JSTMU Journal of Shifa Tameer-e-Millat University

Shifa Tameer-e-Millat University
شفا تعمیرِ ملّت یونیورسٹی

Volume 03 | No. 2 | Dec 2020

Web: https://j.stmu.edu.pk
Email: editor@j.stmu.edu.pk

ISSN 2617-8095 (Print)
ISSN 2617-8109 (Online)

JSTMU Journal of Shifa Tameer-e-Millat University

ISSN 2617-8095 (Print) ISSN 2617-8109 (Online)

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EDITORIAL

COVID-19 raises threatening scenario for otorhinolaryngology and rehabilitation

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Cite this article as: Mumtaz N, Saqulain G. COVID-19 raises threatening scenario for otorhinolaryngology and rehabilitation. JSTMU. JSTMU. 2020; 3(2):62-63.

Keywords: *COVID-19, health care, otolaryngology*

COVID-19 Pandemic has the potential to test the mettle, resilience and strength of each and every facet and aspect of health care system worldwide.[1] The contours, parameters and extent of this mutable pandemic are still hazy and what is more alarming is that the treatment protocols are not universally standardized nor defined. Health professionals are improvising constantly and the advice of the World Health Organization is a generalist approach which is suggestive of the notion that this organization lacks expertise or is unable to coordinate efforts to contain COVID-19 globally. So does this imply "each to his own ".

The healthcare system has never faced such an unprecedented and blunt challenge due to the pandemic with health care professionals in developing countries like Pakistan facing threat of contracting Covid-19 by them and their families due to lack of provision of proper personal protective equipment (PPE)s.[2] Knowledge gaps related to infection control measures, procedures with high risk including aerosol generating procedures, compromised training as well as professional and administrative support not being complemented by research and educational interventions.[3] Maunder RG et al. supports the postulate that such category of health and allied health care professionals were directly and routinely exposed to substantially higher risk of chronic stress or traumatic spinoffs.[4]

Otolaryngology symptoms like a simple cough, a sore throat, breathing difficulty, even anosmia or hyposmia, may be a precursor of severe COVID-19 disease.[5] The ear, nose and throat (ENT) profession is in high risk strata as regards COVID-19 spread due to the fact that it entails hovering near the mucous membrane of upper airway, sections, drops and aerosols generated from the airway during procedures as well as surgical interventions. It is essential that in order to prevent infection and keep ENT's safe improved screening, suspension of non-emergent consultations and clinical examination and elective procedures be resorted to.[6]

This specialty is susceptible for contracting disease from asymptomatic cases in their clinics during routine ENT – patient encounters. A local study revealed 90% cases in isolation centers as being asymptomatic and positive for Corona SARS-2 RNA on PCR testing. Functioning of certain specialties, unavoidably involving close proximity with patients, has been severely affected including dentistry.[7] Even medical students are disheartened and their work performance has badly affected [8] besides disrupting their academic progress and acquiring of clinical proficiency. In addition to ENT surgical procedures, routine examination procedures prevalent in otolaryngology including fibreoptic laryngoscopy and naso-endoscopy are all aerosol generating procedures (AGP's). Compulsory usage of N95 respirators, PPE's, elastomeric respirators usually re-usable and hermetically sealed give superior protection then N95.[9]

A semblance of hope is returning to normal dental practice as being witnessed in China,[7] which has claimed containment of the virus perhaps on account of adopting

safety features. For an otorhinolaryngologist PPE's including gowns and gloves being water resistant, glasses and FFP3/N95 mask are recommended for examining patients, however elective surgeries at the same time should be postponed.[5] Lavinsky J et al. in a Brazilian study, have recommended PPE's use in a routine clinical environment, deferring of clinical appointments, examinations and shifting more towards elective procedures on priority so as to reduce spread. Simultaneously it is advisable to alter clinical setting routines in vogue in diverse areas of ENT complemented by extensive adoption of tele--medicine, tele-practice and tele-rehabilitation prevalent as a manifestation of this pandemic as evidenced.[10] For otolaryngology practice meticulous screening may serve to improve personal awareness regarding protection and dissemination of training on appropriate quality of PPE's during high risk procedures.[6] The same approach should be the underlying theme when rehabilitation professionals including speech and language pathologist render short and long term rehabilitation to patients undergoing or past COVID-19.

COVID-19 demands from otolaryngologists an incredible moral and professional forte in reducing exposure as well as extending of adequate care for the patient.[1] As highlighted by Moti & Goon private and public partnership necessarily complement each other's healthcare systems in recovery of both healthcare needs & economy specific to each individual country. Correspondingly a partnership is established, by choice or compulsion, in healthcare between countries as well as globally.[11]

COVID-19 is taking a toll on the global health care systems and established treatment and clinical protocols and processes. The shock and awe engendered by this pandemic is now giving way to a stampede to develop vaccines even if shortening clinical trials. It is difficult to decipher if the developed economies are petrified or the developing nations despite a display of bravado on both sides. Research will entail extensive and sustained financing as the COVID-19 manifestation, its treatment protocols, prognosis and spread over demographically and geographically diverse regions has to be factored in to enable a comprehensive understanding of the seemingly changing and morphing virus.[12]

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ORIGINAL ARTICLE

Causes of mid trimester pregnancy loss in a tertiary care hospital

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[1] Data collection, data analysis, data interpretation, manuscript drafting
[2] Manuscript writing, data interpretation, proof reading
[3] Literature search, data interpretation, write up, proof reading
[4,5] Data collection

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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Cite this article as: Zardar B, Fawad A, Ismail A, Mehreen S, Bibi S. Causes of mid trimester pregnancy loss in a tertiary care hospital. JSTMU. 2020; 3(2):64-69.

A B S T R A C T

Introduction: Mid trimester of pregnancy is relatively a safe time of pregnancy with minimal and no complications. Mid trimester pregnancy loss constitutes 1 to 5 % of total miscarriages. The purpose of this study is to evaluate the causes of second trimester miscarriages so as to improve the outcome in future pregnancies.

Materials & Methods: This was a prospective cross-sectional study. Demographic features, relevant information and risk factors were recorded in a predesigned proforma. Detailed history was followed by thorough clinical examination and appropriate investigations were advised.

Results: Total number of miscarriages admitted in the unit over the period of two years were 336 and among them 30 patients presented with second trimester miscarriages (8.9%). The mean age of the patients was 31.4 years. In 19 patients (63.4%) there were identifiable causes for the miscarriage. 7 patients (23.33%) had fibroids in the uterus, 5 patients (16.67%) had bacterial vaginosis, 4 patients (13.33%) had cervical incompetence and in 3 patients (10%) there were congenital abnormalities in the uterus.

Conclusion: Patients with second trimester pregnancy loss are at significantly increased risk (10 times more likely) for recurrent second trimester loss. In 50 to 70% of patients no cause can be identified. After single loss there is 80% chance of successful pregnancy outcome in future. Even after two and three mid trimester losses still there is 60% chance of alive pregnancy next time, so thorough evaluation and management plan is needed to prevent this mishap in future pregnancies.

