 mm in diameter and with partial-thickness of choroidal involvement.

3. The optic nerve invasion posterior to lamina cribrosa & to the transection line of the nerve (Fig.1C).
4. Scleral or extrascleral involvement (Fig.1D).

Statistical Analysis: The statistical analysis was performed using SPSS version 24.0. Continuous parameters such as age and size of tumor were represented by median (interquartile range) or mean ± SD depending on the normality while categorical parameters such as gender, laterality, histologic grade, anaplasia grade, growth pattern, extent of optic nerve invasion, pathologic staging, tumor involvement of ocular structures and additional findings were represented in proportions. The categorical data were compared using Chi-square (Fisher exact) test as per the need. A p-value of <0.05 was considered statistically significant.

RESULTS

The study included 54 patients of retinoblastoma during the study period. The median age at presentation was 24 months (IQR: 18-36 months). Female preponderance i.e. 53.7% was observed. Review of enucleated eyes with retinoblastoma revealed following histopathological features and high-risk factors (Table-I). Comparison of various factors with degree of differentiation of tumor is displayed in

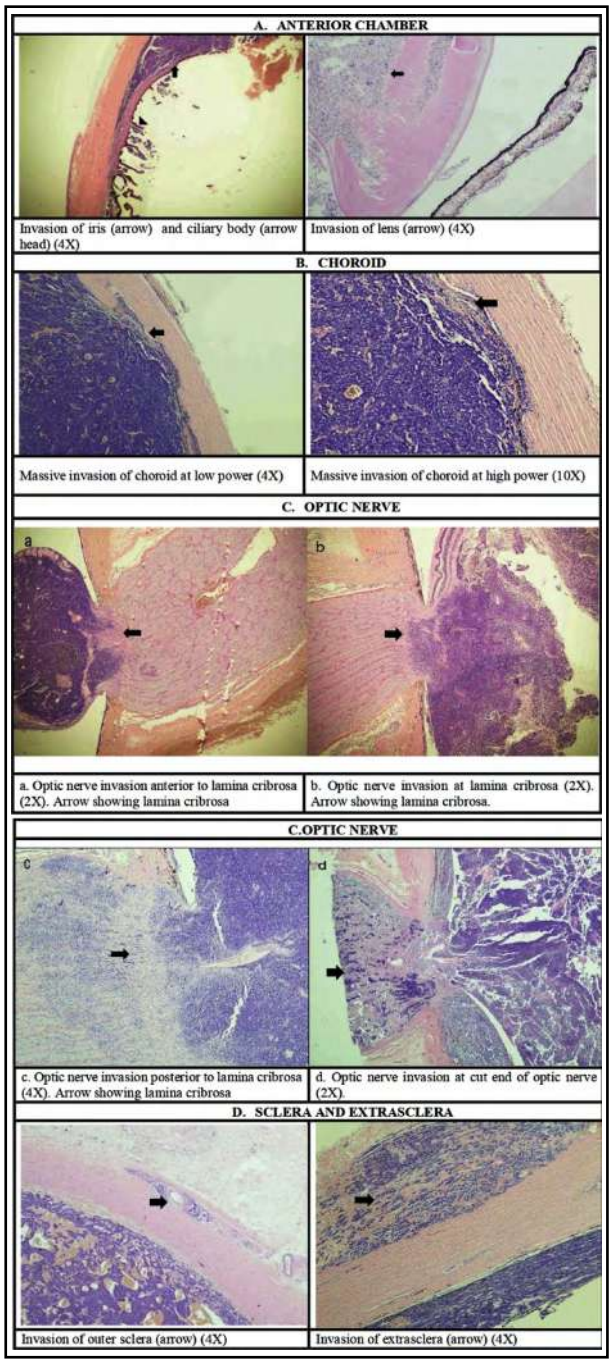

Fig.1

(Table-II). Certain ocular features could not be assessed in few cases due to non-visualisation of these structures as a result of extensive tumor necrosis.

DISCUSSION

Enucleation is one of the oldest form of treatment for retinoblastoma particularly in advanced cases[9] and considered as the best treatment option for patients with unilateral disease and non-salvageable

Table-I: Histopathological features of retinoblastoma

Variables	*Values*
Laterality:	
Unilateral, n (%)	50 (92.6)
Bilateral, n (%)	4 (7.4)
Tumor size, cm	
Median (IQR)	1.7 (1.5-2.0)
Histologic grade (n=51)	
Well-differentiated (G1), n (%)	4 (9.8)
Moderately differentiated (G2), n (%)	34 (64.7)
Moderately differentiated (G3), n (%)	11 (21.6)
Poorly differentiated (G4), n (%)	2 (3.9)
Could not be determined, n (%)	3
Anaplasia grade (n=49)	
Mild, n (%)	20 (40.8)
Moderate, n (%)	29 (59.2)
Severe, n (%)	0
Growth pattern (n=53)	
Endophytic, n (%)	41 (77.4)
Exophytic, n (%)	7 (13.2)
Combined endophytic and exophytic, n (%)	5 (9.4)
Tumor involvement of other ocular structures:	
Vitreous, n (%)	45/52 (86.5)
Optic nerve head, n (%)	24/31 (77.4)
Sub-retinal pigment epithelial space, n (%)	17/27 (63.0)
Sub-retinal space, n (%)	29/47 (61.7)
Optic disc, n (%)	8/20 (40.0)
Cornea, n (%)	1/53 (3.8)
Optic nerve invasion (n=36)	
Anterior to lamina criborisa, n (%)	15 (41.6)
At lamina criborisa, n (%)	5 (13.9)
Posterior to lamina cribrosa, n (%)	15 (41.6)
Up to transection line of ON, n (%)	1 (2.8)
Pathologic staging (n=51)	
pT1, n (%)	20 (39.2)
pT2, n (%)	1 (2.0)
pT2a, n (%)	12 (23.5)
pT3, n (%)	4 (7.4)
pT3b, n (%)	10 (19.6)
pT3d, n (%)	1 (2.0)
pT4, n (%)	2 (3.9).
Additional findings:	
Necrosis, n (%)	44/50 (88.0)
Calcification, n (%)	32/51 (62.7)
Inflammation, n (%)	21/54 (38.8)
Haemorrhage, n (%)	7/54 (12.9)
Retinal detachment, n (%)	2/54 (3.7)
High-risk factors	
Anterior segment structures involvement (n=53)	
Iris, n (%)	2 (3.8%)
Ciliary body, n (%)	2 (3.8%)
Choroidal invasion (n=18)	
≤3mm, n (%)	10 (55.6)
>3mm, n (%)	8 (44.4)
Extent of optic nerve invasion (n=20)	
Posterior to lamina cribrosa, n (%)	15 (75.0)
Up to transection line of the nerve, n (%)	1 (5.0)
Scleral invasion, n (%)	4/54 (7.4)
Extrascleral invasion, n (%)	1/54 (1.9)

Table-II: Univariate analysis of variables with degree of differentiation of tumor

Degree of tumor differentiation	*Number of HRF*					*Presence of HRF*			*Laterality*			*Age categories*		
	No HRF	*1 HRF*	*2 HRF*	*3 HRF*	*p-value*	*No HRF*	*>=1 HRF*	*p-value*	*Uni-lateral*	*Bilat-eral*	*p-value*	*<24 months*	*>=24 months*	*p-value*
Well differentiated (G1); n=4	3 (75)	1 (25)	0	0		3 (75)	1 (25)		3 (75)	1 (25)		3 (75)	1 (25)	
Moderately differentiated (G2); n=33	21 (61.8)	7 (20.6)	6 (17.6)	0		21 (61.8)	13 (38.2)		31 (91.2)	3 (8.8)		21 (61.8)	13 (38.2)	
					0.640			1.000			0.329			0.192
Moderately differentiated (G3); n=11	7 (63.6)	2 (18.2)	1 (9.1)	1 (9.1)		7 (63.6)	4 (36.4)		11 (100)	0		4 (36.4)	7 (63.6)	
Poorly differentiated (G4); n=2	1 (50)	0	1 (50)	0		1 (50)	1 (50)		2 (100)	0		0	2 (100)	

vision. Enucleated eyeball is always assessed for the presence of HRFs. Presence of HRFs warrants the risk of secondary orbital recurrence as well as systemic metastasis, and thus there is a strong indication of adjuvant treatment comprising of chemotherapy and/or External Beam Radiation Therapy (EBRT) which resulted in risk reduction of metastasis to 4% in comparison to 24% who did not receive the treatment according to Honovar et al.[11]

Histopathological features of retinoblastoma have been the focus of many studies.[6-8,12,13] The present study assessed the histopathological features of retinoblastoma with an emphasis on the high-risk factors. Mean age of presentation in the present study was 29.15 ±18.20 months (Median – 24; IQR-18.0 – 36.0 months) which was similar to findings of other regional studies by Zia et al[14], and Gupta et al.[12] also reported that age at presentation greater than 24 months was a predictor for HRFs. In our study, HRFs were noted in 24.0% patients who presented at >24 months of age.

The present study reports presence of well-differentiated tumors in patients who presented at age <24 months in comparison to poorly differentiated tumors who presented in older age group (Table-II). Kashyap et al.[15] also reported poorly differentiated tumors in patinets presenting at an age of >24 months. Present study also reported presence of HRFs in tumors which showed poor differentiation (Table-II) This was similar to another study in which multiple HRFs were observed in poorly differentiated tumors (26%) in comparison to well-differentiated tumors (6.7%).[15]

The HRFs include optic nerve invasion (posterior to lamina cribrosa or to the cut end of the nerve), choroidal, scleral, and extrascleral involvement.[5] The number of patients with ≥1 HRFs in the present study was 35.2% which was similar to the prevalence reported by Kaliki et al.[13] i.e. 38%. Our study reported 1 HRF and >1 HRF in 18.5% and 16.7% patients respectively which was in concordance to a study by Kashyap et al.[15] which reported 18.7% and 22.7% patients for the same. These HRFs have been reported to have a varying prevalence i.e. 6%-28% for invasion of optic nerve posterior to lamina cribrosa and optic nerve to the resection line, 12%-42% for choroidal involvement and 8%-15% for scleral and extrascleral spread.[9] Comparison of the frequency of HRFs observed in our study was compared with other studies from nearly two decades as displayed in Table-III.

The extent of optic nerve invasion is one of the HRFs with incidence of metastasis being reprorted in 12%-42%[9] cases involving posterior to lamina

Table-III: Comparison of studies reporting the prevalence of high-risk factors in retinoblastoma.

Study	*Anterior chamber*		*Choroidal invasion, n (%)*	*Scleral invasion, n(%)*	*Extrascleral invasion, n (%)*	*Retrolaminar ON involvement, n(%)*	*ON to cut end involvement, n (%)*
	Iris, n (%)	*Ciliary body, n (%)*					
Biswas et al.[7] (n==232; 2003)	NA	NA	51 (21.9)	NA	NA	13 (5.6)	NA
Orellana et al.[8] (n=101;2009)	NA	NA	42 (41.5)	9 (8.9)	10 (9.9)	40 (39.6)	NA
Gupta et al.[12] (n=142; 2009)	10 (7)	13 (9)	57 (40.1)	13 (9.1)	9 (6.3)	24 (16.9)	11 (7.7)
Kashyap et al.[15] (n=609; 2012)	65 (10.7)	NA	150 (24.6)	83 (13.7)	25 (4.1)	98 (16.1)	45 (7.4)
Kashyap et al.[17] (n=326; 2012)	29 (9)	23 (7)	71 (21.2)	28 (9)	11 (3.4)	54 (17)	18 (5.5)
Yousef et al.[18] (n=50; 2014)	NA	3 (6)	9 (18)	NA	NA	7 (14)	NA
Rao et al.[19] (n=17; 2014)	5 (29.4)	5 (29.4)	10 (58.8)	5 (29.4)	2 (11.8)	NA	4 (23.5)
Kaliki et al.[16] (n=403; 145 cases, 285 controls; 2015)	12 (8)	17 (12)	96 (66)	20 (14)	8 (6)	71 (49)	3 (2)
Kaliki et al.[9] (331 Indians/193 Americans; 2018)	11 (3.3) / 9 (5)	14 (4.2) /6 (3)	57 (17) / 12 (5)	19 (5.7) / 3 (2)	7 (2.1) / 2 (1)	56 (16.9) / 22 (11)	2 (0.6) / 1 (0.5)
Yahaya et al.[20] (28) (n=234; 2019)	37 (21.5)		47 (27.3)	39 (22.7)	NA	67 (28.5)	NA
Kaliki et al.[13] (n=616; 2020)	28 (4.5)	29 (4.7)	120 (19.5)	30 (4.9)	10 (1.6)	103 (16.7)	11 (1.8)
Present study (n=54; 2021)	2 (3.7)	2 (3.7)	18 (33.3)	4 (7.4)	1 (1.9)	15 (41.7)	1 (2.8)

ON-Optic nerve; NA-Not available.

cribrosa and up to 41%-78% involving transection line.[11] In present study, 66.7% of eyes had optic nerve involvement with variable degree of invasion i.e. both anterior and posterior to lamina cribrosa. An unusual finding in the present study was a very high prevalence (41.7%) of involvement of optic nerve posterior to lamina cribrosa which was similar to the frequency reported by Kaliki et al. (49%)[16] and Orellana et al. (39.6%)[8] (Table-III). The higher frequency of optic nerve involvement were all reported from low middle income countries and thus could be attributed to the fact that patients present at advanced stage of disease due to lack of access to health care facilities while another reason could be lack of awareness among parents and health care providers at primary health care level.

In present study, frequency of choroidal involvement was 33.3% out of which massive invasion of choroid was present in 44% cases. This observation of massive choroidal involvement was similar to the frequency reported by Orellana et al.[8] i.e. 41.3% but was much higher to an Indian study which reported 27.5% cases with choroidal invasion.[9] Choroidal involvement is considered to be a high risk factor for metastases particularly if seen in association with optic nerve involvement.[9]

The involvement of anterior chamber structures i.e. iris and ciliary body also constitutes a HRF. The present study reported the involvement of iris and ciliary body in 3.7% cases each. This finding was found to be similar to the reported frequencies of ciliary body (4.7%) and iris (4.7%) involvement in an Indian study by Kaliki et al.[13]

Scleral invasion is the invasion of the tumor beyond the choroid. Current study reported the frequency of this HRF in 7.4% cases which was relatively closer to the frequencies reported by various Indian studies.[8,12,17] Extrascleral invasion

was seen in 1.9% of the patients which was almost the same as the frequency i.e. 1.6% reported by Kaliki et al.[13] as well in the Indian patients cohort which compared the occurrence of HRFs between American and Indian retinoblastoma patients.[9]

Limitations: The short study span and small sample size may be considered as limitations of our study. Presence of high-risk factors in these patients was not further evaluated by follow-up to assess the impact of their presence on disease progression which warrants further research to analyse outcome in context of presence of HRFs.

CONCLUSION

In conclusion, this is a retrospective data analysis of high risk histopathologic factors in eyes diagnosed with retinoblastoma and treated with primary enucleation from a low middle income country. As our center is a major tertiary care referral hospital, our results might be highly representative of high risk factors in retinoblastoma in our population. The incidence of HRFs has declined over time in studies from developed countries because of early presentation and diagnosis. However, the same is not seen in studies from the developing world. Late presentation of patients, age >24months, and with more advanced disease result in poor outcome in retinoblastoma.

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Original Article

Combining Non-invasive Ventilation with timed position change in the Emergency Department to improve oxygenation and outcomes in patients with COVID-19: A prospective analysis from a low resource setup

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ABSTRACT

Background: Moving away from invasive ventilation towards timed position change and non-invasive ventilation is especially of benefit in low and middle income countries, where judicious use of the available healthcare resources is the need of the day. Our study was conducted prospectively to develop strategies for non-invasive ventilation in combination with timed position change of patients to see its impact on their outcome.

Objectives: Non-invasive ventilation has proven to be of benefit in COVID-19 related acute lung injury. The objective of this prospective, cross sectional study was to develop a protocol for the use of non-invasive ventilation with timed position change to improve COVID-19 patients' outcomes in the Emergency Department (ED).

Methods: All patients presenting with confirmed or suspected COVID-19 were enrolled in the study from March 2020 to October 2020. Data was collected to see the effect of timed position change and non-invasive ventilation on these patients and its effect on delaying or avoiding invasive ventilation.

Results: Of the 207 COVID-19 patients presenting to the IHHN ED, 109(52.7%) had oxygen saturation in the nineties in supine position followed by right lateral in 37(17.9%), sitting up in 30(14.5%), left lateral in 29(14%) and prone position in 2(1%). Maximal oxygenation was achieved with non rebreather mask (NRM) and nasal prongs in 87(42%) of the patients, followed by the use of continuous positive airway pressure (CPAP) in 29(14%).

Conclusion: Most of the patients preferred to stay in the supine position and described it as the position of comfort. When used in combination supine position, patients on NRM with nasal prongs and on CPAP, had oxygen saturation in the nineties. Central obesity was found to be the prime reason for the inability to prone our patients. This needs to be followed up in the current fourth wave of COVID-19 to see the effectiveness of the said modalities.

KEYWORDS: COVID-19, Non-Invasive Ventilation, Supine Position, Prone Position, ARDS.

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INTRODUCTION

With the COVID-19 pandemic now in its fourth wave, critically ill patients are coming to EDs with hypoxia, bilateral lung injury and post COVID sequelae. Since its outbreak in November 2019, many methods for improving oxygenation and patient outcome have been documented in patients

with COVID. Most of these were initially focused on early intubation and ventilation and led to a gross overburden of the health-care system in terms of human resource and availability of intensive care unit (ICU) beds and mechanical ventilators.[1] This led to research to delay or forego invasive ventilation and improve oxygenation through modalities of timed position change and non-invasive ventilation in patients with COVID-19.

Classically, hypoxemic patients with respiratory distress are put in a supine or upright position. Prone position during invasive ventilation has been described in literature as a successful method to increase alveolar recruitment in patients with Acute Respiratory Distress Syndrome (ARDS).[2] COVID-19 patients are postulated to rapidly progress to ARDS with the observation that prone positioning can improve oxygenation even in non-intubated, spontaneously breathing patients.[3] However, as the pandemic has progressed, there are reports that intermittent and timed position change of patients to keep them comfortable and effectively oxygenated, can be an alternative approach, as prone position can be difficult to achieve in certain patients.[4,5]

In Low-Middle Income Countries (LMICs) like Pakistan, the scarcity of available critical care resources has added insult to injury. To date, the total number of COVID-19 cases in Pakistan have been 1.09 million with the largest burden of disease in the province of Sindh with 406,000 active cases.[6] With the rationale of minimizing invasive ventilation and judicious utilization of available resources through assessing the effect of timed position change with non-invasive ventilation modalities, a study was conducted on COVID-19 patients presenting to our ED, located in one of the most crowded vicinities in Karachi, the eleventh most populous city in the world.[7] The idea was to develop pathways that work best for our population during the first wave so that the same can be applied in subsequent waves with wise resource allocation.

The primary objective of this study was to see the effect of improvement of oxygenation by following the position changing protocol in suspected or positive COVID-19 patients with hypoxemia and respiratory distress. The secondary objective was to see the best combination of position change and non-invasive ventilation modalities like nasal cannula, non-re breather mask and CPAP in improving the oxygenation of patients. A follow-up of this study with the use of position preferred by patients and non-invasive ventilation is underway in the current fourth wave.

METHODS

A prospective, cross sectional study was conducted to see the effects of timed position change and non-invasive ventilation modalities in patients with suspected or diagnosed COVID-19, who came to our ED at The Indus Hospital and Health Network (IHHN), Karachi from March 2020 to October 2020.

The target population was suspected or diagnosed COVID-19 patients who had hypoxemic respiratory failure with high work of breathing. All patients above eighteen years, conscious and awake, spontaneously breathing with a respiratory rate of > 24/minutes and on supplemental oxygen were included in the study. All the patients who were already intubated, had immediate need for

Table-I: Patient's health status at baseline

Gender; n=207	
Male	131(63.3)
Female	76(36.7)
Age	
Mean ± SD	56.3±13.6
Min-Max	23-85
Baseline Function class	
I	1(0.5)
II	188(90.8)
III	17(8.2)
IV	1(0.5)
Current function class	
II	15(7.2)
III	39(18.8)
IV	153(73.9)
Presenting complaints	
Fever	155(77.5)
Cough	70(35)
Shortness of breath	162(81)
Runny nose	1(0.5)
Sore throat	2(1)
Chest Pain	6(3)
Diarrhea	2(1)
Other complaints	76(38)
Comorbidities; n=159	
DM	86(54.1)
HTN	99(62.3)
IHD	18(11.3)
COPD/allergy	13(8.2)
history of TB	4(2.5)
Other	80(50.3)
Disposition from ED	
ICU	41(19.8)
Referred out	40(19.3)
Expired in ED	12(5.8)
HDU	101(48.8)
Discharge	6(2.9)
LAMA	7(3.4)

intubation, were hemodynamically unstable (with a Mean arterial pressure (MAP) <65 mmHg) or died within one hour of ED arrival were excluded. An awake positioning protocol for hypoxemic COVID patients which included changing position every two hours was developed. Oxygen saturation (SpO2) was checked by using bedside pulse oximeter with each step of intervention as defined by the protocol, till the time the patients were either admitted, discharged or referred to other facility. Categorical variables like patients' age, gender, presentation and duration of symptoms, co-morbid conditions, functional class on arrival and during hospital stay and vital-signs at triage were retrieved from the electronic health record (EHR). All SpO2 readings were recorded with each intervention (nasal cannula, NRM, application of CPAP) and position (sit-up, supine, left lateral, right lateral and prone). The duration of each intervention was noted and entered into a proforma.

Patients who were admitted to the in-patient COVID-Unit were followed and their location (ward/ High dependency unit (HDU)/ Intensive care unit (ICU)) at admission, date and duration of admission, step-up to ICU, invasive ventilation, step-down and final outcome were recorded. Approval was taken from Institutional review board IRB (IRD_IRB_2020_05_001) and all the participants consented to be enrolled in the study.

RESULTS

A total of 207, COVID-19 positive patients were enrolled in the study with a mean age ± SD of 56.3 ± 13.6 with male predominance (131, 63.3%). Of all patients 188 (90.3%) were in functional class II when they reached the ED, out of which 153 (73.9%) worsened to functional class IV. (Table-I) Hypertension (62.3%) and Diabetes mellitus (54.1%) were found to be the most common comorbidities. Majority of the patients presented with shortness of breath followed by fever and cough (81%, 77.5% and 70% respectively) The disposition included in-patient ICU and HDU admission for 142 (68.6%) patients Table-I. Of the ICU/HDU admissions 130 (91%) did not require invasive ventilation while 12 (9%) went on to be intubated and mechanically ventilated. Non availability of beds resulted in 40 (19.3%) patients referral to other facilities, 7 (3.4%) patients left against medical advice (LAMA), 6 (2.9%) were discharged and 12 (5.8%) expired in

Table-II: Association of Final outcome with gender, basic functional class, and current functional class.

	Final outcome			
	Alive n (%)	*Expired n (%)*	*Total n (%)*	*p value*
Gender				
Male	54(62.1)	50(71.4)	104(66.2)	
Female	33(37.9)	20(28.6)	53(33.8)	0.218□
Total	87(100)	70(100)	157(100)	
Basic functional class				
I	-	1(100)	1(100)	
II	77(60.6)	50(39.4)	127(100)	
III	4(40)	6(60)	10(100)	0.132‡
IV	-	1(100)	1(100)	
Total	81(58.3)	58(41.7)	139(100)	
Current functional class in ED				
II	10(11.5)	-	10(6.4)	
III	19(21.8)	10(14.3)	29(18.5)	0.002*‡
IV	58(66.7)[b]	60(85.7)	118(75.2)	
Total	87(100)	70(100)	167(100)	
Age				
Mean ± sd	52±13.9	59.8±13.2	56.3±13.6	0.001*∫
Min-Max	23-80	36-84	23-85	

*p value <0.05, □ Pearson chi-square test, ‡ Fischer exact test, ∫Independent sample t test.

Table-III: Frequency of intervention and position for maximum Oxygen saturation.

Interventions provided to patients	*N(%)*
NRB mask + Nasal Cannula	120(58)
CPAP	81(39.1)
Nasal Cannula	46(22.2)
Room air	34(16.4)
Intubated + Bag	6(2.9)
Position at which patient reached to maximum oxygen saturation	
Supine	109(52.7)
Left Lateral	29(14)
Right Lateral	37(17.9)
Sit - up	30(14.5)
Prone	2(1)
Intervention at which patient reached to maximum oxygen saturation	
Room air	18(8.7)
Nasal Cannula	36(17.4)
NRB mask + Nasal Cannula	87(42)
CPAP	60(29)
Intubated + Bag	6(2.9)

the ED. (Table-I) The patients who expired were older than the patients who recovered (Mean age ± SD; 59.8 ± 13.2 versus 52 ± 13.9, p=0.001). Gender distribution was similar in both alive and expired patients (p=0.218). (Table-II).

To improve oxygen saturation with an aim to keep it in the early nineties, a timed position changing protocol was used in all the patients. They were asked to change their position every two hours voluntarily and were allowed to stay in the position of maximum comfort. Since a single patient changed multiple positions, it was seen that majority, 109 (52.7%) had oxygen saturation in nineties in supine position followed by right lateral in 37 (17.9%), while 30 (14.5%) oxygenated maximally while sitting up, 29 (14%) in left lateral position and only 2 (1%) patients got maximum oxygen saturation on prone position. (Table-III) The failure to prone ventilate in our cohort is postulated to be due to the body mass index of more than 25 in 129 (62.3%) of our patients with predominant central obesity.

