ISSN-p:2664-5734
ISSN-o:2709-5878

LIAQUAT MEDICAL RESEARCH JOURNAL

Volume 4 Issue 1
1st January 2022 - 31 March 2022

Diagnostic and Research Labortory/
Department of Pathology, LUMHS, Jamshoro Pakistan

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Liaquat Medical Research Journal is the print, online, double blind, peer-reviewed, quarterly released journal devoted to publishing innovative biomedical research and scholastic / academic content from all fields of medical sciences, concentrating on innovative clinical, diagnostic and perspective preventive research.

Aims & Scope

The Journal aims to publish research in all fields of clinical, diagnostic, experimental & preventive areas related to medical sciences to disseminate scholastic work among clinicians and scientists around the globe.

Editorial Office

Liaquat Medical Research Journal,
Diagnostic & Research Lab,
Liaquat University Hospital, Hyderabad,
Sindh, Pakistan.
lmrj@lumhs.edu.pk

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Editorial

GLOBAL DISPARITY IN BREAST CANCER SCREENING GUIDELINES- IS THERE A NEED FOR AN INDIVIDUALIZED APPROACH?

Almasuddin Qazi
Barts Healthcare NHS Trust, London, United Kingdom

Correspondence:
Almas Uddin Qazi
FRCS Barts Healthcare NHS Trust, London, United Kingdom
Email: dralmasqazi@gmail.com

DOI: 10.38106/LMRJ.2022.4.1-01

Received: 20.01.2022
Accepted: 25. 03..2022
Published: 31. 03.2022

ABSTRACT

Breast cancer screening is the key to better clinical outcomes. Cancer diagnosed at the stage where it is still within the ducts has the highest potential for best survival. A screening mammogram is a gold standard for early detection. However, there is variation in the age related guidelines for starting the screening and cessation. Given the rate of breast cancer in the region, the government's economic resources and the priority of the screening service all play a role. Developed countries have benefited from screening mammogram facilities and improved disease outcomes, but underdeveloped countries have not yet introduced national screening programs. Thus nations must take the regional incidence and the biology of breast cancer into account and make evidence-based guidelines.

Key Words: Breast cancer, Mammogram, Screening

INTRODUCTION

Breast cancer is the most common cancer worldwide and the leading cause of death(1). Past few decades, breast cancer mortality has declined to owe to the facility of screening and early detection. To some extent, national breast cancer awareness programs have also played a role. Screening mammogram is the gold standard technique used globally. The mammogram was initially thought to be useful in 1913 but without any promising results; later, much research was conducted between the 1940s and 1970s. Finally, in the 1970s, breast cancer screening using mammograms was introduced(2). Breast cancer screening mammogram is now being used in many countries to detect breast cancer much earlier than it becomes symptomatic. Recently presented data suggested a 40% reduction in mortality in women between 40-74 years of age by taking the benefit of screening mammograms (3). The time elapsed between the development of cancer and its stage is directly proportional; if left untreated for long, the stage of the disease will be advanced. If it is diagnosed at an advanced stage, the survival is poor.

This has been observed that the incidence of breast cancer has racial and regional disparity. Breast cancer has the highest incidence in American women, followed by Europeans(4). Though African women are at relatively lower risk of breast cancer, their tumors are highly aggressive, showing a poor prognosis(5,6). Screening has multifactorial influences, mainly economic, the national incidence, and thus the screening mammogram has different guidelines in different regions. The critical factors that

influence breast cancer screening include age at the start of the mammogram, frequency of the screening mammograms, and the X-ray mammograms' views. Each aspect will be compared here, which is considered by international guidelines.

Starting age of screening mammogram

The breast tissue is dense in young patients; thus, the sensitivity of the mammogram to detect tumors is less(7). In addition, the rate of breast cancer is also relatively lower in younger patients; thus, the screening mammograms start at the age of 40 years in most countries. In the United States of America (USA), women between 50 and 74 years are invited for screening, and between 40 to 50 years should be on an individual basis according to their risk assessment(8). However, National Health Service (NHS) covers mammograms at 47 years by invitation to all average-risk women. The NICE guidelines suggest starting screening at the age of 20 years if there are p53 mutations, at 30 years if there is evidence of BRCA mutations. It is also interesting that the analysis of these mutations is not generally available. The upper age to cease screening mammograms varies from region to region, whereas in the USA, they have a consensus to stop screening at the age of 74 years. The woman will continue to have a screening mammogram if she has a 5-10 years life expectancy. At the same time, women with multiple diseases and a life expectancy of fewer than five years will not get a screening mammogram. The scientific logic to stop screening with less than five years of life expectancy concerns breast cancer biology, which becomes less aggressive with the advancing age within that short span of time. Thus it is less likely that breast cancer becomes lethal in the elderly age group. The mammogram is less sensitive in women <40 years; therefore, alternatives like MRI are advised annually.

Frequency of screening mammogram

There is a consensus to have an annual mammogram in American Societies for screening. While in countries with lower incidence and state-sponsored regions, it is advised to have a mammogram every two years or every three years. It is also recommended that if three consecutive annual mammograms are negative in an average-risk woman, she can have it every two or three years. Countries with poor prognoses and a lower incidence with limited resources always find it challenging to decide about the frequency. It is not yet answered what the frequency of mammograms should be in average-risk women, living in a country with lower incidence of breast cancer.

Screening mammogram views

There are three views of mammograms, including mediolateral (ML), cranio-caudal (CC), and oblique view. Generally, for screening, two views are taken ML and CC. There is an overall consensus on two views.

CONCLUSION

Breast cancer shows regional variation in the incidence and prognosis, and thus screening guidelines should be made accordingly. The countries with high incidence would be safe to continue with more frequent screening tests, but those with lower incidence have not yet decided when to start and how frequently they should be getting their nation screened. The evidence-based approach is the best policy, with regular audits of the service to explore the age for cancer development. In addition, the

aggressiveness of cancer will help in deciding the frequency. For the more aggressive cancer, the mammogram should be more frequent (i.e., Annual); however, the risk of overdiagnosis should be considered.

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Research article

COVID-19 AND HUMORAL IMMUNE RESPONSE IN CONVALESCENT PLASMA DONORS IN PAKISTANI COHORT – ANALYSIS FROM CONVELECENCE PLASMA TRIAL

Jawad Hassan[1], Shahtaj Masood[2], Naveen Fatima[1], Tehmina Nafees[1], Sonia Khan[1], Javed Akram[3],Fridoon Jawad Ahmad[3], Lubna Meraj[4], Ayesha Mahesar[5], Zaratul Ain Malik[1], Nadeem Samad Shaikh[6], Anwar Alam[7], Irfan Ghafoor Baig[1], Muhammad Adil[1], Muhammad Asif[1], Sidra Maqsood[1], Mehjabeen Imam[1], Durenaz Jamal[8], Dilnasheen Safdar[1], Tahir Sultan Shamsi[1]*

[1]National Institute of Blood Disease and Bone Marrow Transplant, Karachi; [2]Hayatabad Medical Complex Peshawar Khyber Pakhtunkhwa; [3]University of Health Sciences, Lahore; [4]Rawalpindi Medical University Rawalpindi; [5]Regional Blood Center, Sukkur; [6]Regional Blood Center, Quetta; [7]Alkhidmat Foundation Blood Bank Lahore; [8]Sindh Blood Transfusion Authority, Sialkot, Pakistan

Correspondence:

Jawad Kazmi
National Institute of Blood Diseases & BMT, Karachi, Pakistan

Email:
Jawadkazmi2003@gmail.com

DOI:
10.38106/LMRJ.2022.4.1-02

Received: 19.02.2022
Accepted: 21. 03..2022
Published: 31. 03.2022

ABSTRACT

Current COVID-19 pandemic has affected the entire globe. While there was no vaccine neither any specific treatment, investigational use of convalescent plasma has been explored in clinical trials. A prospective multicenter study of convalescent plasma was conducted. Donors were tested for total Anti-SARS-CoV-2 antibodies by electrochemiluminescence (ECLIA) and RT-PCR for COVID-19. Enzyme Linked Immunosorbent Assay (ELISA) was used to detect semi-quantitative and quantitative IgG anti-SARS-COV-2 antibodies. IgG Immunofluorescence-based lateral flow immunoassay (LFIA) was used to recheck seronegative donors. A total of 400 donors were enrolled. Twelve donors were SARS-CoV-2 positive by RT-PCR. Nine of 12 donors had developed SARS-CoV-2 IgG antibodies, while in 3 donors antibodies were not developed. A total of 70 donors (17.5%) were deferred due to seronegative status; 64 (16%) of them did not develop antibodies when plasma collection was planned. The IgG semiquantitative ELISA was positive in 282 and quantitative in 284 of 330 donors with a mean value of >1:160 and 44.10±39.22 IU/ml respectively. A total of 116 (29%) donors did not show IgG humoral response to COVID-19 even 28 days from the onset of illness. Subsequently, LFIA method was able to detect IgG antibodies in 20 of 48 (41.6%) seronegative donors and in 20 of 34 (58.8%) ECLIA positive ELISA negative donors. Viral RNA detection in recovered asymptomatic patients with concomitant IgG antibodies indicates recovery. Inability to detect antibodies by different testing kits may be due to their different antigenic targets or sensitivity. Significance of a positive COVID-19 RT-PCR in asymptomatic recovered patients is yet to be determined.

Key Words: Anti-SARS-CoV-2, Convalescent plasma, Covid-19 pandemic, Passive immunization

INTRODUCTION

World Health Organization (WHO) declared COVID-19 as a pandemic and as of 29th June 2020, with 10,004,707confirmed cases and 500,000 deaths reported in 216 countries around the world (1). In Pakistan, around 206,512 people have been diagnosed with COVID-19 and 4,167 deaths have been reported as of now, with the mortality rate of around 2.0%(2). Given the absence of any approved treatment for COVID-19 and vaccine, investigational treatment regimens have emerged as therapeutic options to be considered as a cure.

Passive immunization refers to a process of transferring antibody preparations derived from sera or secretions of immunized donors via systemic or mucosal route to non-immune individuals. Plasma collected from recovered patients of a given infectious illness during convalescence period is referred to as convalescent plasma. It has been used over many decades for a variety of different infectious agents such as pneumococcal pneumonia(3), poliomyelitis(4), measles28, influenza(5) in the past century, and H1N1 influenza(6), Ebola(7), SARS(8)and MERS(9) in this century. In the current SARS-COV-2 pandemic, anecdotal reports have shown efficacy of convalescent plasma(10-12).

A number of published studies have reported the detection of viral RNA of SARS-COV-2 many weeks after documented recovery(13-18,19-22). Clinical significance of persistence or re-emergence of virus is not well understood. Utilization of convalescent plasma, as a way of providing neutralizing antibodies to severely ill patients, has been approved by regulatory authorities in many countries including Pakistan in a setting of clinical trial or as expanded access program. Seronegativity of recovered COVID-19 patients have also been reported in different studies; its clinical significance remains to be seen. This may be due to lower sensitivity of the testing kits, different antigenic targets used or different techniques used. With this background, this study was designed to find out the rate of anti- COVID-19 antibodies and to check seroconversion in recovered COVID-19 patients after convalescence period and compare different antibody detection methods in seronegative patients.

METHODS

The trial was approved by National Bioethics Committee (NBC) and Drug Regulatory Authority of Pakistan (DRAP). It was conducted in accordance with ICH-GCP guidelines. This trial protocol was registered at www.clinicaltrials.gov (trial number: NCT04352751) as experimental use of COVID-19 convalescent plasma for the purpose of passive immunization in current COVID-19 pandemic in Pakistan 2020. Convalescent Plasma Donors were selected according to WHO criteria as given in Figure 1. COVID-19 recovered patients who volunteered to donate convalescent plasma were selected. The patients had a history of COVID-19 during last 4-8 weeks, followed by negative RT-PCR for SARS-COV-2 RNA on 2 consecutive samples 24 hours apart. They had recovery at least 2-weeks before they donate. The participants were between 18-60 years of age weighing >50kg for men and > 45kg for women. At least a week been passed since last use of glucocorticoids. They all must met all the criteria for a regular blood donor (i.e. negative for hepatitis B, C, HIV, Syphilis and RT-PCR negative for SARS-CoV-2). Once they fulfill all the criteria informed consent was signed

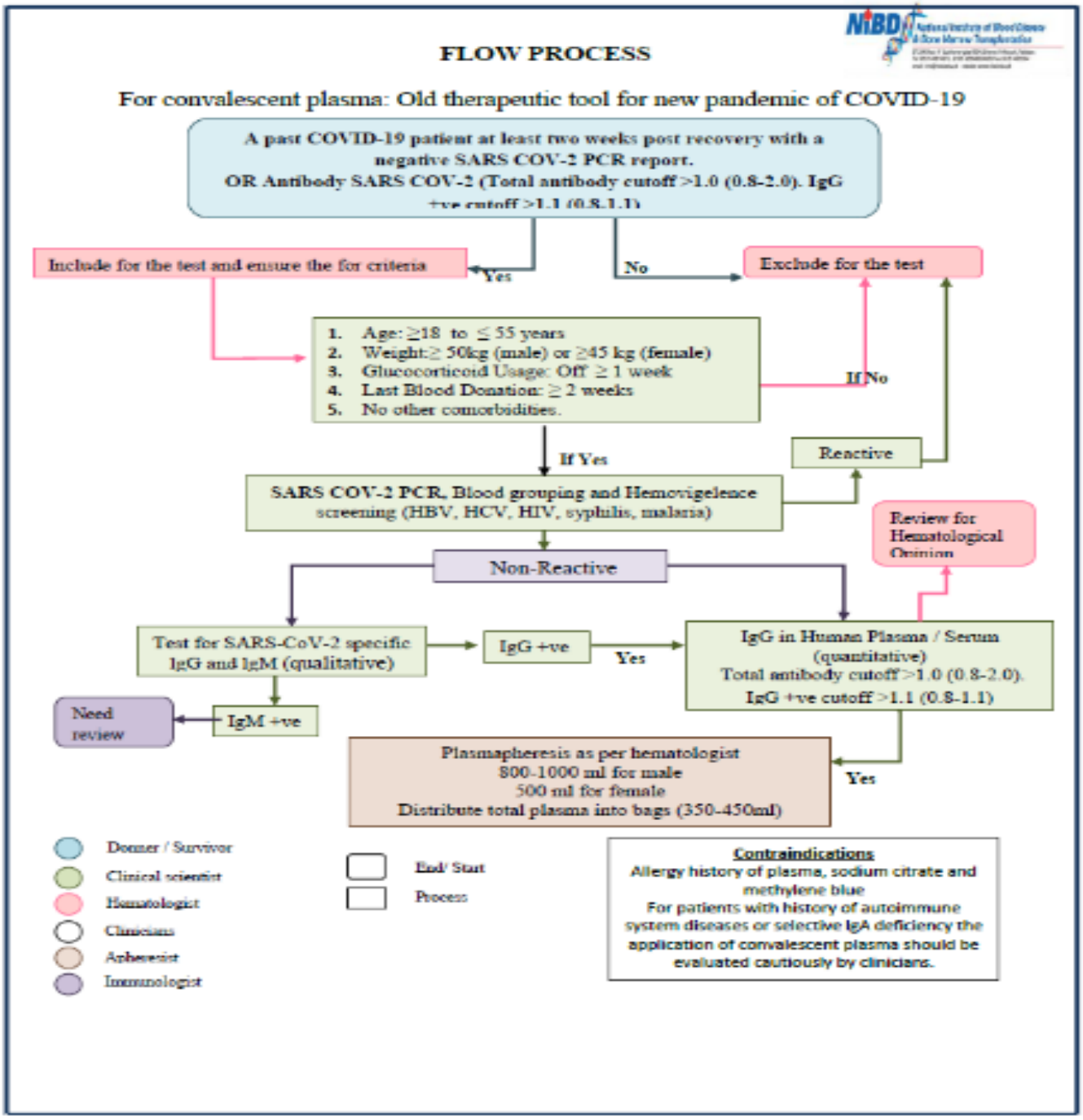
before donation. Moreover, multiparous female donors were excluded from the study. The flow-chart of the patients selection is given in Figure 1.