Keywords: *Mid trimester miscarriages, fibroid uterus, bacterial vaginosis, cervical incompetence, congenital uterine abnormalities*

Introduction

A second trimester miscarriage is defined as loss of pregnancy after 12 weeks' period of gestation and before 24 completed weeks. Mid trimester miscarriage is uncommon, comprising 1 to 5 % of total pregnancy loss. Second trimester miscarriage needs detailed evaluation especially where loss is recurrent to prevent such mishap in future pregnancies. In majority of patients (50 to70 %) the cause cannot be identified but it depends upon the resources available for thorough investigations.[1]

Sometimes there is more than one cause operating in one patient. The presence of multiple risk factors further increases the chances of mid trimester miscarriage and preterm labor. Common causes of second trimester miscarriage are incompetent cervix, abnormalities of uterus (fibroids, intrauterine adhesions), infections,

chromosomal and structural abnormalities in the fetus, chronic maternal medical disorders like uncontrolled hypertension, diabetes and disorders of thyroid gland, congenital uterine abnormalities, autoimmune diseases in mother, antiphospholipid syndrome and thrombophilias.[2]

Screening protocol includes detailed history, clinical examination and relevant investigations. In present pregnancy the period of gestation at which patient presented, along with her symptoms like history of uterine contractions, per vaginal bleeding, history of rupture of membranes and fever should be noted. Dating scan and anomaly scans should be reviewed along with any screening tests performed. Past medical history should involve enquiry about chronic maternal illnesses like hypertension, diabetes and disorders of thyroid gland. Family history of autoimmune diseases, thrombophilia, chromosomal abnormalities and congenital abnormalities should be noted. Past obstetrical history should be taken in detail especially regarding previous pregnancy losses, preterm deliveries, previous modes of deliveries and outcome of previous pregnancies. Examination should include both general physical examination and systemic examination. Abdominal examination should be followed by pelvic assessment. Vaginal swab should be taken for culture and sensitivity and ultrasound should confirm fetal viability.

Incompetent cervix classically presents with painless cervical dilation in absence of uterine contractions and alive fetus on scan. Studies have shown that fibroids in uterus, both submucosal and intramural, cause second trimester miscarriages. Congenital uterine abnormalities are uncommon but can be found in mothers with recurrent pregnancy losses. Screening for autoimmune diseases, antiphospholipid syndrome and thrombophilias should be done in mothers with recurrent second trimester pregnancy losses.[3]

This study was aimed to find out the cause of second trimester miscarriage for proper counselling and management of patients and to prevent recurrent losses in future. This study will aid to the existing knowledge about the subject and the results will be useful for practitioners to do evidence-based practice.

Methodology

This was a prospective cross-sectional study conducted in Ayub Teaching Hospital, Abbottabad, OB/Gyn A unit, on patients who got hospitalized in the unit over the period of two years from January 2017 till December 2018. All the patients with first and second trimester miscarriages were included in the study. Written informed consent was taken and confidentiality was maintained. Study was conducted after getting approval from hospital ethical and research committee. Non probability consecutive sampling technique was used. Patients with twin gestation and polyhydramnios were excluded from the study.

Detailed history was taken followed by clinical examination. Previous history of miscarriages and preterm births was taken. History of congenital abnormalities and fibroids in the uterus as diagnosed on ultrasound was inquired. Clinical examination was done to exclude uterine myomas. Per vaginal assessment helped to exclude vaginal discharge and to determine cervical length and dilatation. Relevant investigations were sent which included abdominal ultrasound scan and high vaginal swab for culture and sensitivity. Data was collected by using a predesigned pro forma. Data was entered in and analyzed by using SPSS version 16. Mean was calculated for numerical variables like age. Frequencies and percentages were used for categorical variables. All results were presented in the form of tables.

Results

Over the period of two years, the total number of miscarriages admitted were 336 including both first and mid trimester miscarriages. Among them there were 30 patients with second trimester miscarriage (8.9%) and 306 patients with first trimester miscarriages including threatened miscarriages. Among 30 patients with second trimester loss, in 11 patients (36.67%) no cause could be identified while in 19 patients (63.4%) there were identified causes. 07 patients (23.33%) had fibroids in uterus, 05 patients were diagnosed to be having bacterial vaginosis (16.67%), 04 patients (13.33%) had cervical incompetence and 3 cases (10%) had congenital uterine abnormalities. Majority of the patients were in age range of 25 to 35 years. Mean age was 31.4 years. 12 patients

were primigravidas (40%) and 18 patients were multigravidas (60%). Majority of patients had pregnancy loss between 18 to 20 weeks of gestation. The most common abnormality found was fibroids in the uterus, followed by bacterial vaginosis and cervical incompetence. Congenital uterine abnormalities were least common.

Table 1: Age of Patients (n=30)

Age	Frequency	Percentage
21- 25 years	5	16.67%
26-30 years	7	23.33%
31-35 years	8	26.67%
36-40 years	10	33.33%
Total	30	100%

Table 2: Gravidity (n=30)

Gravidity	Frequency	Percentage
Primigravida	12	40%
Multigravida	18	60%

Table 3: Period of Gestation (n=30)

Period of gestation	Frequency	Percentage
Less than 15 weeks	8	26.66%
18 to 20 weeks	15	50.00%
21 to 23 weeks	7	23.33%
Total	30	100%

Table 4: Causes of Miscarriage (n=30)

Cause of miscarriage	Frequency	Percentage
Unknown cause	11	36.67%
Fibroids	7	23.33%
Bacterial vaginosis	5	16.67%
Cervical Incompetence	4	13.33%
Congenital uterine abnormalities	3	10%
Total	30	100%

Discussion

Second trimester pregnancy loss is uncommon but it is a distressing event in a patient's obstetrical history. It is the loss of pregnancy between 13 weeks to 23 weeks and 06 days' period of gestation. Patients with mid trimester loss are at significantly increased risk of recurrence (10 times more likely) of second trimester loss or preterm delivery in future pregnancy. In 50 to 70 % of patients no definite cause can be identified but it depends upon how thoroughly a patient has been evaluated and investigated. We received 30 patients with second trimester pregnancy loss over the period of two years and among them in 11 patients (36.6%) no definite cause could be identified.[4,5]

In 7 patients out of 19 (36.8%), there were fibroids in the uterus, both submucosal and intramural as diagnosed by ultrasound scan. A study was conducted in department of obstetrics and gynecology, CMH Lahore by Sarwat Navid and her team. They found 80 patients with fibroid uterus (equal to or more than 5 cm in size) in 10,842 OPD patients (0.74%). In this study 8/80 patients (10 %) had miscarriages. The conclusion of the study was pregnancy with fibroids is a high risk pregnancy with many complications including low lying placenta, placental abruption, breech presentation, cord prolapse, retained placenta, post-partum hemorrhage and need for emergency hysterectomy.[6,7]