It was observed that out of the 109 patients who preferred to stay in the supine position, the maximal oxygen saturation was obtained in 21 (19%) patients with associated NRM use at 15 liter O2 and nasal

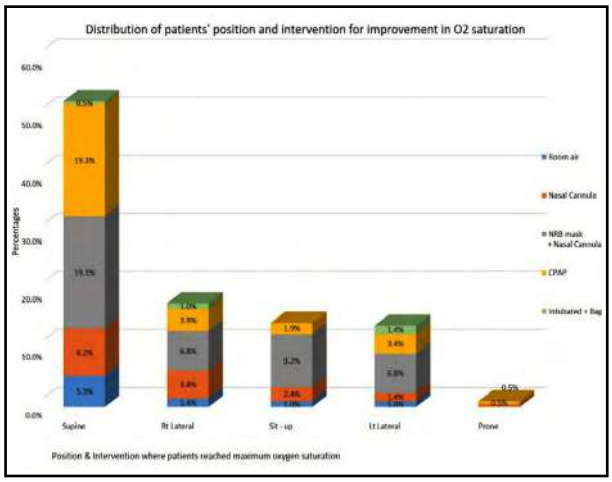

Fig.1

prongs use at 5 liters and in those on CPAP. Similar results of maximal oxygenation in the nineties percent were observed with NRM and nasal prongs use in patients kept in the right lateral (6.8%), left lateral (6.8%) and sitting up (9.2%) positions. Therefore, in our study, maximal oxygenation was achieved with NRM and nasal prongs in 87 (42%) of the patients out of 207 patients followed by the use of CPAP in 29 (14%). (Table-III) (Fig.1).

Out of the 142 patients who were admitted to critical care setup (ICU + HDU), 130 did not require invasive ventilation. Of these 73 (56%) had preferred the supine position, 17 (13%) had stayed in the right and left lateral positions and 23 (18%) preferred sitting up. Although it was the favored position in our study population, all the 12 (9%) patients who were intubated later and had to be invasively ventilated, had also preferred to stay in the supine position.

DISCUSSION

Our study was initially conducted to see the effect of prone positioning on patients with COVID-19, through the use of timed position protocol. However, our patients were not able to tolerate the prone position for more than 15 minutes and predominantly preferred the supine position. This was mostly due to central obesity that has been documented in literature as one of the reasons for failure of prone positioning.[8] Supine position, right and left lateral and siting up were paired with the use of various modalities of non-invasive ventilation. NRM with supplemental oxygen and application of CPAP was found to work best with supine position. Like other published data, our patients were not able to tolerate prone

position with the application of NRM and CPAP, mainly because of lack of beds that can facilitate prone positioning, limited personnel and patient discomfort.[9] Pressure ulcers and anxiety were other factors that deterred patients from staying prone over prolonged periods.[10]

Covid-19 has been the curve ball no one saw coming. The burden on the healthcare system in terms of preparedness and dealing with the pandemic has been enormous. The effect has been particularly devastating in LMIC where limited resources and lack of established disaster management systems, resulted in catastrophe.[11] The uncertainty associated with COVID-19 due to lack of previous experience, led to development of many treatment modalities and pathways that have altered over time. This also led to published data with small sample sizes that did not have the required background and insight due to the novelty of the disease and therefore lacked generalizability. A meta-analysis of thirty-five studies (n= 1712 patients) showed improved PaO2/ FiO2 ratio with better SpO2 and lower mortality rates in patients who were prone as compared to those in the supine position.[12] Many similar studies describing the prone positioning protocol came forth and were well received.[13] Using the findings of our own study and keeping abreast with the current literature, we hope to extrapolate these results to develop protocols that can be time and cost effective and can improve our patient outcome.

CONCLUSION

Most of the patients preferred to stay in the supine position and described it as the position of comfort. When used in combination supine position, patients on NRM with nasal prongs and on CPAP, had oxygen saturation in the nineties. Central obesity was found to be the prime reason for the inability to prone our patients. It is our hope that through this cross sectional follow up, we can develop best practice protocols in our ED for patients with COVID-19 in future. This will help us in maximal utilization of our limited resources to improve patient outcome and prevent and/or delay invasive ventilation through a combinations of position change and non-invasive ventilation. This can also lead to generalization of these protocols for limited resource setups and wise use of healthcare resources.

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Open Access

Original Article

Knowledge and perception of Sepsis among Doctors in Karachi Pakistan

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ABSTRACT

Objectives: To assess knowledge and perception among Pakistani physicians towards sepsis.

Methods: This cross-sectional study was conducted in Indus Hospital and Health Networks from September 2020 to March 2021. The International Sepsis Survey questionnaire was adapted, and its link was sent to trainee physicians as well as specialists, and consultants practicing in various hospitals via social media. Knowledge and perception were scored and 50% was considered the cut-off score for adequacy. Data was analyzed using SPSS version 26.

Results: Analysis was done on 222 respondents who completed the survey. 37.9% of the participants had adequate knowledge. Knowledge regarding sepsis was significantly associated with specialty, ICU/CCU/HDU, and work experience (P-value <0.0001). More recent trainee physicians and those with more experience in critical care areas demonstrated better knowledge. Over 2/3rd of the respondents strongly agreed that sepsis remains one of the unmet needs in critical care today.

Conclusion: A common belief exists that sepsis remains a challenge to treat among doctors. Moreover, there is consensus that it is the most frequently miss diagnosed condition in critical care and a dire need exists for its early diagnosis. Additionally, prompt management of presumed sepsis is imperative to improve outcomes.

KEYWORDS: Sepsis, Septic Shock, Critical Care, Intensivists, Physicians knowledge.

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INTRODUCTION

Sepsis is considered one of the most life-threatening situations in critically ill patients. Being a medical emergency, delayed diagnosis and management are associated with higher mortality rates. Despite evidence-based management guidelines, sepsis remains a leading cause of death with mortality rate ranging between 22.8% to 48.7%.[1-6] Identifying sepsis is challenging, given that its clinical presentation is variable and there is no gold standard for diagnosis. Additionally, the complexity and diversity of the disease further increases the difficulty for health care providers to diagnose it.[7]

Sepsis-related morbidity and mortality can be reduced through early treatment using protocols with well-established therapeutic targets. However, early intervention calls for

prompt recognition by the team managing the patient. Studies have been conducted to assess the ability to recognize patients with sepsis and have suggested that knowledge of sepsis and its clinical forms of presentation is limited among health care professionals. A large Brazilian study showed a significant difference in knowledge existed among physicians with those working at university hospitals having better knowledge when compared to those in public hospitals.[8]

A recent study from Karachi concluded that half of the resident physicians included had excellent knowledge of the sepsis bundle.[9] Another study conducted in Nepal showed that the healthcare workers who were or had previously worked in the critical areas such as emergency and ICUs, had better knowledge (31.7%) than those who were working in less critical or general areas (14.2%).[10]

There is a need for physicians from all specialties to recognize the early signs of sepsis, and make timely diagnosis and treatment possible for a better prognosis.[7,8] A thorough understanding of its definitions and a more comprehensive perception about the disease itself is crucial to prepare our doctors for better management of sepsis. This research aims to establish the gaps in the knowledge and perception of healthcare professionals regarding sepsis and their ability to identify sepsis.

METHODS

A cross-sectional survey was conducted between September 2020 to March 2021. The survey questions were adapted from the International Sepsis Survey[7] after discussion with a senior internal medicine consultant. An electronic form was designed using REDCap software and the survey link was then sent to doctors working in different hospitals in Pakistan. Specifically, the survey was circulated via media links, such as email and other social media platforms like WhatsApp and Facebook to trainee physicians at the postgraduate level, specialist physicians and consultants of Internal Medicine, Critical care, Anesthesia, General Surgery, Orthopedics. Undergraduate medical students, nurses, paramedical staff, physiotherapists, and other non-healthcare-related personal were excluded from the study. Ethical approval was taken from our Institutional Review Board (IRD_ IRB_2019_11_001)

Data was entered and analyzed by using SPSS statistical package version 26 software. Mean ± SD or median (IQR) was computed as appropriate for all the quantitative variables. Frequencies and percentages were calculated for all the categorical variables. The pre-coded questionnaire was adapted with questions regarding misattribution of sepsis symptoms to other conditions, definitions of sepsis, and knowledge of bacterial culture for diagnosis were used to assess knowledge (q17, 22, 23, 24, and 32.1) whereas the remaining questions of the Poeze et al's survey questionnaire[7] were used to assess perception and attitude of physicians regarding diagnosis and treatment of sepsis. Responses to the International Sepsis survey evaluating knowledge were based on SIRS, SOFA, and qsofa scoring systems.[11] In the knowledge section, participants who correctly answered 50% of the questions were considered having adequate knowledge as 50% was the cutoff for positive or negative perception. Chi-Square test was applied as appropriate to detect the significant associations of covariates with knowledge and perception. P-value <0.05 was considered significant.

RESULTS

In this survey, 355 doctors participated, and only 222 (62.52%) completed the study. The analysis is based on 222 participants. Over 58% of the respondents were women. Mean age was 30±4.2 years, with nearly 80% who responded being 30 years or younger. The mean duration of practice was 5 ±4 years. Nearly ¾ of those who responded were practicing in private institutes. Most of the respondents were residents (86.5%), with less than half being year-1 residents (42.3%). Half of the respondents (54.4%) had working experience in either ICU, CCU, or HDUs. (Table-I).

Overall, 38% had adequate knowledge regarding sepsis, and 69% had a positive perception regarding current sepsis diagnosis and treatment. A significant association was found between specialty (ICU/CCU/HDU), working experience, and knowledge, regarding sepsis ($p<0.0001$). Furthermore, compared to other age groups, a greater proportion of participants in the 31-40-year age group had inadequate knowledge related to sepsis compared to younger respondents. Moreover, the doctors working in the private settings had more knowledge (71%) as compared to the doctors of public hospitals. In terms of the departments, the Internal medicine department had the highest proportion of doctors with adequate knowledge (37%), followed by

Table-I: Demographic Characteristics of the Study Participants.

Variable	*n (%)*
Age (in years)	
20-30	179 (80.6%)
31-40	34 (15.3%)
More than 40	09 (4.1%)
Gender	
Female	128 (57.7%)
Male	94 (42.3%)
Type of Institute	
Private	159 (71.6%)
Public	63 (28.4%)
Position	
Consultant/ Specialist	30 (13.5%)
Resident	192 (86.5%)
Residency Status	
R1	94 (42.3%)
R2	56 (25.2%)
R3	30 (13.5%)
R4 and above	12 (6.3%)
Specialty	
Anesthesiology	34 (15.3%)
Emergency	23 (10.4%)
Family Medicine	21 (9.5%)
General Surgery	21 (9.5%)
Internal Medicine	67 (30.2%)
Pulmonologist	16 (7.3%)
Others	40 (18.02%)
Medical practice duration	
2 or less years	25 (11.3%)
3-5 years	150 (67.6%)
6 years or more	47 (21.2%)
Working experience ICU/CCU/HDU	121 (54.5%)
Knowledge regarding sepsis	
Adequate knowledge	84 (37.9%)
Inadequate knowledge	138 (62.2%)
Perception regarding sepsis diagnosis & treatment	
Negative perception	69 (31.1%)
Positive perception	153 (68.9%)

anesthesiology (21%) Table-II.

Regarding questions assessing knowledge, one fourth (¼) of the participants identified the infection as the leading cause of sepsis, followed by bacteremia/bacteria (20.7%) and immunocompromised state (13.5%). When asked about sepsis's major signs and symptoms, more than half of the participants identified the three major symptoms correctly, i.e., fever (82%), tachycardia (54.5%), and hypotension (54%) (Table-III). When asked about misattributing the symptoms of sepsis to other conditions, only 32.9% of the participants strongly agreed to it (Table-IV).

In response to questions assessing the study participants' perceptions, 63% of the participants strongly believed that sepsis is a leading cause of mortality compared to other conditions. Furthermore, 72% of the doctors believed that patients are often being treated too late to reverse the onset of sepsis, and 84% of the participants agreed that patients need better monitoring to catch sepsis at the earliest possible stage (Table-IV).

DISCUSSION

A significant association was found between specialties, ICU/CCU/HDU working experience, and knowledge regarding sepsis, with half of the respondents having adequate knowledge regarding the detection and management of sepsis. Participants working in fields with less interaction with a sepsis patient, such as Family Medicine, Radiology, Cardiology, Pediatric Medicine had inadequate knowledge compared to the other specialties like Anesthesia, Surgery, Internal Medicine, and Pulmonology. Similar results were reported by a Nepalese study where almost 46% of the participants who had worked in intensive care areas had adequate knowledge regarding sepsis.[10]

In our study, younger age group respondents had better knowledge than the older respondents. Our study also found that residents had more knowledge regarding sepsis than the consultants. Similar results were reported by a study conducted in Malaysia[12] This could be because younger respondents were mainly residents who may have studied sepsis more recently, had more frequent encounters with septic patients due to their long hours of training, as well as differences in curriculum.

Almost 69% of the physicians in our study either strongly or somewhat believe that sepsis symptoms can easily be misattributed to other conditions. Similar results were reported by an international survey[7] concluding that many

Table-II Association of participant characteristics with Sepsis related Knowledge and Perception.

Variables		*Knowledge*		*P values*	*Perception*		*P values*
		Inadequate n=138	*Adequate n=84*		*Negative n=69*	*Positive n=153*	
Age Groups	20-30	111 (80.4%)	68 (81%)	0.44Ŧ	58 (84.1%)	121 (79.1%)	0.39Ŧ
	31-40	23 (16.7%)	11 (13.1%)		10 (14.5%)	24 (15.7%)	
	> 40	04 (2.9%)	05 (06%)		01 (1.4%)	08 (5.2%)	
Gender	Female	82 (59.4%)	46 (54.8%)	0.49Ŧ	43 (62.3%)	85 (55.6%)	0.34Ŧ
	Male	56 (40.6%)	38 (45.2%)		26 (37.7%)	68 (44.4%)	
Type of Institution	Private	99 (71.7%)	60 (71.4%)	0.96Ŧ	54 (78.3%)	105 (68.6%)	0.14Ŧ
	Public	39 (28.3%)	24 (28.6%)		15 (21.7%)	48 (31.4%)	
Position	Consultant/Specialist	21 (15.2%)	09 (10.7%)	0.34Ŧ	08 (11.5%)	22 (14.4%)	0.57Ŧ
	Resident	117 (84.8%)	75 (89.3%)		61 (88.4%)	131 (85.6%)	
Year of residency	R1	62 (44.9%)	32 (38.1%)	0.18Ŧ	28 (40.6%)	66 (43.1%)	0.83Ŧ
	R2	28 (20.3%)	28 (33.3%)		19 (27.5%)	37 (24.2%)	
	R3	18 (13%)	12 (14.3%)		11 (15.9%)	19 (12.4%)	
	R4 and above	09 (7.7%)	03 (4%)		03 (4.9%)	09 (6.8%)	
Specialty	Anesthesiology	16 (11.6%)	18 (21.4%)	<0.0001Ŧ**	12 (17.4%)	22 (14.4%)	0.23Ŧ
	Emergency	14 (10.1%)	09 (10.7%)		04 (5.8%)	19 (12.4%)	
	Family medicine	20 (14.5%)	01 (1.2%)		10 (14.5%)	11 (7.2%)	
	General surgery	12 (8.7%)	09 (10.7%)		06 (8.7%)	15 (9.8%)	
	Internal medicine	36 (26.1%)	31 (36.9%)		18 (26.1%)	49 (32%)	
	Pulmonologist	04 (2.9%)	12 (14.3%)		03 (4.3%)	13 (8.5%)	
	Others	36 (26.1%)	04 (4.7%)		16 (23.2%)	24 (15.7%)	
Practice duration	2 or less years	19 (13.8%)	06 (7.1%)	0.28Ŧ	07 (10.1%)	18 (11.8%)	0.93Ŧ
	3-5 years	92 (66.7%)	58 (69%)		47 (68.1%)	103 (67.3%)	
	6 years or more	27 (19.5%)	20 (23.8%)		15 (21.7%)	32 (20.9%)	
Working experience ICU/CCU/HDU		62 (44.9%)	59 (70.2%)	<0.0001Ŧ**	28(40.6%)	93 (60.8%)	0.005Ŧ*

Ŧ Chi-Square, * p-value<0.05, **p-value<0.0001.

disorders and syndromes mimic the presentation of sepsis.[13] Thus making it difficult for physicians to address sepsis when it might be present.

Our study concluded that there is a lack of a standard definition of sepsis, and if a common definition is applied globally, it will help in the early detection and treatment of sepsis, with around three fourth (¾) of the participants agreeing to it. Other studies have found that although guidelines and definitions are in place, adherence to these guidelines is more of a concern and needs to be regularly audited.[14]

Bacterial culture was ranked as the most effective method for diagnosing sepsis by physicians. The second most effective method for diagnosing sepsis was hemodynamic monitoring, similar to previous study results.[7,12] Although bacterial cultures are the most reliable method to diagnose infections, it hinders the early detection and treatment. Several studies have shown that early detection and treatment with antibiotics can reduce sepsis-related mortality.[14] Therefore, other diagnostic modalities and strict monitoring of the early sign and symptoms should be incorporated more into practice for early detection of sepsis.[14,15]

Our study detected a statistically significant association between working experience of

Table-III: Based upon everything you know about sepsis?

Responses	*Frequency (%)*
State of dysregulated host response to infection	140 (63.1%)
Infection leading to organ dysfunction/ failure	56 (25.2%)
Life threatening/ Critical condition that leads to potentially organ dysfunction caused by deregulated host response to infection	55 (24.8%)
Sepsis is a Systemic inflammatory response syndrome (SIRS)	49 (22.1%)
Multi-organ failure in response to bacteremia/ infection	42 (18.9%)
Severe Infection causing organ failure/ MODS/ SIRS/ circulating failure	25 (11.3%)
Clinical conditions (e.g. Vital instability, fever, increases TLC and SOFA score, abnormal heart and respiratory rate, metabolic collapse, poor immunity)	23 (10.4%)
Infection causing circulatory collapse	15 (6.8%)
Bacterial infection in blood	8 (3.6%)
Causes of sepsis	
Infection	57 (25.7%)
Bacteremia/Bacteria	46 (20.7%)
Immunocompromised state	30 (13.5%)
Micro organisms	25 (11.3%)
Low/poor immunity	23 (10.4%)
Pathogens	12 (5.4%)
Release of inflammatory markers	11 (5%)
Bacteria viruses	5 (2.3%)
Inflammation	2 (0.9%)
Other	20 (9%)
Sign and Symptoms of sepsis	
Fever	183 (82.4%)
Tachycardia	121 (54.5%)
Hypotension	120 (54.1%)
Tachypnea	56 (25.2%)
Altered mental status	23 (10.4%)
Respiratory distress	21 (9.5%)
Increased TLC	16 (7.2%)
Low GCS	10 (4.5%)
Unstable vitals	8 (3.6%)
Decrease urination/ AKI	9 (4.1%)
Organ/s failure	8 (3.6%)
Raised wbc count	5 (2.3%)
Low leukocyte count	3 (1.4%)
Shock	2 (0.9%)
Thrombocytopenia	2 (0.9%)
Any symptom of SIRS	2 (0.9%)
Lethargy	2 (0.9%)
Which of the following therapies do you yourself use to treat these sepsis patients?	
Antishock/organ support therapy	114 (51.4%)
Antibiotics	76 (34.2%)
Invasive surgical/radiological therapy	25 (11.3%)
Depend upon the patient	7 (3.2%)

critical areas (ICU/CCU/HDU) with knowledge similar to other studies.[10] The reason behind this phenomenon could be that the doctors working in critical areas get more exposure to patients with sepsis. They frequently get hands-on practice in detecting and managing patients suffering from sepsis compared to the doctors working in the less critical areas.

Table-IV: Sepsis related perception of study subjects.

Responses	*Strongly agree*	*Somewhat agree*	*Somewhat disagree*	*Strongly disagree*	*Don't know*
Sepsis is a leading cause of mortality compared to other conditions	141 (63.5%)	75 (33.8%)	5 (2.3%)	0 (0%)	1 (0.5%)
Sepsis treatment is one of the unmet needs in critical care today	149 (67.1%)	64 (28.8%)	7 (3.2%)	1 (0.5%)	1 (0.5%)
Sepsis is a significant burden on the healthcare system in my country	172 (77.5%)	43 (19.4%)	2 (0.9%)	1 (0.5%)	4 (1.8%)
The symptoms of sepsis can be easily misattributed to other conditions	73 (32.9%)	84 (37.8%)	24 (10.8%)	38 (17.1%)	3 (1.4%)
Patients need better monitoring in order to catch sepsis at the earliest possible stage	187 (84.2%)	34 (15.3%)	1 (0.5%)	0 (0%)	0 (0%)
Patients are often being treated too late to reverse the onset of sepsis	159 (71.6%)	52 (23.4%)	9 (4.1%)	2 (0.9%)	0 (0%)
Families of sepsis patients find it difficult to understand sepsis	174 (78.4%)	42 (18.9%)	4 (1.8%)	2 (0.9%)	0 (0%)
The current treatment options for sepsis are not adequate.	24 (10.8%)	92 (41.4%)	88 (39.6%)	16 (7.2%)	2 (0.9%)
Doctors are eager for a breakthrough in treating sepsis?	151 (68%)	57 (25.7%)	12 (5.4%)	1 (0.5%)	1 (0.5%)
Sepsis is among the most challenging conditions a doctor can treat	151 (68%)	65 (29.3%)	6 (2.7%)	0 (0%)	0 (0%)

In light of the results of our study, we recommend training physicians in critical care areas more frequently to prepare them in detecting and managing sepsis. We would also suggest that the internationally accepted sepsis guidelines be implemented in the hospitals, and regular audits should be conducted to assess physicians' compliance with those guidelines. Furthermore, conducting refresher courses on detection and management of sepsis should be done more often for trainees and consultants to improve their knowledge and familiarize them with the latest detection and treatment modalities.

Limitation: The major limitation of this study was that the sample analyzed was relatively small in terms of the target population, i.e., doctors working in hospitals. As it was an online survey, the response rate was on the lower side. Only 62% of the participants responded and filled the questionnaires sent to them. Secondly, our study did not assess the knowledge and perceptions of nurses who are an integral part of patient care management in the critical areas in our country. Moreover, our study did not assess what was being practiced by the study participants. Assessing practice is an integral part of a study when knowledge and perceptions are being assessed. It should be taken into account to identify the important data gaps to invest more time and resources in that component.

CONCLUSION

Fundamental problems remain the same despite the gap of many years. Sepsis is yet one of the most frequently miss diagnosed condition in critical care, making the need for its early diagnosis imperative. Prompt management of presumed sepsis remains key to improving outcomes. Newer markers for the diagnosis of sepsis are not made readily available everywhere and hence not used as much. Had they been available, would they still have replaced the gold standard of blood culture? Probably not. Much needs to be done regarding early diagnosis, better management, and not to forget its prevention in individuals.

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Authors Contribution:

FA: Conceived, designed, collected data, and prepared the manuscript.
FH: Designed the questionnaire.
AJ: Analyzed and prepared the manuscript.
All authors reviewed and finalized approval of the manuscript.

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Original Article

Epidemiology of in-hospital cardiac arrest in a Pakistani tertiary care hospital pre- and during COVID-19 pandemic

Faiza Ahmed[1], Lubna Abbasi[2], Nida Ghouri[3], Muhammad Junaid Patel[4]

ABSTRACT

Objectives: To determine epidemiology of in-hospital cardiac arrest (IHCA) in a tertiary care hospital, pre- and during pandemic.

Methods: This is a cross-sectional study of inpatients who experienced an in-hospital-cardiac arrest at a tertiary care hospital in Karachi between August 2019 and August 2020. Outcome variables were return of spontaneous circulation (ROSC) and survival to discharge (StD) and analysis was also done comparing pre- and during pandemic period.

Results: A total of 77 patients experienced at least one IHCA event during the 1-year study period. Comparing pre- and during pandemic, ROSC for women was higher during the pandemic albeit not significant (43% vs 50%) in comparison to men (54% vs 10%, p<0.001). During the pandemic, women with IHCA were significantly younger than men (μ ± sd; 36.8 ± 15.3 vs 55.9 ± 12.7, p=0.001,) whereas pre-pandemic, there was no gender differences in mean age. Non-shockable rhythm was more common (92.2%) than shockable rhythm (6.5%). Pre- and during pandemic, there were significant differences in the cause of IHCA for 4H4T (87% vs 100%) and cardiac (36% vs 9%). The proportion of hypoxic patients increased from 50% during pre-pandemic to 91% during the pandemic period, whereas hypo/hyperkalemia decreased from 53% to 34%.

Conclusion: Despite the limitation of a small sample size, our study has provided important information regarding the epidemiology and outcomes of IHCA pre- and during pandemic in a busy Pakistani tertiary care hospital. Our finding that gender differences exist in survival pre- and during pandemic needs to be explored further with more hospitals doing comparative studies.

KEYWORDS: In-hospital cardiac arrest, COVID-19, Gender, Causes of Cardiac arrest.