Specimen Collection and Transportation:

A. Blood Collection:

Whole blood (10 ml) was collected in lavender top (containing K_3EDTA for plasma) and gel tube and plain tube (for serum). Serum or plasma was separated by centrifugation of respective tubes and distributed to 2 to 3 aliquots and sent to respective departments.

Figure 1: Flow Process for convalescent plasma donors



B. Respiratory Specimens Collection for RT-PCR

Nasopharyngeal swab was collected as per CDC guideline; specimens were sent in viral transport media sealed in zip lock bags to the molecular department. All specimens were transported through maintenance of cold chain in reference center for qualitative testing of antibodies against SARS-COV-2.

Lab Investigations:

Complete blood count (CBC) and routine biochemistry investigations were performed as per institutional standard laboratory protocol. Serum samples were tested for qualitative detection of antibodies against SARS-COV-2, using Elecsys® assay kits using ECLIA immunoassay on Cobas e411 immunoassay analyzer by Roche Diagnostics International Ltd, (CH – 6343 Rotkreuz, Switzerland). Qualitative ELISA for IgG antibodies against SARS-CoV-2 was done using Omega Diagnostics IVD, (Genesis Diagnostics Ltd, Cambridgeshire, UK). For quantification, first quantitative kit is developed by AESKULISA SARS-CoV-2 NP IgG (AESKU Diagnostics GmbH & Co., Wendelsheim, Germany), and CE marked. It was used for quantitative measurement of antibodies against SARS-CoV-2. It detects nucleo-capsid protein.

ELISA tests were performed as per suppliers' instructions. Briefly, controls and diluted patient plasma/serum were incubated into individual microplate wells. In a positive test, the specific IgG will bind to the recombinant antigen. Addition of enzyme linked conjugate (anti human IgG) bound the antigen-antibody complex. Chromogen/substrate solution was added in each well for catalyzing a colored reaction. Stop solution was added into each well to inhibit the enzymatic catalyzation. Photometric measurement of the color intensity was made after adding stop solution.

Lateral Flow Immuno-fluorescent Assay kit detects anti-SARS-CoV-2 IgG and IgM (Lateral flow immunoassay) (Shenzhen Lifotronic Technology Co., Ltd, Shenzhen, China). LFIA was used later when the kit became available. ECLIA positive and quantitative ELISA negative as well as both negative donors with LFIA method were tested. RNA extraction was done using dry swab RNA kit FavorPrep viral nucleic acid extraction kit-1 (Favorgen Biothech Corps, Ping-Tung, Taiwan). Amplification was carried out using manufacturer's instructions (Bosphore, Novel Coronavirus (2019-nCoV) detection kit v2, Anatolia geneworks, Istanbul, Turkey). The kit employed multiplex PCR targeting two regions i.e. orf1ab (acquired through FAM filter) and E gene (acquired through HEX filter). For amplification and acquisition of fluorescence Rotorgene –Q (Qaigen) was used.

Statistical analysis

Data was analyzed using SPSS version 21.0. Descriptive statistics including mean and SD were computed for continuous variables. Frequency and percentages were evaluated for categorical variables. Independent *t*-test was applied to identify the difference between the means in two unrelated groups and Chi-square test was used to test a relationship between categorical variables.

RESULTS

A total of 400 donors were enrolled for convalescent plasma donation. There were 304 (76%) males (male to female ratio was 3.1:1), mean age of donors was 36.4±11.3 years. 332 (83%) of them remained home quarantine for a mean duration of 17.7±6.4 days. Follow up COVID-19 RT-PCR was done on a mean of 16.3±6.4day after their first RT-PCR positive test. Viral RNA was not detected on this testing. Plasma collection was done on day 15±14.2 after last negative RT-PCR. Table 1 shows the demographic details of these donors. Of 400 donors, 70 (17.5%) had a travel history abroad as shown in F*igure 2*. Their laboratory investigations were within normal range as shown in Table 1. After all screening and baseline testing 200 patients were excluded and finally 200 donors were recruited for antibody analysis. All selected donors were negative for transfusion transmitted infections such as Hepatitis B, C, HIV, syphilis and malaria parasite.

At the time of donation, 376 out of 400 donors were negative for SARS-COV-2 by RT-PCR. However, out of remaining 12, RT-PCR detected the presence of viral RNA, they were all male. Two of these 12 were hospitalized for a week when COVID-19 was diagnosed while 10 of these 12 were home quarantined. None of these 12 had any associated comorbid. Nine of these 12 showed seroconversion i.e., presence of concomitant anti-SARS-CoV-2IgG antibodies. A total of 70 (17.5%) donors were deferred due to absence of anti-SARS-CoV-2 antibodies in 64 (16%) and detection of viral RNA in 3 (0.75%) without any evidence of seroconversion. In 60 seronegative cases, there were 52 males. Eight of these 60 needed hospitalization while 52 were quarantined at home.

Table 1: Demography & Laboratory Parameters

DEMOGRAPHIC DATA n(%)	
Male Female	152 (76%) 48 (24%)
Low Medium High	8 (4%) 188 (94%) 4 (2%)
Age (years)	36.42 ± 11.34
HEMATOLOGICAL PARAMETERS (Mean±S.D)	
[1]Hemoglobin (g/dl)	14.0 ± 1.5
[2]Hematocrit (%)	40.3 ± 4.6
[3]Red blood cell count (x10^{12}/L)	4.9 ± 0.54
[4]White blood cell count (x10^{9}/L)	7.6 ± 1.5
[5]ALC* (x10^{9}/L)	2.6 ± 0.76
[6]ANC*(x10^{9}/L)	3.9 ± 1.1
[7]Reticulocyte Count (10^{9}/L)	56.2 ±32.3
[8]Platelets (10^{9}/L)	267 ±65.4
[9]IPF® (%)	6.0 ±3.2
BIOCHEMICAL PARAMETERS (Mean±S.D)	
[10]Albumin (g/dl)	4.5 ± 0.27
[11]Calcium (mg/dl)	9.7 ± 0.40
[12]Lactate Dehydrogenase (U/L)	167 ± 32.0
[13]Urea (mg/dl)	24.3 ± 8.3
[14]Creatinine (mg/dl)	0.87 ± 0.16
[15]Sodium (mEq/L)	138.8 ± 2.6
[16]Potassium (mEq/L)	4.1 ± 0.3
[17]Bicarbonate (mEq/L)	25.2 ± 2.52
[18]Chloride (mEq/L)	101.0 ±13.9
[19]Bilirubin Total (mg/dl)	0.56 ± 0.34
[20]Bilirubin Direct (mg/dl)	0.25 ± 0.63
[21]Alkaline Phosphatase (U/L)	47.06 ± 18.8
[22]SGPTº (U/L)	23.2 ± 9.1
[23]Random Blood Sugar (mg/dl)	103 ± 21.7
MOLECULAR ASSAY	
SARS-CoV-2 RT-PCR	Not Detected : 188
Anti-SARS-CoV-2 IMMUNOLOGICAL ASSAYS (Mean ± S.D) in COVID-19 recovered patients	

*Absolute Neutrophil counts, Absolute Lymphocyte counts,®Immature Platelet fractions,ºSerum glutamate pyruvate transaminase ¥Electrochemiluminesence ≠Enzyme Linked immunosorbent Assay **Reference ranges:**[1](M: 13.0-16.5, F:11.5-15.4), [2](M:40-52, F:36-48)

[24] ECLIA¥	35.93 ± 31.4 (165/200) Sensitivity: 82.5% Specificity: 100%
[25]ELISA≠ Qualitative / semi-quantitative	142/165 (86%) Mean: >1:160 fold serum dilution. Range: >1:180 - >1:320. Sensitivity: 71% Specificity: 100%
[26]ELISA Quantitative	141/165 (85.4%) 59.74 ± 35.90 Sensitivity: 70.5% Specificity: 100%

Figure1: Exposure History

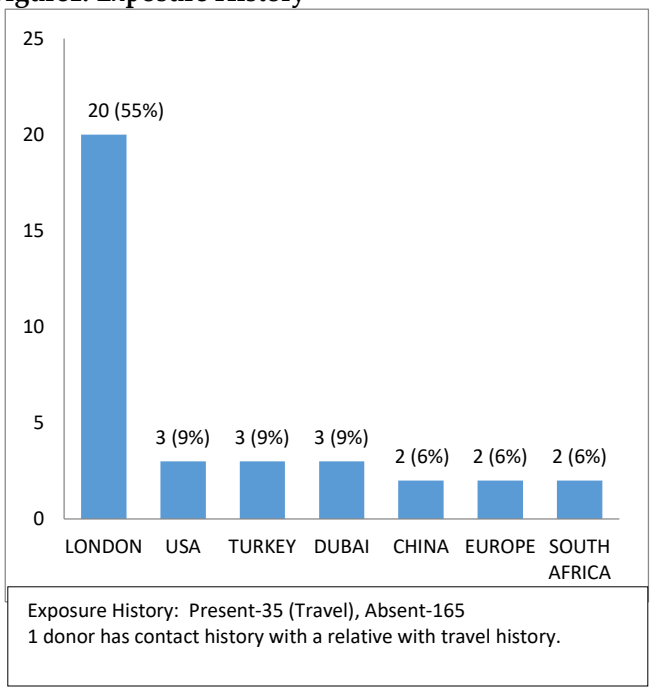


Table 2: Recurrence of SARS-COV-2 in published studies, worldwide

Studies	Diagnostic Tools	Covid-19 Recurrence
Chan D et al(13)	RT-PCR	1 patient
Zhang J Fen et al(14)	RT-PCR	1 patient
Huang P et al(15)	RT-PCR	1 patient
Xiao AT, Tong X, Zhang S et al(17)	RT-PCR	15/70patients
Jian M, Li Y, Han M et al(18)	RT-PCR	6/29 patients
Lan L, Xu D, Ye G et al(16)	RT-PCR	4 patients
Li et al(21)	RT-PCR	18/610 patients
Zhou L, Liu Q et al(22)	RT-PCR	14% patients
Current study	RT-PCR	12*

Mean value of anti-SARS-CoV-2 immunoassay by ECLIA was 35.93±31.4 (This is a qualitative test; significance of this numerical value is not known). Qualitative ELISA for IgG antibodies were positive in 284 out of 330 donors (86%). Mean IgG antibody titer was >1:160-fold serum dilution (range >1:80 - >1:320). Quantitative ELISA for IgG was detected in 282 donors (85.4%) with a mean 59.74 ± 35.90 (cut off: 8.0 U/mL) and range (9.98 - 100 U/mL). This means that further 46 donors did not develop IgG anti-SARS-CoV-2 antibodies. Subsequently, LFIA method was able to detect IgG antibodies in 20 of 48 (41.6%) seronegative donors and in 20 of 35 (58.8%) ECLIA positive ELISA negative donors.

Table 3: Comparison of COVID-19 seropositive and seronegative donors

	ELECYS RESULTS		
	Positive	Negative	*p* value
Age(Mean± SD)	36.43 ± 10.7	34.10 ± 12.3	0.266[a]
Sex Male (n) Female(n)	 126 25	 26 04	0.660[b]

Facility where admitted/Quarantine Hospital (n) Home(n)	 17 134	 4 26	 0.746[b]
Days of Quarantine (Mean± SD)	16.05 ± 6.3	15.50 ± 4.4	0.236[a]
Comorbids Yes No	 13 138	 3 27	 0.806 [b]

[a] = Independent *t*- test, [b]= Chi- square test

Table 4: Performance of LFIA technique in Seropositive and Seronegative COVID-19 Patients

ECLIA Positive & IgG Negative (n=17)	IgG +ve& IgM –ve (n=14)
	IgG -ve& IgM –ve (n=3)
ECLIA Positive & IgG Positive (n=4)	All 4 were IgG +ve and IgM -ve
ECLIA Negative & IgG Negative (n=24)	IgG -ve& IgM –ve (n=12)
	IgG +ve& IgM –ve (n=10)
	IgG -ve& IgM +ve (n=2)

SARS-CoV-2 Assay kit (Lateral flow immunoassay), Shenzhen Lifotronic Technology Co., Ltd, Shenzhen, China

DISCUSSION

Convalescent plasma donation is one of the experimental treatment options for COVID-19 and has been approved as a trial in a number of countries like United States of America and Britain. The therapeutic benefits of convalescent plasma were studied formally in animal models in early 20th century. In 1916, convalescent plasma from polio survivors was administered to poliomyelitis patients(27) to determine its efficacy followed by influenza(31)and measles(28, 29) and recently in SARS(34), MERS(35), and Ebola virus diseases(33).

In Pakistan, this trial for experimental use of COVID-19 convalescent plasma for the purpose of passive immunization was approved by national bioethics committee on April 4 and by Drug Regulatory Authority of Pakistan (DRAP) on April 9th, 2020 and the first donation was taken on April 15th.

Detection of COVID-19 RNA was found in a number of published studies, in which after RT-PCR negativity on 2 consecutive samples (Table 2), subsequent RT-PCR testing showed viral RNA again. Our study was designed to make sure that at the time of plasma donation, all the donors should not have any evidence of the presence of COVID-19 RNA and there should be documented evidence of the presence of anti-SARS-CoV-2 antibodies in their serum. Plasma donations were acceptable from the donors who have at least 2 negative PCR reports 24 to 48 hours apart almost 2 weeks prior to donation, as per FDA guidelines(6) .

Total antibodies are considered to be the most sensitive and earliest serological markers and increment in their levels start to appear after the first week of symptoms onset(8). Test using nucleocapsid antigens and receptor binding domain combined are the most sensitive(12). Seventy of our 400 donors did not show IgG antibodies after≥2 weeks of PCR negative results, which is in contrast to the findings in others studies which state that higher levels of IgG and IgM ELISA occur in the second and third week(9,10), and may persist for 2 years(11), however they can be positive as early as on fourth day after onset of symptoms. In contrast, according to CDC's (center for disease control) current guidelines, some patient's body's immune response may take longer time to develop immunity(23), resulting in a negative antibody result.

Another interesting finding was when subsequently, LFIA kit became available, seronegative donors' samples were analyzed who were either seronegative with ECLIA and ELISA kits or showed a positive

reaction to ECLIA but no evidence of IgG on ELISA, a good number of them detected presence of IgG in those sera. This may be due to different sensitivity of these kits, a false positive/negative result or their differing target antigens in the testing system.