A meta-analysis of different studies regarding fibroids and infertility by N Bajekal and T.C.Li has narrated that fibroids are fairly common in women of reproductive age group and are responsible for infertility and pregnancy losses. In women with fibroids, 50 % will conceive after myomectomy and there is a significant reduction in first and second trimester pregnancy loss. A submucosal or intramural fibroid distorting the uterine cavity, fibroids more than 5 cm in size and multiple fibroids are all indications for myomectomy in women planning the pregnancy.[8,9]

Infections have important role to play in mid trimester pregnancy loss and in preterm labor. 10 to 25 % of mid trimester miscarriages are caused by infections as discussed in different studies. Many infections are involved including bacteria, fungi, viruses, spirochetes and protozoa. The most important infection involved is bacterial vaginosis. It is imbalance in vaginal flora with

reduction in lactobacilli and abundance of anaerobes, enterococci, coliforms, staphylococci, fusobacterium, mycoplasma, ureaplasma, group B beta hemolytic streptococci and more importantly gardnerella vaginalis and mobiluncus. Bacterial vaginosis is present in 50% of pregnant women and is a risk factor for mid trimester miscarriage and preterm labor. In our study we found 5 patients out of 19 (26.3 %) with bacterial vaginosis as diagnosed by culture of high vaginal swab. Amsel criteria was used for diagnosis (thin, white, yellow, homogeneous discharge, clue cells on microscopy, pH of vaginal fluid >4.5). Treatment of bacterial vaginosis will reduce the incidence of mid trimester miscarriages and preterm deliveries. Studies have shown the beneficial effects of treatment for bacterial vaginosis if started before 20 weeks of pregnancy, so starting treatment early in second trimester is recommended.[10-12]

When cervical dilatation and effacement occurs without the presence of uterine contractions during second or third trimester before term, it is referred to as cervical insufficiency. True cervical weakness is an accepted cause of mid trimester pregnancy loss and preterm labor. In our study during the period of two years we received 4 patients out of 19 (21.2%) in which miscarriage occurred due to cervical incompetence as diagnosed by typical history of painless cervical dilatation and expulsion of alive pregnancy.

Ultrasound (transvaginal) assessment of cervical length is an effective prognostic indicator of mid trimester pregnancy loss and preterm labor especially in women with previous history. Cervical length less than 2.5 cm is best indicator in high risk patients. Such patients benefit more from cervical cerclage. A 02 years' study conducted in Ayub Hospital complex, Abbottabad showed high success rate of cervical cerclage applied in properly selected cases with previous history of mid trimester miscarriages and preterm deliveries, with sonographic evidence of cervical shortening, dilatation and cone formation.[13] A study conducted by Huma Naz and her team in Fatima hospital Baqai medical university Karachi studied beneficial effects of cervical cerclage in 33 patients. Patients with previous history of mid trimester pregnancy loss and preterm deliveries and those with cervical length less than 2.5cm on ultrasound were included in study. Pregnancy prolongation with delivery at term occurred in 87.8% of patients.[14] Similar beneficial effects have been observed in several other studies.[15,16]

Elective cervical cerclage early in second trimester overcomes the risk of emergency procedure. A study conducted in Independent University Hospital Faisalabad over the period of two years included 50 patients with previous history of recurrent mid trimester miscarriages due to incompetent cervix. Effectiveness of cerclage was more than 90%. Elective procedure gives better fetomaternal outcome.[17] Elective cervical cerclage has definitely a beneficial role to play in patients with repeated mid trimester pregnancy losses, previous preterm deliveries with sonographic evidence of short cervix.[18,19,20] Although having beneficial effects for properly selected patients, the surgical procedure of cervical stitch application is not without risks. Saba Mubashir and her team studied the morbidities associated with this procedure in Agha khan university hospital Karachi. It is 2 years' study which included 70 patients who underwent cervical stitch. Morbidities included rupture of membranes, miscarriages, preterm labor, chorioamnionitis and displacement of suture. Risk of maternal infection also rose by two fold. They reported that after cervical stitch application the risk of rupture of membranes was 10% and risk of miscarriage was 8.6%.[21]

In our study congenital abnormalities of the uterus were diagnosed in 3 patients of mid trimester miscarriages out of 19 (15.7%). There were 02 cases of bicornuate uterus and 1 case of unicornuate uterus as diagnosed by ultrasound scan. Structural abnormalities of the uterus are divided into the congenital abnormalities caused by abnormal fusion of mullerian ducts and acquired abnormalities which include fibroids in uterus, endometrial polyps and intrauterine adhesions. Uterine abnormalities cause miscarriages, preterm labor and intrauterine growth restriction. Congenital abnormalities of uterus include agenesis, hypoplasia, unicornuate uterus with or without rudimentary horn, uterine didelphys, complete or partial bicornuate uterus, complete or partial septate uterus and arcuate uterus.[22-25] Congenital abnormalities of uterus are diagnosed by 3 D ultrasound, hysterosalpingography and hysteroscopy.26,27 The mean incidence in general population is 04% and in women with recurrent miscarriages the incidence is 06%. The true incidence in population is difficult to diagnose because

diagnostic tests are invasive and are done only in patients with infertility or recurrent pregnancy loss.[28-30] The role of hysteroscopy is both in the diagnosis and in treatment. Beneficial effects are seen in patients with repeated pregnancy losses after excision of intrauterine septum and adhesiolysis. Bicornuate uterus has highest incidence of first and second trimester pregnancy loss. Hysteroscopic resection is valuable in women with repeated losses.[31,32]

In first trimester of pregnancy 70% of miscarriages are due to chromosomal abnormalities while in second trimester 20 % are caused by this. Defects are usually trisomy, triploidy and monosomy. Ideally chromosomal make up of fetus and parents should be checked in recurrent first and second trimester miscarriages but this is not cost effective. In couples carrying balanced translocations, the risk of unbalanced translocation in the fetus is just 01% and live pregnancy rate is 70%, similar to general population. The presence of chromosomal abnormalities in the fetus or in parents' needs help of clinical geneticist and prenatal genetic diagnosis can be offered.[33,34]

Chronic maternal illnesses like uncontrolled hypertension, diabetes and disorders of thyroid gland all increase the chances of both first and second trimester miscarriages. Relevant history, clinical examination and appropriate investigations will help in diagnosis and management.[35] Antiphospholipid syndromes is present in 15% of patients with recurrent miscarriages. It is an auto immune hypercoagulable state caused by antibodies against cell membrane phospholipids that provoke blood clots both in arteries and veins. Antiphospholipid syndrome is associated with miscarriages, still births, preterm deliveries and severe pre-eclampsia. It is diagnosed by the presence of lupus anticoagulant and anticardiolipin antibodies in the serum.[36,37]

Thrombophilia screening should be done in all the patients having history of recurrent miscarriages in both first and second trimester. Low dose aspirin and low molecular weight heparin are treatment of choice if thrombophilia is associated with antiphospholipid syndrome.[38] Due to limitation of resources and poor socioeconomic status of our patients we were not able to perform some relevant investigations like screening for chromosomal abnormalities, thrombophilia and antiphospholipid syndrome as investigations for these are not available inside hospital laboratories and pathology department.