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INTRODUCTION

In-hospital cardiac arrest (IHCA) is a major cause of death worldwide yet, data on the epidemiology of IHCA is limited.[1] Cardiac-related causes such as heart failure, arrhythmia or myocardial infarction account for the majority of the cases (50%-60%) followed by respiratory insufficiency as a leading cause.[2] Survival outcomes after an IHCA event vary between 0% to 42% globally.[3] Some major patient-related factors age, gender, initial presentation, underlying conditions; whereas major healthcare related factors include response time of emergency team, location of event, duration and method of resuscitation.[1,4-7] Studies have reported that patients with a shockable rhythm have upto 2 to 3 times higher survival to

hospital discharge (StD) in comparison to patients with a nonshockable rhythm.[8,9]

The recent COVID-19 pandemic is further impacting the epidemiology and outcome with some studies indicating an increase in the burden of cardiac arrest in COVID-19 patients.[3] A US-based study showed that during the first peak of the pandemic, there was an almost five-fold increase in incidence of IHCA as compared to the same period in the previous year.[10] In the first meta-analysis comparing outcomes in patients with IHCA before and during the COVID-19 pandemic, concluded that even though cardiac arrests in COVID-19 patients was higher, the return of spontaneous circulation (ROSC) was similar in the pre- and COVID-19 periods as was overall mortality.[11]

There is evidence elsewhere that recognizing the cause of arrest by the emergency team as well as minimizing health-care related risk factors may help in improving survival outcomes.[2] With limited published literature from Pakistan on the epidemiology of IHCA in adults and evidence that the COVID-19 pandemic is associated with a higher incidence of arrests with worse survival rates, in the present study, we aimed to investigate the profile and outcomes of IHCA patients pre- and during the COVID-19 pandemic.

METHODS

A cross-sectional study was conducted on patients who experienced an IHCA event at the Korangi Campus of the Indus Hospital and Health Network between Aug 2019 and Aug 2020. It included patients admitted in Emergency (ER), wards, intensive care unit (ICU), critical care unit (CCU), high dependency unit (HDU) and COVID-19 ICU. Only the initial cardiac arrest was taken if any patient had more than one.

A pre-coded questionnaire was used to capture data. Sociodemographic variables included were age, gender, and comorbidities whereas IHCA event variables were initial cardiac rhythm, Hs & Ts, event location, pre-arrest cerebral performance and any underlying factors present prior to arrest. Pre-pandemic period was defined as August 2019 to Feb 2020 and during-pandemic was from March 2020 to August 2020. An IHCA event was defined as a cardiac arrest that occurs in a hospital and for which resuscitation was attempted with chest compressions, defibrillation, or both. Outcome variables were return of spontaneous circulation (ROSC) and survival to discharge (StD).

All patients included in the study were age 14 and above. In our hospital, 14-17 years are treated as adults. Patients excluded were those below 14 years, those who had an out-of-hospital-cardiac-arrest, were transferred in-patients from another hospital with a history of arrest prior to arrival to our hospital, patients on Temporary Pacemaker (TPM) or Permanent Pacemaker (PPM) and those post cardiac catheterization. Approval from Institution Review Board was taken (IRD_IRB_2019_06_006).

Data was entered and analyzed using software SPSS 26. Mean ± SD was calculated for age based on normality. Frequency and percentage were calculated for all the categorical variables. Chi-square or Fischer exact test was applied to see the association of all the categorical variables with ROSC, StD and period of cardiac arrest.

RESULTS

A total of 77 patients (57% men) experienced at least one IHCA event during the 1-year study period Table-I. Overall, 39% IHCA patients achieved return to spontaneous circulation (ROSC) and 36% survived to discharge (StD) from the hospital. Majority of the cardiac arrest for those who survived was in the Emergency department (57%) followed by ICU (13%). ROSC and StD was significantly higher in non-ICU patients as compared to ICU patients ($p<0.0001$, Table-I. It was also observed that women who underwent cardiac arrest during the pandemic were significantly younger than men (μ ± sd; 36.8 ± 15.3 vs 55.9 ± 12.7, $p=0.001$) whereas before the pandemic, there was no differences in their mean age (Fig.1). Non-shockable rhythm was more common (92.2%) in these patients than shockable rhythm (6.5%).

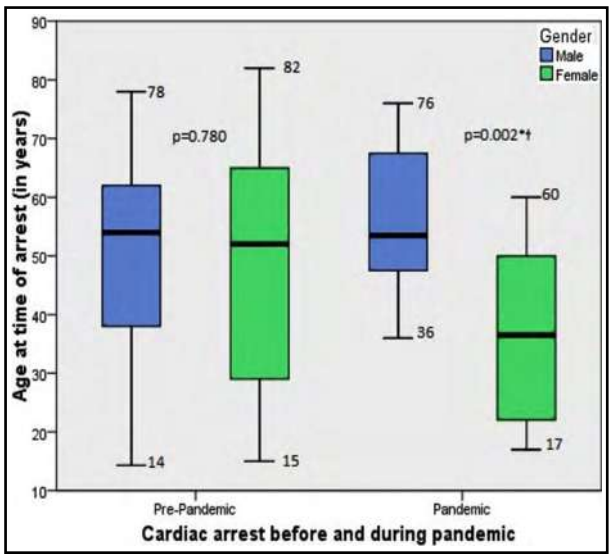

Fig.1: Association of age and gender with IHCA.

Table-I: Characteristics and outcomes of patients who experienced an IHCA in a tertiary-care hospital in Karachi Pakistan, 2019-2020.

Variables	*All*	*ROSC*	*p-value*	*Survival at Discharge*	*p-value*
	n (%)			*n (%)*	
All IHCA patients, n (%)	77	30 (39)	-	28 (36.4)	-
Gender; n(%)					
Male	44 (57.1)	15 (50)	0.312□	14 (50)	NS
Female	33 (42.9)	15 (50)		14 (50)	
Location of cardiac arrest; n(%)					
Emergency department (ED)	20 (26.0)	17 (56.7)	0.000**‡	17 (60.7)	0.000**‡
Intensive care unit (ICU)	21 (27.3)	4 (13.3)		4 (14.3)	
COVID ICU	23 (29.9)	3 (10)		1 (3.6)	
Other (ward, HDU, etc)	13 (16.9)	6 (20)		6 (21.4)	
Initial cardiac rhythm; n(%)					
Shockable rhythm					
Ventricular fibrillation	4 (5.2)	2 (6.9)	NS	2 (7.4)	NS
Pulseless ventricular tachycardia	1 (1.3)	-		-	
Non-shockable rhythm					
Pulseless electrical activity	10 (13)	1 (3.4)		1 (3.7)	
Asystole	61 (79.2)	26 (89.7)		24 (88.9)	
Pre arrest cerebral performance; n(%)					
Mild to no neurological disability	51 (66.2)	22 (75.9)	NS	20 (74.1)	NS
Moderate disability	7 (9.1)	1 (3.4)		1 (3.7)	
Severe disability	5 (6.5)	2 (6.9)		2 (7.4)	
Coma or vegetative state	12 (15.6)	4 (13.8)		4 (14.8)	
Brain death	1 (1.3)	4 (13.8)		-	
Factors present prior to Arrest; n(%)					
Mechanical ventilation	31 (44.9)	4 (15.4)	0.005*□	3 (12)	0.001*□
Renal insufficiency	36 (52.2)	11 (42.3)		10 (40)	
Hepatic insufficiency	10 (14.5)	4 (15.4)		4 (16)	
Sepsis	34 (49.3)	12 (46.2)		12 (48.0)	
Malignant disease	2 (2.9)	-		-	
Hypotension	29 (42.0)	9 (34.6)		8 (32.0)	

* p<0.05, **p<0.0001, NS not significant, □ Chi square test, ‡ Fisher exact test.

Approximately 58% of the IHCA events occurred pre-pandemic. Pre-pandemic for both ROSC as well as StD nearly half of our patients recovered. However, ROSC dropped to 25% and StD to 18.8% during the pandemic. Even though not statistically significant, there was an increase in the proportion of 30-39 year old age group experiencing an IHCA for men and women. There were also differences in ROSC between men and women pre-and during pandemic. For men, there was statistically significant reduction in recovery from 54% in pre-pandemic to just 10% during pandemic. However, for women, there was no difference in recovery pre- and during pandemic (43% vs 50%) Table-II.

Within non-shockable rhythm, PEA as a cause decreased from 18% to 6% pre- and during-pandemic, whereas unexpectedly, asystole as initial cardiac rhythm increased from 73% to almost 91% during pandemic. Pre- and during pandemic, there were significant differences in the

Table-II: Causes of patients who experienced an IHCA in pre pandemic and during pandemic.

Variables, n (%)	*Time of cardiac arrest*			
	Pre-Pandemic (Aug '19 – Feb '20) n=45	*Pandemic (Mar-Aug 2020) n=32*	*Total n=77*	*p-value*
ROSC	22 (48.9)	8 (25)	30 (39)	0.034*□
Survive to discharge	22 (48.9)	6 (18.8)	28 (36.4)	0.007*□
Age (years)				
Male				
<30 year	4 (16.7)	-	4 (9.1)	NS
30-39 year	2 (8.3)	3 (15)	5 (11.4)	
40-59 year	11 (45.8)	9 (45)	20 (45.5)	
60-69 year	4 (16.7)	3 (15)	7 (15.9)	
70 and above	3 (12.5)	5 (25)	8 (18.2)	
Female				
<30 year	6 (28.6)	4 (33.3)	10 (30.3)	NS
30-39 year	3 (14.3)	3 (25)	6 (18.2)	
40-59 year	3 (14.3)	4 (33.3)	7 (21.2)	
60-69 year	6 (28.6)	1 (8.3)	7 (21.2)	
70 and above	3 (14.3)	-	3 (9.1)	
Gender and ROSC; n (%)				
Male	***n=24***	***n=20***	***n=44***	
ROSC	13 (54.2)	2 (10)	15 (34.1)	0.002*□
Female	***n=21***	***n=12***	***n=33***	
ROSC	9 (42.9)	6 (50)	15 (45.5)	NS
Gender and survival; n (%)				
Male	***n=24***	***n=20***	***n=44***	
Survived to discharge	13 (54.2)	1 (5)	14 (31.8)	0.000**□
Female	***n=21***	***n=12***	***n=33***	
Survived to discharge	9 (42.9)	5 (41.7)	14 (42.4)	NS
Initial cardiac rhythm				
Shockable rhythm				
Ventricular fibrillation	3 (3.8)	1 (3.1)	4 (5.3)	
Pulseless ventricular tachycardia	1 (2.3)	-	1 (1.3)	
Non-shockable rhythm				NS
Pulseless electrical activity	8 (18.2)	2 (6.3)	10 (13.2)	
Asystole	32 (72.7)	29 (90.6)	61 (80.3)	
Predominant cause of IHCA; n (%)				
Cardiac	16 (35.6)	3 (9.4)	19 (24.7)	0.009*‡
4H4T	39 (86.7)	32 (100)	71 (92.2)	0.038*□
Sepsis	23 (51.1)	13 (40.6)	36 (46.8)	NS
Breakdown of 4H4T; n (%)				
Hypoxia	20 (50)	29 (90.6)a	49 (68.1)	0.006*□
Hypovolemia	1 (2.5)	-	1 (1.4)	
Hypo/Hyperkalemia	21(52.5)	11 (34.4)	32 (44.4)	
Thrombosis/pulmonary embolus	2 (5)	1 (3.1)	3 (4.2)	
Toxication	2 (5)	2 (6.3)	4 (5.6)	
Hydrogen ion (acidosis)	25 (62.5)	16 (50)	41 (56.9)	

* p<0.05, **p<0.0001, □ Chi square test, ‡ Fisher exact test, † Independent sample t test.

cause of IHCA for cardiac (36% vs 9%, p=0.0009) and 4H4T (87% vs 100%, p=0.04) respectively. The proportion of patients with sepsis remained the same (51% vs 41%). Within 4H4T causes, the proportion of hypoxic patients increased from 50% during pre-pandemic to 91% during the pandemic period, whereas hypo/hyperkalemia decreased from 53% to 34% (p=0.006, Table-II).

DISCUSSION

A few publications have started emerging regarding outcomes of in-hospital cardiac arrest during the COVID-19 pandemic yielding information regarding gender, age, common initial rhythm, survival to discharge, or achievement of ROSC.[3,10-14] To the best of our knowledge, this is the

first study reporting the epidemiology and outcomes of IHCA pre- and during pandemic in Pakistan.

The number of IHCA episodes that took place pre- and during pandemic at our hospital were comparable. As expected, the proportion of those who survived cardiac arrest reduced during the pandemic. Sandroni et al aptly summarized some reasons for the pandemic affecting the epidemiology of in-hospital cardiac arrest.[3] The authors summarized that some possibilities of reduced survival could be due to restrictive guidelines for the management of cardiac arrest which may include extra donning and doffing of protective gear leading to delays in starting CPR as well as a large influx of severely ill patients which overwhelmed the hospital systems. Lim et al's review study noted during the pandemic, in-hospital cardiac arrest incidence of COVID-19 patients varied between 1.5% and 5.8% among hospitalized patients and specifically between 8.0–11.4% among patients in ICU. In-hospital cardiac arrest occurred more commonly in older male patients while most common initial rhythms were non-shockable (83.9%, [asystole = 36.4% and pulseless electrical activity = 47.6%]).[13] The proportion in our data also showed that during non-shockable was nearly 91%; however, the asystole was much higher (91%) as compared to PEA which was just 6%. Another study conducted during the COVID -19 pandemic showed asystole as the most common initial rhythm. It is odd to note this such that the expected rhythm should have been Pulseless electrical activity as it is the commonest result of respiratory failure and hypoxia[15] as expected from COVID-19. Our sample size was too small and more work needs to be done to investigate if asystole is also as common in hypoxia and whether this is limited to COVID-19 related hypoxia alone.

Our finding was similar to other studies in terms that a larger proportion of men have a cardiac arrest.[16] However, we found that during the pandemic, the proportion of men who did not achieve ROSC dropped significantly whereas that was not the case for women. We do not have an explanation for this finding. It is possible that men were more likely to have been exposed to COVID-19 as opposed to the women presenting in the Emergency. This hypothesis cannot be verified since it is not common practice to do a post-mortem or even a COVID-19 test on people who die in emergency in Pakistan. Our study shows survival to discharge and achievement of ROSC were both higher among non-ICU patients, similar to a previous study where return of spontaneous circulation (ROSC) was achieved in 60% of ICU and 70.2% of non-ICU patients.[17] Our study also had a greater proportion of non-ICU patients (31.9%) survive in comparison to ICU (20%) but probably not statistically significant due to a small sample size.

Most of the in-hospital arrests noted were in COVID ICU possibly due to SARS-COV2 contributing to a greater severity of disease leading to arrests in the COVID unit. Thus making frequency of arrests more common in the ICU setting as opposed to wards when compared to previous studies.[1]

Mean age of patients undergoing IHCA in our study was similar in pre pandemic period, where men were affected than women[3,13,18] but unlike a recent Finish study[19] where sudden cardiac arrest was greater in the pre-menopausal and early postmenopausal women than younger ones, our data showed an increase in younger women getting an IHCA event. Possible causes protecting women include better hand hygiene and more likely to seek preventive care. From our study, we cannot comment if in general women access our tertiary care facility more; however, there is some evidence from primary care facilities that women access basic health units more frequently than men in Pakistan.[20]

As expected, our study also showed that lesser proportion of patients who were on mechanical ventilation achieved ROSC and STD as compared to others who were not on mechanical ventilation.[21]

4Hs and 4Ts were a common cause of poor outcomes as expected. The most common etiology of arrest in one such study was respiratory failure.[22] Most patients during the pandemic were noted to have hypoxia making it the most common cause, because of the respiratory implications of the virus. However, since we did not note the COVID-19 status of those in Emergency, we can only presume that they were also COVID-19 positive.

Limitations: A limitation of our study was the small sample size as well as not having COVID-19 status of those who died in Emergency. However, despite the sample size, we were able to show some differences in pre- and during pandemic epidemiology of IHCA. A limitation is our inability to have a covid-19 status on all the patients and so some explanations were not possible.

CONCLUSION

As expected, fewer people achieved ROSC and StD during the pandemic period in comparison to the pre-pandemic period. The role of age and

gender in similar sociodemographic population needs to be further explored and tertiary facilities are encouraged to analyze and compare their IHCA outcomes pre- and during pandemic.

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Authors' Contribution:

FA: Conceived, designed, collected data and prepared the manuscript.
NG: Analyzed data and wrote some sections of manuscript.
All authors did review, final approval of manuscript an are responsible for integrity of the study.

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Original Article

Duration of respiratory sample stability at -80ºC for SARS-CoV-2 PCR

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ABSTRACT

Objective: To determine the stability of respiratory samples for SARS-CoV-2 PCR at standard laboratory ultra-freezer temperatures (-80˚C).

Methods: Five hundred and sixty-five archived, SARS-CoV-2 PCR positive patient specimens received at the Pathology Department of the Indus Hospital & Health Network between January 2021 and June 2021 were retested in June 2021. Samples had been stored at -70˚C or below throughout this duration. Sample integrity following storage was assessed as the percentage of samples with reproducible results, and as consistency of cycle threshold (Ct) values between the original testing and the repeat testing.

Results: Of the 565 samples evaluated in this study, 86% gave reproducible results upon retesting. However, there was no correlation between the duration of storage and result reproducibility, though the majority (69% for PCR Target-I and 78% for PCR Target-II respectively) of non-reproducible results had Ct values above 30. Similarly, there was a consistent increase of Ct values upon storage at ultra-freezer temperatures, though the effect again was more contingent upon freezing the sample in the ultra-freezer rather than the duration of storage.

Conclusion: SARS-CoV-2 positive respiratory specimens for PCR can be stored for up to six months at -70˚C or below without loss of sample integrity, though there is some loss of PCR-detected viral targets as evidenced by an immediate increased in the PCR-generated Ct values. In addition, samples with initial Ct values above 30 are more likely to give non-reproducible results.

KEYWORDS: COVID-19, SARS-CoV-2, PCR, specimen retention, respiratory, ultra-freezer, biorepository.

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INTRODUCTION

Clinical laboratories are mandated by guidelines of accrediting agencies (CLIA, CAP, TJC) to have plans in place for patient specimen retention and storage. Such retention serves several purposes including repeat or additional testing when needed, further investigation for public health purposes, quality control procedures, new test validation, and subsequent research if needed.[1]Specimen storage conditions, including appropriate temperatures and durations, need to be defined in order to ensure that specimens remain uncompromised throughout the retention period, and any subsequent analyses on the specimens generate valid results.

While specimen storage in clinical laboratories is desirable, it is nevertheless resource-intensive, including the requirement for uninterrupted power supply and storage space in freezers and refrigerators. A specimen storage plan should thus ideally balance wastage of this precious resource against wastage of laboratory resources required to store specimens. This necessitates the systematic testing of the upper time limits of storage at standard storage temperatures of laboratory refrigerators and freezers, as storage beyond these temperatures would involve use of resources without any benefit to the clinical laboratory.

CDC guidelines recommend storage of respiratory specimens at 2-8°C for up to 72 hours after collection, while if a delay in testing or shipping is expected, such specimens are recommended to be stored at -70°C or below.[2,3] This is a general recommendation, however, for all respiratory samples, and not specifically for samples to be tested for SARS-CoV-2 through PCR. In addition, the recommendation does not include an upper time limit for storage at -70°C that can safely be undertaken without compromising sample integrity. One FDA recommendation states that respiratory samples can be stored at -70°C or below for up to 8 weeks without any deterioration.[4] It is unclear, however, if respiratory specimens remain viable beyond this time.

With reference to SARS-CoV-2 detection through PCR in respiratory specimens specifically, there are several studies aimed at evaluating sample integrity following short-term storage at room temperature and at refrigerator temperatures (2-8°C).[5-9] There is, however, a paucity of studies evaluating sample viability upon long-term storage at standard ultra-freezer temperatures (-70 to -80°C). Guidelines for the SARS-CoV-2 PCR kits used in this study also state that respiratory specimen stability at standard refrigerator and freezer temperatures has not been established.[10] Moreover, in the current pandemic, these samples may especially be needed for research purposes, for example, to study the evolution of the virus and its mutation pattern. However, since such storage is not without cost to a clinical laboratory, there is a need to determine the duration for which samples remain viable at the standard ultra-freezer temperatures (below -70°C) employed for bio-repositories associated with clinical laboratories. The primary aim of this study was thus to determine the duration for which samples for SARS-CoV-2 PCR remain viable at standard ultra-freezer temperatures in clinical laboratories.

METHODS

Five hundred and sixty-five randomly selected, anonymous, archived, SARS-CoV-2 PCR positive nasopharyngeal patient specimens stored in viral transport, media were used in this study. These specimens had been sent to the Pathology Department at Indus Hospital & Health Network, Karachi, after approval by the Institutional Review Board (IHHN_IRB_2021_07_001) for routine testing for SARS-CoV-2 between January 2021 and June 2021. Samples had been stored at 4°C from the time of collection to the time of testing, in accordance with standard recommendations. Storage time at 4°C before the initial testing ranged between two hours and 24 hours. After PCR testing, the remnant samples were stored at -80°C until their evaluation for this study.

Real-time PCR testing on these samples was done either on Roche Cobas 6800 using cobas SARS-CoV-2 kit or on GeneXpert using Xpert® Xpress SARS-CoV-2. Both systems are fully automated, including sample preparation (nucleic acid extraction and purification) followed by PCR amplification and detection systems. In addition, both systems detect two targets in the virus genome – a 'Target-I' which is a nucleic acid sequence specific to SARS-CoV-2, and a 'Target-II' which is a nucleic acid sequence not specific to SARS-CoV-2, but is common to all Sarbecoviruses.

Samples selected for the study were re-run in June 2021. Thus, the storage period of these samples at -70 to -80°C ranged two prepositions between one and six months. Xpert® Xpress SARS-CoV-2 was used for the repeat run on all samples. None of the samples were thawed in between the first and the repeat runs, while the storage temperature was also monitored as part of the routine laboratory procedures to ensure that there is no significant deviation from the recommended storage temperatures of ultra-freezers. Table-I gives the number of samples selected from each month for inclusion in the study. Reproducibility of positive results and cycle threshold (Ct) values of samples at the time of the initial run, in comparison with those of the repeat run were used to evaluate sample integrity. Cycle threshold (Ct) is a numerical value generated during a RT-PCR test. It refers to the number of cycles needed for a

Table-I: Reproducibility of positive results on repeat testing.

	Jan-21	*Feb-21*	*Mar-21*	*Apr-21*	*May-21*	*Jun-21*
No. of samples	84	100	81	100	100	100
% Reproducibility	99	92	70	93	82	80

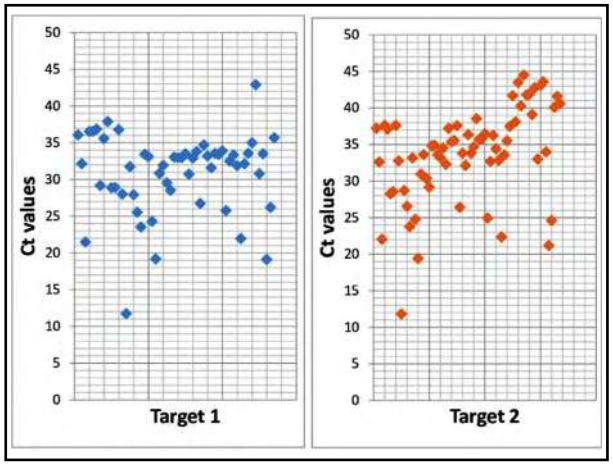

Fig.1: Distribution of initial Target-I and Target-II CT values of discrepant results i.e., positive results which turned negative on repeat testing.

sample to amplify and cross a threshold (cut-off) to be considered detected/positive.[11] In addition, Ct values of samples, in general, are inversely correlated with pathogen load, infectivity, and severity of disease, as a lower Ct value means a higher amount of the target.[12,13] Ct values at the time of testing were computed from already existing laboratory records, while Ct values after storage of samples were recorded after the second run on each sample undertaken for the purpose of this study. All values were computed using MS Excel, which was also used for data analysis.

Fig.2: Difference in average CT values between the first run and the repeat run of samples of SARS-CoV2 PCR.

RESULTS

The overall percentage reproducibility of SARS-CoV-2 PCR results was 86%. Table-I shows the reproducibility of results from the month-wise time points included in the study.

Overall, 69% and 78% of discrepant results, i.e. positive results which turned negative on repeat testing, had a Ct value above 30 for Target-I and Target-II respectively. Fig.1 shows the distribution of initial Ct values obtained with discrepant positive results.

The average Ct values obtained for Target-I and Target-II during the initial run and subsequent run, along with the standard deviation and coefficient of variation are presented in Table-II.

From the above data, it is evident that there is a consistent increase of Ct values targets upon retesting after storage at ultra-freezer temperatures. The average increase of Ct values for each of the targets across the month-wise time points is depicted in Fig.2.

The temperature chart of the freezer used to store samples was maintained throughout at the recommended temperature of -70°C or below. All critical equipment at the study site is backed up with alternate power supplies. In addition, ultra-freezers are equipped with alarm systems in case their temperatures cross unacceptable limits. No untoward incident related to ultra-freezer use to

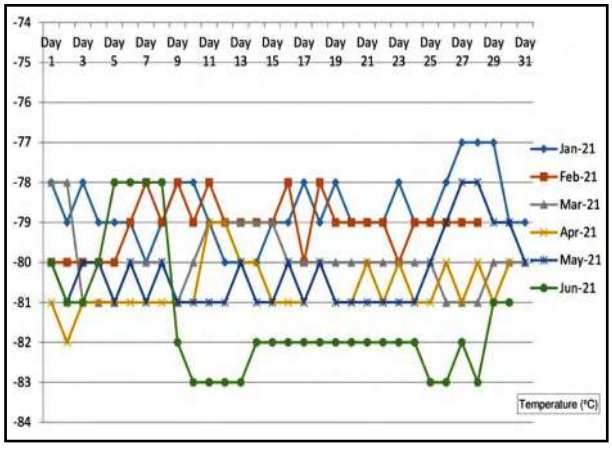

Fig.3: Temperature log of the ultra-freezer used of the study sample storage.

store samples was reported in the study period. Fig.3 depicts the daily monitored temperature log of the ultra-freezer in which samples for this study were stored.