In our study, viral RNA for SARS-COV-2 was detected in 12 donors. Out of these, 9 had concomitant quantitative IgG antibodies (ELISA) for SARS-CoV-2 and 3 showed negative antibody results. According to a study RT-PCR has been detected even beyond week 6 following the first positive test(7).

Our results showed a lower number of seroconversions (82.5%) as compared to Chinese studies. If we add up LFIA detected IgG results in the initial cohort, then IgG positivity has risen to 89%. This may be due to the fact that most of our donors (89%) had milder disease and did not require hospitalization. In contrast, Chen D *et al*(13), Zhang J Fen *et al*(14), Huang P *et al*(15) reported recurrence of RT-PCR positivity on oropharyngeal swab specimen in one patient each, after 2 consecutive negative PCR results. Another study reported 4 patients with COVID-19, who met criteria for hospital discharge or discontinuation of quarantine, to be positive on RT-PCR, 5 to 13 days later(16). Other studies, however reported a higher trend of recurrence, as 21.4% (15/70) and 20% (6/29) by Xiao AT (17) and Jiang M (18), respectively.

All these studies suggested that initial negative results may be due to various reasons such as variable viral load, sample site, technical expertise, effect of antiviral drugs, hormonal therapy taken, sensitivity of nucleic acid detection kit, false negative results or prolonged nucleic acid conversion.

Given the chance of recurrent positive SARS-CoV-2 RNA in the clinical course and to minimize the risk of spread in other COVID-19 cases, together they suggested that different specimen types to be analyzed at a time, such as oropharyngeal/nasopharyngeal, etc, larger samples to be taken, more than one method like serology testing should be considered combined with RNA testing. The patients in recovery phase should also be regularly tested for assessment of infectivity, all discharged patients should be ensured for at least 14 days home quarantine and RT-PCR test results of pharyngeal swab specimens should not be considered as the only one indicator for diagnosis, treatment, isolation, recovery or discharge and transferring for hospitalized patients. RT- PCR detection of viral traces cannot always be correlated with the ability of transmission(13,14,18,21,22).

In a report on 9 patients, viral isolation attempts in culture were un-successful beyond day 8 of onset of illness , which points towards decline of infectivity beyond the first week(24). That is why the "symptom-based strategy" of the Centers for Disease Control and Prevention (CDC) indicates that health care workers can return to work, if "at least 3 days (72 hours) have passed since recovery defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath); and, at least 10 days have passed since symptoms first appeared".(25)

This is a large scale study with concomitant antibody testing with RT-PCR, use of 2 different assays for the detection of anti-SARS-CoV-2 antibodies, selection of patients at least 14 days after last PCR negative or 28 days from start of symptoms.

However, use of single nasopharyngeal/oropharyngeal swab sample only in each patient, current RT-PCR techniques for SARS-COV-2 detection has almost 25-30% chance of false negative results were the limitations of the study. Inability to check for neutralizing antibodies at the time of this paper submission and a possible patient selection bias cannot be completed excluded, as all the donors were healthy volunteers recovered from COVID-19.

CONCLUSION

We conclude that 29% recovered COVID-19 patients did not show IgG humoral immune response at least 2 weeks after negative RT-PCR result in our cohort. Although, additional testing with LFIA kit reduced it to 11% only. However, a majority of them had concomitant IgG antibodies and only 0.75% had isolated PCR positivity in asymptomatic recovered patients from COVID-19 donors. Current serological diagnostic kits

have limitations as they are first generation kits. COVID-19 is a novel disease and scientific data is adding up on daily basis. Better kits are needed to accurately diagnose seroconversion status for COVID-19 in general population.

Conflict of Interest statement

All the authors declared no conflict of interest.

Trial Registration: DRAP Registration No: F.NO.17-8/2020 DD (PS), NBC Registration No: NBC-472 COVID19-03, NIH ID: NCT04352751

ACKNOWLEDGEMENT

We acknowledge the humanitarian support by convalescent plasma donors and well-wishers who motivated the donors. Sindh Blood Transfusion Authority and Dr Mesum Abbas for their technical support. We are also thankful to staff of passive immunization , NIBD especially: Waqas Javed, Asif Samad, Abdul Wahab, Nazim Hussain, Neha, Faraz Ali, Urooba Aslam, Aimen Muzammil, Shakir Ahmed, Anila Ali and all supporting staff from across the country sites for untiring work for this project. Hilton Pharma provided an unrestricted research grant for this clinical trial in this testing time of pandemic. Special thanks to Dr AhsonQavi and Dr Neeta Maheshwari of Hilton Pharma Medical Department for providing technical support in this trial.

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Research article

IMPACT OF INTELLECTUAL DISABILITIES OF CHILDREN ON MENTAL HEALTH OF PARENTS

Zahoor Ahmad, Kinza Anwar, Hafsah Gul, Nadia Ishtiaq, Hafsah Arshad
University Institute of Physical Therapy, Department of Allied Health Sciences, University of Lahore, Pakistan

Correspondence:
Zahoor Ahmed
University Institute of Physical Therapy, Department of Allied Health Sciences, University of Lahore, Pakistan

Email:
zahoor_riphah@hotmail.com

DOI:
10.38106/LMRJ.2022.4.1-03

Received: 29.11.2021
Accepted: 21. 03..2022
Published: 31. 03.2022

ABSTRACT

Parents of disabled children face unique challenges in their daily lives resulting in stress. This study was conducted focusing on the parents of children living with intellectual disability to evaluate the rate of anxiety and depression. This cross-sectional study included the parents of children who attend the Health and Wellness Physiotherapy Rehabilitation center and Physiotherapy rehabilitation center of NCS University. There were 290 parents who consented and participated in the study. The participants were given a questionnaire with pre-designed questions about the socio-demographic characteristics of the family. Furthermore, the Beck's Depression Inventory (BDI) scale and State trail Anxiety Inventory were used to assess the level of depression and anxiety in our study population. Data was analyzed through Statistical Package for Social Sciences (SPSS- version 22.0). Out of 290 participants, 179 (61.7%) were males and 111 (38.7%) were females. With respect to BDI the number of Mild Mood disturbance was reported in 20 (6.9%), borderline clinical depression in 50 (17.2%), moderate depression in 82 (28.3%), severe depression was 113 (39%) and extreme depression was seen in 25 (8.6%). Likewise, 21 (7.2%) participants denied any anxiety, 32 (11%) were in mild anxiety level, 114 (39.3%) were in somewhat anxiety level but 123 (42.4%) were in high anxiety level of state trail anxiety inventory scale. According to the study's findings, parents of disabled children were considerably affected by anxiety and depression.

Key Words: BDI Scale, Birth Disables, Depression, District Mardan, STAI Scale

INTRODUCTION

Intellectual disabilities are extremely common in children around the world, and rates are expected to rise in the upcoming years due to advanced medical facilities and improved infant survival rate (1, 2). The rate of intellectual disability in children is reported to be particularly high in developing countries and late diagnosis is reported from less developed regions of the world. In Kenyan children, rates of neurological disability are estimated to be as high as 9.3%, which also includes intellectual disability (3). Raising a child with such a disability is a challenge for parents at times giving them anxiety and depression. The association of caring for a child with intellectual disability and development of

anxiety and depression in parents has been explored mostly in the developed-countries with social support systems (4). According to the studies conducted in less developed countries such as Kenya, Kuwait, Qatar, Pakistan, and India, the parents of such children have shown 47 to 50% prevalence of psychological disorders (5-7). Raising and caring for a child having intellectual disability may result in challenges in family bonding, stress, and warrant a need to adopt a different parenting style as compared to parenting a normal child (8). Stress has been linked to negative couple attributions about marital satisfaction, as well as the impact of stress on family functioning (9). There are reports suggesting that these challenges can also result in divorce and financial constraints (10). The experts in the field believe that the stress level which arises from a situation; comes with caring a disabled child due to lack of the knowledge and experience of dealing with the situation and understanding the child's needs. There are a number of studies looking at factors influencing parents of intellectually disabled children and causing psychological distress. These factors include but not limited to lower socioeconomic status with compromised financial support (11), single parent(mostly mother)(12, 13), feminine gender(14), perceived burden of care(13), lack of psychosocial support system(15) and inadequate knowledge of the child's disability(16). In case of familial problems when there are multiple disabled children in the family, it also raises the risk of depression in parents. In situations when the younger child is having disability and certain disorders, such as autism, are reportedly associated with high stress levels in parents (11).

Most of the literature focusing on the subject is reported from developed countries, while there is limited literature available from under-developed countries. On the other hand, less developed area estimates are relatively higher and limited services are available. It is therefore crucial to explore the level of the problem in less developed countries with limited social support. Thus, this study was designed to explore anxiety and depression levels among parents of disabled children living in Mardan District of Pakistan

METHODS

This was a prospective cross-sectional study approved by institutional review board, and ethical committee of NCS University Swabi Campus. This was a questionnaire-based survey and data was collected on a pre-designed questionnaire to find out the rate of depression and anxiety among parents of children with Intellectual disabilities. A non-probability convenient sampling technique was adopted in the study. Both parents of children with intellectual disabilities, attending services at Health and Wellness Physiotherapy Rehabilitation Center, NCS Physiotherapy Rehabilitation Center and Private Clinic of District Mardan Pakistan, were invited to take part in the study. A total of 290 parents consented to participate in this study. The data was collected for a period of 6 months, from 1st February 2021 till 30th August of 2021. Beck's depression inventory (BDI) questionnaires, STAI and written informed consent were provided to Parents of children with Intellectual disabilities. Those parents who agreed to provide the information and signed the consent form were invited to provide information in the questionnaire. The parents with limited literacy were provided assistance in filling up the responses.

Beck et al. (1) created and revised the BDI; the test–retest reliability of BDI was 0.86. This mental health tool consists of 21 items, each of which describes depressive symptoms and asks the respondent to rate their relevance to the symptom and how much it bothered them in the previous week. The

response was recorded on a four-point scale. The sum of the total responses ranging from 0 to 63. The higher scores suggest a higher level of depression. Spielberger et al. created the STAI inventory, which is used to assess predisposition to anxiety (trait) and existing levels of apprehension in the respondents. It has 40 items that need to be reported by the respondent where 20 items assess state anxiety and 20 items evaluate anxiety predisposition. The score for each item rated from one to four. The response score of each item is added together to get the total score. The higher the score, the higher the level of anxiety.

All the parents of children with intellectual disabilities were briefed about the study along with harms and benefits and were explained about the confidentiality of the data they will be providing. They were also assured that they are free to leave the study if they wanted to leave the study at any time without any legal bonding.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS version 22.0). The responses were recorded and presented in the scores. Frequency distribution was presented in graphs.

RESULTS

The total participants were 290; including 179 (61.7%), males and female participants were 111 (38.7%). Age was distributed in three categories; the participants between the age of 21 to 30 years were 28.3 % (n=82), between the age of 31 to 40 years were 44.1 % (n=128) and above the age of 40 years were 80 (27.6%). Around 31 (10.7%) single parents were living without a partner (i.e. divorced). Majority of the families belonged to the middle socio-economic class (n=93, 32.1), while 66 families were poor (i.e. 22.8%) and 50 parents reported to be from a strong financial background. Majority of the participants had 1 child (n=270, 93.1%) in their families and while 6.9% had 2 children in their families.

The mean and SD in BDI was 3.97± 0.99; the mean and SD of BDI in male was 4.38 ±1.19 and in female was 4.03 ±0.76, but the mean and SD of BDI in participants living with partner was 4.17± 1.08 and in divorced participant living without partner was 4.87± 0.42. Although, the mean and SD was in STAI was 3.16±0.89; the mean and SD of STAI in male was 3.49± 0.50 and in females was 2.64±1.11 but the mean and SD of STAI in participants living with partner was 3.15±0.93 and participant living without partner (divorced) was 3.25± 0.44. (Figure1 and 2).

With respect to BDI the number of mild mood disturbance were n=20 (6.9%), borderline clinical depression was 50 (17.2%), Moderate depression were n=82 (28.3%), severe depression were n=113 (39%) and extreme depression were n=25 (8.6%). Therefore, the majority of participants were in a severe depression level of the BDI scale. Likewise, the n=21 (7.2%) were in Not At All Anxiety level, n=32 (11%) were in little anxiety level, n=114 (39.3%) were in somewhat anxiety level but n=123 (42.4%) were in very much anxiety level of state trail anxiety inventory scale.