Conclusion

Second trimester miscarriage is a distressing event in any woman's obstetrical history. Detailed history, clinical examination and relevant investigations will help to find out the cause, so as to prevent future pregnancy loss.

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ORIGINAL ARTICLE

Psychological impact of COVID-19 pandemic on Pakistani doctors

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Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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Cite this article as: Aslam W, Habib M, Habib M, Aziz A. Psychological impact of Covid-19 pandemic on Pakistani doctors. JSTMU. 2020; 3(2):70-74.

A B S T R A C T

Introduction: The COVID-19 pandemic has caused a significant burden on healthcare system and adversely affected the health care professionals all over the world including Pakistan. Therefore, the short- and long-term effects of this pandemic on mental health of Pakistani medical doctors need to be established.

Objective: This study aimed to assess the mental health status and associated factors among doctors exposed to COVID-19 in Pakistan.

Methodology: An online survey was carried among doctors working in different government hospitals. A Questionnaire was developed which comprised of three different sections. Mental health was assessed on basis of scoring in three Likert scales including Generalized anxiety disorder -7 scale (GAD-7), Insomnia severity index (ISI-7) and Patient health questionnaire (PHQ-9). Cluster analysis was used, and chi-square test was applied for comparison of characteristics.

Results: Study was conducted on 73 specialists /consultants working in different government hospitals of the country. 54.8% of them suffered from subthreshold mental disturbances while 23.3% had mild disorders, 12.3% had moderate disorders and 9.6% suffered from severe mental disturbances. Various factors having significant relationship with psychological status of doctors were identified.

Conclusion: COVID-19 outbreak has significantly affected the psychological health of Pakistani doctors. The factors adversely affecting the mental health of our health care professionals need to be addressed by providing psychological support to them.

Keywords: *COVID 19, mental health, health care workers, psychological support*

Introduction

Coronavirus (COVID-19) outbreak in Wuhan, China in December 2019 has progressed to a global health issue. It has adversely affected approximately 169 countries of the world including Pakistan.[1,2] It was declared as PHEIC (Public Health Emergency of International Concern) on Jan 30, 2020 by WHO who officially named it Corona Virus Disease 2019 COVID-19.[3-5] Pakistan's first case was reported on 26 February 2020 [6] but approximately after four weeks, the number of cases in Pakistan were 784 as declared by WHO and the situation is worsening till date.[1]

Currently, the Pakistani doctors are not only facing physical exhaustion due to work overload but there is an additional social pressure by media, myths, inadequate safety equipment, concerns regarding contagion exposure to family and much more.[3] This has led to many psychological issues including sleep disturbances, anxiety and depression etc.[3]

Pandemics are associated with drastic civilization alternating consequences. The psychological effects of infectious pandemics can be devastating on the society, especially on the health care workers. Stress, fear, anxiety and other psychological consequences of the

disease are seen more often when it is highly contagious and fatal.[3] Doctors are the frontline workers and many studies conducted worldwide have shown that doctors have been adversely affected by it not only leading to significant mortalities, but most importantly causing them psychological distress and other mental health ailments including anxiety, depression and post traumatic syndrome.[3,6] This study aims to understand the psychological impact of Covid-19 outbreak on Pakistani doctors and to identify various factors linked to mental health of Pakistani doctors, working in an already under-resourced constrained environment.

Methodology

This cross-sectional survey-based study was conducted from 15 May to 15 June 2020. After taking approval from institutional review board of Atomic Energy Cancer Hospital (NORI), an open-ended questionnaire was constructed. It was piloted on 10 specialist doctors for its ease of understanding, reachability and technicality. The responses of those 10 consultants were not included in the study. The questionnaire consisted of three sections. Section one was concerned with demographic details of the participants including gender, age as well as serving institution and speciality/department, section two comprised of questions assessing the risk and degree of exposure to COVID -19 while section three addressed the mental health of the participants by using three different Likert scales along with questions on utilization of psychological resources in the form of books, social and electronic media as well as getting psychotherapy in times of stressful conditions. Generalized Anxiety Disorder Scale was used (GAD-7) which is an easy-to-use tool and is used to assess the anxiety and panic disorder. It uses 7 questions and scores are calculated by assigning points to different response categories. Severity ranges from minimal /no disorder (score 0-4), mild (score 5-9), moderate (score 10-14) and severe disorder with scores ranging from (15-21). Second scale was Patient Heath Questionnaire PHQ-9. It is comprised of 9 questions and on the basis of scores calculated is categorized into minimal/no disorder (score 0-4) mild (score 5-9), moderate (score 10-14) and severe depressive disorder (score 15-21). Third scale was Insomnia Severity Index ISI-7, it is used to determine the extent of insomnia, based on points for different questions, it is classified into normal (score 0-7), subthreshold insomnia (score 8-14), moderate (score 15-21) and severe insomnia (score 22-28). All the above-mentioned scales are self-administered, easy to use screening tools for assessment of mental health having good and reliable sensitivities and specificities. The questionnaire was created on Google forms and distributed through social media among different specialists/consultants of various Government hospitals of Pakistan. All the data collected in the study was voluntary and anonymous. All the doctors who were consultants /specialists working in Government organizations were included in the study. All the junior doctors and doctors working in private institutes were excluded from the study. Sample size was not preplanned; an iterative approach was considered. All the responses received fulfilling the inclusion criteria in the desired time period were included in the study. Frequencies were calculated for demographic data. All the participants were divided into 4 groups by using Ward method by utilizing Euclidian squared root distance as measurement parameter. The scores of all the three scales were clustered by using K-Means Cluster analysis. Then Chi-Square Test was used to find association between different groups and categorical variables. The data was analyzed by using SPSS version 22.

Results

The google form was sent to 95 consultants/ specialists, out of which 73 health care professionals, which filled and returned the form were included in the survey. Results revealed that majority of doctors who participated in the study were females. All the participants were divided in four age groups. Frequencies and percentages were calculated for continuous variables as shown in Table 1.

Doctors working in various fields with different specialties participated in the study, which allowed us to gather data from health professionals working under varied circumstances and exposure in relation to Covid-19. Specialties of doctors who participated in the study are shown in Figure 1.