DISCUSSION

Overall, the results of our study suggest that samples positive for SARS-CoV-2 through PCR remain viable at -70°C or below for at least up to six months. There are, however, two caveats in this general conclusion. Firstly, 14% percent of the initially positive samples turned out to be negative on re-evaluation. It must be noted, however, that most of these samples had a Ct value of 30 or above on initial testing. Ct values above 30 obtained from SARS-CoV-2 PCRs have been shown to correlate

Table-II: Month-wiseean, SD, and CV of sample Ct values at collection and following storage.

Six months	*Target-I-Original run (Jan-21)*	*Target-I- Re-run (Jun-21)*	*Target-II-Original run (Jan-21)*	*Target-II- Re-run (Jun-21)*
Mean	28.96	29.87	31.00	32.00
Standard deviation	4.36	6.03	5.14	6.96
Coefficient of variation	15.07	20.19	16.59	21.76
Five months	*Target-I-Original run (Feb-21)*	*Target-I- Re-run (Jun-21)*	*Target-II-Original run (Feb-21)*	*Target-II- Re-run (Jun-21)*
Mean	28.42	30.12	29.11	31.98
Standard deviation	5.17	6.30	5.79	6.52
Coefficient of variation	18.18	20.91	19.89	20.38
Four months	*Target-I-Original run (Mar-21)*	*Target-I- Re-run (Jun-21)*	*Target-II-Original run (Mar-21)*	*Target-II- Re-run (Jun-21)*
Mean	29.63	31.37	31.28	33.77
Standard deviation	3.74	5.98	5.68	6.17
Coefficient of variation	12.52	19.08	18.15	18.26
Three months	*Target-I-Original run (Apr-21)*	*Target-I- Re-run (Jun-21)*	*Target-II-Original run (Apr-21)*	*Target-II- Re-run (Jun-21)*
Mean	27.62	29.17	28.68	31.73
Standard deviation	4.65	6.80	5.44	6.91
Coefficient of variation	16.83	23.31	18.95	21.77
Two months	*Target-I-Original run (May-21)*	*Target-I- Re-run (Jun-21)*	*Target-II-Original run (May-21)*	*Target-II- Re-run (Jun-21)*
Mean	27.55	30.99	28.70	33.08
Standard deviation	4.64	6.63	5.55	6.71
Coefficient of variation	16.85	21.41	19.34	20.27
1 month or less	*Target-I-Original run (Jun-21)*	*Target-I- Re-run (Jun-21)*	*Target-II-Original run (Jun-21)*	*Target-II- Re-run (Jun-21)*
Mean	28.39	30.94	32.34	32.73
Standard deviation	9.06	7.24	7.06	6.82
Coefficient of variation	31.90	23.39	21.84	20.85

with samples containing non-viable virus. This may explain why discrepant results were mostly obtained with samples exhibiting Ct values above 30[14]. Notably, though there is a trend towards higher Ct values in discrepant results, no correlation was found for the percentage of discrepant results with sample storage duration. If anything, the samples stored for the longest period of time analyzed in the study – samples from January 2021 – showed the least number of discrepant results.

Secondly, there is a trend towards increased Ct values with sample storage, even in ultra-freezers. An increase in Ct value by 3.3 indicates approximately a 10-fold decrease in target amount, indicating that even storage at the standard laboratory ultra-freezer temperatures fails to prevent some loss of SARS-CoV-2 target constituents for PCR[15]. It must be noted that this loss starts immediately after storage, evidenced by the observation that Ct values increased even for samples with the shortest storage duration of less than a month, regardless of the duration of storage. However, the exact Ct values notwithstanding, samples generally found positive upon initial testing would generally again give a positive result.

Most existing guidelines on the appropriate storage of samples for SARS-CoV-2 PCR recommend storage of respiratory specimens at 2-8°C for up to 72 hours after collection. While it is clear that if a delay beyond 72 hours is anticipated, samples should be stored in ultra-freezers with temperatures of -70°C or below. There nevertheless remains a gap in defining the upper time limit of such storage, particularly with reference to SARS-CoV-2. Thus, there have been several studies evaluating SARS-CoV-2 PCR sample integrity over refrigerator and room temperatures,[5-9] we have not come across any published, publicly available, study or data with which we could perform a direct comparison of the results obtained in this study.

Limitations of the Study: While this study has provided evidence to fill an important knowledge gap pertaining to SARS-CoV-2 sample storage in ultra-freezers, it has certain limitations which are as follows: Firstly, this study has not evaluated sample viability beyond 6 months of storage at temperatures tested in this study. This could not be accomplished due to the limitation in the resources available to the laboratory, particularly the kits available for PCR testing. It could have been possible to reduce the number of samples for each time period and to include more samples from prior time points, but this would have reduced the confidence in our results obtained.

Furthermore, the same specimen was not used for repeat testing, which would have shown a more standardized month-wise progression of Ct values. This could not be accomplished for practical reasons since actual remnant patient samples were used for this study. These would not have provided sufficient material for the 6 successive data points needed for this study.

Another limitation of the study was that it included only the initially positive samples, while negative samples were excluded from the study. This was done considering a resource-limitation regarding the number of tests which could have been performed for this study. Inclusion of negative samples would have divided the sample, the sample size for each analysis by half and hence reduced confidence in our results. Additionally, it is more practicaly significant to generate such data for positive samples, since these are more likely to be needed for any subsequent analyses. We also do not see any reason why the applicable results of initially positive samples cannot be extrapolated to the initially negative ones.

Lastly, although both of the PCR systems used for this study (Roche Cobas 6800 using cobas SARS-CoV-2 kit or on GeneXpert using Xpert® Xpress SARS-CoV-2) were fully automated and sensitive systems, use of a single system for the study would have increased the precision of results. Again, as the clinical laboratory uses multiple systems, and actual patient specimens were used for this study, the limitation could not be avoided for the purpose of this study.

CONCLUSION

Initially, positive samples for SARS-CoV-2 PCR retain their integrity for up to six months following storage at standard laboratory ultra-freezer temperatures of -70°C or below. However, samples with a Ct value above 30 are more likely to give discrepant results after storage at these temperatures, though the likelihood of discrepant results appears to be unrelated to the duration of storage. In addition, there appears to be some loss of viral targets detected by real time PCR upon storage, as evidenced by a consistent increase of Ct values with storage. Interestingly, this increase of Ct values happens soon after storage and appears to be unrelated to the duration of storage within a timeframe of 6 months.

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Conflicts of Interest: None.

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Author`s Contribution:

JA and MD conceived and designed the study.
JA wrote the manuscript and is responsible for the integrity and accuracy of this study.
FN did data collection, statistical analysis and prepared the figures.
SJ did the editing, final review and approval of manuscript.

Open Access

Original Article

Susceptibility pattern of *Mycobacterium tuberculosis* over a period of five years at Indus Hospital and Health Network, Karachi, Pakistan

Nazia Khursheed[1], Sunil Asif[2], Safia Bano[3], Maria Mushtaq Ali[4], Fareeha Adnan[5]

ABSTRACT

Objective: To determine the susceptibility pattern and frequency of isolation of multidrug, pre-extensively drug and extensively drug resistant TB in a tertiary care hospital in Karachi, Pakistan.

Method: A cross-sectional study was designed. Samples received in the lab were processed for growth and sensitivity testing of *Mycobacterium tuberculosis*. Isolation of MTB was done on Mycobacteria growth indicator tube (MGIT) followed by identification using MPT64. Samples were than evaluated for drug sensitivity against first and second-line antimycobacterial drugs. Statistical analysis was performed using SPSS version 24.0.

Results: Of the 20014 samples received, 23.1% were identified as *Mycobacterium tuberculosis*. Drug sensitivity testing was performed on 95.9% isolates. Fifty-two percent samples were from males and 48% female patients. The study found statistically non-significant relationship between gender and likelihood of disease with drug-resistant (DR)-MTB organisms. The rate of isolation of MDR-TB was highest (43%) among ages 25-55 years and previously treated patients compared to newly diagnosed patients (62% vs 36%). Among MTB positive samples, 91.5% were pulmonary while 8.5% were extrapulmonary samples. Extrapulmonary samples were more likely to be sensitive to antimycobacterial drugs. The highest resistance was observed against Isoniazid (pulmonary=58%; extrapulmonary=12.7%), Rifampicin (pulmonary=58.7%; extrapulmonary=8.2%), and Levofloxacin (pulmonary=29.2%; extrapulmonary=20%).

Conclusion: A considerable number of drug resistant tuberculosis cases were identified in the present study. It is essential to develop further strategies to reduce the spread of this disease.

KEYWORDS: *Mycobacterium tuberculosis*, Drug-resistance, Pulmonary and Extrapulmonary tuberculosis.

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INTRODUCTION

Mycobacterium tuberculosis (MTB) is the 9th leading cause of death with annually 10 million new cases and 1.7 million deaths worldwide.[1] Among 30 high TB burden countries Pakistan has been ranked at fifth position according to WHO Report 2020.[2] According to WHO Eastern Mediterranean Regional Office (EMRO) reports (2019), there were approximately 265 incidences of TB per 100,000 population in Pakistan. Moreover, there were 15, 5537 (new and previously treated) cases of TB reported during 9 months in 2020 in Pakistan. Although, TB is a curable and preventable disease, with 85% cure rate,[3] emergence of Multidrug resistance (MDR) strains worsens the situation. Pakistan ranks fourth among the 27 high MDR-TB burden countries.[4]

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In Pakistan, the per capita cost for the treatment of TB is $307.74. In this scenario, surveillance study will be helpful in evaluating the effectiveness of TB prevention and control programs and highlight the emerging resistance pattern in the community. Surveillance of frequency and drug resistance profile provide clinicians with a background of MTB drug susceptibility and assist in designing modifications in their approach to DR-TB transmission control and in creating effective regimens and treatment strategies for DR-TB patient management based on WHO guidance. Taking in to account the above context, the present study is designed to analyze the frequency and susceptibility pattern of MTB in clinical isolates from 2016 to 2020 at the Indus Hospital and Health Network (IHHN), Korangi campus, Karachi, Pakistan.

METHOD

This retrospective study was conducted at the IHHN, located in Karachi, Pakistan. It has supported tuberculosis control efforts in Pakistan since 2007. The study was approved by the Institutional Review Board (IRB) of IHHN (study number IHHN_IRB_2021_04_019).

All MTB isolates from pulmonary and extra-pulmonary samples received during 2016 – 2020 were processed for culture and drug susceptibility testing (DST). Data were extracted using the Hospital Management Information System (HMIS), which included patient medical record number, age, gender, date of isolation, specimen-type and susceptibility pattern of TB against first- and second-line mycobacterial agents.

Microbiological methods: All specimens were processed at the Microbiology Laboratory of IHHN. The specimens were digested and decontaminated using the N-acetyl-L-cysteine-NaOH method and smears were prepared according to the standard protocols, subjected to auramine O staining and examined under Light Emitting Diode (LED) fluorescence microscope. For the growth of *M. tuberculosis,* specimens were inoculated on both Mycobacteria growth indicator tube (MGIT) and Lowenstein Jensen (LJ) medium (Becton Dickinson). Growth from the positive LJ slant and MGIT vials were stained with Ziehl nelson. Identification of *M. tuberculosis* was done by MPT64.

Drug Susceptibility Testing: Susceptibility testing was performed using BACTEC MGIT 960 method by following the standard procedure of the manufacturer.[5] Final drug concentrations used were 1.0 µg/ml for streptomycin, 0.1 µg/ml for isoniazid, 1.0 µg/ml for rifampicin, 5.0 µg/ml for ethambutol and for pyrazinamide 100 µg/ml, for kanamycin and capreomycin 2.5 µg/ml, amikacin 1 µg/ml, ofloxacin 2 µg/ml, moxifloxacin 1 µg/ml, 0.25 µg/ml and levofloxacin at 1 µg/ml. The relative growth ratio was determined by comparing the fluorescence between the two tubes by the system's software algorithm. Susceptibility results were determined by comparison of analysis of fluorescence in the drug-containing tubes and Growth Control tube. To interpret the results for first line and second line drugs, the standard protocol recommended by manufacturers was followed for DST by the MGIT 960 method. When the growth unit (GU) of the growth control reaches 400 within 4–13 days, the GU values of the drug-containing vials were assessed.; the result was reported as susceptible and resistant strains, when the GU of the drug-containing tubes were found to be 100 and >100 respectively.

Quality controls: Quality control of each batch of culture and drug susceptibility pattern (DST) performed with the reference strain H37Rv (ATCC 27294), which is susceptible for all standard anti-tuberculosis drugs.

Statistical analysis: The data were analyzed by using SPSS 24.0.[6] Quantitative variables were calculated as mean ± std, whereas, descriptive statistics were used to calculate the frequency and percentage of drug resistance tuberculosis cases by age, gender and history of patients. Comparisons of categorical variables were performed by using $\chi 2$ test. P-value < 0.05 was considered as statistically significant.

RESULTS

Twenty thousand and fourteen samples were received during the study period. Among them 4652 (23.1%) were flagged positive as Mycobacterium species, 14836 (74.1%) were negative, 519 (2.5%) were contaminated and 7 (0.03%) were rejected according to the rejection criteria of the laboratory. Out of 4652 positive samples, DST was performed on 4463 (95.9%) isolates identified as MTB, 115 (2.4%) were identified as MOTT (Mycobacterium other than MTB), while 74 (1.5%) were MTB positive with contamination. These 189 samples were excluded from the analysis. The frequency of MDR, pre-extensively drug resistant (pre-XDR), extensively drug resistant (XDR) and sensitive Mycobacterium tuberculosis were found to be 40%, 15%, 1% and 44% respectively.

Among positive samples male preponderance was found in 2327 (52.1%) samples and 2136

(47.9%) samples were from females. Mean age of the sampled patients was 33 (std ± 16.7) years with minimum <1 year and maximum 95 years. The pulmonary samples were 4086 (91.5%) and extra pulmonary samples were 377 (8.5%). Of the positive samples those from newly enrolled patients were 3743 (83.8%) and previously treated patients were 706 (15.8%).

Among MDR-TB cases, comparison has been done between age groups < 15, 15-24, 25-34, 35-44, 45–55 and above 55 years. Age groups 25-34, 35-44 and 45-55years were the most affected groups with MDR-TB as compared to other age groups (Table-I). MDR-TB, pre-XDR and XDR isolates were statistically more prevalent in previously treated than in newly diagnosed patients, shown in (Table-I).

Among PTB samples, tested for first-line drugs, showed highest resistance against Rifampicin (58.7%) and Isoniazid (58.0%) followed by Pyranzinamide (20.7%), Ethambutol (13.0%), and Streptomycin (12.4%). For second-line drugs, high resistance was observed for Ofloxacin (30.2%) and Levofloxacin (29.2%) (Fig.1a).

Extra pulmonary samples showed high sensitivity as compared to pulmonary samples. In EPTB samples highest resistance was observed for Isoniazid (12.7%), followed by Rifampicin (8.2%), Streptomycin (5.0%), and Pyrazinamide (4.5%) among first line antituberculosis drugs. In second-line drug similar to PTB samples, highest resistance was observed against Levofloxacin (20%). However, EPTB samples showed 100% sensitivity to Ethambutol and Moxifloxacin (Fig.1b).

DISCUSSION

This study reports the susceptibility pattern of MTB after laboratory record review. The frequency of isolation of MTB was found to be 23.2% (4652/20014) in the current study. Whereas a study conducted in Punjab reported low incidence rate of 14%, on the contrary, 0.002 incidence rate was observed from developed countries.[7]

Our study reports a high rate of MDR–TB isolates (40%) which is analogous with a local study which reported a rate of 38.7%.[8] Inconsistent with our findings, a study done in Punjab reported only 9.3% of MDR-TB. The high prevalence of TB in Karachi (Sindh) as compared to Punjab might be because Karachi is a densely populated city and also an economic hub where people come from many different regions, often live in close quarters, and this increases TB transmission in the

Table-I: Association of types of TB and Demographics.

	MDR (%)	*Pre-XDR (%)*	*XDR (%)*	*Non-MDR (%)*	*Total*	*P value*
Type of TB						
PTB	1767 (43.2)	650 (15.9)	28 (0.68)	1641 (40.1)	4086	0.000
EPTB	25 (6.6)	8 (2.1)	0 ()	344 (91.2)	377	
Total	1792	658	28	1985	4463	
Gender						
Male	948 (40.7)	33 (14.3)	17 (0.73)	1029 (44.2)	2136 (100)	0.586
Female	844 (39.5)	325 (15.2)	11 (0.51)	956 (44.7)	2327 (100)	
History of treatment						
Previously Treated	439 (62.1)	152 (21.5)	11 (1.5)	104 (14.7)	706 (100)	
Newly Enrolled	1348 (36)	499 (13.3)	17 (0.45)	1879 (50.2)	3743 (100)	0.000
Unknown	5	7	0	2	14	
Age Groups						
<15	147 (37.5)	38 (9.7)	0 (0)	206 (52.6)	391 (100)	
15-24	475 (37.8)	185 (14.7)	6 (0.47)	588 (46.8)	1254 (100)	
25-34	416 (43.0)	154 (15.9)	6 (0.62)	390 (40.3)	966 (100)	0.000
35-44	269 (43.3)	92 (14.8)	6 (0.96)	254 (40.9)	621 (100)	
45-55	290 (43.6)	106 (15.9)	4 (0.60)	264 (39.7)	664 (100)	
>55	195 (34.3)	83 (14.6)	6 (1.0)	283 (49.9)	567 (100)	

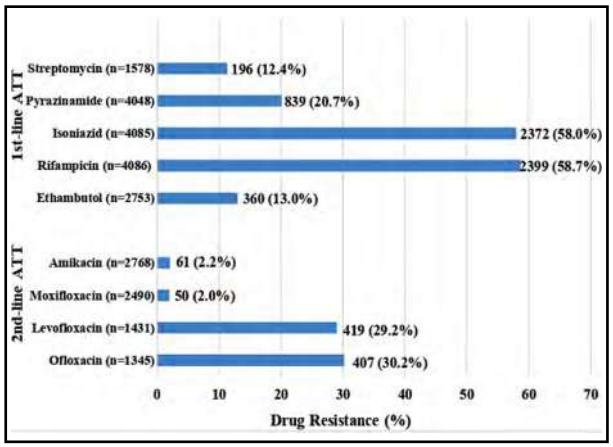

Fig.1a: Antibiotic susceptibility pattern of MTB in PTB samples.

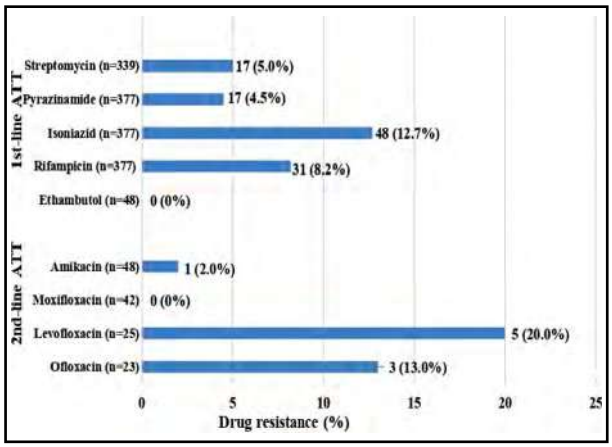

Fig.1b: Antibiotic susceptibility pattern of MTB in EPTB samples.

community. The Indus Hospital has been an MDR-TB referral and treatment site since 2007 another reason for a higher rate of MDR-TB. Multiple studies from different regions of the world have reported 4-50% incidence rate of MDR-TB.[9]

Among first line antimycobacterials, the highest resistance was observed for Rifampicin and Isoniazid. The findings in present study are similar to the studies conducted in Bangladesh and South Africa that showed high rates of resistance to Isoniazid and Rifampicin.[10,11] However the high rates of resistance to streptomycin and Isoniazid observed in these studies is not in concordance with our results.[11] An alarming finding is the high resistance observed against Levofloxacin (29.2%) and Ofloxacin (30.2%), as quinolones are important components of DR-TB regimens. The reason for this upsurge is probably excessive and unregulated use of these antibiotics.

Ineffectively managed MDR TB cases mutate into XDR-TB. Our data showed 15% pre-XDR-TB and 1% XDR-TB strains. Our results are similar to studies conducted in India for instance Sharma and colleagues reported 18.4% pre-XDR prevalence.[12] In comparison, a study conducted by Sameer Adwani et al., from India, from a similar population density and setting as Karachi, reported a higher prevalence of pre-XDR-TB (55.9%) and XDR-TB (4.8%).[13] The emergence of pre-XDR and XDR strains is alarming since treatment options are limited, costly and outcomes are poor.

In this study no statistical significance was found between gender and different categories of drug resistance. This is consistent with a study done by Aarain et al.[10] In contrast, a study conducted in Bangladesh reported three times higher TB prevalence in males.[14] A study in Israel also stated males as a risk factor to DR-TB.[15] Another study conducted in Karachi reported high drug resistance in male gender which is not in accordance with our findings. The significance of gender with respect to drug resistance needs to be further explored. The conflicting results was observed with higher degree of vulnerability of the female gender to DR-TB in Pakistan and the Republic of Georgia.[16,17]

In contrast to gender, age was found to be associated with drug resistant TB. The highest frequency of MDR- TB was observed in the age group of 24 -55 years. Previous studies documented a higher rate of MDR- TB in the 10-25 year age group.[18] Our results can be supported by the fact that this age group is more exposed to the community consequently, making them more vulnerable. It might also be accredited to other activities connected to the phase of development where social and cultural factors gain importance in their lives, financial constraints, and TB-related stigma. In addition, a lower resistance in under five and above 55 years of age is possibly due to lower level of exposure and inactive lifestyle which subsidizes the risk of cross-transmission of MDR strains. In contrast to our findings, some investigations have not shown any association between the risk of MDR-TB and age.[19-21]

In the current study, the overall occurrence of PTB was 91.5%, similar to the results observed in Chiniot, where 90.5% of cases were reported as PTB, significantly higher percentage compared to other studies (40% to 44% cases) conducted in Khyber Pakhtunkhwa, Pakistan.[22] Furthermore, a study conducted in Ethiopia reported a 40.9%

prevalence of PTB.[23] According to the Global TB report EPTB contributes to 15% of the all TB cases.[24] However, the proportion of EPTB among TB patients varies from country to country and ranges from 5% (China) to 29% (Afghanistan). Interestingly it also differs from province to province in Pakistan. The ratio is observed to be higher in Khyber Pakhtunkhwa and FATA, in comparison to Punjab and Sindh.[25] Herein, of the total isolates 8.5% were EPTB. This proportion is lower than the developing countries such as US (21%), Italy (32%), and Australia (39%). These differences might be attributed to different factors including differences in socio-demographic features, failure of early diagnosis or under-estimation of EPTB in developing countries.[26] Extrapulmonary-TB samples showed higher sensitivity (91.2%) to the antituberculosis drugs. This finding is further strengthened by another study conducted in Europe where a high rate of MDR-TB was associated with PTB. In India, a study conducted by Mourya et al reported a drug resistance rate of 13.4% in EPTB samples that is higher than the rate observed in the present study. On the contrary, a significantly low rate (2.2%) of MDR-TB in EPTB samples was reported in another study conducted in Pakistan.[25] Higher sensitivity in EPTB samples might be because it does not contribute considerably to the transmission of the disease, consequently, there is a low chance of spreading drug resistance strains.

Collectively, the higher occurrence of MDR, pre XDR, and XDR TB was observed in previously treated patients. A similar pattern was observed in a meta-analysis done in Ethiopia for sub-Saharan African countries that reported the high prevalence of drug resistance TB strains in previously treated patients as compared to newly diagnosed cases.[27] The major reason contributing to the high rate of drug resistance in previously treated patients is non- adherence to antituberculosis treatment strategies. While secondary reasons could be low literacy levels, discriminatory behavior by health care providers, deferrals in care seeking behavior and self-denial due to disgrace experienced by TB patients.

Although, different parts of the world reported variable patterns of drug-resistant TB, these dynamics in the resistance profile may be due to very different modes of living habits, poor application of TB infection control policy, inadequate and irregular treatment, and the dissemination of drug-resistant strains.

Strength: The strength of this study is that it is sharing the current frequency and susceptibility pattern of *MTB*. This information can be used to observe evolving patterns of drugs resistance which could help in modifying treatment guidelines.

Limitation: The main limitation of this study is the retrospective collection of data. For the majority of patients, we were not able to retrieve a detailed clinical history, X-ray findings, and treatment outcome. Another limitation of our study is that it is a single centre study, therefore, it cannot be generalized for the whole population and possesses selection bias.

CONCLUSION

The ongoing transmission of DR-TB strains in the community is a serious public health problem as treatment is often prolonged and newer drugs are not easily available and costly making treatment completion difficult to achieve. The major risk factors for the development of DR-TB identified in the present study are age and history of previous TB treatment. Hence, there is an urgent need for surveillance programs, availability of new molecular tests at district level, effective TB programs, extensive research to explain the factors concomitant with DR-TB.