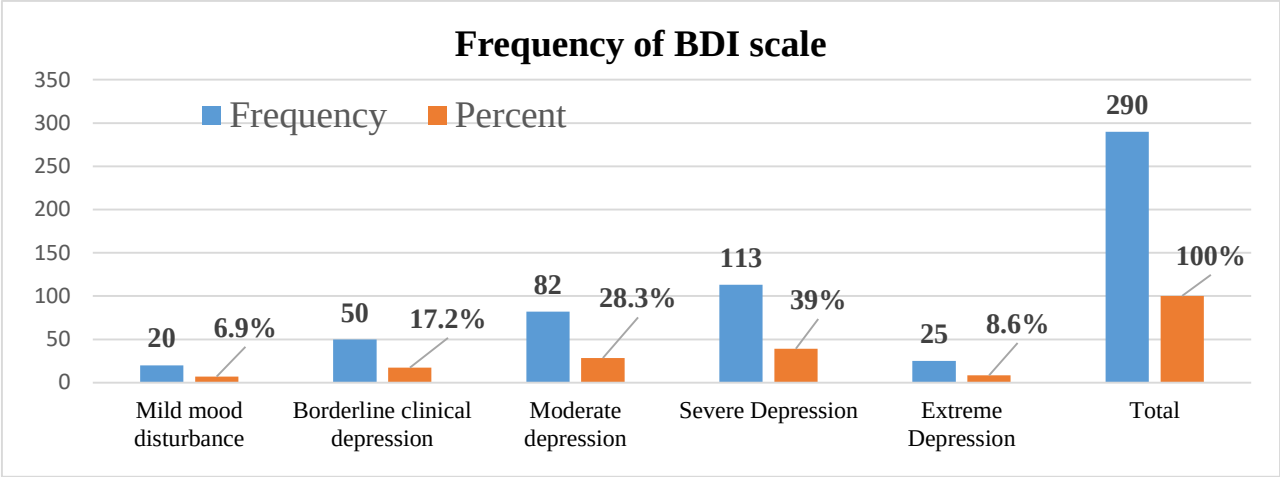

Figure 1: Showing the Frequency of Beck's Depression Inventory Scale

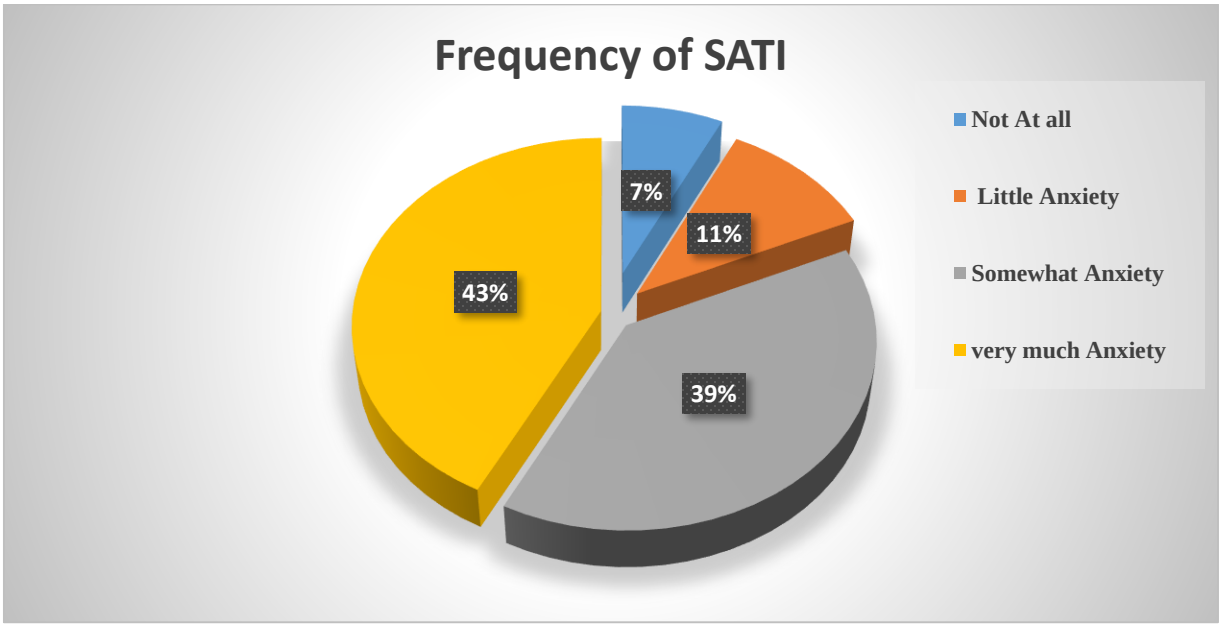

Figure 2: Showing the frequency of SATI Scale

DISCUSSION

The results of our study showed a considerable level of anxiety and depression in parents raising children with intellectual disability and more than 40% showed a level of distress higher than the normal level. The results of the study demonstrates that a considerable number of parents of such children suffer from undiagnosed and untreated mental illnesses. According to previous research, the rate of mental health issues among disabled children's parents range from 32 to 89 percent (18, 19). Our study's high prevalence rate is consistent with the previously reported undiagnosed distress and mental health issues of parents. The situation gets even worse due to the lack of emotional and technical support provided by health facilities in Pakistan. Especially given the scarcity of trained mental health care providers in this country. The importance of health care providers addressing mental health issues of parents having intellectually compromised children is highlighted by this finding. The high prevalence found in this study is consistent with existing literature. Our findings

are lower than those reported in Kenya, where a prevalence rate of 79 percent has been reported (20). Differences in data collection instruments could be a reason for this discrepancy. The BDI was used in our study, which is a self-report proforma with a chance of misinterpretation of the feelings and a risk of reporting bias. In terms of social demographics, many of the study participants were in their thirties. This is primarily due to the family system in our country where people normally get married in their twenties or early thirties and have children during the respective age range; similar findings in relation to age have been previously reported (17, 21). There were far more women in this study than men. It is again related to the family unit design in our country where women generally take a role as primary caregivers for children and in case of separation and divorce mothers continue to take charge of the growing child(22). Husbands may distance themselves from the disabled child in some cases, and in certain situations mothers may be blamed for having the disabled child (23). Even if other caregivers from the extended family support in child care, the mother is the one with highest responsibility. It is unquestionably critical to implement programs that benefit women in particular and train them to care for their children appropriately. Designing and facilitating psychological interventions that address issues focusing mothers of such children particularly.

A considerable number of participants in this study were jobless, and a high proportion belonged to a low socioeconomic class. There has been a well-established association reported between a child's disability and social status of the parents (24). It is also seen in our sample too. This said relationship has multiple factors in relation to joblessness and poverty. This can jeopardize mothers' health and also related to late provision of perinatal services. The poverty has association with low birth weight and birth asphyxia, which in turn have established causal relationships with intellectual disability in children. Among families living with a disabled child, up to 88 percent of caregivers find it difficult to meet the basic needs of their disabled child (25). Families in Mardan who were from a higher socioeconomic class, with educated parents, and received social support had less psychological distress, according to our research. These factors are associated with the economic situation of parents included in our study. Despite being somewhat rural, the population of Mardan is more educated, and as a result, people in Mardan will have better livelihoods because of better employment. People with a higher socioeconomic status and educated parents are more likely to seek and receive better material and psychological support, according to studies (26, 27). In this study, a high perceived responsibility of care for the child was linked to a higher level of stress and anxiety, most likely as a result of being a single parent. This may be due to reduced informal sources of support (i.e., friends, relatives and social support groups), which have shown to reduce stress in caregivers of disabled children (28-31). High stress level has been shown to be inversely proportional to the level of confidence in managing such a child. This is in line with previous reported literature, which has found that less confidence level reduces parental self-efficacy in child management, putting parents and their families under stress (32, 33).

CONCLUSION

Parents raising intellectually disabled children in Mardan face a significant psychological burden. Residence in Mardan city, low socioeconomic status, understanding of a child's disability, lack of confidence and training, burden of care, and limited social and psychological support are all associated with this high stress level. In Mardan, parents of children with intellectual disabilities require contextualized psychosocial interventions. Financial difficulties had an effect on the level of

depression and anxiety as well. Depression and anxiety levels were found to be higher in facing negative societal attitudes.

Conflict of interest

All authors declare no conflict of interest

Funding

No funding acquired for this project

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Research article

EVALUATION OF THE PATTERN OF CONTRAST SENSITIVITY IN GLAUCOMA PATIENTS

Muhammad Asif, Sania Raheem, Abdul Hameed Talpur, Mehak Nazeer, Muhammad Karim, Um-e-Farwa
ISRA School of Optometry, Al-Ibrahim Eye Hospital, Karachi, Pakistan

Correspondence:
Muhammad Asif
ISRA School of Optometry, Al-Ibrahim Eye Hospital, Karachi, Pakistan
Email:
Mohammadasif75050@yahoo.com

DOI:
10.38106/LMRJ.2022.4.1-04

Received: 09.12.2021
Accepted: 12. 03.2022
Published: 31. 03.2022

ABSTRACT

This prospective cross-sectional study was conducted to measure the contrast sensitivity in different types of glaucoma patients. The patients for this study were identified using a non-probability convenient sampling method from 01st February 2020 to 30th August 2020. The diagnosis and sensitivity were tested using lea contrast sensitivity, Snellen visual acuity charts, trial box, and occluder. The data were analyzed using Statistical Package for Social Sciences (SPSS version 20.0). Out of 60 patients, including 37 males and 23 females, between 16-80 years of age. 33 (55 %) patients were diagnosed with Primary Open Angle Glaucoma(POAG), 17 (28.3 %) patients with Primary Close Angle Glaucoma, 7 (11.7%) patients with Acute Closure Glaucoma(PCAG), and 3 (5%) patients with Secondary Glaucoma. Similarly, with glasses, 46 (76.7 %) patients had visual acuity 6/6 to 6/12, 11 (81.3%) patients had 6/18 to 6/36 and 3 (5 %) patients had 6/60. According to contrast sensitivity 30 (50%) patients had 1.25% (80%), 21 had 2.50% (40%) and 9 had 5% (20%). 15 subjects had 1.25% (80%), 13 subjects had 2.5 %(40%) and 5 subjects had 5% contrast sensitivity in POAG. Around 11 subjects had 1.25% (80%), 4 subjects had 2.5 % (40) and 2 subjects had 5% contrast sensitivity in PCAG, 3 subjects had 1.25% (80%), 3 subjects had 2.5 % (40) and 2 subjects had 5% contrast sensitivity in PCAG. There was a reduction in contrast visual acuity with and without refraction. Most of the patients had variation at the level of Contrast Visual Acuity in POAG.

Key Words: Contrast Sensitivity, Close Angle, Glaucoma, Intraocular Pressure, Open Angle,

INTRODUCTION

Glaucoma is an ocular illness that damages the optic nerve and gradually progresses to blindness. Rising pressure inside the eye (i.e. raised intraocular pressure) damages the optic nerve, failing to transmit images to the brain, resulting in blindness (1). Increased intraocular pressure is a significant risk factor (2). The pathogenesis of glaucoma is not yet understood; however, the rising intraocular pressure is thought to cause retinal ganglion cell necrosis. There is an imbalance between aqueous humor secretion from the ciliary body and its drainage. Aqueous humor is normally drained through two independent pathways:

1. The trabecular meshwork,
2. The uveoscleral outflow pathway

The rate of flow through these pathways determines the intraocular pressure. Open-angle glaucoma is related to increased resistance in the trabecular meshwork resulting in reduced outflow (3,4). The significant risk factors for glaucoma include age over 45 years, Family history or personal history of raised intraocular pressure, reduced corneal thickness and rigidity, ocular injury, and diabetes mellitus (5,6).

Glaucoma has been categorized into five major types, including:

1. Open-angle or chronic glaucoma: This is the most common glaucoma presenting with gradual vision loss without any other sign symptoms (7,8).
2. Angle Closure (acute) glaucoma: It is an emergency where the flow of aqueous humor fluid is blocked suddenly, causing a rise of fluid pressure causing pain and visual impairment (9).
3. Congenital glaucoma: It is the embryonic development defect in the angle of the eye, where an abnormally developed angle of the eye shows slow or complete blockage of fluid drainage. This type of glaucoma has a familial predisposition and presents with cloudy eyes, excessive tearing, or sensitivity to light in children(10).
4. Secondary glaucoma: It is not a primary defect in the aqueous humor production or drainage but rather a complication of injury or any other eye condition, i.e., cataracts or even ocular tumors, and certain drugs such as corticosteroids may also cause glaucoma (11,12).
5. Normal-Tension glaucoma: It occurs without increased intraocular pressure. The exact cause is unknown, but extreme sensitivity or a reduced blood flow to the optic nerve could be a possible cause (13,14).

Contrast sensitivity deals with the ability to see fine points at low contrast levels. When a person can see minute details at very low contrast, it suggests their high contrast sensitivity, while otherwise, if a person doesn't see that case. Contrast sensitivity is directly related to three-dimensional (3D) vision or Binocular Single Vision (BSV)(15).

Contrast sensitivity is vital in communication, orientation, and mobility, performing everyday tasks, particularly near vision tasks such as reading and writing. The vision in patients with age-related macular degeneration (ARMD) and glaucoma gets better in bright light (11). There is literature available suggesting variation in contrast sensitivity in different types of glaucoma. However, there is low-level literature available suggesting measures of contrast sensitivity in each type of glaucoma. Thus, this study measured contrast sensitivity in different glaucoma patients using visual acuity and visual field.

METHODS

A prospective cross-sectional study was conducted at Glaucoma clinic at Al- Ibrahim Eye Hospital Malir, Karachi, Pakistan, from 1st February 2020 till 30th August 2020. Sixty patients with various glaucoma types were included using a non-probability convenient sampling technique. These patients were between the ages of 16 to 80 years, with a confirmed diagnosis of glaucoma without any other ocular disease. After obtaining written consent, all patients were assessed in standardized room illumination with Snellen's chart. Contrast sensitivity was evaluated with lea symbols contrast sensitivity chart (low contrast flip Chart), visual acuity was checked using Occluder and Snellen visual acuity chart. The findings of the examination were recorded on a pre-designed proforma.

Statistical analysis

Statistical package for social sciences (SPSS) version 20.0 was used for data analysis. All continuous

variables are presented as terms of mean± and Standard Deviation (±SD), and categorical variables are presented as frequency and percentages in graphs and tables.

RESULTS

Total 60 patients with a confirmed diagnosis of glaucoma consented to be part of this study, including 37 males and 23 females (Figure 1). The mean onset age was 38.4 years, ranging from 16 to 80 years. Out of 60 patients, 33 (55 %) patients were diagnosed with Primary Open Angle Glaucoma (POAG), and 17 (28.3 %) patients were Primary Close Angle Glaucoma (PCAG), 7 (11.7%) patients were Acute Closure Glaucoma (ACG), and 3 (5%) patients were Secondary Glaucoma (SG) (Figure: 02). Visual Acuity with glasses 46 (76.7 %) patients had 6/6 to 6/12, 11 (81.3%) patients had 6/18 to 6/36 and 3 (5 %) patients had 6/60 (Table: I). Contrast Sensitivity with glasses 30 (50%) patients had 1.25% (80%).21 patients had 2.50% (40%), 9 patients had 5% (20). (Table: I)

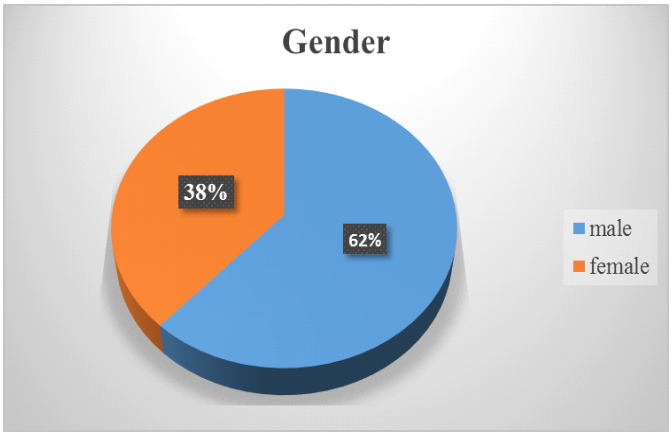

Figure 1. Gender distribution of the patients presenting with glaucoma

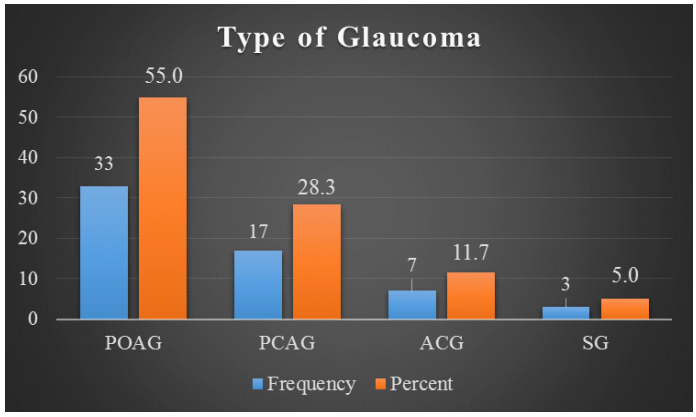

Figure 2: Distribution of the types of glaucoma

Contrast Sensitivity of 15 patients was 1.25% (80%), 13 patients had 2.5% (40) and 5 patients had 5% in POAG. 11 patients had 1.25% (80%), 4 patients had 2.5% (40), and 2 patients had 5% in PCAG. 3 patients had 1.25% (80%), 3 patients had 2.5% (40) and 2 patients had 5% in ACG. 1 patient had 1.25% (80%), 1 patient had 2.5% (40), and 1 patient had 5% in SG (Figure: 03)

Visual Acuity with Glasses	Frequency	Percent
6/6-6/12	46	76.7
6/18-6/60	11	18.3
6/60	3	5
Total	60	100
Contrast Sensitivity with Glasses	Frequency	Percent
5%	9	15.0
2.5%	21	35.0
1.25%	30	50.0
Total	60	100.0

Table 1: Visual Acuity with glass in patients with confirmed diagnosis of glaucoma

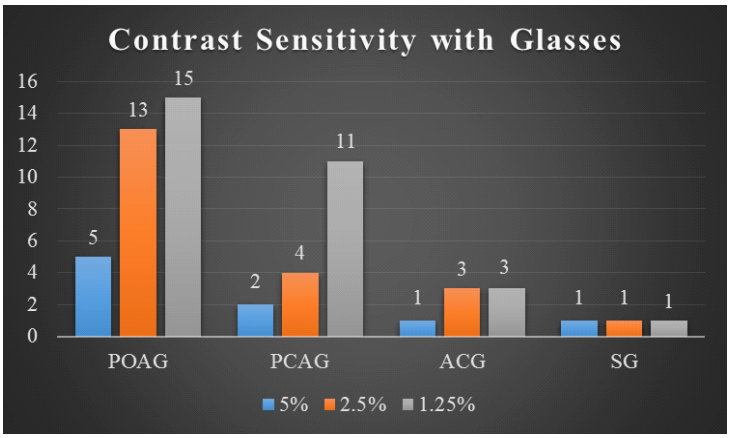

Figure 3. Distribution of Contrast sensitivity in each type of glaucoma

DISCUSSION

In our study, 60 patients were included having confirmed glaucoma diagnosis, their visual acuity was checked, and a contrast sensitivity test of each patient was performed.