Table 1: Demographic Data

Variable	Frequency	Percentage
Gender		
Male	14	19.2%
Female	59	80.8%
Age		
22-30 years	5	6.9%
31-39 years	42	57.5%
40-47 years	19	26.0
> 47 years	7	9.6%

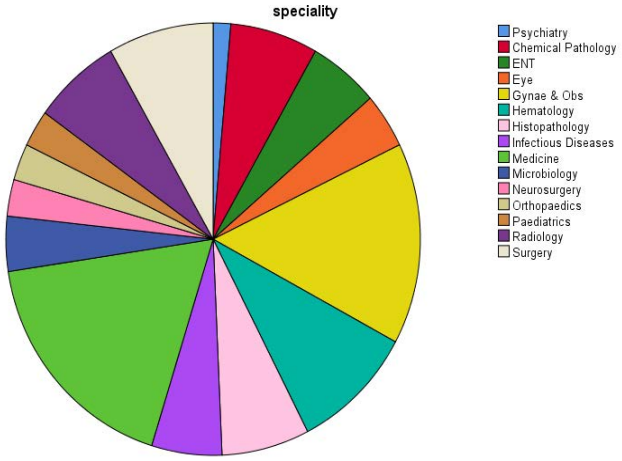

Figure 1: Distribution of doctors according to their specialty.

All the participants of the study were divided into four clusters on the grounds of their scores of three Likert scales GAD-7, PHQ-9 and ISI-7 used. Of the total 73 participants, 40 (54.8%) had subclinical mental health problems, 17 (23.3%) had mild mental health problems, 9 (12.3%) had moderate mental health problems while 7(9.6%) had severe mental health problems. Distinct allocated clusters had statistically different Likert scale scores as shown in Table 2.

Table 2: Cluster analysis arrangement

Variables	1	2	3	4	*p* - value
Frequency/ percentages	40/ 54.8%	17/ 23.3%	9/ 12.3%	7/ 9.6%	<.001
GAD-7mean	3	10	11	15	<.001
ISI-7mean	3	6	14	22	<.001
PHQ-9mean	3	9	9	23	<.001

Comparison of properties of variables among different clusters was done and it was found that no statistically significant differences were observed when comparing some variables like age and gender. However statistically significant differences were found when few variables like being front line worker and taking help from psychological resources at periods of stress were compared. Complete and detailed comparison among various variables in relation to cluster groups along with their P-values is shown in Table 3.

Table 3: Comparison of properties of variables among clusters

Variable	Response	Clusters				Total	p value
		1	2	3	4		
Age (yrs.) 22-30 31-40 41-47 >47		 5 17 12 6	 6 9 2 0	 3 3 3 0	 1 3 2 1	 15 32 19 7	0.34
Gender	Male Female	11 29	3 1 4	0 9	0 7	14 59	0.13
Speciality	Medicine Psychiatry ENT EYE Obs & Gynae Haematology Microbiology Chemical pathology Histopathology Surgery Inf. diseases Orthopaedics Radiology Neurosurgery Paediatrics	5 0 2 1 3 5 2 5 3 3 3 2 2 2 2	5 0 0 1 4 1 1 0 1 1 1 0 2 0 0	1 1 0 1 2 0 0 0 1 2 0 0 1 0 0	2 0 2 0 2 1 0 0 0 0 0 0 0 0 0	13 1 4 3 11 7 3 5 5 6 4 2 5 2 2	0.51

Variable	Response	Clusters				Total	p value
		1	2	3	4		
Front line worker	Yes No Maybe	6 28 6	4 11 2	2 4 3	5 2 0	17 45 11	0.03
Financial constraints	Yes No Maybe	10 27 3	5 12 0	3 6 0	2 3 2	20 48 5	0.27
Diagnosed with COVID19	Yes No	2 38	0 17	3 6	4 3	9 64	<.05
Friend with COVID-19	Yes No	26 14	13 4	7 2	5 2	51 22	0.78
Use of Psychological resource material	Yes No	11 29	12 5	2 7	1 6	26 47	0.006
Psychotherapy Sessions	Yes No	10 30	8 9	2 7	0 7	20 53	0.10

Discussion

Since the advent of pandemic COVID-19, the health care professionals worldwide have directly or indirectly suffered by it. Previously the percentage of infected corona population was low in Pakistan as compared to other parts of the world. However due to multiple factors such as negligence and lack of awareness in general population, the cases of people infected with corona virus have increased steadily and has reached almost a peak in Pakistan. With the increase in suspected cases, the burden on healthcare system of Pakistan has increased substantially as well .The study is designed and conducted especially at this time to identify and address the psychological effects of this pandemic on Pakistani doctors. As with every passing day, not only the number of people infected with Corona virus is increasing but the proportion of doctors being infected by Corona virus is increasing as well. This study included the doctors working in government hospitals, providing healthcare services to people residing in densely populated areas. The doctors working in government setups are exposed to increased number of patients and they have limited resources to work with. Moreover, psychological support in the form of awareness seminars, addressing common psychological problems and psychotherapies are also scarcely available in most of government institutes.

The results of this study revealed that situation arising due to COVID-19 has significantly influenced the mental health of Pakistani health care professionals. More than half of the participants had subthreshold mental disturbance, followed by 23 and 12% having mild and moderate mental health problems respectively, while 7% suffered from severe mental health disturbances. These results are in concordance with study conducted by Sethi et al.[7] Self quarantine and social distancing have further increased the incidence of psychological problems. Regarding the comparison of demographic data with anxiety and depressive disorders, our study did not show significant relationship between age, gender and increased incidence of mental health disorders. This is in accordance with an international study conducted by Liang et al.[8] which showed that no significant relationship existed between age and incidence of mental health problems. Similarly, a local study conducted by Saqlain et al.[9] concurs with our findings. However, this was in contrast to a local study conducted on college students by Salman et al.[10] which revealed a significant positive correlation between the age and incidence of mental health disturbance. Our study showed that dealing with corona virus infected patient as a frontline worker had significant correlation with the increased incidence of psychological problems. The same results were revealed by a study conducted in China by Lai et al.[11] Relatively fewer studies have been done to identify the psychological impact of this pandemic on healthcare workers in Pakistan since this pandemic reached its recent peak, caused by abrupt substantial increase in number of cases of COVID-19. To our knowledge our study is the first one reporting the association of many variables with anxiety and depressive disorders targeting our population of interest, the specialist doctors working in government hospitals. There was a significant correlation between getting infected from Corona virus and increased chances of suffering from anxiety and depressive disorders. However, there was a negative correlation between exposure of friends or neighbors with COVID 19 and increased mental stress. This may be due to increased spread of disease among masses, as the people around us are increasingly been infected. We found a positive correlation between the use of psychological resources in times of increased stress and lesser chances of developing mental disorders. This is in accordance with study conducted by Mukhtar et al.[12]

Similarly a study by Rahman et al,[13] supported and urged the need for increased availability and usage of psychological resource material and setting up psychological guidelines for use in pandemics to reduce its devastating psychological effects.

Limitation of Study

One of the limitations of the study is the use of convenience sampling which may affect the generalizability of findings. Another limitation is the inherent design of the study with sampling technique being restricted to doctors with internet access only. However, despite these limitations, our study is the first of its kind in Pakistan which recognizes different factors affecting the mental health of Pakistani doctors working in Government hospitals during COVID-19 outbreak. Further larger longitudinal studies need to be conducted that would aid the policy makers in addressing various factors influencing the mental health of Pakistani doctors during outbreak of Corona virus disease 2019.