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Authors' Contribution:

NK conceived, designed and critically review of manuscript.
SA and SB did data collection and analysis.
MMA did data analysis and manuscript writing.
FA did critical review of manuscript.
NK takes the responsibility and accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Open Access

Original Article

Effect of Remdesivir on mortality and length of stay in hospitalized COVID-19 patients: A single center study

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ABSTRACT

Objectives: To see the difference in mortality among hospitalized COVID-19 patients given Remdesivir (RDV) with those who were not given RDV.

Methods: A prospective cohort study was conducted on patients who were admitted to the COVID-19 isolation unit at The Indus Hospital, Korangi Campus Karachi between March and June 2020.

Results: Groups were similar in age and gender distribution. RDV group was more hypoxic, had severe ARDS and needed higher Oxygen support compared to non-RDV group (p=0.000). Median SOFA score was 2 in RDV vs 5 in non-RDV (p=0.000). More than moderate COVID pneumonia was found in 92% of the RDV group while 89% of non-RDV group (p value=0.001). Median day of illness to administer Remdesivir was 10. There was no difference in mortality (45.5% in RDV vs 40.4% in non-RDV; p=0.4) between the two groups. Median length of hospital stay was 12 days (IQR=7.5-14.5) in RDV group compared to 10 days (IQR=6-14) in non-RDV group (p=0.009).

Conclusion: RDV did not show any difference in in-hospital mortality in our patients. More patients had severe ARDS in the RDV group while patients in the non-RDV group had higher SOFA score and multi-organ failure. Length of stay was longer in patients receiving Remdesivir.

KEYWORDS: COVID-19, Remdesivir, mortality, ARDS.

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INTRODUCTION

The novel coronavirus disease (COVID-19) emerged in December 2019 and rapidly became a pandemic. Globally, as of now 203,178,675 people are infected, including four million deaths.[1] This led to the search of desperate public health measures including the quest for effective treatments. Despite the fact that a number of therapeutic agents have been tested for the treatment of Covid-19, no antiviral drug has proved to be efficacious.[2] Experts from the World Health Organization initiated mortality trials comparing four drugs including Remdesivir, Hydroxychloroquine, Lopinavir, and interferon beta-1a.[3] The rate of mortality, initiation of ventilation, and length of hospital stay were not definitely reduced by any of the trial drug.[3]

One of the many promising candidates for this purpose was Remdesivir, which is a drug with effective antiviral properties.[4] Remdesivir has a broad spectrum of activity and acts by inhibiting RNA-dependent RNA polymerases (RdRp) and subsequently causes arrest in RNA synthesis.[5] It has been used to treat Filo viruses, Corona viruses, paramyxoviruses and pneumoviridae.[5] In Wuhan, China the first randomized, placebo-controlled trial of Remdesivir among patients with COVID-19 was begun. Unfortunately, they were unable to access the efficacy of Remdesivir as the trial was unable to successfully complete recruitment.[6] However, results from a large randomized, double-blind clinical trial showed that a 10-day Remdesivir course had significantly faster recovery time (11 days) in COVID 19 patients when compared to those who received placebo (15 days).[2] Contradicting this evidence, the WHO led SOLIDARITY trial in over 40 countries worldwide showed no benefit of Remdesivir on mortality or length of hospital stay.[3] Despite such conflicting results, on 1st May 2020, Remdesivir was granted Emergency Use Authorization by the US Food and Drug Administration for the treatment of patients with severe COVID-19.[7] Later this was expanded to include non-severe patients. Final approval was given on the basis of three Randomized controlled trials which showed benefit of Remdesivir over placebo in reducing mortality.[2,4,8] Hundred and Eight clinical trials of Remdesivir for COVID-19 are currently registered with U.S National Library of Medicine.[9] The only contraindications to the use of Remdesivir are severe hepatic dysfunction (ALT >5 times of upper limit of normal), renal dysfunction with GFR <30 ml/min and neonates.

Currently, Pakistan has entered the fourth wave of COVID-19. So far, there have been about 21 thousand deaths due to COVID-19 all over the country.[10] It is extremely crucial to aim for effective therapeutic regimes for COVID-19 along with prevention strategies. In this paper, we share our experience with Remdesivir use in COVID-19 hospitalized patients at the Indus Hospital, Korangi Campus, Karachi during the first wave of COVID-19 in the country.

METHODS

We conducted a prospective cohort study on all COVID-19 admissions (positive nasopharyngeal RT-PCR for COVID-19) at the Indus Hospital, Korangi campus in Karachi. The study was approved by the IRB under approval number IRD_IRB_2020_04_002. All consecutive patients who were admitted to the COVID-19 isolation unit and were at least 18 years old were enrolled between 24th March and 19th June 2020. Disease severity was assessed using the National COVID-19 management guidelines 11. Disease severity was classified as "severe COVID-19" if on admission the respiratory rate was more than 30/min, oxygen saturation was 90% on room air or Chest X-ray showed more than 50% of lung fields involved while "Critical COVID-19" if along with the criteria for severe disease they manifested ARDS, Septic shock or multisystem organ failure (MSOF). Remdesivir was administered to patients who fulfilled the criteria for severe disease as per the international recommendations at that time. Since the drug was not easily available in Pakistan at that time, the choice of patients for therapy was largely dependent on availability of the drug. Later, Remdesivir was being manufactured in Pakistan and was easily available. Only contraindications to the use of Remdesivir were pre-existing hepatic dysfunction as manifested by Alanine Aminotransferase (ALT) levels more than 5 times the upper limit of normal and reduced Glomerular filtration rate (<60 ml/min). Hence, those COVID-19 severe disease patients who received Remdesivir were analyzed in Rem group while those who could not receive Remdesivir due to unavailability or contra-indications were analyzed in Non-Rem group. Those patients who did not receive Remdesivir due to unavailability of the drug in the early days or any contraindication to its use were used as a comparison group for the purpose of this analysis. We recorded patient's demographics, clinical details and laboratory parameters at admission. The main outcome of interest was in-hospital mortality. All data was entered on a REDCap database and Stata version 14 was used for analysis. Mean (SD) were reported for continuous data after checking normality. Median (IQR) was used for non-normally distributed data. Categorical variables were reported as numbers and percentages. Either Student's t-test or Mann Whitney U test were used to compare continuous data. Chi square or Fischer's Exact test was used to compare categorical data. P-value ≤ 0.05 was considered significant.

RESULTS

A total of 268 patients were enrolled in the study. Remdesivir was given to 102 patients while 166 were in the non-Remdesivir group. The

Table-I: Characteristics of COVID-19 patients admitted at The Indus Hospital-Korangi Campus.

Variable	*Remdesivir n(%) n=102*	*Non-Remdesivir n(%) n=166*	*p-value*
Age[β]	55.0 ± 12.8	56.2 ± 13.3	0.485
Gender			
Male	75 (73.5)	130(78.3)	0.370
Female	27(26.5)	36(21.7)	
Hypertension			
Yes	47(46.1)	72(43.4)	0.665
No	55(53.9)	94(56.6)	
Diabetes			
Yes	52(51.0)	74(44.6)	0.308
No	50(49.0)	92(55.4)	
Heart Disease			
Yes	11(10.8)	17(10.2)	0.888
No	91(89.2)	149(89.8)	
Fever			
Yes	86(84.3)	139(83.7)	0.900
No	16(15.7)	27(16.3)	
Cough			
Yes	51(50.0)	101(60.8)	0.089
No	51(50.0)	65(39.2)	
Shortness of breath			
Yes	76(74.5)	139(83.7)	0.066
No	26(25.5)	27(16.3)	
Systolic BP^ mmHg	138(118-151)	139(123-153)	0.437
Diastolic BP^ mmHg	80(71-80)	80(72-90.5)	0.847
Pulse^ b/min	100(86-110.5)	106(92-117.5)	0.233
Respiratory Rate^ /min	32(26-38)	30(24-36)	0.147
Oxygen Saturation^ %	86(78-90)	88(76-93)	0.032*
SOFA Score^	2(2-3.5)	5(4-8)	<0.0001**
PaO2/FiO2 Ratio^	115 (72.9-242.5)	187.5 (104.3-268.3)	0.032*
Clinical Severity			
Moderate	8(7.8)	18(10.8)	0.001**
Severe	27(26.5)	15(9.0)	
Critical	67(65.7)	133(80.1)	
Invasive ventilation			
Yes	37(36.3)	66(39.8)	0.569
No	65(63.7)	100(60.2)	
ARDS			
Severe ARDS	41(40.2)	30(19.2)	0.002*
Moderate ARDS	20(19.6)	52(33.3)	
Mild ARDS	24(23.5)	46(29.5)	
Not Present	17(16.7)	28(17.9)	
Oxygen Requirement			
≥5 Litres	83(81.4)	84(50.6)	<0.0001**
< 5 Litres	19(18.6)	82(49.4)	
Non Invasive Ventilation			
Yes	39(38.2)	63(38.0)	0.963
No	63(61.8)	103(62.0)	

^Median (IQR), [β]Mean (SD), P value *<0.05, **<0.001

baseline characteristics of both Remdesivir and non-Remdesivir groups are shown in Table-I.

Overall more than three fourth (76.5%) of the patients were male and there was no difference in gender or age distribution of the two groups. Distribution of major comorbid conditions like diabetes mellitus, hypertension and heart disease was not different between the two groups. Most patients presented with fever, cough and shortness of breath as presenting symptoms in both groups (p>0.05). Among the physical parameters in emergency room, median peripheral oxygen saturation (Spo2) was significantly lower in the Remdesivir group (86% vs 88%; p=0.032). Similarly, the median Pao2/ Fio2 ratio was much lower for the Remdesivir group (115; IQR=72.9-242.5) at presentation compared to the non-Remdesivir group (187; IQR=104-268) (p=0.032). In the Remdesivir group, 40% patients had severe ARDS while in the non-Remdesivir group only 19% had severe ARDS (p=0.002). Patients with clinical severity of moderate, severe and critical were included in the study as those with less than moderate disease were not admitted to hospital for management. Remdesivir group had more patients (92%) with combined severe disease and critical disease while the non-Remdesivir group had a majority of patients with critical disease (80%) (p-value=0.001). Need for high flow oxygen at least 5 L was more in the Remdesivir group (81% vs 50.6%; p=0.000). However, both the groups had similar need for invasive ventilation and non-invasive ventilation (p>0.05). Median SOFA score was much higher in non-Remdesivir group depicting multiorgan dysfunction compared to the Remdesivir group (5 vs 2; p=0.000).

There were no major differences in baseline laboratory parameters (Table-II), however, inflammatory markers like Ferritin and IL-6 were markedly raised in the non-Remdesivir group compared to Remdesivir group (p < 0.05). Median D-dimer was 0.6 ng/ml in Remdesivir group while 1.8 ng/ml in the non-Remdesivir group (p=0.000). Pro-calcitonin was significantly higher in the non-Remdesivir group (p=0.013). Chest X-ray findings were scored using RALE scoring and the median RALE score was 6 (IQR=5-8) in Remdesivir group while 5 (IQR=4-7) in the non Remdesivir group (p value 0.002).

When mortality was compared between the two groups (Table-III), no major difference in hospital mortality was observed (46% in

Table-II: Baseline Laboratory parameters.

Variable	*Remdesivir*	*Non-Remdesivir*	*p-value*
	Median (IQR)	*Median (IQR)*	
Hemoglobin (mg/dl)	12.8(11.8-14.1)	13.2(11.4-14.5)	0.921
White blood cells (x109/L)	15.6(9.5-17.8)	12.5(7.9-17.5)	0.883
Neutrophils (%)	87.6(82-90.9)	85.3(80.3-90.2)	0.809
Lymphocytes (%)	6.3(5.4-11.6)	8.2(7.1-12.8)	0.924
Platelet (x109/L)	293(106.5-367.5)	202(131-341)	0.227
Creatinine (mg/dl)	1.0(0.8-1.3)	1.1(0.9-1.9)	0.018*
IL6 (pg/ml)	24.2(10.2-50.5)	46.3(24.8-164.8)	0.059
CRP (mg/L)	151.7(47.7-206.8)	135.7(77.1-214.9)	0.401
Ferritin (ng/ml)	730.1(393.7-1076.5)	1623(606.9-1675.6)	<0.0001**
Pro-calcitonin (ng/ml)	0.2(0.1-0.4)	0.6(0.2-2.2)	0.013*
LDH (U/L)	423.5(341.3-579.3)	529.5(453.8-767)	0.772
D-dimer (ng/ml)	0.6(0.4-1.9)	1.8(0.7-6.9)	<0.0001**
RALE Score (CXR)	6(5-8)	5(4-7)	0.002*

CXR= chest x-ray, P value *<0.05, **<0.001.

Remdesivir group vs 40.4% in non-Remdesivir group; p=0.46). Median length of hospital stay was 12 (IQR=7.5-14.5) days compared to 10 days (IQR=6-14) in non-Remdesivir group (p=0.009).

With regards to adjunctive therapies, (Table-IV) there was no significant difference in the use of Tocilizumab between the two groups (p>0.05). Use of antibiotics was higher in non-Remdesivir group (p=0.000) while use of methyl prednisolone was higher in Remdesivir group (p=0.001). Similarly, the use of therapeutic anticoagulation was significantly higher in the non-Remdesivir group compared to Remdesivir group (p=0.001).

The median number of doses used for this cohort was 5 (IQR=2-5), which corresponds to 600mg Remdesivir per patient. The median duration of

Table-III: Outcome COVID_19 patients by use of Remdesivir.

	Remdesivir	*Non-Remdesivir*	*p-value*
In-hospital complications$^{\beta}$	***n(%)***	***n(%)***	
None	36(38.3)	78(50.0)	
Cardiac Abnormalities	22(23.4)	27(17.3)	
Nosocomial Infection	16(17.0)	30(19.2)	
CNS Abnormalities	3(3.2)	5(3.2)	
Septic Shock	6(6.4)	32(20.5)	<0.0001**
MODS	15(16.0)	23(14.7)	
AKI	10(10.6)	46(29.5)	
Thromboembolism	0	7(4.5)	
Barotrauma	0	4(2.6)	
DIC	1(1.1)	9(5.8)	
Length of hospital stay^ (days)	12(7.5-14.5)	10(6-14)	0.009*
Mortality			
Alive	55(53.9)	99(59.6)	0.406
Dead	47(46.0)	67(40.4)	

^Median (IQR), $^{\beta}$does not add up to 100, P value *<0.05, **<0.001.

Table-IV: Use of adjunct therapies in both groups of COVID-19 patients.

Variable	*Remdesivir n(%)*	*Non-Remdesivir n(%)*	*p-value*
Tocilizumab			
Single Dose	25(25.3)	34(20.5)	
Two Doses	4(4.0)	9(5.4)	0.615
Not Given	70(70.7)	123(74.1)	
Antibiotics			
Yes	46(46.0)	142(86.6)	<0.0001**
No	54(54.0)	22(13.4)	
Anticoagulation			
Therapeutic Doses	29(29.0)	77(47.2)	
Prophylactic Doses	68(68.0)	73(44.8)	0.001**
Not Given	3(3.0)	13(8.0)	
Methylprednisolone			
Yes	97(97.0)	135(82.8)	0.001**
No	3(3.0)	28(17.2)	

symptoms at which the Remdesivir was administered was 10 days (IQR=8-11). The maximum Alanine amino transferase after administration of Remdesivir was 81 (IQR=42-136) wile maximum creatinine was 1.1 (0.9-2.2) in our patients.

DISCUSSION

We believe this is the first report of the use of Remdesivir from our country. Randomized Clinical Trials have shown some benefit of Remdesivir in COVID- 19 pneumonia.[2,4,8] However, our data is from the first wave of COVID-9, when practitioners did not have much idea regarding the optimum dosing and duration of therapy as well as expected side effects of this uncommon drug. With more data emerging on the management of COVID-19, it is now evident that Remdesivir is one of the mainstay therapies for halting the progression of COVID-19 pneumonia.

Although our data shows no effect of Remdesivir on mortality, we have only been able to look at in-hospital mortality while a recent meta-analysis published in January 2021 suggests that 28 day mortality and oxygen support through 14-28 days is affected by the use of Remdesivir.[12] Hence, it is quite possible that our groups would have shown a difference if they were followed for a longer period of time. Secondly, our treatment groups were not balanced to begin with. The Remdesivir group was characterized by marked hypoxia and features of ARDS due to COVID-19 pneumonia allowing easy decision making for using the drug. On the other hand, the non-Remdesivir group seems to be more severely sick as indicated by higher median SOFA scores and high pro-calcitonin suggesting the onset of multi organ dysfunction and possible secondary bacterial infection complicating their outcomes and prognosis. The use of Remdesivir was abandoned in this group due to presence of multi organ dysfunction and probable liver and renal injury contraindicating the use of Remdesivir. However, the overall mortality reported from another one of our recently published papers from this cohort was 39% which was not very different from the Remdesivir group here.[13]

One important difference to highlight in our data is that Remdesivir was being administered to people at a median 10th day (IQR=8-11) of illness during the first wave of COVID-19. Later, published data indicated that this was probably already late. Hence, guidelines adapted the 10 day rule and now it is understood that Remdesivir benefit is maximized by giving it in hypoxic patients within 10 days of illness.[11] In fact, some data suggests the use of Remdesivir in non-hypoxic patients earlier in the course of the disease if there is evidence of COVID-19 pneumonia.[14] We did not identify any major side effects of Remdesivir in our patients. Maximum ALT and serum creatinine were not significantly raised.

Our study has a number of limitations including non-random treatment allocation leading

to selection bias. Co-administration of other compassionate therapies like antibiotics, steroids and anticoagulation (both prophylactic as well as therapeutic doses) could also confound the results. These effects are not easy to tease out because of the observational nature of the study. An interesting observation was that most patients in the non-Remdesivir group were given antibiotics, had higher pro-calcitonin levels and higher SOFA scores indicating the onset of secondary bacterial infection or an already complicated clinical course with multi-organ failure. Hence this group, was never a candidate for Remdesivir therapy. While most patients in the Remdesivir group had pure hypoxia, need for high flow oxygen and severe ARDS without evidence of multi-organ failure as evidence by a lower SOFA score. Even in this group, we see a high mortality and no benefit of Remdesivir in our patients. We believe this group of patients were too late to receive Remdesivir, as has been discovered later in multiple studies, hence we were not able to see any improvement in outcomes.[14] However, the study is unique in being one of the first local reports on Remdesivir from our region where prospective data collection was done to follow patients for in-hospital mortality and side effects. Our recent data on the use of Remdesivir in non-hypoxic, moderate COVID pneumonia patients is soon to be published showing significant difference by the use of Remdesivir. It is in the light of this data that our institution's guidelines were modified to include the use of Remdesivir in moderate COVID-19 pneumonia patients (unpublished).

Although our results are not encouraging in favour of the use of Remdesivir but due to the limitations highlighted above we believe further randomized controlled trials and prospective data on early administration of Remdesivir in COVID-19 pneumonia are needed to provide evidence of effect. Moreover, longer follow up studies on long term outcomes and safety are needed. COVID-19 is currently the biggest healthcare problem and we still do not have enough effective therapies for this disease. Hence, the search for better therapeutic modalities and optimum timing of therapy is important in management of COVID-19 patients.

Conclusion: Remdesivir did not show any mortality benefit among severe COVID-19 patients in our data. Randomized controlled trials are needed to define the effectiveness of the drug early in the course of the disease.

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QS: Conceived, designed, data collection, data analysis, manuscript writing.
SS: Conceived, designed, data collection, manuscript review.
AR: Designed, data collection, data analysis, results writing.
MH, RS & SS : Designed, data collection, manuscript review.

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Original Article

The Effects of live- in rehabilitation on ARV adherence, abstinence from drugs and lifestyle modification in people who inject drugs (PWID) Living with HIV – A clinic review

Aneela Hussain[1], Anum Rahim[2], Anila Sheikh[3], Ahsun Jiwani[4]

ABSTRACT

Background & Objective: HIV/AIDS is mostly seen in people who inject recreational drugs (PWID). Adherence has to be optimum for its treatment to be effective. Compliance to HIV medication has been problematic in PWID making HIV control difficult. Many studies in the past have validated educational activities like rehabilitation programs beneficial in maintaining regularity in medication intake. This brought us to the question of looking at such programs and its effects on our population. This study was conducted to assess the impact of other perspectives of abstinence and adherence including family support and employment status on a person's willingness for treatment continuation and avoidance of drugs.

Methods: A retrospective chart review of 241 PWID was conducted to assess adherence to antiretroviral agents (ARVs) and abstinence from recreational drugs post visit to the rehabilitation center. Associations with family support, marital status, employment, income and back to work status were also assessed.

Results: Adherence to ARVs had significant statistical association with marital status (p=0.025), starting work again (p=0.001), family support (p=0.009), employment status (p=0.009) and monthly income (p=0.025). While family support (p=0.033), employment status (p<0.0001), Going back to work (p<0.0001), mode of travel to Rehabilitation center (p<0.0001) and monthly income (p=0.004) were associated with abstinence from drugs. Duration of rehabilitation or age had no effect on adherence or abstinence in our patient population of PWID.

Conclusion: Family and spousal support and employment promote optimal ARV compliance and should be encouraged when starting ARVs. Enrollment in a long-term complementing educational program would further enhance ARV intake and abstinence.

KEYWORDS: HIV, Rehabilitation, Adherence.

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INTRODUCTION

Human immunodeficiency virus (HIV) infection causes a decrease in immunity, and predisposes to superadded infections and long standing illness.[1] A survey done in the end of 2016, revealed that a population of 36.7 million are living with HIV/AIDS and 2.1 million comprised of those younger than 15 years. Since June 2017, the number of HIV positive people accessing antiretroviral therapy (ART) globally rose up to 20.9 million from 15.8 million in June 2015, 7.5 million in 2010, and less than one million in 2000.[2] In Pakistan as many as 133,000 people are infected with HIV.[3] It is estimated

that people who inject drugs (PWID) are 22 times more likely to acquire HIV than the rest of the population.[2] There are approximately 11.8 million PWID worldwide, and 13.1% of them are thought to be living with HIV.[4] In Pakistan, 105,000 people are drug injectors out of which 37.8% roughly are infected.[5] A high level of adherence around >95% is required for antiretroviral therapy (ART) to be effective.[6,7] Adherence is a patient's ability to follow a treatment plan, take medications at prescribed times and frequencies, and follow restrictions regarding food and other medications.[8] Rehabilitation is any service or activity that can address the health related challenges that people living with HIV (PLHIV) can face, it provides support to lead effective lives in communities. As per WHO, drug adherence counselling programs optimize treatment goals and outcomes,[9] Psychoeducational interventions have been reported during the past year as promoting adherence to antiretroviral agents (ARV). However, a study showed that the effect of the educational intervention was not durable suggesting long-term or repetitive interventions to produce a lasting impact on adherence, lifestyle modification and recreational drug sobriety.[10,11] In Pakistan a study also showed around 55% effects of rehabilitation on adherence in PWID.[12]

This study was conducted to assess the impact of other perspectives of abstinence and adherence including family support and employment status on a person's willingness for treatment continuation and avoidance of drugs.

METHODS

This study is a retrospective medical chart review conducted at the, HIV Clinic of IHHN, which is a tertiary care hospital in Karachi. The study population is a cohort of PWID living with HIV active or previous IV drug use who have been to a rehabilitation unit at the start of the treatment. After approval by the Institutional Review Board (IRD_IRB_2019_05_006), all patients fulfilling the inclusion criteria from 1st October 2016 till 30th September 2018 were included in the study and were followed for adherence to medicines and, abstinence from recreational drugs for almost 1-year post rehabilitation center visit. Demographic variables like marital status, age, mode of travel to the clinic, employment and monthly income were assessed along with abstinence and adherence variables. Adherence to ARV was checked by pill count of remaining ARV by a healthcare provider, pharmacy refills/ pick up and self-reporting by the patient or their caregivers. While, abstinence from recreational drugs was checked by inquiring about it from patients or their attendants. PLHIV (confirmed by WHO approved rapid tests) 15 years and above who were currently injecting drugs or had in the past were included in the study while those not willing to take ARV were excluded.

Statistical Analysis: For adherence and abstinence, age, duration of rehabilitation, duration of IV drug use and back to work were compared using Kruskal Wallis test at less than 3 months, 3 to 6 months, 7 to 10 months and greater than 10 months. For adherence, Pearson's chi square test was applied for work status, Fisher exact for monthly income, financial status, mode of travel, marital status and gender. While likelihood ratios were reported for family support. However, for abstinence, back to work and mode of travel were assessed using Pearson's chi square while gender and marital status were assessed with Fisher exact test. Lastly, likelihood ratios were reported for family support, financial status and monthly income. P value of less than equal to 0.05 was considered significant for all variables.

RESULTS

The data of 241 individuals was included in the analysis. Majority of the patients were males 222 (92.1%). The median age of the study participants was 31 (27-36) years. Almost half of the patients were single 114 (47.7%), followed by married individuals 107 (44.8%). More than half of the study participants did not have any family support 122 (51%) during the period of undergoing therapy, followed by those who had support from their parents 43 (18%). In terms of mode of travelling to antiretroviral therapy center (ARTC), the travelling for almost half of the participants was facilitated by different voluntary NGOs, followed by those who came to the ARTC on their own 84 (35%). The majority of the participants 41 (58.5%) had a monthly income of 10,000-30,000 PKR, followed by those who had a monthly income of >60,000 PKR 54 (22.4%). The median duration spent in rehab was 45 (40-60) days. Similarly, the median duration of IV drug abuse was 1095 (365-2007.5) days.