The required methods for diagnosing and evaluating glaucoma progression include visual field measurement and optic disc evaluation (3). In addition, psychophysical tests are also helpful to explore each part of the visual pathway's functional status for assessment and monitoring of the disease progression. The deterioration in longitudinal contrast sensitivity in glaucoma patients has been reported in multiple studies.

A test Lea contrast can quickly measure contrast visual acuity by measuring the distance between the eye and clear visibility of the symbols at 25%, 10%, 5%, 2.5%, and 1.25% contrast (10). For the interpretation, the 0.10 visual acuity corresponds to the visibility of 10M symbols at 1 meter, similarly 0.05 at 0.5 meters, and 0.3 at 0.3 meters. Thus, visual acuity values are easy to calculate and interpret, and there is also a table to convert these findings in Snellen equaling VA values (4). There are six pages and response keys available; the contrast to the Peli-Robsin chart test, the obtained results are more reliable and reproducible. The other limitation of the Peli-Robsin chart tests is the measurement of the spatial frequency of 1 cpd at a distance of 1 meter, while patients with ocular hypertension and glaucoma present with contrast sensitivity loss frequencies of 0.25 and 8cpd.

Although in the current study, a decline in the contrast sensitivity with glasses in glaucomatous patients had a maximum of 1.25% contrast sensitivity of high percentage of patients compared to the study conducted by Maria et al. reported in 2016, that contrast sensitivity was affected more in glaucoma patients than high-contrast visual acuity (16). Previously reported studies did not provide such evidence to support contrast sensitivity as a measure for early detection of glaucoma. The contrast sensitivity has been reported to correlate with the perimeter deviation. It is also believed that contrast sensitivity and visual field testing could help identify functional changes in glaucoma patients earlier when they still have good visual acuity.

Onal et al. 2008 investigated spatial-contrast sensitivity (CS) as a measure for diagnosing early glaucoma in patients whose visual acuity was still within normal limits. The study results suggested significantly lower contrast sensitivity at all spatial frequencies in glaucoma patients compared to the controls. The results in our study in terms of Visual Acuity with glasses were 46 (76.7 %) patients had 6/6 to 6/12, 11 (81.3%) patients had 6/18 to 6/36, and 3 (5 %) patients had 6/60. And if we compare contrast sensitivity between both studies, contrast sensitivity measurement was around 50%, while specificity ranged between 68 and 100%. FACT contrast sensitivity scores of less than 22 at 12 cpd spatial frequency provided sensitivity and specificity values concomitantly exceeding 60% to Contrast Sensitivity with glasses 30 (50%) patients had 1.25% (80%).21 patients had 2.50% (40%), 9 patients had 5% (20%).

Contrast Sensitivity has a high percentage in POAG; approximately 33 patients with decreased contrast sensitivity about 15 subjects had 1.25% (80%), 13 subjects had 2.5% (40). Five subjects had 5% than PCAG approximately 11 subjects had 1.25% (80%), four subjects had 2.5% (40), and two subjects had 5% in PCAG after than in ACG approximately three subjects had 1.25% (80%), three subjects had 2.5% (40) and two subjects had 5% in ACG (13). Low percentage in SG approximately 1 subject had

1.25% (80%), 1 subject had 2.5% (40), and 1 subject had 5%. Still, there was no evidence of current previous studies about the types of glaucoma affecting contrast sensitivity.

The study was prospective and conducted in a specialized hospital for eye diseases, having standardized methods and techniques used for the study; however, small sample size is appreciated as a limitation of this study.

CONCLUSION

In this observational study, the result showed a reduction in contrast visual acuity with and without refraction. Most patients had variation at the level of contrast visual acuity in primary open-angle glaucoma. Therefore, it is recommended that contrast sensitivity be performed in patients with refractive errors; in glaucoma patients, visual acuity compared to contrast ability can determine the asymptomatic disorder of eyes.

Routine clinical tests for high and low contrast sensitivity should be done to evaluate patient detail resolving ability and disturbs daily activities, thus patients must be counselled.

Conflict of interest:

All the authors declared no conflict of interest.

Funding

No funding was received for this project

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Research article

LONG TERM RECOVERY ASSESSMENT OF POST-COVID-19 LOSS OF TASTE AND SMELL- A POPULATION-BASED SURVEY

Sana Shahzad[1], Faisal Jamil[2]
[1]St.Helen's and Knowsley NHS Trust, United Kingdom, [2]Medway Maritime Hospital, Gillingham, United Kingdom

Correspondence:
Faisal Jamil
Consultant Physician
Medway Maritime Hospital, Windmill Road, Gillingham, United Kingdom
ME7 5NY

Email:
faisal.jamil@nhs.net

DOI:
10.38106/LMRJ.2022.4.1-05

Received: 03.02.2022
Accepted: 26. 03..2022
Published: 31. 03.2022

ABSTRACT

Coronavirus Disease (COVID-2019) has remained a pandemic for more than two years and has badly affected human lives. It was a novel disease without even knowledge of its symptoms. It has caused millions of deaths all around the world. It involves multiple organ system with a variety of symptoms but sense of taste, smell, were commonly affected. This was a prospective population-based survey conducted by using a pre-defined questionnaire. About 218 COVID -19 RT-PCR positive patients were treated at home without any significant illness. There were 141 and 125 patients who recovered completely with return sense of smell and taste respectively, while 11 patients had both dysfunctional senses. Females had a significantly higher rate of complete recovery of sense of taste but smell had no association with gender. Our study showed a significant proportion of patients showing incomplete recovery of the taste and smell. Further studies on the neurological pathways are recommended to explore it in depth and develop interventions to cure the disability.

Key Words: COVID-19, Long COVID, Sense of smell and taste

INTRODUCTION

Coronavirus Disease (COVID-2019) is a viral infection caused by an RNA virus named SARS-CoV-2. The infection was first reported in Wuhan city of China in 2019; it causes mild symptoms to severe respiratory illness and causes death. According to a World Health Organization (WHO) report, since its discovery in 2019, it accounts for more than 6 million deaths worldwide. Many patients develop the infection without showing any symptoms, while others develop debilitating disease causing hospitalization and even respiratory failure. Following complete recovery, some patients have mild symptoms ranging from mild myalgia to severe dyspnea.

More than half of the patients reported a loss of taste and smell as the most common symptoms (1). Later, long COVID was reported initially from the support groups then confirmed by the scientific community(2). Nevertheless, mechanism and pathogenesis of development of long COVID are not yet understood. Still, it is precisely reported to be with the persistence of the virus for a long time and damage to the nervous and respiratory systems(2). Further reports suggest the involvement of all body systems in long COVID (3), including the immune, musculoskeletal, nervous, gastrointestinal,

cardiovascular and renal systems. Thus no system is spared. Altered taste and smell are the most commonly reported symptoms of long COVID(4). A previously reported study suggested a loss of taste and smell in 28% of cases six months post-COVID(5). Another study from Faroe Island included non-hospitalized, PCR positive COVID 19 patients (n=180). Over 53% of participants reported having at least one symptom after 125 days of recovery. Out of these,>20% of participants reported having a persistent loss of taste and smell(6). In another study, 25.5% of COVID recovered patients reported to have smell and taste disorders more than six months after recovery from the acute phase(7). Initial reports also suggested up to 30% prevalence of smell and taste dysfunction after one-year post-COVID recovery (8).

The available literature includes all patients with COVID-19. There is limited literature available on patients of all levels of severity. There is little literature on patients who had mild symptoms and did not receive aggressive therapy for COVID symptoms. Therefore, this study was designed to evaluate smell and taste dysfunction persistence in patients with mild symptoms.

METHODS

This questionnaire-based survey, including RT-PCR nasal swab confirmed COVID-positive patients diagnosed between 1st April 2020 and 30th April 2021. All patients self-reported having mild symptoms, and no hospitalization was required. The patients who had a loss of smell and taste at the first diagnosis were included in this study, and they were requested to participate. Those who consented after informed consent were included. The self-administered structured questionnaire was designed and requested from the patients who came in contact at least one year after recovery(n=455), and 218 questionnaires were returned filled with informed consent. The questions were asked regarding smell and taste recovery. The questions included recovery of both the senses as complete, incomplete, and dysfunctional. Both senses were questioned separately, and also loss of both senses together.

The data was entered and analyzed using the Statistical Package for Social Sciences (SPSS version 21.0). The questions were reported as categorical variables and presented as frequency distribution in numbers and percentages. Gender was correlated with recovery of both senses by using Ch-squared test, and a p-value <0.05 was considered significant.

RESULTS

A total of 218 participants consented to be part of our study, including 54.1% (n=118) males and 45.9% (n=100) females. The mean age of the participants was 38.73 years (range 21 to 65 years ±SD= 11.01). All of these patients had PCR positive COVID-19, and the median duration of diagnosis was 18.6 months. All of these patients had experienced a loss of taste and smell, out of which 97 patients had complete recovery and return of both senses. 141 (64.7%) had complete recovery of the sense of smell, and 125(57.3%) had complete

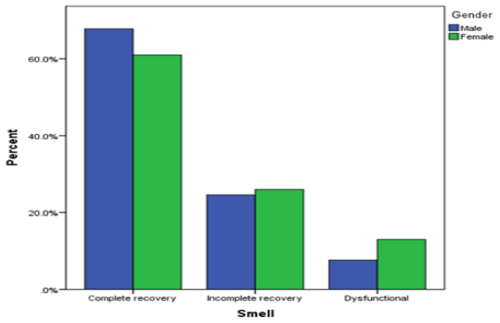

Figure 1. Association of gender with recovery of sense of smell

recovery of taste. 55 (25.2%) had incomplete recovery of smell sense, and 70 (32.1%) had incomplete recovery of taste. 11 (5.0) had both senses dysfunctional. Among dysfunctional senses, patients mentioned cacosmia in the majority of cases. Gender did not show a significant association with the recovery of the sense of smell. Still, the taste was significantly influenced by gender, where female patients had a significantly higher recovery rate (p-value=0.03) (Figures 1 and 2).

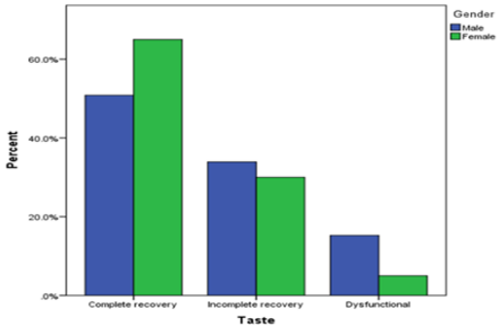

Figure 2. Association of gender with recovery of sense of taste

DISCUSSION

COVID-19 has developed into a systemic problem with some lethal complications resulting in millions of deaths. However, a significant majority recovered completely without any devastating effects on health. Loss of taste and smell were the most commonly reported symptoms in earlier days of the diagnosis. This study focused on the long-term recovery of the taste and smell senses. Though a significant majority in our sample had complete recovery. A considerable number is still suffering from the incomplete return of these senses, and a small number had dysfunction.

Previously reported studies focused on short-term recovery, where 38% and 41% lost taste and smell, respectively, out of which 74% had severe symptoms(9). A large study on the impact of olfactory sense loss on respiratory recovery should show a strong association between the two. Around fifty percent of patients showed recovery of the sense of smell within 40 days of onset(10). Another retrospective study conducted using a questionnaire reported complete recovery of the sense of smell in 85.71% of participants within 3-61 days while around 8% reported persistent hyposmia. Another small study, including 61 patients, reported that 28% of patients continued to have a loss of taste and smell after six months of recovery(5). A cohort study conducted in Melbourne focused on the recovery of taste and smell after COVID showed that 74% of COVID-19 positive patients complained of loss of taste and smell, out of which 34% had a persistent loss of smell after recovery and 28% had complaints of loss of taste(11). Another study reported that around 17% of patients reported having a loss of smell and taste even after nine months of recovery(12). Yet another study reported complete recovery of smell and taste functions in 52% and 61.5%, respectively, after 229 days (13). Our findings of recovery and persistent symptoms post-COVID are consistent with the existing literature.

Loss of smell is widespread during viral infection involving the respiratory system. However, the recovery from the loss of smell corresponds to the recovery of the respiratory symptoms. However, the case was different in COVID patients, where many recovered patients continue to have these symptoms even after biologically confirmed recovery. The exact cause of the loss is not yet understood. Still, specific mechanisms are thought to be involved, such as inflammatory response damaging mucosa or neuronal pathways of smell and taste(14). However, patients with no or minimal stress or depression, or cognitive dysfunction post-COVID are less likely to have a central nervous system problem. Theoretically, it is more likely to be the response at the organ/ mucosal level at the nose and tongue where there is damage to the nerve ending as part of the inflammatory response. Though it is not yet understood. An electrophysiological study was done on the sensory system and

suggested no metabolic activation of the brain after an olfactory stimulus. Thus further detailed analysis would be helpful in exploring the cause and find out the cure of the disability.

CONCLUSION

Our study suggests a considerable chance of having loss of smell and taste even after one year of complete recovery from COVID-19 viral infection. The exact mechanism of the loss is not yet fully understood, and further studies to explore the pathophysiology of the long-term effects of COVID-19 are essential to make it understood.

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Research article

RIGHT VERSUS LEFT COLON CANCER- ARE THEY DISTINCT ENTITIES?