Conclusion

Pandemic COVID-19 had a strong impact on mental health of Pakistani doctors. Various factors having a negative influence on their mental health were identified. The effect of these factors should be minimised by devising methods aiming to reduce devastating psychological effects of this outbreak on our healthcare workers. Psychological help should be available at local and national level and should be provided to doctors working in all the hospitals across the country.

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ORIGINAL ARTICLE

Dysmenorrhea in students: Characteristics and predictors

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Article Info.

Conflict of interest: Nil

Funding Sources: Nil

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Cite this article as: Abid F, Aamer M, Faiz S, Azam F, Shaheed A, Javed, N. Dysmenorrhea in students: characteristics and predictors dysmenorrhea in students. JSTMU. 2020; 3(2):75-80.

A B S T R A C T

Introduction: Dysmenorrhea is a very common reproductive issue present in young females that severely impacts their life.

Objectives: To determine the prevalence of primary dysmenorrhea amongst undergraduate students of Pakistan, the association of dysmenorrhea with various factors, and the impact on academic performance.

Methodology: An observational study was carried out at different Pakistani universities. The data was collected using a self-designed, pre-tested questionnaire. which was distributed online. The data was analyzed using IBM Statistical Package for Social Sciences (SPSS) version (Armonk, NY) 26.0. Descriptive statistics were applied for qualitative variables. Mean and standard deviation were calculated for quantitative variables. Chi-square was applied to determine if the differences in cycle length were significantly related to dysmenorrhea. T-tests were applied to determine if there were significant differences in age and body mass index in participants with dysmenorrhea.

Result: There were 226 students who had participated in the study. There were 193 (85.40%) participants who reported experiencing dysmenorrhea out of which 97 students (50.26%) took a drug or a combination of drugs to alleviate the pain. There was a high prevalence of stress symptoms associated with dysmenorrhea with fatigue after sleep ($p<0.05$). Physical activity did not have any effect on dysmenorrhea. Physical activity, the average grade of pain, and the presence of pain in each cycle were significant predictors of dysmenorrhea ($p<0.05$).

Conclusion Physical activity and characteristics of pain, such as cyclical nature and intensity, are predictors of dysmenorrhea.

Keywords: *Dysmenorrhea, undergraduate students, stress, BMI, physical activity*

Introduction

The prevalence of primary dysmenorrhea, a common problem in reproductive females, is usually underestimated and difficult to determine as the majority of the women and young females consider pain as a normal component of menstruation. Hence, their health can be seriously compromised leading to consequences in reproductive health in the future. On a global level, almost 71% of adolescents and women under 25 years of age experience dysmenorrhea.[1] In Pakistan, almost 78% of women report dysmenorrhea. With female adolescents being 51% of the global population, health facilities providing medical and psychological care are required to cater to the needs of this increasing population.[2,3]

Primary dysmenorrhea is defined as a cramping pain of varying severity in the lower abdomen before or during menstruation with no underlying cause. It may be accompanied by dizziness, headache, nausea, fatigue, vomiting, and diarrhea.[4,5] It frequently develops in adolescence and usually affects those in schools or universities, being a leading cause for absenteeism. It also has a significant effect on social relationships, mental status, academics, daily activities, sleep, and mood causing anxiety and depression.[6] The pain usually lasts for 8 to 72 hours and radiates to the lower back or back of the legs. Usually starting before menstruation, the severity is greatest for the first and second days of the cycle. This pain is attributable to the release of prostaglandins released during endometrial degeneration leading to myometrial contractions. The prostaglandin theory is further strengthened by the effectiveness of non-steroidal anti-inflammatory agents (NSAIDs) in alleviating symptoms of primary dysmenorrhea. Prostaglandin production is inversely related to the secretion of progesterone so as menstruation begins, progesterone levels drop and prostaglandins level increase thus leading to dysmenorrhea.[6]

Numerous factors affect the duration and severity of primary dysmenorrhea, such as family history of dysmenorrhea, low BMI, lack of physical activity, early age at menarche, heavy menstrual flow, irregular menstrual cycles, nulliparity, high levels of stress, smoking, disruption of social networks, depression and anxiety.[5] Regarding dietary intake, a study suggested that high levels of fish, eggs, and fruit in the diet was associated with a low frequency of primary dysmenorrhea.[7] According to a study conducted in India, a high prevalence of dysmenorrhea was seen in girls living in rural areas who had low BMI.[8]

Women with high-stress levels are twice more prone to primary dysmenorrhea compared to women with low-stress levels especially those with a history of dysmenorrhea.[9] Stress causes an impaired secretion of adrenaline and cortisol that affects prostaglandin synthesis. It also down-regulates the production luteinizing hormone and follicular stimulating hormone causing impaired follicular development, leading to a low secretion of progesterone that alters the synthesis of prostaglandins.[10]

In the management of primary dysmenorrhea, NSAIDs play a very important role as the first-line therapy to relieve the painful symptoms as NSAIDs block the formation of the enzyme cyclooxygenase that forms prostaglandins.[11] Contraceptive hormones are also used as they inhibit ovulation and decrease endometrial proliferation. These cause immediate relief from symptoms associated with dysmenorrhea.[12] Additionally, non-medicinal treatments are also used widely, such as topical heat application, mild exercises, using herbal remedies and the use of ginger and cinnamon, meditation and other stress-relieving activities in the daily routine.[13]

Therefore, the objective of the study was to determine the prevalence of primary dysmenorrhea amongst undergraduate students of Pakistan, the association of dysmenorrhea with various factors, and the impact on academic performance.

Methodology

An observational study was carried out at different universities of Pakistan, after approval from the Institutional Review Board of Shifa International Hospital (IRB#1188-464-2018). The sample size was calculated to be 226 using an online software with a probability of 50%, confidence interval of 95%, and a design effect of 1.0. A non-probability sampling technique was used because our study targeted females. The time for the study was one year. The data was collected using a pre-tested, self-designed questionnaire. The questionnaire had a total of 38 questions which were divided into four domains. The first domain was concerned with the basic demographic data. The second domain included menstrual history i.e. age of menarche, regularity of cycles, duration and flow of bleeding, pain intensity (assessed using NPRS scale), and associated symptoms. The third and fourth domains assessed stress levels and physical activity using preformed but summarized questionnaires respectively. Stress was assessed using a 9 question section on our questionnaire, inquiring about deadline stress, low self-confidence, insufficient sleep, fatigue after sleep, appetite change, irritability upper back pain, difficulty in concentrating, and caffeine dependency. The stress questionnaire was tailored according to the International Stress Management Association (ISMA), picking those questions that would be most relevant in the current

setting. The intensity of physical was measured on a scale of 0 to 5 with 0 being none and 5 being the maximum. Nine activities were measured: lifting weights, digging, climbing stairs, cycling, jogging, running, walking, gym and others. The data collected was analyzed using IBM Statistical Package for Social Sciences (SPSS) version (Armonk, NY) 26.0. Descriptive statistics were applied for qualitative variables. Mean and standard deviation were calculated for quantitative variables. Chi-square was applied to determine if the differences in cycle length were significantly related to dysmenorrhea. T-tests were applied to determine if there were significant differences in age and body mass index in participants with dysmenorrhea.