Adherence to ART: The participants were divided in different groups according to the time they adhered to the ART (i.e., <3 months, 3-6 months, 7-10 months and more than 10 months). Kruskal Wallis test, Pearson chi-square/fisher exact test, and likelihood ratio test was applied as appropriate to assess significant association of the independent variables with the time adhered to ART. Table-I

Table-I: Adherence to ART.

	<3 Months	*3-6 Months - n(%)*	*7-10 Month - n(%)*	*>10 Months - n(%)*	*Total - n(%)*	*P value*
Duration in rehabilitation/ Days^	40	45 (40-60)	60 (40-60)	45(40-60)	45(40-60)	0.739¥
Duration of IV drug use/Days^	1460 (456.3-3467.5)	1460 (365-1825)	1460 (365-2920)	730 (365-1835)	1095 (365-2007.5)	0.063¥
Age/ Years^	32(26-42)	31(26-36)	30.5(26-37.5)	32(27-35)	31(27-36)	0.891¥
Back to work^	2	40(2-60)	60(40-60)	45(40-60)	45 (35-65)	0.14¥
Gender						
Male	10(83.3)a	90(91.8)a	33(91.7)a	89(93.7)a	222(92.1)	0.211€
Female	0a	2(2)a	0	4(4.2)a	6(2.5)	
Transgender/MSM	2(16.7)a	6(6.1)a,b	3(8.3)a,b	2(2.1)b	13(5.4)	
Marital Status						
Single	4(33.3)a	53(54.6)a	17(47.2)a	40(42.6)a	114(47.7)	0.025€
Divorced	0a,b,c	1(1)c	3(8.3)b	1(1.1)a,c	5(2.1)	
Married	6(50)a,b	35(36.1)b	16(44.4)a,b	50(53.2)a	107(44.8)	
Separated	2(16.7)a	8(8.2)a,b	0b	3(3.2)b	13(5.4)	
Work status/Back to work						
Yes	3(27.3)a	45(47.9)a	19(54.3)a	65(73)b	132(57.6)	
0.001Ŧ						
No	8(72.7)a	49(52.1)a	16(45.7)a	24(27)b	97(42.4)	
Mode of travel to the ARTC						
Self	2(18.2)a,b	27(27.6)	10(27.8)b	45(47.4)a	84(35)	<0.0001€
Family	5(45.5)a	4(4.1)b	1(2.8)b	11(11.6)b	21(8.8)	
NGO	4(36.4)a	67(68.4)b	25(69.4)b	39(41.1)a	135(56.3)	
Family Support						0.009 λ
Parents	0a	15(15.3)a	6(16.7)a	22(23.7)a	43(18)	0.009 λ
Siblings	5(41.7)a	13(13.3)b	5(13.9)b	8(8.6)b	31(13)	
Spouse	3(25)a	7(7.1)b	3(8.3)a,b	17(18.3)b	30(12.6)	
Other	1(8.3)a	4(4.1)a	1(2.8)a	7(7.5)a	13(5.4)	
No support	3(25)a	59(60.2)b	21(58.3)b,c	39(41.9)a,c	122(51)	
Employment Status						0.009€
Employed	5(41.7)a,b	50(51)b	18(50)b	66(69.5)a	139(57.7)	0.009€
Unemployed/Not supported lives with family	0a	7(7.1)a	4(11.1)a	3(3.2)a	14(5.8)	
Unemployed supported by family	7(58.3)a	24(24.5)b	11(30.6)a,b	22(23.2)b	64(26.6)	
Street Based	0a,b	17(17.3)b	3(8.3)a,b	4(4.2)a	24(10)	
Social Status (monthly Income)						
<10000	0a	11(11.2)a	4(11.1)a	11(11.6)a	26(10.8)	0.025€
10000-30000	8(66.7)a,b	47(48)b	24(66.7)a,b	62(65.3)a	141(58.5)	
30000-60000	0a	7(7.1)a	2(5.6)a	11(11.6)a	20(8.3)	
>60000	4(33.3)a	33(33.7)a	6(16.7)a,b	11(11.6)b	54(22.4)	

Ŧ Pearson's chi square test, € Fisher Exact Test, λ Likelihood Ratio test, ¥ Kruskul Wallis Test, ^Median(IQR).

shows statistically significant associations between adherences to ART and marital status (p= 0.025), starting work again (p=0.001), mode of travel to ARTC (p= <0.0001), having family support during therapy (p=0.009), employment status of the study participants (p= 0.009) and monthly income (p= 0.025). Adherence to ART for longer time periods was found consistently higher among individuals who were either single or married than those who were either separated or divorced. Furthermore, the individuals who were provided the transportation facility by the NGOs were found to adhere to ART for longer duration. Moreover, long term adherence was found among those individuals who

had a monthly income of 10,000 PKR-30,000PKR. Statistically significant associations were not found between adherence to ART and gender, age, duration in rehabilitation, duration of IV drug use, and going back to work.

Abstinence from Drugs: For the analysis of second objective i.e. abstinence from drugs, the participants were divided in different groups according to the time they abstained from IV drugs (i.e. <3 months, 3-6 months, 7-10 months and more than 10 months). Kruskal Wallis test, Pearson chi-square/fisher exact test, and likelihood ratio test was applied as appropriate to assess significant association of the independent variables with the time the participants adhered from drugs. Table-II shows significant associations between abstinence from IV and recreational drugs and having family support during therapy (p=0.03), Mode of travel to ARTC

Table-II: Abstinence from drugs.

	<3 Months - n(%)	*3-6 Months - n(%)*	*7-10 Month - n(%)*	*>10 Months - n(%)*	*Total - n(%)*	*P-value*
Duration in rehabilitation/ Days^	45(38.5-60)	60(40-60)	52(40-60)	40(40-60)	45(40-60)	0.195¥
Duration of IV drug abuse/Days^	912 (60-2555)	1277 (365-1825)	1460 (730-2920)	912.5 (265-2281.25)	1095 (365-2007.5)	0.801¥
Age/ Years^	29(27.25-32.75)	32(27-35)	31(27-39.75)	31(26-35)	31(27-36)	0.079¥
Back to work^	40(15.5-56.25)	60(40-60)	60(40-60)	45(40-60)	45 (35-65)	0.065¥
Gender						
Male	36(97.3)a	102(99.0)a	37(97.4)a	32(100)a	207(98.6)	0.514€
Transgender/MSM	1(2.7)a	1(1.0)a	1(2.5)a	0	3(1.4)	
Marital Status						
Single	19(52.8)a	54(52.4)a	13(34.2)a	13(40.6)a	99(47.4)	0.357€
Divorced	0	4(3.9)a	2(5.3)a	0	6(2.9)	
Married	14(38.9)a,b	40(38.8)b	22(57.9)a	17(53.1)a,b	93(44.5)	
Separated	3(8.3)a	5(4.9)a	1(2.6)a	2(6.3)a	11(5.3)	
Work status/Back to work						
Yes	15(42.9)a	48(46.6)a	24(66.7)b	29(93.5)c	116(56.6)	<0.0001ϒ
No	20(57.1)a	55(53.4)a	12(33.3)b	2(6.5)c	89(43.4)	
Mode of travel to the ARTC						
Self	9(24.3)a	24(23.3)a	11(28.9)a	21(65.6)b	65(31.0)	<0.0001ϒ
Family	5(13.5)a	7(6.8)a	4(10.5)a	4(12.5)a	20(9.5)	
NGO	23(62.2)a	72(69.9)a	23(60.5)a	7(21.9)b	125(59.5)	
Family Support						
Parents	8(21.6)a	21(20.4)a	7(19.4)a	6(18.8)a	42(20.2)	0.033 λ
Siblings	9(24.3)a	10(9.7)b	2(5.6)b	5(15.6)a,b	26(12.5)	
Spouse	4(10.8)a	9(8.7)a	4(11.1)a	6(18.8)a	23(11.1)	
Other	1(2.7)a,b	1(1.0)b	4(11.1)a	4(12.5)a	10(4.8)	
No support	15(40.5)a	62(60.2)b	19(52.8)a,b	11(34.4)a	107(51.4)	
Employment Status						
Employed	20(54.1)a,b	46(44.7)b	25(65.8)a	28(87.5)c	119(56.7)	<0.0001 λ
Unemployed/Not supported lives with family	1(2.7)a	9(8.7)a	0a	2a	12(5.7)	
Unemployed supported by family	12(35.1)a	29(28.2)a	11(28.9)a	2(6.3)b	55(26.2)	
Street Based	3(8.1)a,b	19(18.4)b	2(5.3)a,b	0a	24(11.4)	
Social Status (monthly Income)						
<10000	5(13.5)a	13(12.6)a	6(15.8)a	1(3.1)a	25(11.9)	0.004 λ
10000-30000	21(56.8)a,b	53(51.5)b	25(65.8)a,b	23(71.9)a	122(58.1)	
30000-60000	1(2.7)a	6(5.8)a	4(10.5)a,b	6(18.8)b	17(8.1)	
>60000	10(27)a	31(30.1)a	3(7.9)b	2(6.3)b	46(21.9)	

ϒ Pearson's chi square test, € Fisher Exact Test, λ Likelihood Ratio test, ¥ Kruskul Wallis Test, ^Median(IQR).

(p=<0.0001), employment status (p=<0.0001), and monthly income (p=0.004). Individuals who received transport to ARTC via NGOs were more likely to have longer duration of drug abstinence. Abstinence from drugs was found consistently higher among individuals who had family support. Similarly, abstinence was found consistently higher among employed individuals compared to those who were unemployed or street based. Furthermore, longer abstinence duration was found among those individuals who had a monthly income of 10,000 PKR-30,000 PKR. Statistically significant associations were not found between abstinence from drugs and gender, age, duration of rehab, duration of IV drug use and marital status.

DISCUSSION

According to this study, most of our study population belonged to the younger age group, with the ratio of single to married almost similar, with a low income, and lesser number had family support. According to our findings marital status, employment status, family support system and a reasonable income were the main reasons for adherence to ARV. Highest adherence to ARVs has been at >10 months of follow up (73%) in PWID who have rejoined their respective occupations. At 3 to 10 months of follow up we noticed adherence of > 65% ,similar to a meta-analysis ,done in low and high income countries, which showed a healthy association with employment.[13] Furthermore, ARV adherence at > 10 months of follow up was actually very good (65.3%) among those employed and had an income of 10,000 - 30,000 PKR (which is middle income group). Interestingly in our study , those without any social support have been adherent to their medications much more (60%) at 3 to 10 months of follow up which is contrary to many studies which showcase social support as a big factor for adherence.[14,15] Regularity with ARVs has been more amongst married people (53%) when followed up for more than 10 months. We also saw a positive relationship between marriage and adherence at less than three months of follow up (50%). A further elaboration on this would be the quality of the relationship as a study done by Johnson et al emphasized a harmonious commitment to fare well in the level of adherence as well as virological suppression.[16]

When it comes to abstinence from drugs, similar results were found in the middle income group (71.9%). Those abstinent from drugs > 10 months had a positive association with self-transport (65%) which probably shows their commitment to getting well. Those who went back to work also were abstinent from drugs (93.5%) which makes going back to work a major factor to stay off recreational drugs, similarly those who were employed were also more inclined towards drug abstinence (87.5%). Most people with no social support were abstinent for 3 to 10 months only which dipped after that duration in our cohort which may show a need for family support to prevent relapsing. In addition, abstinence from recreational drugs was related favorably with job status, family support, a good income and clinic visit support. Unlike other studies, abstinence had no significant association with being married in our study.[17]

This negates our initial hypothesis that getting patient rehabilitated in a rehabilitation center is beneficial for adherence to ARVs and establishes abstinence to recreational drugs. Prior studies on the same subject synchronized with our findings that the effect of isolated educational interventions was not durable, suggesting that long-term or repetitive interventions may be required to produce a lasting impact on adherence and lifestyle modification as well as abstinence from drugs.[11] Goujard et al. resonated with our findings of a reasonable income leading to better adherence in HIV treatment, however their findings of an educational system leading to good medication adherence were in contrast to our[18] findings (which were of short-term 4 to 8 weeks of rehabilitation and education), and suggests that long term and repetitive rehabilitation and educational interventions are needed for sustained adherence. ARV adherence is casual if the person is homeless and without family support as suggested by our study in sync with a Canadian study.[19] Alcohol use and depression have been found to be a cause of lax attitude towards ART.[20] High pill burden and dosing frequency are also well studied factors for non-adherence[21] which our study was not looking into.

Limitations of the study: We did not look at the quality of the marital life, depression and anxiety, other medical conditions along with HIV and education level of the PWID which may also impact adherence to ARV and abstinence to drugs. Another aspect which needs to be looked at is why most of our PWID are men and not women which our study fails to delineate. The strength of the study lies in exploring associations of various factors apart from rehabilitation only, which gives us an outlook on other aspects which may affect both adherence and abstinence.

CONCLUSION

Our study concludes that for sustained ARV adherence rehabilitation programs and educational interventions must take place at regular intervals throughout the life of the patient. Furthermore, at each clinic visit family support system must be encouraged and revisited throughout therapy. Also efforts must be taken to encourage employment when starting treatment. However more research is needed to understand how long educational and rehabilitation programs should continue and whether it should be clinic/ organization based or community based, one on one or group sessions and how frequently to assess for psychological ailments.

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Authors Contribution:

AH: conception of the idea, designing the study, literature search, data compilation, write up and reviewing the article and responsible for the accuracy and integrity of this manuscript.
AR: data analysis, reviewing the article, write up
AS: data collection, compilation, data cleaning and management, reviewing the article
AJ: data Analysis, reviewing the article.

Open Access

Review Article

Rapidly progressive glomerulonephritis in children

Khemchand N Moorani[1], Madiha Aziz[2], Farhana Amanullah[3]

SUMMARY

Rapidly progressive glomerulonephritis (RPGN), characterized by a rapid development of nephritis with loss of kidney function in days or weeks, is typically associated histologically, with crescents in most glomeruli; and is a challenging problem, particularly in low resource settings. RPGN is a diagnostic and therapeutic emergency requiring prompt evaluation and treatment to prevent poor outcomes. Histopathologically, RPGN consists of four major categories, anti-glomerular basement membrane (GBM) disease, immune complex mediated, pauci-immune disorders and idiopathic /overlap disorders. Clinical manifestations include gross hematuria, proteinuria, oliguria, hypertension and edema. Diagnostic evaluation, including renal function tests, electrolytes, urinalysis/microscopy and serology including (anti GBM antibody, antineutrophil cytoplasmic antibody (ANCA)) starts simultaneously with management. An urgent renal biopsy is required to allow specific pathologic diagnosis as well as to assess disease activity and chronicity to guide specific treatment.

The current guidelines for management of pediatric RPGN are adopted from adult experience and consist of induction and maintenance therapy. Aggressive combination immunosuppression has markedly improved outcomes, however, nephrotic syndrome, severe acute kidney injury requiring dialysis, presence of fibrous crescents and chronicity are predictors of poor renal survival. RPGN associated post infectious glomerulonephritis (PIGN) usually has good prognosis in children without immunosuppression whereas immune-complex-mediated GN and lupus nephritis (LN) are associated with poor prognosis with development of end stage kidney disease (ESKD) in more than 50% and 30% respectively.

Given the need for prompt diagnosis and urgent treatment to avoid devastating outcomes, we conducted a review of the latest evidence in RPGN management to help formulate clinical practice guidance for children in our setting.

Information sources and search strategy: The search strategy was performed in the digital databases of PubMed, Cochrane Library, google scholar, from their inception dates to December 2020. Three investigators independently performed a systematic search using the following search terms "Rapidly progressive glomerulonephritis" "children" "crescentic glomerulonephritis" "management" at the same time, backtracking search for references of related literature.

KEYWORDS: RPGN, Acute glomerulonephritis, Crescentic GN, Acute kidney injury, Immunosuppressive therapy.

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BACKGROUND

RPGN without prompt optimal management is a setup for morbidity and mortality.[1] Different pathologic mechanisms can lead to crescent formation, inflammation and scarring and present as RPGN (also known as crescentic GN or cGN). When more than half the glomeruli

are involved it leads to acute kidney injury (AKI) with more than 50% loss of renal function within a few days to weeks.[2] The clinical severity varies from AKI to advanced uremia depending upon degree of glomerular involvement with crescents.[1]

EPIDEMIOLOGY

The true incidence of RPGN is unknown due to its variable definitions and multiple underlying etiologies. The estimated incidence of RPGN is seven cases per million annually in the United States. It constitutes 3.2% and 5.5% of renal biopsies in adults from Saudi Arabia and India respectively.[3,4] A study conducted at a major kidney diseases Institute in Karachi found that 46% (29/63) children with mesangiocapillary GN on biopsy presented with RPGN, indicating immune mediated GN as an important cause of RPGN in our setting. More than half the children with RPGN had poor outcomes despite treatment.[5] It is important to understand thatcrescentric glomerulonephritis (cGN) is a pattern that can occur in a variety of glomerular diseases.[6] A recent study that analyzed biopsies of 60 children with RPGN/cGN found immune complex GN in 75%, ANCA-associated pauci-immune GN in 17% and anti-glomerular basement-membrane GN in 2%. The same study found that cGN was detected in 7.5% (61/808) renal biopsies performed in children at their center.[6] In children most RPGN is seen in the setting of immune complex (IC) mediated GN (PSGN, SLE, IgA, HSP).[7,8] An Indian study showed a higher prevalence of pauci immune (PI) mediated RPGN compared to IC (71.7% vs 28.3%)[9] raising the concern that PI is also an important cause of RPGN in children.[10]

ETIOLOGY OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

The most appropriate classification of RPGN is based on histopathology and on the presence, localization, and characteristics of immune deposits on immunofluorescence (IF) staining and is divided into three major categories; Type-I: Linear antibody (IgG) deposition disorders: Anti-glomerular basement membrane (GBM) disease, Type-II: GN caused by deposition of immune complexes (i.e., in IgA nephropathy (IgAN), lupus nephritis (LN), PIGN, Henoch Schonlein Purpura nephritis (HSPN)) and Type-III: Pauci-immune GN (caused by ANCA vasculitis). Etiologies underlying RPGN are further listed in Table-I.

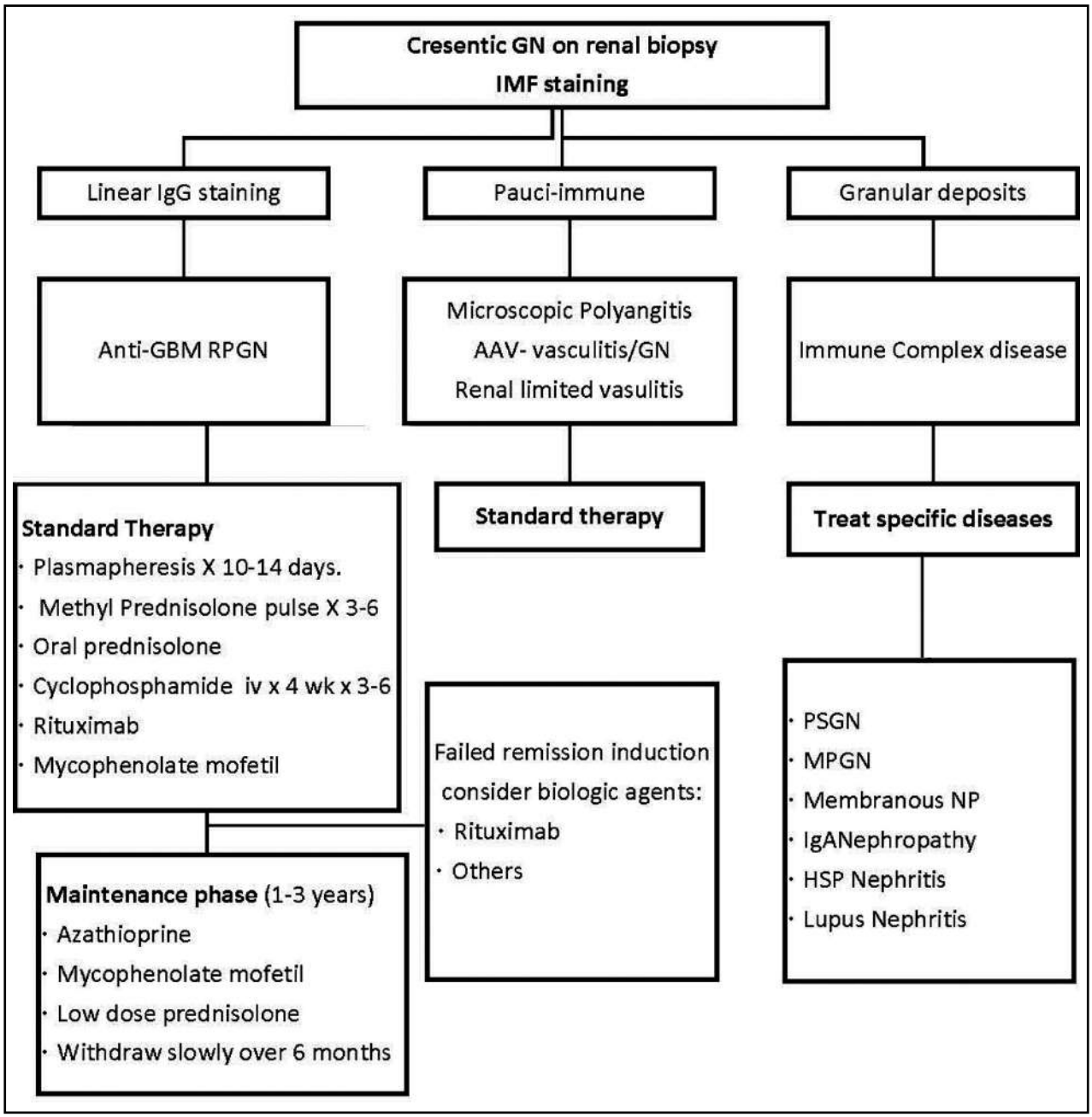
PATHOGENESIS OF CRESCENTIC GLOMERULONEPHRITIS

Crescent formation represents a nonspecific response to severe injury to the glomerular capillary wall. There are three stages of crescent formation (Fig.1). During the first stage, there is induction of gaps or rents in the glomerular capillary wall and GBM by macrophages and T-cells. This is followed by movement of plasma proteins (fibrinogen) and inflammatory cells which release interleukin-1 (IL1) and tumor necrosis factor alfa (TNF alfa)

Table-I: Etiology of RPGN (Crescentic GN) in Children.

Anti-GBM linear (IgG deposits) GN
Anti-GBM Nephritis
Goodpasture Syndrome
Post renal transplantation in Alport's Syndrome
Immune complex (granular deposits 80%) GN
Post infectious GN
Post streptococcal GN
Infective endocarditis
Shunt nephritis
Staph aureus sepsis
Other infections: HIV, Hepatitis B and C
Systemic disease
SLE nephritis
HSP nephritis
Mixed connective tissue disorder
Primary GN
IgA nephropathy, MPGN, membranous nephropathy, C1q nephropathy
Pauci-immune (negative IF or few deposits) GN
Microscopic polyangitis
Granulomatosis with polyangitis (Wegener's granulomatosis)
Renal limited vasculitis
Eosinophilic granulomatosis with polyangitis (Churg-Strauss disease)
Idiopathic crescentic GN
Medications: penicillamine, hydralazine
Post-renal transplant (recurrence)
IgAN, HSP, MPGN, SLE
RPGN like clinical picture but without crescents
Hemolytic uremic syndrome, acute interstitial nephritis, diffuse proliferative GN

Adapted from: Peadiatric kidney Disease - Chapter on RPGN 2016.



Algorithm-1: Treatment of Crescentic /Rapidly Progressive Glomerulonephritis.

and pro-coagulant factors into the bowman's space.[11,12] Crescents are the final common pathway of severe inflammatory glomerular disease. These include immune complex disease (like LN, IgA nephropathy, post infectious GN (PIGN)) as well as anti-GBM or ANCA related disorders.

The second stage is of active proliferative inflammation resulting in the development of cellular, fibrocellular and then fibrous crescents with the passage of time. Fibroblast growth factors promote fibroblast proliferation and collagen deposition. Transforming growth factor-beta may also play an important role. Apart from macrophages and T-cells, parietal and visceral epithelial cells also contribute in active crescent formation. This final fibrous stage is unlikely to respond to immunosuppressive therapy and has a high risk of ESKD.[1,13,14]

Types of Crescentic Glomerulonephritis: Three mechanisms of glomerular injury are known that

can result in activation of podocytes and epithelial proliferation to form crescents.