Fayaz Hussain Mangi1, Jawaid Naeem Qureshi2
1Department of Oncology, NIMRA Cancer Hospital Jamshoro, Pakistan, 2Department of Surgery, Indus Medical College, Tando Mohammad Khan, Sindh, Pakistan

Correspondence:
Jawaid Naeem Qureshi
Department of Surgery
Indus Medical College, Tando Mohammad Khan, Pakistan

Email: drjnq@hotmail.com
DOI: 10.38106/LMRJ.2022.4.1-06

Received: 14.01.2022
Accepted: 15. 03.2022
Published: 31. 03.2022

ABSTRACT

Colon cancer is among the most commonly occurring cancers globally and is linked with a poor prognosis. The incidence and prevalence of cancer is expected to rise more in the upcoming years. Right-sided colon cancer reportedly related with poorer survival as compared to the left-sided cancer. This study was conducted to compare both-sided cancers in the Pakistani population. A retrospective analysis of the case files was conducted, including 119 colon cancer patients (i.e. Right colon cancer=41, left colon cancer=78). Left-sided colon cancer showed a lower grade and less rate of metastases. The results showed no significant influence of sidedness on survival outcome, though there was a non-significance difference in favor of right colon cancer. Further studies are required to explore biological differences in cancers arising from both sides of colon.

Key Words: Colon Cancer, Sidedness, Clinical outcome

INTRODUCTION

Colon cancer is among the most commonly occurring cancers around the globe, with a poor prognosis in a majority of patients(1). Anatomically colon and rectum are designed in such a pattern that a large mass can be accommodated for a long time without presenting any specific symptoms. Thus, colon cancer patients are likely to be diagnosed at a late stage. The adult colon is 5 feet long, divided into different sections. The right colon starts with the cecum as first part, then ascending colon, hepatic flexure (under liver where colon makes a turn), then continues as the transverse colon. The middle of the transverse colon demarcates the right and left colon. Therefore, the left half of the transverse colon, splenic flexure, descending colon, and sigmoid colon make the right colon. The rectum is the last part in continuation with the sigmoid colon and ends up with the anal canal. It is suggested that the prevalence of the colon cancer is higher on the left side as compared to the right side(2).

The available literature suggests the influence of colon cancer on clinical outcomes where colon cancer on left side demonstrates better overall survival. In advanced disease, the survival was not influenced by the side of the tumor (3). Similarly, results from the AIO KRK-0104 trial suggested that the left-sided colon was associated with more favorable survival. However, the influence was associated with KRAS mutations, while no influence was seen without taking KRAS into account(4). The NCIC CO.17 trial included metastatic colon cancer and reported that survival in metastatic colon cancer is not

influenced by the side of the primary tumor (5). Data also suggested variation in the biological characteristics of colon cancer depending on the location of cancer (6). Thus the survival difference might have multifactorial influencers from essential characteristics to more complex molecular mechanisms.

The right-sided colon cancer presents with advanced stage, thus being associated with poorer survival than the left colon(7). There has been a consideration that the right and left colon might be separate entities. Therefore, this study was conducted to compare basic characteristics of the colon cancer developing on right and left sides of the colon.

METHODS

A total of 119 colon cancer patients were diagnosed and treated during ten years (between 2008-2018) at NIMRA hospital, and their complete clinical information was available. Out of these, 41 were right-sided colon (i.e, Cecum, ascending colon, and right half of the transverse colon and 78 were left-sided colon (i.e, left half of transverse colon, descending colon, and sigmoid colon) were identified from database in recruited in this study. All the patients had surgery after diagnosis or underwent emergency surgery, or in some inoperable cases, only a biopsy was taken. The data were retrospectively collected from case files. Basic histopathological parameters, including primary site, tumor size, metastases status, and histological grades, were recorded. Histological grade was defined as well-differentiated as grade I, intermediately differentiated as grade II, and poorly differentiated as grade III tumors. Demographic characteristics and basic histological characteristics of right sided colon cancer were compared with that of the left-sided colon cancer. Survival was calculated as the time from date of diagnosis to the date of the last follow-up or death and both sides were compared. Statistical package for social sciences (SPSS version 24.0) was used for data collection and analysis. A comparison was made using the Chi-squared test, and the Kaplan- Meier method was used to compare survival between right and left colon cancer. A p-value <0.05 was considered significant.

RESULTS

The patients (n=119) with complete clinical information available from case files, including 41 right colon and 78 from the left colon were analyzed in this study. Out of which 30.8% of males while 38.9% were females had right-sided colon cancer. Similarly, among left-sided colon cancer, 69.2% were males, and 61.1% were females (Figure 1). On right-sided colon cancer, 19.1% were negative for lymph node metastasis, and 30.8% of left sided had lymph node metastases. Five patients (14.3%) and two (2.6%) were presented with systemic metastases on the right and left-sided colon cancer respectively. Histological grade distribution among right and left colon are shown in Figure 2. Median survival for right-sided colon cancer was 30 months, while 25 months for the left-sided colon. There was no significant difference in the survival of both sides (Figure 3).

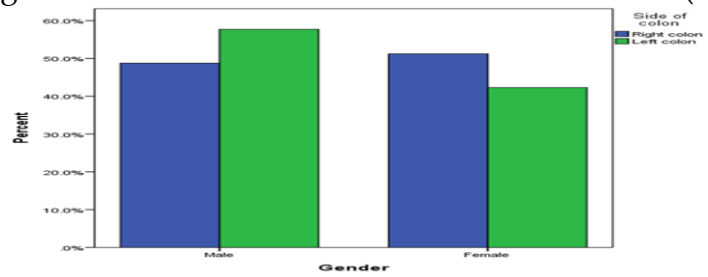
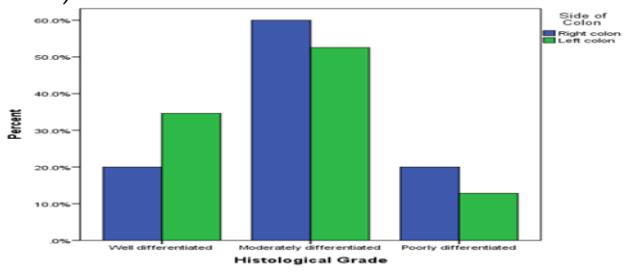


Figure 1. Association of sidedness of colon cancer with gender



Figuer2. Association of sidedness of colon cancer with histological grade

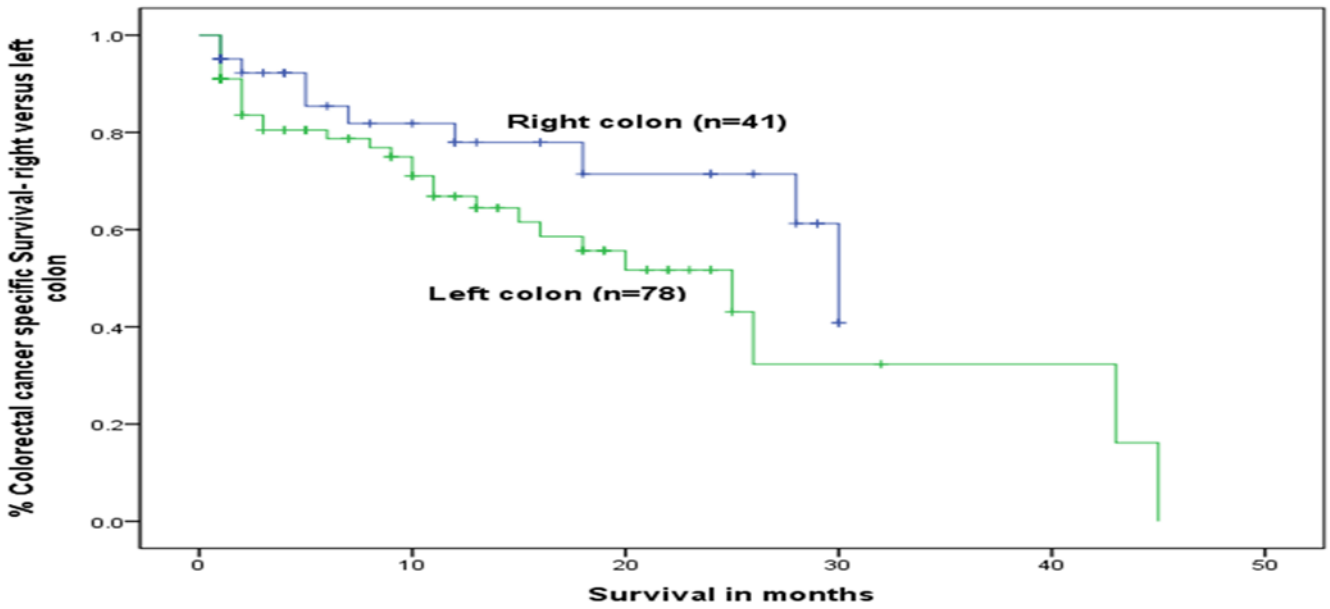


Figure 3: Colon cancer specific survival- Right sided versus left sided

DISCUSSION

The study showed higher rate of left-sided colon cancer in males and presented with a more favorable histological grade. However, the survival difference did not reach a significant level. Left-sided colon cancer reportedly shows better survival in the previously conducted studies. The difference in survival appears to be influenced by biology, which differs according to the location.

Previously reported data suggest that colon cancer in the Pakistani population is associated with a poor prognosis showing shorter survival(8). Biology is also aggressive in the Pakistani population(8). Previously reported studies have suggested that left-sided colon cancer enjoyed better survival, however, this may not be entirely related to the side, but this might influence the development of symptoms. The left-sided colon cancer is nearer to the anal canal; thus, the passing of bloody stool and change in bowl habits develop earlier than the right-sided colon. Obstruction and metastases were more common on the right side, which is most likely attributed to the delay in diagnosis. Cecum has the largest diameter in the entire colon; thus, it can accommodate a large tumor; therefore, the changes of advanced stage at diagnosis are highest. John M Creasy et al. studied 907(3) colorectal cancer patients. They followed them up for 11 years left-sided colon cancer patients showed better overall survival, but there was no significant difference in the disease-specific outcomes. A previously reported study showed that the right-sided colon cancers were significantly more extensive and poorly differentiated than the left colon cancer(9). The same study said that right-sided colon cancer had poor overall and colorectal cancer-specific survival(9). In our study, the survival of both sides was poor, and the sample was even smaller in right-sided colon cancer; thus, it could not reach a significant level. A randomized controlled trial was conducted, including 69 patients, out of which 52 proved to have RAS wild-type metastatic cancer; out of these 84% had left sided disease(10). Though the trial concluded that the sidedness was influencing the disease outcome, actually the mutation was influencing, and wild-type RAS was more prominent on left-sided cancer and showed earlier shrinkage of the tumor and better progression-free survival. In contrast, post-Hoc analysis of the

OPTIMOX3 DREAM Phase III study showed better survival in left-sided metastatic colorectal cancer irrespective of KRAS status(11).

The results of the AIO KRK-0104 trial were suggestive of the same finding as reported in other studies where left-sided colon cancer achieved a favorable survival outcome compared to right-sided colon cancer. KRAS mutation and the sidedness of colon cancer were significant factors influencing survival outcomes (12). Yet another study looked at the influence of the primary tumor resection and compared both sides of the colon, and showed no significant difference in survival if the primary tumor was resected(13). The Spanish TTD trial compared KRAS wild type right-sided colon demonstrated lower efficacy than the left-sided colon cancer(14).

This was a single center-based study where pathological reports were retrieved from the same laboratory using the same definitions of the parameters. All patients were treated using the same guidelines at any given time. However, the study's retrospective nature and a small sample size are considered as the study's limitation.

CONCLUSION

This study showed a non-significant difference in the pathological parameters and survival of colon cancer arising from right and left sides. However, cancer arising from right side of the colon showed a lower rate of occurrence, more undifferentiated tumours and inferior survival as compared to the left-sided colon cancer. Further large-scale prospective studies are required to explore the biological differences in the sidedness of the colon cancers.

Conflict of interest:

All the authors declared no conflict of interest.

Funding

No funding was received for this project

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Research article

AWARENESS OF MOTHERS REGARDING USE OF NATURAL PROBIOTICS IN SCHOOL GOING HEALTHY CHILDREN'S DIET

Fasiha Shah[1], Nabia Shah[2], Faisal Hyder Shah[3]
School of Social work, Faculty of Social Sciences, Universiti Sains Malaysia, Penang, Malaysia, [2]Department of Education and [3]Department of Social Work, University of Sindh, Pakistan

Correspondence:
Fasiha Shah, School of Social work, Universiti Sains Malaysia Penang, Malaysia

Email:
fasiha.sw@gmail.com

DOI:
10.38106/LMRJ.2022.4.1-07

Received: 01.01.2022
Accepted: 18. 03.2022
Published: 31. 03.2022

ABSTRACT

Probiotics are recently getting popular as immunity enhancers, and being investigated to treat acute infections, including gastroenteritis. Commonly used probiotics have been in practice for ancient periods. This study was thus conducted to evaluate the knowledge of mothers of school-going children regarding the use of probiotics in their children's diet. Our results showed that 23% of women were aware of probiotics and their health benefits out of 200 women surveyed, while 16% had never heard of probiotics. However great majority were taking probiotic-rich food, including yogurt, buttermilk, and cheese, in their diet. The knowledge of the use of probiotics in mothers was significantly associated with mothers' level of education. We conclude that there is limited knowledge of probiotics and their health benefits in mothers, but given the anecdotal evidence and inherited dietary patterns, probiotics are part of the daily diet of the school-going children in our study population.

Key Words: Probiotics, Children, Mother's knowledge

INTRODUCTION

Probiotics are living micro-organisms that produce health benefits when taken in a certain quantity. The probiotics are mainly bacteria that resemble normal organs' normal flora, including the gastrointestinal tract, mouth, and skin. Using antibiotics and other conditions that can affect normal flora make patients further susceptible to infections most commonly observed are gastroenteritis. Growing children have higher nutrition demands and protection from infections. Probiotics boost immunity significantly strengthen gut flora to reduce gastrointestinal tract infection.

On the other hand, gastrointestinal infection is the most common cause of illness in children of all age groups. A meta-analysis and systematic review including 34 studies of 4911 patients concluded that probiotics were beneficial in acute diarrhea in children(1). It has been suggested that the use of probiotics not only improves autistic symptoms but also improves gut health in young children (5 – 9 years old)(2). Another interesting study included 120 children with recurrent respiratory tract infections and added probiotics. They showed that probiotics improved gut health by balancing gut flora, thus reducing respiratory tract infection(3). This is probably because of the post- antibiotic effect in gut flora; therefore, the use of probiotics maintains normal intestinal flora.

Yogurt, cheese, pickles, kefir/ fermented milk are commonly used food having a live culture of micro-organisms, and these are everyday dietary items used around the globe. Yogurt has been used since ancient times to improve health and is used as supportive therapy in gastrointestinal disease. There is evidence about fermented food like Kefir showing evidence of modulation of gut flora and reducing the risk of non-communicable disease(4).

There is literature available suggesting using probiotics in children to reduce the risk of infection(5). However, there is still a lack of understanding of parents in using probiotics in the regular daily diet of growing children. Therefore, this study was conducted to evaluate the knowledge of mothers of school-going children about probiotics and the pattern of probiotic-rich food in school-going children's nutrition.

METHODS

This was a questionnaire-based cross-sectional study conducted in two junior schools in Hyderabad. Questionnaires were sent to the mothers of children in junior school classes 1 to 5. The questionnaire had two sections one section had information regarding mothers' knowledge about probiotics and food containing probiotics and their health benefits on the growth and well-being of school-going children. The second part of the questionnaire was related to probiotic-rich food and the frequency of the mentioned food per week. The foods included yogurt, buttermilk, cheese, and pickle.