Results

There were 226 participants in the study. All of the participants were female. There were 193 participants who had dysmenorrhea. The demographic data and menstrual history are detailed in Table 1.

Table 1: Demographic details and menstrual history

Characteristics		Measure	Dysmenorrhea (n=193)	p-value
Age (Mean±SD)		20.10±1.10	20.50±1.20	0.05
Age at menarche in years (Mean±SD)		12.80±1.50	12.80±1.70	0.86
BMI (Mean±SD)		21.40±3.60	21.80±4.00	0.55
Average length of cycle (n, %)	<21 days	3 (9.09)	20 (10.36)	>0.05
	21-28 days	15 (45.45)	94 (48.70)	0.84
	28-35 days	11 (33.33)	64 (33.17)	0.93
	>35 days	4 (12.13)	15 (7.77)	0.55
Duration of bleeding (days) (Mean±SD)		5.00±2.00	5.00±1.00	>0.05
Number of pads used (Mean±SD)		3.00±1.00	3.33±3.14	0.25
Average grade of pain (Mean±SD)		3.00±2.60	6.20±4.10	<0.05
Physical activity score (Mean±SD)		42.09±8.09	42.70±6.53	0.63
Stress score (Mean±SD)		15.19±2.95	16.06±2.93	0.10

There were 110 students studying medicine, 4 studying dentistry, 8 studying pharmaceutical sciences, 27 students studying arts, 19 students studying commerce and 58 students were enrolled in other courses.

Table 2 shows stress symptoms among the participants with dysmenorrhea. The chi-square for differences in participants reporting fatigue after sleep was significant ($p<0.05$) with more participants reporting fatigue in the dysmenorrhea group as compared to the other group.

Table 2: Stress levels among the two groups

Stress symptom	No dysmenorrhea	Dysmenorrhea	p-value
Deadline stress	18	120	0.66
Low self confidence	25	152	0.41
Insufficient sleep	12	92	0.23
Fatigue after sleep	17	134	0.04
Appetite change	23	141	0.85
Irritability	21	124	0.95
Non-specific pain	13	104	0.12
Difficulty in concentrating	25	147	0.88
Caffeine dependency	9	80	0.12
Stress scores (Mean±SD)	15.19±2.95	16.06±2.93	0.10

Table 3 shows a comparison of physical activity with dysmenorrhea. The mean physical score did not vary significantly amongst the two groups ($p>0.05$).

Table 3: Physical activities among the two groups.

Activity done in past week	No Dysmenorrhea	Dysmenorrhea	P-value
Lifting weights	8	34	0.57
Digging	0	5	NA
Climbing stairs	28	180	0.73
Cycling	1	13	0.92
Jogging	7	46	0.81
Running	11	66	0.88
Walking	30	183	0.68
Gym	1	18	0.85
Other	11	49	0.73

NA: Not Applicable

Symptoms such as mood swings (74.80%), headaches (76.00%), irritability (71.20%), insomnia (21.00%), lower backache (66.00%), and breast tenderness (40.00%) were also recorded. A logistic regression model was used to assess independent predictors for dysmenorrhea. The estimates were also adjusted for other variables. Table 4 shows the results of the model.

The participants used a variety of methods to help alleviate the pain. There were 97 participants (50.26%) who used pharmacological methods for the pain. Out of the 97 participants, 23.30% used acetaminophen, 11.40% used NSAIDs, 7.30% used mefenamic acid, 2.10% used butylscopolamine bromide and 1% used some other medicine. There were 12 participants (5.20%) who had to use a combination of medicines to soothe the pain.

Table 4: Logistic Regression Model

Variables	Unadjusted Estimates			Adjusted estimates		
	Risk	CI	p-value	Risk	CI	p-value
Age	0.99	0.61-1.62	0.98	1.09	0.59-2.03	0.76
BMI	0.79	0.63-0.99	0.04	0.76	0.58-1.01	0.06
Age of menarche (years)	0.81	0.56-1.16	0.25	0.82	0.54-1.25	0.36
Cycle length (days)	1.64	0.75-3.59	0.21	1.89	0.81-4.41	0.14
Duration of bleeding (days)	1.07	0.67-1.71	0.78	1.22	0.69-2.16	0.49
Pad usage	0.56	0.28-1.11	0.10	0.72	0.35-1.49	0.38
Pain in each cycle	12.11	2.48-59.03	<0.05	14.51	2.16-97.50	0.01
Intensity of pain varies in each cycle	1.94	0.51-7.40	0.33	1.92	0.40-9.25	0.42
Average grade of pain	0.58	0.42-0.81	<0.05	0.51	0.34-0.76	<0.05
Physical activity	0.92	0.84-1.01	0.07	0.88	0.79-0.98	0.02
Stress	0.97	0.78-1.20	0.80	0.98	0.76-1.28	0.92

BMI-body mass index, CI-confidence interval

Discussion

In this study, among 226 participants the overall prevalence of primary dysmenorrhea in medical students was exceedingly high (85.4%) as compared to the studies carried out in the international literature reviewed. One of the most common symptoms suffered by females was pain in the lower abdomen that radiated to the back and upper thighs. These symptoms were almost similar to a study carried out in King Khalid University of Saudia which suggested lower abdomen, leg and back pain were one of the most common locations.[3,4,14]

Various studies show that there is an inconsistent relationship between the age of menarche and dysmenorrhea and our results show that no significant association was found between the age of menarche and dysmenorrhea.[15] These variations are probably due to sociocultural and lifestyle factors. In addition to this, various studies showed that cycle irregularity and heavy

menstrual blood flow had a strong relation with dysmenorrhea.[16,17] A study carried out among students in Egypt showed that girls with longer cycle length and heavy blood flow experienced dysmenorrhea in comparison to those with normal or shorter cycle length, however, we did not find any association of cycle length with dysmenorrhea in our study.[18] This discrepancy could be since most of the participants in this study had a normal duration and flow of menstruation than others.

Another important factor affecting dysmenorrhea in young females in physical activity. Literature shows significant relation of physical activity with the volume of menstrual flow and intensity of dysmenorrhea.[10] Females who were more physically active had fewer symptoms of dysmenorrhea as compared to those who exercised less, due to endorphin release.[19] Another study focusing on physical activity showed a significant difference in physical symptoms and pain in the two groups.[20] Our study contradicted this hypothesis which could be attributed to the fact that physical activity is usually restricted by females due to dysmenorrhea and other social factors. Most females due to lack of awareness and cultural beliefs prefer resting during their cycles and avoid heavy work.

Low BMI indicates poor nutritional levels which is a causative factor for dysmenorrhea as shown in a study carried out in India.[7] Low caloric intake, body weight, and fat mass disturb pulsatile secretion of pituitary gonadotropins leading to an increase in the rate of dysmenorrhea.[21] The obtained values for BMI of this present study are not in a range depicting severe malnutrition hence, the relation of BMI with the prevalence of dysmenorrhea could not be well-explained as suggested by another study carried out in Iran which showed no significant association of BMI with dysmenorrhea.[22] This could be due to different geographical and sample characteristics.