***Type-I*: Anti-GBM (Goodpasture syndrome)**-constitutes circulating antibodies IgG directed against the non-collagenous domain of alpha-3 chain of type IV collagen, present in the GBM and/or alveolar basement membrane. It accounts for 10%-15% of all diffuse crescentic GN and may present as GN alone or in combination with pulmonary hemorrhage (Goodpasture syndrome) and as ANCA associated "dual antibody disease".[14] Reported pediatric cases are very rare (n=31) with a higher prevalence in girls (M/F ratio 1:4).[15]

***Type-II*: Immune complex mediated injury**-Multiple stimuli lead to crescentic proliferative GN including infections, systemic diseases, and preexisting primary GN. In most cases the serology and histology help diagnose the underlying disease, such as, presence of IgA deposits on IF in IgA nephropathy, antistreptococcal antibody positivity and sub epithelial deposits in PIGN, antinuclear antibodies (ANA) positivity and a "full house" (IgG, IgA, IgM, C3 and C1q) positivity on IF in LN. IC mediated RPGN is the most common and severe form, particularly in children with PIGN, IgA nephropathy/vasculitis and LN.[14]

***Type-III:* Pauci-immune necrotizing and crescentic GN**: is characterized by few or no immune deposits on immunofluorescence and is usually associated with systemic vasculitis. ANCA associated vasculitis (AAV) is characterized by the destruction of small and medium-sized arterial vessels, in the presence of circulating autoantibodies toward the cytoplasmic region of the neutrophil (ANCA) predominantly against proteinase-3 (PR3) and myeloperoxidase (MPO). AAV includes granulomatosis with polyangitis (GPA), microscopic polyangitis (MPA) and eosinophilic granulomatosis with polyangitis (EGPA) and renal-limited vasculitis and drugs-associated ANCA positive GN. In AAV, these circulating autoantibodies (against PR3 or MPO) are found in 80-90% and are presumably produced in response to either respiratory infections or environmental factors. ANCAs induce activation of neutrophils resulting in release of inflammatory cytokines, reactive oxygen species and lytic enzymes and also initiate formation of neutrophil extracellular traps (NETs). These NETs along with inflammatory cytokines cause vasculitis affecting the respiratory tract and kidneys. ANCA positivity varies according to type of vasculitis, GPA usually shows anti-PR3 ANCA in 60–80% and produce a cytoplasmic pattern (c-ANCA). MPA, renal limited vasculitis and drug induced crescentic GN may show anti-MPO ANCA in 80–90% and produce perinuclear staining (p-ANCA). EGPA may also show anti-MPO ANCA in 35–40% of cases. Patients with MPA may have both types of ANCA. Ten percent of patients with GPA or MPA may have ANCA-negative GN limited to the kidneys and are taken under this spectrum with similar clinical features, biopsy findings and prognosis.[13,14]

The histological classification: focal (50% normal glomeruli), crescentic (>50% cellular crescents), sclerotic (>50% sclerotic glomeruli) and mixed (any other combination) has significant prognostic value. Validation studies have confirmed the predictive value of this system in adults and in children.[16] In the pediatric study, the probability of having an estimated GFR of >60 ml/min/1.73 m2 at 2 years was 100% in the focal group, 56% in the crescentic/mixed group, and 0% in the sclerotic group. Most children present in adolescence with a female preponderance. In the setting of an inflammatory insult, PR-3 and MPO are translocated to the cell surface of neutrophils and monocytes where they interact with ANCA and stimulate neutrophils to undergo a respiratory burst and release their primary granule contents leading to tissue inflammation and endothelial damage.[17]

CLINICAL MANIFESTATIONS OF RPGN

A nationwide RPGN survey from Japan showed that in children 0-18 years of age clinical manifestations included, proteinuria (60-72%) hematuria (68-83%) renal failure (average eGFR 41±34 ml/min/1.73m^2) lung involvement (16%).[18] RPGN in older children may present more commonly with complications like hypertensive emergencies, volume overload, pulmonary edema and cardiac failure.[14]

There may be features of underlying systemic diseases with skin (vasculitic rash), joint (arthritis), nervous system (convulsions and altered sensorium) and upper airway (sinusitis, septal perforation) /pulmonary involvement (hemoptysis and pulmonary hemorrhage).[11,14,19]

Anti-GBM RPGN is rare in children. Clinical manifestations may follow upper respiratory infection, with nonspecific symptoms or severe renal and pulmonary manifestations.

Renal involvement is a severe manifestation in ANCA associated RPGN (GPA, MPA), and

can present as slowly progressive GN or AKI and often leads to ESKD, causing significant morbidity and mortality. MPA may present with isolated renal-limited form or overlap with polyarteritis nodosa, which may result in multi-organ involvement including renal, pulmonary, mesenteric, coronary artery and central nervous system. Renal involvement is seen in 94–100% of patients at onset of MPA and 50-100% in GPA but not in EGPA.[14,19]

LABORATORY EVALUATION IN A CHILD WITH RPGN

All patients suspected with RPGN need investigations including serology and urgent biopsy.

- Urinalysis especially microscopy will show microscopic hematuria, RBC casts
- Renal function- always impaired in varying proportion.
- Serum electrolytes may be abnormal depending upon degree of AKI.
- Complete Blood Counts -anemia, neutrophilia and thrombocytosis are common.
- C-reactive protein (CRP)
- Spot urine protein to creatinine ratio may be elevated to nephrotic range (>3)
- Serologies-Anti-streptolysin O titer (ASOT)/anti-DNAase B (poststreptococcal glomerulonephritis), hepatitis B- virus surface antigen (HBsAg) and anti-HCV antibody
- Complement- C3, C4 (normal in Pauci-immune, anti-GBM disease and IgAN, low in PIGN (C3), lupus nephritis (C3, C4), CH50, anti-nuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-ds DNA) for lupus, serum IgA levels for IgAN, anti-GBM IgG antibodies, ANCA levels. ANCA screening is done by indirect immunofluorescence (IF) and ELISA for PR3 ANCA as first step and later IF for MPO.
- Radio-imaging: Chest X-Ray PA view, Echocardiography, Ultrasound kidneys and CT scan as indicated.
- Renal Biopsy: to confirm etiology (crescents in >50% of glomeruli), to identify underlying cause on IF to help classify patients into IC, PI and anti-GBM mediated RPGN (Table-II), to assess the degree of renal damage (percentage of glomeruli with crescents, type of crescents

Table-II: Clinical and Laboratory Features of Common Causes of RPGN.

Cause	*Typical features*	*Serology*	*Complement*	*Biopsy*	*Outcome*
Poststreptococcal glomerulonephritis	Sore throat/impetigo, gross hematuria, edema, oliguria, HTN	ASO, anti-DNase B antibodies	Low C3, normal C4	Granular immune deposits	Recovery in 2 weeks. No relapse
Lupus nephritis (diffuse proliferative, class IV)	SLE, gross hematuria, proteinuria, HTN	ANA, anti–ds-DNA	Low C3, low C4	Granular immune deposits	Prolonged course, Relapses & remission. Mortality and ESKD
IgA disease	Persistent /episodic gross hematuria, proteinuria, HTN	Negative	Normal	Granular immune deposits	Varies with biopsy findings
Anti–GBM disease	Macroscopic hematuria and hemoptysis, acute kidney injury	Anti–GBM antibodies	Normal or increased	Linear staining for IgG and C3	With PLEX better outcome, No relapses high mortality if lung involvement.
AAV Microscopic polyangiitis Granulomatosis with polyangiitis (Wegener)	Non-specific, upper airway obstruction, arthralgia; hemoptysis, purpura, polyarthritis nodosa	p-ANCA c-ANCA	Normal or increased	Few/pauci-immune	Relapses may occur but less in MPA compared to Wegener, need long term follow up and immunosuppressive therapy

HTN-hypertension, ASO-anti-streptolysin O, ANA-antinuclear antibodies, anti–dsDNA-anti–double-stranded DNA, P-ANCA-perinuclear antineutrophil cytoplasmic antibodies, C-ANCA- cytoplasmic ANCA, SLE-systemic lupus erythromatosus, ESKD-end stage renal disease, PLEX-plasma exchange. ***Adapted from:*** Critical Care Nephrology, Chapter 47 2017.

(cellular, fibrocellular and fibrous) to predict the reversibility of renal damage (activity and chronicity index, active proliferative with cellular crescent).[6,13]

- Genetic studies for idiopathic or primary MPGN, atypical HUS and should be done where facilities are available.

MANAGEMENT OF CHILDREN WITH RPGN

A) Supportive Care:

All children with RPGN require strict monitoring for complications of AKI, respiratory support and underlying systemic disease management in the intensive care unit. Control of hypertension, dialysis for uremia to stabilize renal function along with electrolyte abnormalities, correction of anemia, treatment of intercurrent infection and care of nutrition are essential measures for any sick child with RPGN. Use of antiplatelet agents to prevent thrombotic complications associated with systemic vasculitis, prophylaxis for osteoporosis and gastric protection may be necessary in long term management. Decision for dialysis and renal biopsy as well as initiation of aggressive immunosuppressive therapy should be done on a priority basis.[6,13]

B) Specific Treatment: (Algorithm 1)

Untreated, RPGN typically progresses to ESKD over a period of days, weeks or a few months. Patients with fewer crescents may have a slower more protracted course. Treatment regimens and management strategies have been extrapolated from adult studies due to limited experience in children.[19,20] The European League against Rheumatism and European Renal Association-European Dialysis and Transplant association (EULAR-ERA EDTA) recommendations and the SHARE project findings suggest intravenous high dose steroids and cyclophosphamide (CYC) for 3–6 months as first-line therapy in children.[19,20] Rituximab (RTX) is an alternative for children with refractory or relapsing disease.[19,20] Mycophenolate mofetil (MMF) has also been used as induction therapy. Plasma exchange is an optional treatment in rapidly progressive renal failure or when alveolar hemorrhage is present.[20,21] Given high risk of severe infection, infertility and secondary malignancy risk with CYC, alternative agents like MMF, or RTX and biological agents are being evaluated.

INDUCTION OF REMISSION

a) Standard Approach

A combination of high dose glucocorticoids and either CYC or RTX and therapeutic plasma exchange are included in the initial treatment for remission induction.[14,20]

Glucocorticoids remain a cornerstone in remission induction and maintenance. The optimal dose, route, and duration of glucocorticoids remains uncertain. The common regimen used includes IV pulses of methylprednisolone (MP 15–30 mg/kg, maximum 1 g/day) for 3–6 days, followed by high-dose oral prednisone (1.5–2 mg/kg daily) for 4 weeks, with tapering to 0.5 mg/kg daily by three months and alternate day prednisone for 6–12 months.[1]

Cyclophosphamide (CYC) is an alkylating agent that causes broad immunosuppression and has been used widely for RPGN. Despite good response rates, the risk of relapse and toxicity has led to multiple studies comparing oral daily with IV pulse cyclophosphamide.

CYCLOPS an open label multicenter randomized controlled trial (RCT) in ANCA-associated vasculitis showed that IV CYC was non-inferior to oral CYC with respect to time to remission over 18 months and was associated with lower cumulative dose but higher relapse rates (50% higher than oral on follow up study).[21,22] Oral dose of CYC varies from 2–3 mg/kg/day for 8– 12 weeks, with a maximum 150 mg/kg cumulative dosage and intravenously 500–750 mg/m^2 mg/dose every two weeks with total 6 doses. The dose should be adjusted to maintain a leukocyte count of 3000–4000/cu mm or an absolute neutrophil count of $\geq$ 1500.[14,19,23]

Rituximab (RTX) is a B-cell depleting anti CD20 monoclonal antibody found effective in induction of remission usually in cases of AAV with active crescents. RTX is preferred over CYC as first line remission induction therapy for patients in whom CYC is contraindicated or presents a risk of infertility.[22] It appears to be a more promising therapy for AAV.[22-24] The Rituximab in AAV (RAVE) trial (197 patients) compared rituximab with standard CYC and RITUXIVAS study (44 patients) compared addition of RTX in standard regimen (MP pulse, CYC) with standard regimen and found that RTX was as effective as CYC for induction of remission in newly diagnosed cases of AAV and appeared to be superior in patients with relapsing disease.[22] High cost, availability of monitoring (CD19 levels) and relative risk of

infections given prolonged immunosuppression are limiting factors for RTX use and CYC remains a cornerstone of therapy for many developing countries including Pakistan. RTX has been used as 375 mg/m^2/week for 4 weeks with target being CD19 counts of less than 1%.[25]

Methotrexate (MTX) and MMF have also been studied for induction of remission. The trials NORAM and MYCYC showed that MTX and MMF may be used to induce remission in selected cases in whom conventional therapies have failed or are contraindicated and are at lower risk of relapse.[19,21]

Plasmapheresis (PLEX) has been used for the treatment of crescentic RPGN with variable success. The rationale of using PLEX is the rapid removal of antibodies which are involved in pathogenesis and to decrease the severity of vascular injury and end-organ damage. Therapeutic plasmapheresis is recommended for patients with pauci-immune crescentic GN, anti-GBM GN, and life-threatening pulmonary hemorrhage, and it might be beneficial for patients with refractory immune complex RPGN (due to SLE or severe proliferative GN).[20,21,26] Intensive plasma exchanges for two weeks has been recommended for children with pulmonary hemorrhage requiring dialysis or with unsatisfactory response to induction treatment.

PLEX in AAV: The MEPEX trial showed reduced mortality and improved renal function in the PLEX arm (compared to IV MP and CYC) earlier on, however at four years there was no difference in ESKD and death.[27] The PEXIVAS study reported that PLEX does not reduce the risk of ESKD or death in patients with severe AAV.[28] The current evidence from PEXIVAS, MEPEX and other case series does not suggest a beneficial role of PLEX long term over standard of care in AAV. PLEX also incurs high cost and resources.

PLEX in Anti -GBM disease: Is the initial treatment of choice to remove circulating antibodies. Followed by immunosuppressive therapy with high dose MP and CYC or RTX to reduce antibody production.[27] KDIGO guidelines for GN recommend PLEX with 60 ml/kg volume replacement daily in anti-GBM disease for 14 days or until anti-GBM antibodies are undetectable.[29] Anti-GBM disease does not usually have a relapsing course. long-term maintenance therapy is not required however low dose prednisone, azathioprine (AZA), or MMF may be used as needed. Postponing transplantation for at least six months after antibodies have become undetectable reduces the recurrence rate significantly and is the accepted guideline. [30]

MAINTENANCE OF REMISSION

The maintenance therapy for RPGN based on consensus recommendation are low dose oral prednisolone, AZA, MTX, MMF and more recently RTX.[20,21]

AAV: In the maintenance phase, a combination of low-dose steroids and AZA, RTX or MMF can be used for an undefined follow-up period. The vast majority of patients with AAV will achieve remission with induction therapy, but about a third of them will relapse by 18 months and another third will remain in relapse-free remission for more than a decade.[19,21]

CYCAZAREM (CYC versus AZA for Early Remission phase of vasculitis) trial found no difference in relapse rates at 18 months.[31] The IMPROVE trial (International MMF Protocol to Reduce Outbreaks of Vasculitides) found AZA to be superior to MMF for maintenance of remission.[32] RTX has been increasingly used as maintenance therapy in AAV and is considered a safe and effective alternative to AZA.[21] MAINRITSAN (Maintenance of Remission using Rituximab in Systemic ANCA-associated Vasculitis) showed sustained remission at month 28 with RTX compared to AZA.[33]

Duration of maintenance therapy (prednisolone and AZA) is usually for 18–24 months and may be withdrawn slowly over 6 months if patient has maintained remission for 12 months.[34] This duration of therapy may be extended to 3–5 years in patients with either relapses or elevated ANCA titers.[1]

TREATMENT OF FAILED INDUCTION

With adequate therapy, remission can be achieved in 60% of patients.[35] Failure of induction of remission require more aggressive therapeutic agents depending upon which protocol already used, availability of resources and expertise. Multiple agents like MMF, MTX, RTX, PLEX, TNF alfa receptor blocker (etanercept), TNF monoclonal antibody (infliximab), cytotoxic T lymphocyte associated antigen 4 (CTLA-4) IgG (abatacept), human anti-CD52 monoclonal antibody (alemtuzumab), anti-IL-6 receptor human monoclonal antibody (tocilizumab), and anti-IL-5 human monoclonal antibody (mepolizumab) have been used with promising results in adults and children.[19,21,22]

TREATMENT OF RELAPSING DISEASE

Relapse is defined as either a rapid rise in serum creatinine along with active urinary sediments and or glomerular crescents on follow-up renal biopsy. In addition, manifestation of new extra-renal symptoms or worsening of existing symptoms may occur in relapsing AAV. Treatment is to increase the dose of corticosteroids and a change in disease-modifying agent, after excluding non-compliance. Second or third-line therapeutic agents for induction and/or maintenance like MMF, MTX, anti-TNF agents, RTX or tocilizumab should be considered.[36]

OUTCOME OF RPGN

The outcome is determined by the severity of renal failure at presentation, promptness of intervention and the underlying renal pathology. Overall long term prognosis has improved with aggressive combination immunosuppressive therapy. Majority (60-70%) show normal renal functions[1]. However, it depends on multiple factors and poor prognostic factors include nephrotic syndrome, AKI requiring dialysis, large fibrous crescents, and a high chronicity index.[31,35]

Most children with RPGN from PIGN have an excellent prognosis without any specific treatment and >90% regain normal renal function at short-term follow-up with a risk of CKD up to 31% in developing countries.[35] The worst renal prognosis is seen with IC mediated GN and LN with ESKD at 54% and 29% respectively. Renal outcomes in patients with RPGN with >80% crescents, tubular atrophy and interstitial fibrosis are poor with >50% risk of ESKD.[37] The mortality rate in Goodpasture's is about 30% mainly due to severe pulmonary hemorrhage. Pediatric AAV is associated with a high relapse rate, longer maintenance therapy and significant organ damage. Identifying optimal strategies that balance the adverse events and cost of maintenance therapy with active disease morbidity and treatment are critical areas of research. The development of novel agents and optimization of existing therapeutics are evolving research areas in all types of vasculitis. Several agents targeting different components of immune /complement mediated or genetic GN are under investigation and may change the paradigm of future management of RPGN.

CONCLUSION

RPGN that presents with gross hematuria, oliguria, hypertension, edema and AKI, though uncommon in children, is a management challenge and is limited to tertiary nephrology centers. Timely referral, diagnosis and urgent treatment are essential for optimal renal outcome. In our health set up, high dose methyl prednisolone and cyclophosphamide pulses are the initial therapy followed by low dose prednisolone and azathioprine or mycophenolate mofetil as maintenance therapy. Rituximab and plasmapheresis may be used in select cases. Long-term follow-up and monitoring for relapses, adverse events, renal function, hypertension, infections and growth is recommended for all children.

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Case Report

Congenital Pouch Colon in a Neonate

Sana Niaz[1], Sahira Naz[2], Rumaissa Abdul Raziq[3]

ABSTRACT

Congenital Pouch Colon (CPC) is a rare anorectal malformation (ARM) in which a part of or the entire colon is replaced by pouch-like dilatation. Males are more likely to be diagnosed with the condition compared to females. The highest incidence of the disease is in South Asia, with a significant number of cases reported from India. Early diagnosis can be made when there are hypoechogenic lesions on antenatal ultrasound scans. We report a case of a neonate with routine antenatal scans who presented with a distended abdomen and inability to pass feces. The diagnosis was made in the early neonatal period, followed by surgical management.

KEYWORDS: Congenital pouch colon, Anorectal malformation, Pouch colon syndrome, Invertogram .

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INTRODUCTION

Congenital Pouch Colon (CPC), also known as short colon syndrome, is a rare anorectal malformation predominantly seen in people from Northern India, with a reported incidence of 5-10%.[1] The condition occurs predominantly in males with a ratio varying from 2.25:1 to 7:1.[2,3] B Mirza conducted a retrospective study with a sample of 21 children. The study aimed to decipher the incidence of CPC anorectal malformation in Pakistan. Out of 21, 18 were suffering from CPC with high ARM and three with low ARM. The study reported an incidence of 6.73%.[4]

In CPC, part or whole of the colon is replaced by a dilated pouch which communicates via a fistula with the genitourinary tract.[1] It is classified into five types depending on the length of colonic involvement (Table-I). Associated genitourinary anomalies may accompany and include hydronephrosis, hydroureteronephrosis, renal agenesis, vesicoureteral reflux, cryptorchidism, and hypospadias. Other conditions may also co-exist like congenital heart disease, sacral agenesis, Meckel's diverticulum, and colon duplication.[4] Treatment involves surgical management which in turn depends on the length of colonic involvement and type of CPC. Here we report a case of a 2-day-old male child with type-1 congenital colonic pouch.

CASE REPORT

A 2-day-old male infant was brought to the Emergency Department of the Indus Hospital and Health Network, with the complaint of failure to

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pass stool since birth. Abdominal distension was observed on the 1st day of life by parents. They also noted meconium in urine. Medical history revealed that he was delivered at full term by normal vaginal delivery with no antenatal and postnatal complications; to a third gravida mother with two alive and healthy children. The mother's antenatal scans were normal. Furthermore, there was no history of premature rupture of membrane or gestational diabetes mellitus. Family history revealed a non-consanguineous marriage between parents with no history of gastrointestinal anomalies, sudden infant death or miscarriages.

On physical examination, the baby's weight was 2.9 kg; he appeared dehydrated, lethargic, with gross abdominal distension and had no anal opening. A nasogastric tube was passed to rule out associated tracheoesophageal fistula, which passed effortlessly and was visualized in the stomach on a radiograph. Moreover, an invertogram (Fig.1) and abdominal radiograph (Fig.2) were performed, which confirmed a high type of anorectal malformation and an air-fluid level with a large bowel loop, respectively. Ultrasound abdomen and echocardiography were done to rule out other associated anomalies, but were normal.

After initial stabilization, appropriate antibiotic initiation, and anesthesia fitness evaluation, he was shifted to the operation theater for a laparotomy. Perioperative findings were suggestive of a type 1 pouch colon and no normal colon could be identified. A large thick muscular fistula communicating with the bladder (posterior wall) was identified and an ileostomy was performed 25cm above the rectum. Diagnosis of "congenital pouch colon associated with imperforate anus and recto-vesical fistula" was made. Postoperatively, the baby remained vitally stable; stoma started to function, feeding was started and progressively increased, and later direct breastfeeding was started which he tolerated well. Following a detailed assessment, the attending physician and surgeon counseled the infant's parents regarding his diagnosis, likely prognosis, follow-up and home care plans and future surgical plan. The baby was discharged home on out-patient follow up.

DISCUSSION

Early diagnosis of the syndrome plays a significant role in reducing mortality and morbidity. In our case, the baby was diagnosed with CPC, a rare condition in the early neonatal period. Due to low incidence and therefore awareness in Pakistan and no family history, it may have been missed resulting in a poor outcome.

In 1912, Spriggs originally described Congenital Pouch Colon in a London Hospital Museum, on a specimen that manifested absence of half of the colon and rectum.[5] The name, Pouch colon syndrome, was suggested by Narsimha Rao et al. in 1984.[6] Since then, different theories have been conducted to unravel its etiology. Wakhlu et al postulated that it is due to the combination of defective development and failure of rotation of the gut during intrauterine life.[7] Some have proposed vascular impairment as the cause. Genetic factors like Wnt, NOTCH and Hedgehog gene mutation and environmental factors like vitamin B and iodine deficiency are also associated with CPC.[8] The most straightforward classification of CPC was proposed by Saxena and Mathur (Table-I) in 2008. It classified CPC into five types depending on the length of colonic involvement. Another classification by Gupta DK classified CPC

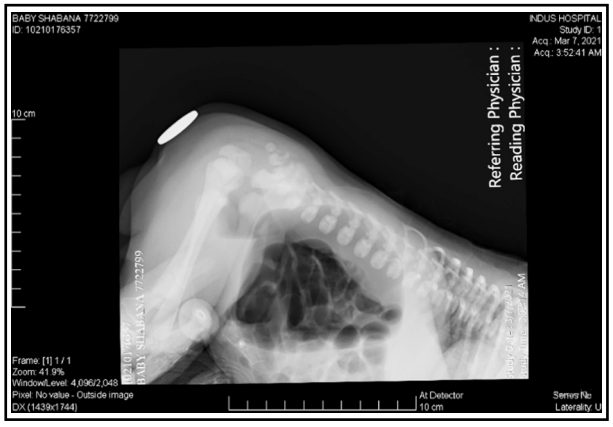

Fig.1: Invertogram.

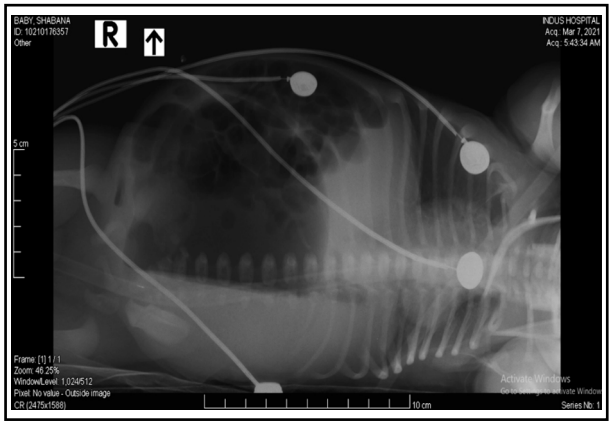

Fig.2: Radiograph abdomen (lateral decubitus view).

Table-I: Types of Congenital Pouch Colon (CPC).

Types of CPCS	*Classification*
Type-1	Normal colon absent and ileum opens into pouch colon
Type-2	Ileum opens into a normal cecum which opens into the pouch colon
Type-3	Normal ascending colon and transverse colon opens into the pouch colon
Type-4	Normal colon with recto-sigmoid pouch
Type-5	Double pouch colon with short normal inter-positioned colon segment

as complete and incomplete depending upon the length of the colon left to perform the pull-through procedure.[1]

In contrast with a normal colon, CPC varies anatomically, histologically, and functionally. On gross examination, the normal anatomical findings of *Taenia coli*, smooth muscle, haustration, and appendices epiploicae were absent along with a small pouch with rudimentary mesentery, indicative of the true CPC. The vascular supply of the pouch is from the branches of the superior mesenteric artery. Histopathologically, the muscle wall of the pouch is un-differentiated between the inner circular muscles and outer longitudinal muscles. Mature ganglion cells present in most cases; however, giant ganglia are also present in 10% of cases.[1]

The clinical presentation of CPC can be made early in the neonatal period. However, it may vary due to associated factors like the gender of the baby, type of CPC, and size of the fistulous connection between the colon and genitourinary tract. In most of the cases, males may present with imperforate anus and abdominal distension, and in 50% cases, fecaluria may be seen. On the other hand, females often present with abdominal distension, but sometimes urinary incontinence, constipation, and enterocolitis may follow.[1]

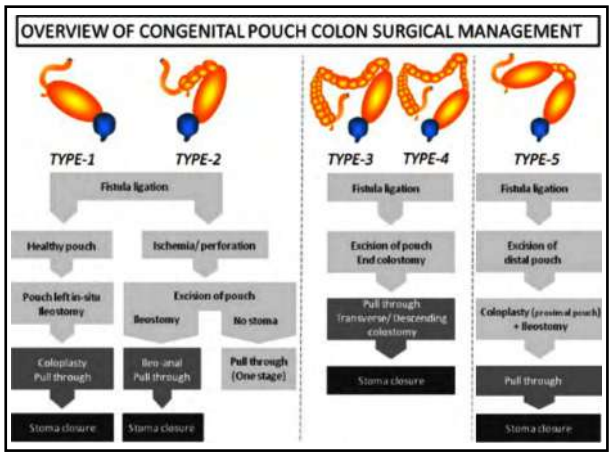

Fig.3: Surgical Management of CPC.