The responses were recorded as categorical variables. Data were analyzed using SPSS version 22. The frequency of responses was recorded as frequency distribution and presented in tables and graphs and 0.05 was taken as a cut-off for significance.

RESULTS

A total of 200 mothers consented to be part of the study with 285 children. The mean age of children was 7.2 years (range 5- 11.5 years). Out of 200 mothers who participated, 38 were working women, and all the children were city dwellers. Educational level ranged from primary level to masters. The mother's education level was significantly associated with the understanding of the probiotics and their benefits on the health of children (Figure 1). Yogurt was the most frequently used probiotic source, and buttermilk was the least used probiotic source. A summary of the results is given in Table 1.

DISCUSSION

The study suggested that mothers with high education levels were aware of the health benefits of probiotics; yogurt was the most commonly and frequently used source of probiotics included in the diet of school-going children regardless of the mothers' knowledge.

A study reported from Turkey assessed knowledge of women regarding probiotics during pregnancy and for their infants. The study participants demonstrated inadequate ability, significantly associated with age, socio-economical status, educational level(6). The results regarding mothers' knowledge were consistent with our study, and though the children in this study were younger and in the infant group. Similarly, the Alberta Pregnancy Outcomes and Nutrition (APrON) analysis was conducted on 413 Canadian mothers of two years and younger infants. One-third of mothers were not well aware of probiotics, though a great majority heard of probiotics. A considerable number was taken by themselves, but half of the mothers were not giving them to their infants as they were not aware of health benefits in infants(7). Thus the lack of awareness of probiotics is a global issue.

Previously reported systematic review suggested that the parents received information from the internet or the other family members. However, many children were taking probiotics as part of their diet(8). A meta-analysis published in 2019 suggested that using probiotics as an adjuvant in acute diarrhea in children is useful for management(1).

The educational level of mothers	N=200
Up to Primary	56(28%)
Matric	71(35%)
Bachelors	20(10%)
Masters and above	53(26.5%)
Knowledge of probiotics	N=200
Never heard	32(16%)
Heard but don't know the details	122(61%)
Know well	46(23%)
Yogurt	N=200
Not used	35(17.5%)
At least once a week	71(35.5)
More than three times a week	94(47%)
Buttermilk	N=200
Not used	158(79%)
At least once a week	30(15%)
More than three times a week	12(6%)
Cheese	N=200
Not used	62(31%)
At least once a week	92(46%)
More than three times a week	46(23%)
Pickle	N=200
Not used	168(84%)
At least once a week	21(10.5%)
More than three times a week	11(5.5%)

Table 1: Summary of the knowledge of mother's regarding use of probiotics in diet of school going children

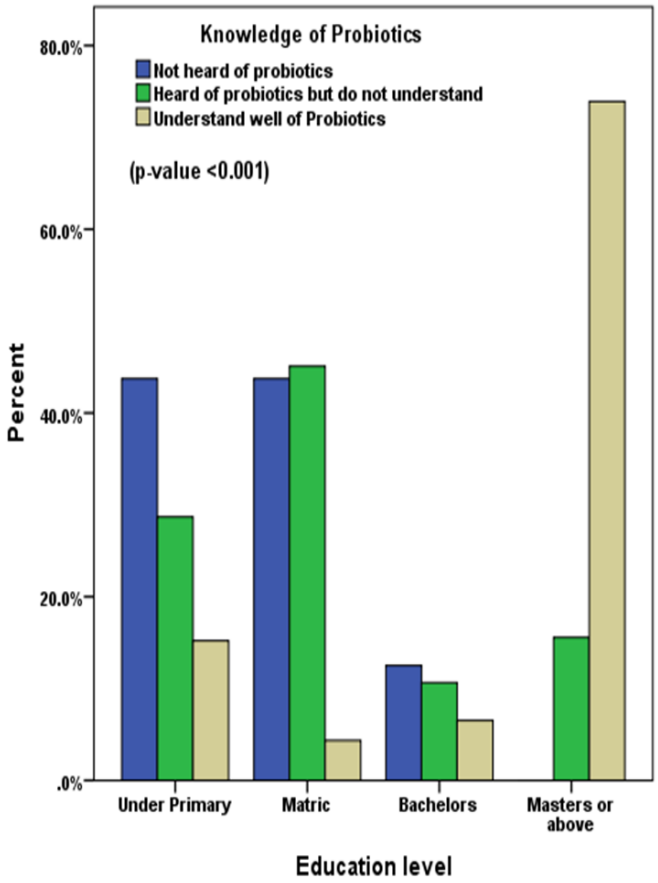

Figure 1. Association of the education level of mothers regarding use of probiotics in the diet of school going children

Interestingly, probiotics suggest a preventive role then therapeutic as a meta-analysis including 33 studies showed a protective role in children's antibiotic-associated diarrhea. Thus knowledge of parents and caretakers is essential in providing enough quantity. A double-blind placebo-controlled trial looked at the efficacy of yogurt in preventing antibiotic-associated diarrhea and showed promising results(9). There is data available evaluating the effectiveness of the probiotics where there are favorable reports in general. However, there is a limited role as a therapeutic agent. Regardless of the use, the priority is safety, and the reported studies suggest that probiotics are well tolerated and that there were no significant reported issues (10).

The study evaluated mothers for their knowledge regarding probiotics in their school-going children. The small sample size was considered a limitation, though the prospective nature of the study is a strength.

CONCLUSION

A considerable number of children take probiotics as part of their regular diet. However, most mothers were not aware of the probiotics—the knowledge of probiotics in mothers associated with the level of education. However, using a probiotic-rich diet is inherited as the dietary habits based on anecdotal evidence. Further studies are required to assess the preventive role of probiotics in children's growth.

Conflict of interest

All the authors declared no conflict of interest.

Funding

No funding was received for this project

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Research article

FREQUENCY OF DIFFERENT INDICATIONS AND FINDINGS FOR COLONOSCOPY IN A TERTIARY CARE HOSPITAL

Jalpa Devi, Nandlal Seerani, Amerta Bai, Rabia Farooque, Hira Laghari, Riaz Hussain Awan, Akram Bajwa, Komal Kumari, Seema Nayab

Department of Gatroentrology, Liaquat University of Medical and Health Sciences Jamshoro, Pakistan

Correspondence:
Jalpa Devi,
Department of Gastroentrology, Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan

Email:
devijalpadj@gmail.com

DOI: 10.38106/LMRJ.2022.4.1-08

Received: 01.02.2022
Accepted: 21. 03.2022
Published: 31. 03.2022

ABSTRACT

Colonoscopy is one of the most important diagnostic tools to assess the structural abnormalities of the large intestine and distal ileum. To date, there is a paucity of data in Pakistan on indications and findings of colonoscopy. Therefore, our study aimed to evaluate the indications and endoscopic findings of patients who underwent colonoscopy at a tertiary care hospital in interior Sindh, Pakistan. This prospective cross-sectional study of 125 patients who underwent lower gastrointestinal endoscopy was conducted in the Endoscopy Unit of LUMHS Civil Hospital Hyderabad / Jamshoro from April 2020 to September 2020. To be eligible participants had to be 14 years or older, of either gender and giving informed consent. Data regarding demographic characteristics, indications, and endoscopic findings were gathered on a pre-designed proforma.

A total of 125 participants were recruited with a mean age of 39 ± 20, out of which 60% were males. Rectal bleeding was the most common indication (70.4%) followed by abdominal pain (9.6%), chronic diarrhea (8%), altered bowel habits (6.4%), constipation (2.4%), post-cancer surveillance (1.6%), weight loss, and anemia (0.8%) each. The most common colonoscopy findings were hemorrhoids (29.6%),and suspected tumor/growth (14.4%), while 22.4% were normal. The most common indication in our study was per rectal bleeding with hemorrhoids as the most common endoscopic finding on colonoscopy.

Key Words: Colonoscopy, Hemorrhoids, Rectal bleeding

INTRODUCTION

Colonoscopy is one of the most important tools to assess the structural abnormalities of the large intestine and distal ileum. It is a safe and effective procedure and plays a pivotal role in the diagnosis of myriads of large intestinal disorders such as infective colitis, colonic adenomas, polyps, inflammatory bowel disease, and carcinomas. Also, it is an essential tool in therapeutic intervention

including polypectomy, electrocoagulation, stricture dilation and stent placement. (1-3). It is a gold standard screening tool for early detection of colorectal carcinoma which has been shown to improve disease outcomes (3-5).

Although it's a relatively safe procedure, some complications have been noted in rare instances. The post colonoscopy complications like perforation, bleeding and mortality rate range from 0 to 1.7/ 1000, 0 to 22.3/1000, and 0 to 2 /1000 colonoscopies respectively. Globally, different gastrointestinal professional societies have adopted the safety standards for colonoscopy practice to minimize post colonoscopy complications (6-10).

Throughout the world, there is a high demand for colonoscopy services (11). In a resource-poor and highly populated countries, there is an utmost need to identify colonic disease burden and to ascertain that colonoscopies are performed only in appropriately indicated cases such as suspicious malignancy and other high-risk abnormalities (12).

To date, there is a paucity of data in Pakistan on indications and findings of colonoscopy. Therefore, we aimed to evaluate the indications and endoscopic findings of patients who underwent colonoscopy at a tertiary care hospital in interior Sindh, Pakistan.

METHODS

This was a prospective cross-sectional study, carried out at the endoscopy unit of Liaquat University of Medical and Health Sciences, Hyderabad / Jamshoro from April 2020 to September 2020. One hundred and twenty-five patients were included, which were referred from inpatient, outpatient, and emergency department. It was carried out after approval by the Institutional Ethical Review Committee.

The patients of either gender, who gave informed consent were included in the study while non-consenting patients were excluded. Data regarding demographic characteristics including age, gender, indications, colonoscopy findings, and the type of therapeutic intervention was recorded on a predesigned proforma. All the colonoscopies were performed without sedation.

As per indications, colonoscopy was performed to observe abnormalities and to send biopsy samples for histopathology. The preparation for the procedure included a digital rectal examination to rule out any contraindication and bowel preparation. For bowel preparation, patients were kept on a liquid diet, bisacodyl 5 mg tablets, 6-10 tablets of sodium docusate 100 mg per-oral, and sodium phosphate (Kleen enema) 24 hours before the procedure. All patients were kept under observation for 2 hours after the procedure, and discharged with counseling on restarting normal diet and reporting any complication immediately. The histopathological findings were not included as the objective of this study was to document indications and colonoscopic findings only.

Statistical analysis was done with IBM SPSS software (version 22 for windows Inc., Chicago, IL, USA). A descriptive analysis was done for demographic features, which were presented as mean ± the standard deviation for quantitative variables and number (percentage) for qualitative variables.

RESULTS

There were 75 (60%) males out of 125 patients. The mean age of patients was 39 (Standard deviation (SD) ± 20) years. Seventy-six (60.8%) patients were in the age group 20-50 while 33 (26.4%) were greater than 50 years of age. The demographics for age, gender, and ethnicity are described in table 1. Eighty-

one (64.8%) patients were referred from the outpatient department while the rest were from different inpatient departments.

Per rectal bleeding (Hematochezia) was the commonest indication (*n*=88; 70.4%) followed by abdominal pain representing 12 (9.6%) patients. Other common colonoscopy indications are shown in Table 1.

Colonoscopy findings showed that 28 (22.4 %) of the patients had normal colonoscopy while many different abnormalities were detected in the 97 (77.6%) patients. The most common findings were hemorrhoids (32.2 %), and suspected tumor/growth (14.4%), followed by other findings which are shown in Table 2.

Table 1. Summary of the primary characteristics and indication of colonoscopy

Age group (years)	**Frequency (%)**
<20	15 (12%)
20-50	76 (60.8%)
>50	34 (27.2%)
Total	125 (100%)
Gender	**Frequency (%)**
Male	75 (60%)
Female	50 (40%)
Ethnicity	**Frequency (%)**
Sindhi	85 (67.5%)
Urdu	15 (11.9%)
Punjabi	9 (7.1%)
Balochi	8 (6.3%)
Pathan	5(4%)
Siraiki	4 (3.2%)
Indication	**Frequency (%)**
Hematochezia	88 (70.4%)
Abdominal pain	12 (9.6%)
Chronic diarrhea	10 (8%)
Altered bowel habits	8 (6.4%)
Constipation	3 (2.4%)
Postcancer Surveliance	2 (1.6%)
Anemia	1 (0.8%)
Weight loss	1 (0.8%)

In patients that presented with hematochezia (Rectal bleed), the most frequent colonoscopic abnormalities were hemorrhoids in 31 (35.2%), suspected colorectal tumor/growth in 12 (13.6%), normal in 10 (11.4%), and rectal polyps also in 9 (10.2%) patients. Among patients with abdominal pain as their indication, the findings were normal in 7 (58.3%), hemorrhoids in 4 (33.3%), and stricture in 1 (8.3%) patients. The colonoscopy findings found in patients that presented with chronic diarrhea were normal and ulcers in 4 (40%) patients each, suspected colorectal tumor/growth, and hemorrhoids in 1(10%) patient each.

The colonoscopy was diagnostic in 118 (94.4%) patients and therapeutic interventions were carried out in 7 (5.6%) patients. Therapeutic procedures included polypectomy.

Table 2. Summary of the diagnosis made on colonoscopy

Findings	Frequency (%)
Hemmorhoids	37 (29.6%)
Normal	28 (22.4%)
Suspected growth	18 (14.4%)
Ulcers	10 (8%)
Rectal polyp	9 (7.2%)
Polyp at other location	4
Ulcer + Hemmorhoids	4
Loss of vascularity+Erythema	3
Fissure in ano + Hemmorhoids	3
Stricture	2
Anal Fissure	1
Colopathy	1
Hard impacted stool	1
Growth + Hemmorhoids	1
Ulcers + Loss of vascularity+pseudopolyps	1

DISCUSSION

Colonoscopy is frequently used for diagnostic, and therapeutic purposes, and as well as the screening tool for colorectal carcinoma in patients older than 50 years as recommended by guidelines (5).

Our study had a majority of male patients (60%) which was consistent with the finding of Olokoba et al. (1), Mohammad et al. (3), Akere et al. (4), Betes M et al. (13), Imperial T et al. (14), Salamat et al.(15) and Mudawi et al. (16) Shrestha et al. (17) while Joukar F et al. (18) and Manzoor et al. (19) had more female patients compared to men.

Furthermore, the mean age of participants was observed to be 39 (± 20) years, in which the majority were in the 21-50 years age group, while in other studies the mean age is quite variable. In a study conducted at Ghulam Muhammad Mahar Medical College and Teaching Hospital, Sukkur, Pakistan in 2019, the mean age was found to be 56 (± 17) years, majority proportion was above 50 years (3), while another study conducted at Military Hospital, Rawalpindi, Pakistan in 2007 had a mean age of 50 years (15). Rehman et al. (20) and Farhan et al. (21) had mean age of 44.86 (±16.22) and 43.7 years.