For better diagnosis, preoperative radiographic investigations, like an erect skiagram and an invertogram are required which generally show a large air-fluid level in the bowel loop; a suggestive radiographic finding of meconium.[4] For co-existing anomalies ultrasound of abdomen and echocardiograph along with voiding cystourethrography must be performed. Out of the many complications found to be associated with CPC post-operatively, diarrhea, urinary tract infections, failure to gain weight, bowel stenosis, rectal or bowel prolapse, wound dehiscence, enterocolitis, and septicemia are among the most common.[1] The prognosis of the syndrome depends on several factors, like type of CPC, age at presentation, presence of associated anomalies, and presence of septicemia and gut perforation.

The standard treatment for patients with CPC is resection of the pouch with abdominoperineal pull-through in multiple stages.[9] The surgical management of CPC is explained in Fig.3.[10]

The baby in our case had presented with typical CPC features of abdominal distention and inability to pass feces since birth. A pre-operative diagnostic invertogram was performed along with an abdominal ultrasound to arrive at the correct diagnosis. Confirmatory diagnosis of type 1 CPC was made based on per-operative findings. The parents were counseled regarding the child's condition to ensure timely follow-up and further staged surgical plans.

CONCLUSION

As CPC is a rare syndrome, it can be missed by obstetricians in the prenatal period. Detailed antenatal and postnatal evaluation leads to prompt diagnosis and consequently minimal complications. It also allows early screening and management

of associated conditions. Timely diagnosis and management have a significant impact on overall prognosis and reduction of associated mortality.

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Authors Contribution:

SNI: conception of idea, designing the study, literature search, data compilation, manuscript writing and review.
SNA: conception of idea, literature search, manuscript writing, review and is responsible for integrity of the study.
RAR: Literature search, manuscript writing and review.

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Case Report

Disseminated cryptococcal infection in a lymphoma suspected patient

Nazia Khursheed[1], Amna Umer[2], Fareeha Adnan[3]

ABSTRACT

Cryptococcus neoformans is an opportunistic pathogen, mainly responsible for meningitis in immunodeficient individuals. We report a rare case of dessiminated cryptococcosis in a six years old boy, patient was being evaluated for lymphoma. In the present case the causative agent was *Cryptococcus neoformans*. It was diagnosed through Bactec, aerobic blood culture bottle. The cause of hospitalization of the patient was fever with abdominal pain. Blood and CSF culture revealed the presence of *Cryptococcus neoformans* which was further confirmed by urease test and corn meal tween agar (CMT). In the present case fungus was unusually isolated earlier from blood culture rather than cerebrospinal fluid.

KEYWORDS: *Cryptococcus neoformans*, Lymphoma, Sepsis.

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INTRODUCTION

Cryptococcus neoformans (C. neoformans) is a ubiquitous and opportunistic fungal pathogen, primarily acquired via respiratory tract. It is an encapsulated (30 µm thick) unicellular yeast, about 5-12 µm in diameter [1], primarily responsible for cryptococcal meningitis.[1] According to the Centers for Disease Control and Prevention (CDC), USA, annually there are almost one million new cryptococcal meningitis cases reported worldwide, therefore, is an important global health concern. Clinical case studies suggest that conditions that impair host cell-mediated immunity such as human immunodeficiency virus (HIV) infection[2] autoimmune diseases, immunosuppressive therapy, liver cirrhosis, lung diseases, lymphoproliferative malignancy and hematological malignancy,[3] play a central role in the pathogenesis of cryptococcal infections.[4] These infections with variable clinical presentations have been reported in a variety of immunocompromised patients from different regions of Pakistan[5] and it is less frequently seen in children than adults.[6] Herein we report a case of cryptococcosis in a child with lymphoma.

CASE PRESENTATION

A six years old child from a remote area, presented with a history of intermittent fever, abdominal pain, distension, vomiting, and crusted skin lesions all over his face for 6 months. The symptoms were gradual in onset for which he received certain medications from a local health center and referred to our tertiary care hospital. His previous treatment was unknown. He was semiconscious and tachypneic, therefore admitted to the pediatric intensive care unit. On examination

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he was icteric, on auscultation, the chest was clear with no murmurs heard, on palpation, abdomen was soft with hepatosplenomegaly and cervical lymphadenopathy.

CT scan with contrast was advised. The imaging appearances of hepatosplenomegaly with cervical, axillary, mediastinal, inguinal and multiple mesenteric lymphadenopathy suggested lymphoproliferative disorder like lymphoma. There was also evidence of left renal and multiple pulmonary deposits. The cervical lymph node was sent for biopsy. It exhibited complete effacement of nodal architecture by sheets of foamy macrophages and multinucleated giant cells along with chronic lymphoplasma cystic infiltrate. Numerous round to oval organisms were seen in the cytoplasm of these foamy macrophages and giant cells, which were highlighted on special stain PAS, GMS, PAS Alcian blue and fontanna masson.

He was treated with teicoplanin 200mg/IV/ QDS/24 hrs (10 days), fluconazole, two mg/ ml/50ml (14 days), and meropenem 660mg/8 hourly (12 days). CBC reports revealed anisopoikilocytosis, target cells, schistocytes (2%), and large platelets with thrombocytopenia. Procalcitonin was 1.73 ng/ml.

Suspecting a fungal infection in immunosuppressed patient B-d glucan (BDG) was requested which was reported as negative. Simultaneously blood and urine cultures were sent for culture and sensitivity. Urine culture was negative; however aerobic blood culture came positive on the third day of his admission. The gram stain showed rare budding yeast cells. Initially, all the plates were negative only a few small colonies on sheep blood agar grew on the second day of incubation that was not well appreciated (Fig.1a). However, there was no growth on Macconkey and chocolate agar plate. The plates were reincubated for another 24 hrs to confirm the growth of any other pathogen. The colonies observed were creamy and mucoid. The gram stain from colonies showed budding yeast cells. The case was clinically correlated and it was decided to set urease and germ tube test (GTT) on the same day. The urease test was found to be positive within four hours however, slide examination of GTT revealed it to be negative. The same day the sabouraud dextrose agar (SDA) was inoculated. The colony and morphology of yeast on SDA were creamy white with smooth margins (Fig.1b). This was followed by incubation on cornmeal tween agar (CMT). It was interpreted on 3rd day of incubation. Microscopic examination of CMT showed large spherical blastoconidia of different sizes without hyphae. These typical findings confirmed the presence of ***Cryptococcus. Neoformans*****:** After reporting *C. neoformans*, the patient was immediately treated with the combination of fluconazole and amphotericin B, 25 mg/IV/24hr for 23 days.

Subsequent blood cultures were done to distinguish between the true fungemia and contamination, but they all turned out to be negative. Meanwhile, the patient developed signs of meningitis. CT brain showed prominent temporal horns of bilateral ventricles hydrocephalous. No abnormality like parenchymal or meningeal enhancement was observed. CT abdomen revealed hepatosplenomegaly with generalized lymphadenopathy and renal deposits. Pulmonary deposits were observed on a chest scan. This was followed by cerebral spinal fluid (CSF) culture. The CSF detailed report showed 29% neutrophils, 65% lymphocytes, 6% monocytes, and budding yeast cells. Numerous RBC were seen because of the traumatic tap. Gram staining, CSF culture, wet prep, and India ink were performed. Donut-shaped yeasts on India ink were seen (Fig.1c). Rapid Cryptococcus antigen test was performed on the CSF sample, with positive and negative controls to assure the presence of yeast, which was also positive (Fig.1d).

The patient was in distress and antifungal fluconazole had already been started. Multiple blood cultures and three consecutive tracheal

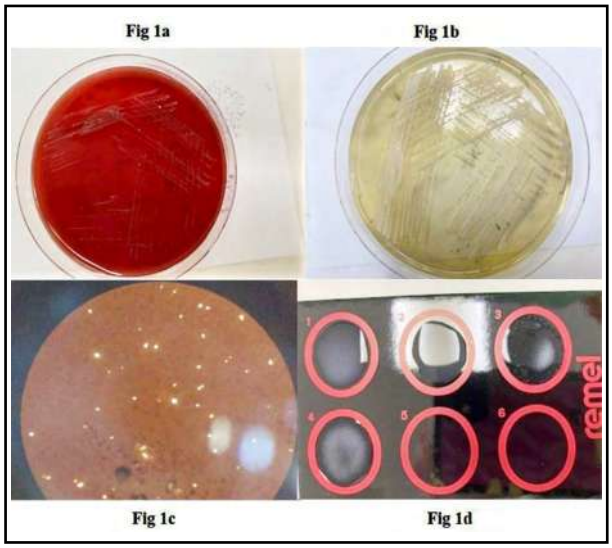

Fig.1a: Sheep blood agar, 1b: SDA, 1c: India ink, 1d; (1) negative control, (2) weak positive control, (3) strong positive control, (4) strong agglutination.

cultures were sent which turned out to be negative. Histopathology of skin biopsy also revealed the presence of Cryptococcus neoformans.

Initially, he was kept euvolemic. Fundoscopy was done to check papilledema. Patient had an intermittent temperature (37.6 - 39*C) and developed hypernatremia during his stay. He was taken off from the ventilator, once his oxygen level was normalized. No central venous catheter was inserted. Despite aggressive treatment measures the child could not survive and expired within a month of admission.

DISCUSSION

The threat of cryptococcosis is becoming a global health problem with deadly consequences particularly in immunocompromised individuals.[7] Cryptococcal infection starts with the inhalation of yeast with the CNS as the main site of infection but it can propagate and cause infection at any site in the body.

In this case *C. neoformans* was isolated from blood culture. It has been observed that it causes fungemia before it crosses the blood brain barrier.[8] From the present study it is clear that cryptococcus can be isolated from blood in the early phase of dissemination. The 7-day incubation of blood culture bottle at 37*C can facilitate its growth of yeast. The expected reason for earlier detection in blood followed by negative and later on positive CSF culture is that patient might develop sepsis after inhalation of organism which later crossed blood brain barrier and caused meningitis.[8] In the case of suspected meningitis, CSF and blood cultures should be performed simultaneously. This will enhance the chances of isolation of pathogen at early stage.

CONCLUSION

This report proposes that in immunocompromised patients cryptococcosis should be considered in the differential diagnosis if there is persistent fever and ineffective antibiotic treatment. Empirical administration of antifungal agent may be necessary. *C. neoformans* antibody test, blood culture, CSF culture and surgical excision biopsy is needed for early diagnosis

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NK Critically reviewed case report.
FA Prepared manuscript draft.
AU Information collection and prepared initial draft of manuscript.

Open Access

Case Report

Lemierre's syndrome in a child

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ABSTRACT

Lemierre's Syndrome (LS) is a rare syndrome most frequently due to an anaerobic organism, Fusobacterium Necrophorum. It is commonly a complication of an acute oropharyngeal infection, but there are exceptions to its presentations. In our case the cause of LS was otitis media caused by Streptococcus species. This is a rather unusual presentation of LS. LS is caused due to septic complications of oropharyngeal infections, which lead to thrombophlebitis of internal jugular vein leading to thrombosis formation. In this case report, we present a case of Lemierre's syndrome in a seven-year-old male child. The patient presented with high grade fever spikes and earache, which were unresponsive to oral antibiotics. LS was diagnosed in this patient on the basis of clinical, microbiological and radiological findings. After the diagnosis, treatment involved using broad spectrum antibiotics and anticoagulants, followed by surgery. Though role of anticoagulants is controversial in LS, but there is no specific guideline contraindicating the use of anti-coagulants. In our case, timely diagnosis and management enabled us to discharge the patient without any symptoms.

KEYWORDS: Lemierre's syndrome; Fusobacterium Necrophorum; Septic thrombosis.

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INTRODUCTION

Andre-Alfred Lemierre first reported a combination of clinical features in twenty young patients.[1] The clinical features included peritonsillar or pharyngeal abscess secondary to an anaerobic infection which led to thrombosis in internal jugular vein and septicemia. These symptoms were later coined as "Lemierre's Syndrome (LS)". Since the first reported case in 1936, LS became very rare due to development of antibiotics, and was once even termed as the "Forgotten Disease". However, since the last two decades an increasing number of cases have been reported.[2] It is unclear if this rising trend in cases is due to advancement in diagnostic techniques, decreased number of tonsillectomies or increased antibiotic resistance to organisms.[3,4]

We present a case of a 7-year-old boy, admitted with complaints of ear discharge and persistent fever spikes, which was later confirmed as a case of Lemierre's syndrome on the basis of positive culture and radiological findings.

CASE REPORT

A 7-year-old boy, with no significant past medical history, was admitted in the pediatric unit of our hospital with complaints of fever and right earache since eight days, along with

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mucopurulent discharge from the same ear for the last one day. On examination, he was a febrile, malnourished child with palpable cervical lymph nodes on the right side. The largest lymph node measured about 1.5 cm, was tender, smooth but hard in consistency. Detailed right ear examination revealed conductive hearing loss with a congested and perforated tympanic membrane with mucopurulent discharge.

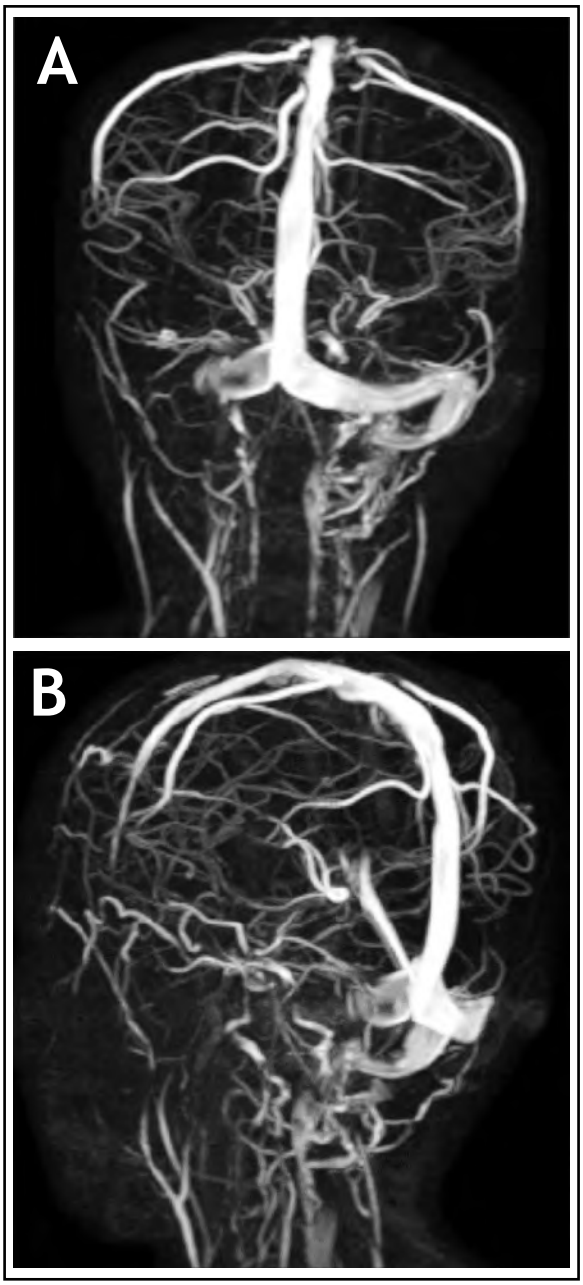

Fig.1a and b: Posterior and lateral MRV images showing cerebral venous sinus thrombosis, involving right transverse sinus with extension into sigmoid sinus and internal jugular vein.

On the basis of history and examination, our provisional diagnosis was otitis media. Intravenous injections of ceftriaxone and vancomycin were started, after which fever spikes spaced out, but persisted. Blood cultures which were sent on admission, came out positive for Streptococcus species which was sensitive to ceftriaxone. Culture of his ear discharge and repeated blood cultures were all negative, but due to persistent fever spikes, leukocytosis (TLC: 20.2 x 10^9/L) and thrombocytopenia (105 x 10^9/L). MRI and MRV showed cerebral venous sinus thrombosis, involving right transverse sinus with extension into sigmoid sinus and internal jugular vein (Fig.1a & 1b), along with focal right sided cerebellar meningeal and tentorial enhancement (Fig.2).

Explorative mastoidectomy revealed middle ear full of granulation tissue, extending to the mastoid antrum. Long process of incus was also eroded, while head of stapes was covered with granulation tissue. Lateral semicircular canal and facial canal were intact. Chest X-ray and echocardiography was done to screen for emboli in heart and pulmonary vasculature, which came out normal. The thrombus evident on MRI was treated with intravenous enoxaparin. After ten days of injection enoxaparin, our patient was switched to oral rivaroxaban to prepare him for discharge as his symptoms were starting to resolve. Later, he was discharged on oral antibiotics and was advised to continue anticoagulants for six more weeks. On follow up, his symptoms had completely resolved upon completion of treatment. We plan to follow him again after six months to plan for tonsillectomy.

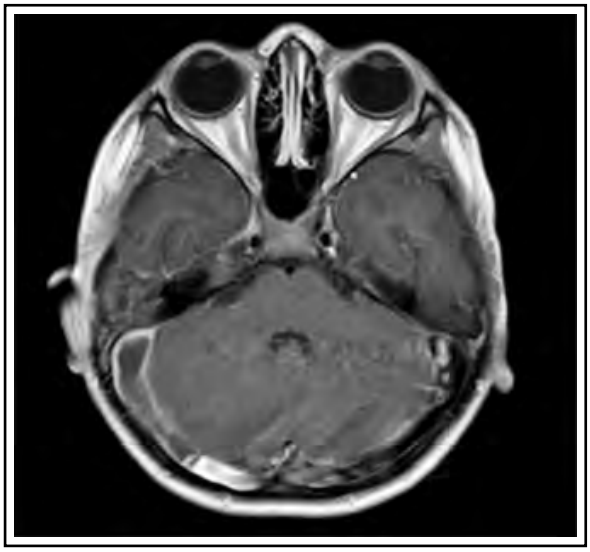

Fig.2: Post contrast enhancement in right cerebellar region.

DISCUSSION

Lemierre's Syndrome is also known as postanginal septicemia because sepsis usually manifests after an oropharyngeal infection.[5] It usually begins as a local oropharyngeal infection, and presents with fever, dysphagia and neck swelling.[6,7] Later during the course, infection spreads via blood stream to other organs. This spread of septic emboli usually presents with chest pain, hemoptysis and dyspnea in 79 to 100 percent cases,[7] while less commonly deranged liver functions, arthralgia, and coagulopathies have also been reported.

The most commonly reported pathogen in LS is Fusobacterium spp., especially Fusobacterium Necrophorum.[7] In a study published, of the 96 patients diagnosed with LS 52 percent were culture positive for Fusobacterium spp. The remaining cases is this study were positive for Streptococcus spp. (18%), and Staphylococcus aureus (6.3%), respectively.[7] There are very few cases reported from Pakistan, especially in pediatric population.[8] One of these reports, defined an unusual presentation of LS with Fusobacterium spp, but absence of jugular vein thrombosis.[6] Another study was done in Abbottabad, where patients admitted with tonsillopharyngitis were screened for LS, and only two cases (1.28%) were identified. The first patient had throat swab culture positive for bacteroides and pseudomonas, while second patient's culture showed no organism growth.[9] In our case, LS was caused by Streptococcus species, which most likely was due to our patient's unvaccinated status.

LS is diagnosed by a combination of clinical signs, positive blood cultures and radiological findings. Its treatment also involves broad spectrum antibiotics, surgical removal of septic focus and anticoagulants. Use of anticoagulants is still debatable, as no specific guidelines on treating LS are present.[10,11] Many recent cases reported in pediatric population have used some form of anticoagulants,[12-14] which seemed to have reduced or slowed the progression of thrombosis. The use of anticoagulants is still questionable though, as there is lack of evidence. Removal of thrombosis via surgery is hardly ever indicated, however surgery is indicated in removal of abscess in parapharygeal and tonsillar region, along with empyema of lungs or septic joints.[10] These medical and surgical treatment options can be used separately or in combination to treat LS. In our case, due to persistent symptoms despite use of appropriate antibiotics, surgery was performed to remove infection. It is very important to treat LS at an early stage as delay in the treatment can be life threatening. The mortality rate of LS can vary from 5 to 18 percent.[7,10]

CONCLUSION

LS is rather an unfamiliar syndrome with serious complications that can even cause death. It was once considered a rare syndrome, but due to increasing number of reported cases recently, it is important to spread awareness about this syndrome. It is vital to catch LS during its early stage to avoid any formidable complications. LS is usually reported after an oropharyngeal infection, but as seen in our case, it can occur as a sequelae to otitis media. It is therefore important to evaluate for LS in any patient presenting with a neck swelling or any other signs of inflammation after an oropharyngeal infection or otitis media.

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Authors' Contribution:

FH: Conception of the idea, literature search, data compilation, write up and reviewing the article.

AN, SH, SS: Conception of the idea, review and final approval of the manuscript.

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Voice against tobacco: A call for integrated action for effective change

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The use of tobacco amongst the youth of Pakistan is an increasingly concerning issue. Approximately 1,200 children between the ages of 6 and 15 start smoking each day.[1] As smoking and tobacco use is the single most avoidable cause of death globally, engaging all stakeholders in tobacco control has never been more imperative to improve tobacco control measures and save the future of our youth.

The medical community is well informed of the health hazards of smoking. With lung cancer being an indisputable consequence, tobacco-induced illnesses such as cardio- and cerebrovascular disease, chronic obstructive pulmonary disease and oral cancers are just a few of the other possible outcomes. Particularly for the youth, unique risks include lifelong addiction, sustaining a customer base for the tobacco industry. Pakistan has recently been identified as a business hub by British American Tobacco[2] and, along with Philip Morris International, actively promotes novel tobacco products in Pakistan. These include electronic devices, 'heat-not-burn' tobacco and nicotine lozenges such as Velo, making tobacco use modern and trendy. To address the tobacco industry's innovation and targeted advertising, integrated methods must be leveraged and awareness created around risk perceptions of young people to subsequently fuel tobacco control efforts.

Interventions by health workers may be highly effective in individual smoking cessation efforts, with even a 3-minute counselling session resulting in benefits. Behavioural change and pharmacological interventions are also available. Beyond this, health professionals can involve themselves by building relationships with stakeholders and policy makers, speaking up or writing about the issue at hand. In Pakistan, however, where tobacco has become a cultural norm, physicians do not fully exploit this power to enable actionable change in tobacco uptake. Realizing their role as important societal leaders who can 'denormalise' tobacco use, particularly amongst youth, is critical.

Pakistan is a signatory to the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC), supporting the implementation of comprehensive tobacco control programs through MPOWER. MPOWER employs the following strategies: Monitor tobacco use and interventions, protect people from tobacco smoke, offer help to quit tobacco use, warn about the dangers of tobacco, enforce bans on tobacco advertising, promotion and sponsorship, and Raise tobacco taxes and develop sustainable alternatives to tobacco growing. Yet the complex tobacco tax structure in Pakistan, providing economic favor to the tobacco industry, appears counterintuitive to this.

A 10% increase in prices would reduce tobacco use in teenagers by 18%.[3] Therefore, because the youth is more sensitive to the price of goods, making tobacco products less affordable is likely to have a direct impact on their consumption. Disconnected tobacco control advocacy and intense lobbying by the tobacco industry leads to

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an impasse and so, groups must band together in an effort to raise awareness about required policy changes. A de facto coalition must include the medical community, civil society organizations, youth groups, academic institutions, public health professionals and policy makers. Only then can individual efforts be unified, strengthened and channeled for effect.

Indus Hospital & Health Network has used the MPOWER framework to create 'Voices Against Tobacco' (VAT). This is a community-centric initiative aimed at supporting positive policy change and empowering Pakistan's youth to take ownership of their health and future. VAT is a direct response to the need for a tobacco control coalition in Pakistan and the objective of this is simple - to provide a common platform for anti-tobacco advocates to amalgamate and support initiatives against tobacco use.

VAT aims to invest in Pakistan's youth by conducting capacity building exercises in school-based tobacco control training. VAT champions will then advocate for enhanced tobacco control measures amongst their communities and collect narratives on tobacco use, advertising and pricing. This will support galvanization of a strong group amongst the youth and project their advocacy efforts through multiple stakeholder engagement sessions and social media campaigns. Community outreach, along with a concurrent media campaign, will support national policy objectives including tobacco taxation, novel products regulation and sustainability of tobacco control through engagement with policy makers.

Protecting the health, well-being and livelihood of Pakistani youth is of utmost importance, for their future and the future of the country. By synergizing multiple groups of value to tobacco control efforts, we can push for effective policy change and facilitate meaningful change in the current state of tobacco in Pakistan.

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