In this study, we found 28 (22.4 %) of the patients had a normal colonoscopy. In literature, we observed a higher rate of normal colonoscopy findings as compared to our study except for a study done in Nepal by Shrestha et al. (17) which found normal findings in 19.3%. Farhan et al. (21) Salamat et al. (15) and Joukar F et al. (18), Akere et al. (4) reported normal colonoscopy in 40%, 38%, 35.5%, and 26% respectively. The normal colonoscopic findings were as significant as abnormal results since they are reassuring for patients and physician. Efforts should be made to properly screen and weigh the risks and benefits of colonoscopy to reduce unnecessary discomfort, complications, and overutilization of already scarce resources.

Our study showed rectal bleeding as the most common indication for colonoscopy accounting for 70.4 %. Salamat et al. (15), Akere et al. (4), and Olokoba et al. (1) had similar observations. However, in the study by Farhan et al.in Lahore Pakistan, the most common indication was altered bowel habits whereas, Elbatea et al. (2) in Egypt, Mudawi et al. (16) in Sudan found abdominal pain to be the most

common indication of colonoscopy. In the study by Wang et al. in Chinese and American hospital (22), screening for colorectal carcinoma was the most common indication which showed how much developing country like ours is still far from preventive medicine.

Hemorrhoids (29.6%) accounted for the majority of cases of colonoscopy findings in our study which is consistent with Mohammad et al. (3), Joukar F et al. (18), Rehman et al. (20), Nazish et al. (23). Whereas, another study conducted by Salamat et al. (15) Farhan et al. (21), Mudawi et al. (16) found hemorrhoids in only 10%, 10 %, 6.4% respectively.

In our study, we found 14.4 % had suspected tumor/ growth whereas, Salamat et al. (15), Mudawi et al. (16), Shrestha et al. (17), Akere et al. (4), and Elbatea et al. observed 10 %, 11%, 11%,12%, 15% respectively. The third most common finding was ulcers (8%) in this study.

The range of various findings on colonoscopy can be explained by variations based on lifestyle, ethnicity, geography, diet, socio-economic factors, and expertise and experience of the gastroenterologist.

The gender discrepancy in terms of male preponderance could be attributed to the lesser tendency of women to undergo such procedures in developing countries with conservative culture, social inhibition, and lack of awareness. This could lead to the underestimation of the actual risk that colonic diseases would be posing on the females. This warrants community interventions to spread awareness and mitigate the risk of colonic cancer and other diseases in womenfolk.

This study, to the best of our knowledge, it is one of the few studies from interior Sindh to delineate the indications and findings of colonoscopy. However, it can't provide the prevalence and incidence in the population since it's a single hospital-based study. Several such large-scale multi-center studies and population-based registries are required to identify the actual burden of the colonic diseases in the country, which would help to direct the health care services and calculated allocation of limited resources.

CONCLUSION

Per rectal bleeding constituted the most common indication of colonoscopy followed by abdominal pain and chronic diarrhea. Hemorrhoids, suspected growth/tumor, and ulcers were the most frequent pathology in patients who underwent colonoscopy. Approximately, one-quarter of patients had a normal examination of colonoscopy.

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Letter to Editor

ARTIFICIAL INTELLIGENCE IN AID EFFICIENT MENTAL HEALTHCARE IN CONTEXT OF STATE-OF-THE -ART SIR COWASJEE MENTAL HEALTH INSTITUTE AT HYDERABAD SINDH PAKISTAN

Aijaz Patoli[1], Shehram Syed[2], Abbas Syed[3], Zafi Sherhan Syed[4]
[1]Sir C.J. Institute of Psychiatry & Behavioral Sciences Hyderabad Pakistan. [2]RMIT University, Australia. [3]University of Louiseville, USA. [4]Mehran University of Engineering & Technology, Pakistan.

Correspondence:
Dr. Aijaz Patoli
Founding C.E.O of Sir C.J. Institute of Psychiatry & Behavioral Sciences Hyderabad Pakistan
Email: draijazq@gmail.com

DOI: 10.38106/LMRJ.2022.4.1-09

Received: 03.01.2022
Accepted: 02. 03.2022
Published: 31. 03.2022

ABSTRACT
Artificial intelligence (AI), often described as the machine simulation of human intelligence, is a branch of computer science that solves problems automatically using computational algorithms. AI systems work by first consuming massive volumes of labeled training data, analyzing it for patterns, and finally using these patterns to make predictions. On the other hand mental health issues are increasing in human thus use of AI in provision of mental health aid would a novel approach.

Key Words: Artificial Intelligence, mental health, machine simulation

INTRODUCTION

Globally, over 70% of adults and younger population live with mental illness without receiving any treatment or approaching mental health care facility (1). There are a number of societal barriers and taboos in receiving mental health care as compared to physical health. Thus there is a huge difference in actual prevalence and treated prevalence of mental health (i.e. treatment gap)(2). Among many reasons for this include; stigma, discrimination, capacity & minimal investment in mental health. Historical lunatic asylums journey tertiary level mental facilities like Sir C.J. Institute of Psychiatry (CJIP) Hyderabad Sindh Pakistan, which was established as an asylum in 1865, could not had an impact until year 2000, with the publishing of World Health Report which estimated the Burden of Disease–Disability Weights. There was a shock for the world, that mental health disorders were included in top five diseases causing disabilities.

Artificial intelligence (AI), is the simulation of human intelligence by machines. It is an area of computer science that uses computational algorithms to solve problems automatically. AI systems work by collecting large amounts of labelled training data, evaluating it for patterns, and then making predictions based on those patterns. AI in mental healthcare has the great potential (3).

It is used to identify behavioral traits of individuals with mental illness and to improve the management of mental healthcare interventions. In fact, mental healthcare is one of the domains in which telehealth and AI can be integrated seamlessly (4).

Academicians from the fields of psychology and computer science have collaborated to use artificial intelligence to gain a better understanding of mental illnesses in order to develop systems that can detect the disease using computational machines (5).

This letter briefly describes the use of four modalities namely; audio, visual, text, and physiological signals in conjunction with AI-powered machine learning systems to spot signs of mental illness. We cite research studies that have demonstrated the efficacy of such solutions. Our letter will focus on AI-based automated depression recognition, as depression is the most common type of disability worldwide, impacting more than 5% of the global adult population, according to WHO. Untreated depression has also been linked to suicide in the past (6).

Human speech consists of linguistic and paralinguistic parts. It has already been demonstrated that AI-based systems can detect human emotions, trustworthiness, and sincerity by using paralinguistic aspects of speech (7). There is an emphasis on investigating how speech can be used as a biomarker of diseases that affect speech production, such as depression (8). The aim is to use the information contained in a paralinguistic speech to build and subsequently deploy AI-based systems to identify depression from everyday conversations. Two important studies in this regard are from Alghowinem *et al.* and Williamson *et al.* who highlighted that computational speech analysis may yield biomarkers for depression(9, 10). The survey from Cummins and colleagues reported a detailed review of speech-based screening for depression and suicide risk.

Natural-language processing (NLP) is a sub-field of AI that is used to evaluate textual documents automatically to infer meanings (11). NLP deals with the linguistic aspects of human communication. It has received a lot of attention recently for its potential in mental healthcare (12). Bathina *et al.* reported that individuals with depression express atypical and distorted language on social media (13). In respect to that, Jain *et al.* demonstrated that NLP can be used to identify social media posts related to depression and suicidal intent, whereas, Rinaldi *et al.* proposed a novel approach to interview transcripts of depressed individuals to provide psycholinguistic insights about the disease (14, 15). These are encouraging signs that show that NLP holds great potential to support the mental healthcare of patients and may be integrated into the AI-based system for automated depression screening.

Facial expressions provide the most powerful, natural, and straightforward way to communicate emotion. Human beings perceive emotional feedback and reciprocate behavior based on recognizing others' facial expressions. However, it is well known that individuals' mental illnesses have atypical facial behavior that can provide cues to mental state. To this end, Girard et al. propose that automated systems can be trained to spot depressive features in people's facial expressions (16). According to Stratou *et al.,* as depression severity grew, respondents in their study showed less facial activity in terms of facial muscle movement and head movement (17). They experienced lesser eye gaze changes, making them appear inattentive and passive and observed that people with depression had facial emotions of hostility, sadness, and a lack of joy (17). These studies suggest that it is possible to screen for individuals with depression based on their facial appearance and movement, and that is the rationale for integrating visual modality for automated depression screening.

Amongst other modalities, multiple studies have shown that physiological signals such as heart rate, blood pressure, electro-dermal activity, and electro-encephalogram offer an alternate way to recognize stress, anxiety, and depression (18). Similarly, body movement information can be used to gauge for psychomotor activities of patients with depression. It should be mentioned here that an automated system to recognize depression can also work by ingesting information from multiple modalities, learning from it, and making predictions of the patient's mental state. In fact, several studies, have shown that integrating multiple modalities can help improve the systems performance. Thus, there is ample evidence to investigate the use of AI-based automated systems for screening depression.

The experimental methodology for automated depression screening is based on conversations that include a clinician and the patients with depression in a hypothetical clinical setup. The setup consists of hardware and software parts. The hardware part includes electronic sensors to acquire audio, visual, physiological and body movement data. The software part consists of algorithms that implement the AI-based system featuring engineering and machine learning parts.

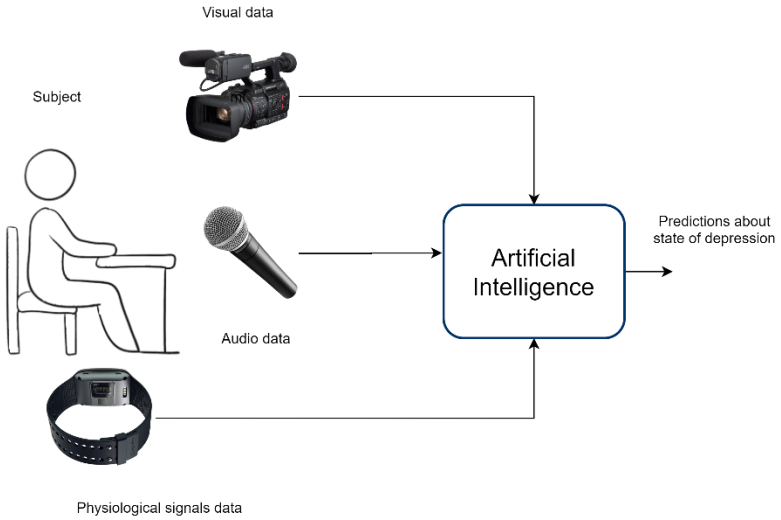

Figure 1: Conceptual setup for data collection where audio, visual, and physiological signals data is acquired from both, the subject and the clinician

Figure 1 illustrates the data collection setup for the task of automated depression screening. This hardware setup is placed in a hospital environment where patients typically meet the clinician to seek medical and/or therapeutic support. The communication between the two is required in the form of video recordings through a video camera and microphone facing the patient – these provide necessary data for audio and visual modalities. A suitable speech transcription tool can be used to generate transcripts for conversation between the clinician and patients. This modality can subsequently be used for NLP, as discussed earlier. Physiological signals such as temperature, blood pressure, heart rate, and electro-dermal activity are recorded through the Empatica E4 band. The efficacy of this module has already been demonstrated with tasks related to stress detection. In addition to physiological signals, the E4 band also records body movement data through the built-in IMU. Thus, the recording setup enables the recording of multimodal signals that can be leveraged for automated depression recognition.

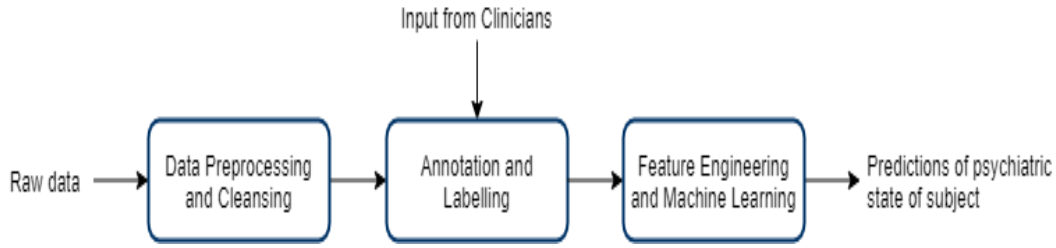

Figure 2: Conceptual framework for signal processing and machine learning pipeline

The conceptual process flow diagram for the signal processing and machine learning pipeline is illustrated in *figure 2*. It starts with data preprocessing and cleansing which ensures that the acquired data is of sufficiently good quality for training AI-based systems. The data so far does not contain ground-truth labels regarding the psychiatric state of subjects, for example, whether the patient is healthy or has depression. Labels can also include depression severity, for example, in terms of the Patient Health Questionnaire-9 score (19). At the annotation and labeling stage of this framework, labels will be assigned to each recording based on the input from clinicians. These labels are provided by the clinician after assessing the patient.

The Feature Engineering and Machine Learning pipeline consist of feature computation, feature selection, and classification based on cross-validation. At the feature computation stage, audio, visual, and physiological signals data is transformed into representations that are meaningful for the classifier. For example, prosody, voice quality, and spectral features are more meaningful for classifiers than raw audio waveforms. Similar transformations are also required for visual and physiological signals data.

At the machine learning stage, the dataset is divided into three parts; training, validation, and test. The sub-datasets are used to train the machine learning model, validate its performance for different hyper-parameters, and finally test its performance on a previously unseen part of data. The choice of a machine learning algorithm depends on the type of labels. If the dataset has been labeled for binary classes of depressed and not-depressed, then a classifier will be used. On the other hand, if the dataset has been labeled for depression severity, then a regressor will be used. Once the machine learning model has been trained, it can be used to recognize the existence of depression as well as its severity in a real-world environment.

The World Health Report 2000 was alarming to developed world even. The stigma, discrimination, capacity & low investment in Low Middle Income Countries (LMICs) like Pakistan face great challenges specially in backdrop of pandemic effects of social psychology (20). Wave of change of policies towards mental health, set in by the World Health Report, can be seen in form of transformation of CJIP Hyderabad into an autonomous multidisciplinary Mental Health facility. Still the technology has fill the gaps in our context specially "The 10/90 Gap" and the treatment gap (20). The 10/90 discovered that during 2002-2004, only 3.7% of research on psychiatry in leading journals was from the least developed countries, whereas they represent >80% of the world population. This means we are relying on the western sociocultural context for our knowledge to address our own mental challenges. This Category fallacy (Kleinman, 1987): Applying a category that makes sense for a particular cultural group in another group, for whom this category may not make sense, creates

treatment gap. So we need to adopt Leapfrog strategy to include Artificial Intelligence in planning and development of state-of-the-art Sir C.J Institute of Psychiatry & Behavioral Sciences Hyderabad for diagnosis, treatment, monitoring & evaluation and recovery.

To conclude, in this letter, we provided a brief overview of multiple modalities through which behavioral cues for mental illness can be recognized. We also discussed the steps of data collection, data annotation, feature engineering, and machine learning for the AI-based system for automated depression screening. We hope this letter encourages collaboration between psychologists, computer scientists, and engineers to begin research into automated depression screening systems in Pakistan.

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Editorial office:

Liaquat Medical Research Journal
Diagnostic & Research Lab,
Liaquat University Hospital, Hyderabad,
Sindh, Pakistan.

Ph #: +92 22 9210 212
Fax #: +92 22 9220 100

Email: lmrj@lumhs.edu.pk
URL:http://ojs.lumhs.edu.pk/index.php/LMRJ