In addition to the aforementioned factors, stress is also an important determinant of the intensity of dysmenorrhea. Women who are stressed are twice more likely to suffer from dysmenorrhea than those who do not experience much stress. Stress alters normal levels of prostaglandins and also down-regulates the production LH and FSH causing impaired follicular development which impairs progesterone synthesis ultimately leading to deranged prostaglandin synthesis.[9] According to the stress scores in our study, the average stress score in females with dysmenorrhea was higher than that of females who were not afflicted with primary dysmenorrhea, supporting the notion that This gave stress can be a risk factor for primary dysmenorrhea.

A study showed that considering many other factors, pain is the most strongly associated factor in sleeping difficulties.[23] The National Sleep Foundation's women and sleep poll from 1998 showed that women reported more sleeping difficulties in the first few days of their cycle due to pain and cramps. In association with lack of sleep, most women presented with daytime fatigue or fatigue after sleep due to a disturbed sleep.[3] In our study, the specific symptom of fatigue after sleep had a strong association with dysmenorrhea giving a p-value of 0.04. However, based on the previous studies reviewed, the role of this association is unclear.

Dysmenorrhea is one of the leading causes of self-medication among young females.[24] Out of the 97 participants, 23.30% used acetaminophen, 11.40% used NSAIDs, 7.30% used mefenamic acid, 2.10% used butylscopolamine bromide and 1% used some other medicine. 5.2% of this population used a combination of three drugs, Acetaminophen, NSAIDs, and mefenamic acid. This indicates the severity of the symptoms suffered by this population in question. According to a study, the usage of NSAIDs showed great efficacy in improving dysmenorrhea symptoms as compared to paracetamol or placebo but was associated with more adverse effects. According to another study that compared the efficacy and safety of over-the-counter NSAIDs, ibuprofen was the optimal drug for usage.[25]

The main limitations of the study were the small sample size. The study did not aim at investigating the impact of various professions or routines on dysmenorrhea. The observational nature of the study poses difficulty in generalizing the results irrespective of time and geography. Similar studies could be carried out on a larger scale to find significant correlations that would help to create greater awareness among young females. Lifestyle modifications and stress management could be a good implementation of this study in helping the community.

Conclusion

Physical activity and characteristics of pain, such as cyclical nature and intensity, are predictors of dysmenorrhea. These factors are important in developing agents that can relieve dysmenorrhea.

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JSTMU Journal of Shifa Tameer-e-Millat University

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Open Access

ORIGINAL ARTICLE

Myths and misconceptions related to CoVID-19 among future health care providers in a private University of Islamabad - An interventional study

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Article Info.

Conflict of interest: Nil

Funding Sources: Nil

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Cite this article as: Naseem S, Naeem Z, Choudhry H, Bareach G, Fafi S, Tahir F, Ahmad Qazi , Mangrio S, Khalil R. Myths and Misconceptions related to CoVID-19 among future health care providers in a private University of Islamabad - An interventional study. JSTMU. 2020; 3(2):81-87.

A B S T R A C T

Background: Erroneous treatments are hovering all over the internet and social media due to non-existence of the ultimate treatment to CoVID-19. There is a need to disseminate correct knowledge and encourage practices based on evidence, which can successfully prevent the spread of this deadly global pandemic.

Objectives: The objective of the study was to explore the myths and misconceptions related to CoVID-19 pandemic in a pre and post health awareness workshop among the future health care professionals in a private medical university in Islamabad, Pakistan.

Methodology: A quasi experimental study was carried out in March, 2020 over a period of two weeks at Shifa Tameer-e-Millat University, Islamabad. The participants included undergraduate medical, nursing and pharmaceutical sciences students, making a total sample size of 315. Simple random sampling was used. Data was collected using a self-designed questionnaire exploring the myths and misconceptions. A pre and post health awareness workshop was conducted and questionnaires filled by the participants. Data was analyzed using SPSS 23.

Result: A change in the frequency of concepts related to myths and misconceptions was observed following the health awareness session, results were statistically significant using McNemar's test in context to majority of the myths and misconceptions, p-value < 0.05.

Conclusion: Health education has very important role in public health especially in times when the health problem is novel. In such situations, emphasis should be paid on the health education as it can modify the behavior regarding myths and misconceptions which can contribute to decrease in morbidity and mortality.

Keywords: *CoVID-19, health education, myths, misconceptions, healthcare providers, Pakistan*

Introduction

CoVID-19 was first uncovered and revealed in Wuhan, China in December 2019 as the epidemic of respiratory illness comprising of breathing problems, fever, cough and pneumonia, with 14 days' incubation period. This infection spreads through droplet infection as a result of coughing and sneezing from person to person. Hence, the prevention of this spread is possible by restraining from effected people.[1] It has been reported that till Sept 2020 there are over 277,333 cases globally and 11,384 fatalities worldwide, and in Pakistan 302,020. The World Health Organization declared the outbreak a Public Health Emergency of International Concern on 30 January, and a pandemic on 11 March.[2]

Erroneous treatments are hovering all over the internet and social media due to non-existence of the ultimate epidemiology & treatment to this disease. The spread, the cause and the cure of CoVID-19 since the spread are recognized as myths and illusions concluding to incorrect facts.[3,4] Social media being the major platform of such myths have heaps of ongoing discussions claiming that the spread can be obstructed by mouthwash, garlic, gargling with bleach, third-generation antibiotics, restriction on Chinese food, frozen food and meat, which is not approved by any local and global health organization what so ever. However, various tests and trials are in progress to define treatment and identify the accurate source of this virus.[5, 6]

World Health Organization (WHO) and various health agencies have taken necessary measures to regulate the information and drive out the misapprehensions of CoVID-19 and its cures. Similarly, surgical and other masks are in use as a protection which is being constantly suggested and is effective.[7,8] An additional subject has been argued, that the virus can spread through parcels and posts arriving from Chinese origin. It cannot be concluded; in fact, the virus cannot survive more than nine days on a surface and can easily be disinfected by antiseptics.[7]

Another misconception is that pets or other animals are source of transmitting the virus, its outspread were linked to the Hunan Seafood Wholesale Market. There is no evidence to believe that any animal or pet is a source of infection. According to Centre for Disease Control (CDC) there is no evidence that animals and pets can be infected with the new corona virus. WHO recommends handwashing with soap and water after contact with any surface and pets? Furthermore, it is widely believed that pneumonia vaccines or third generation antibiotics can protect against CoVID-19.[8]

People of all ages can be infected by CoVID-19. Misconception regarding more susceptibility of older people exists. Though, those who are suffering with chronic medical conditions (such as hypertension, diabetes mellitus, cardiovascular diseases, asthma and other comorbid conditions), appear to be more susceptible and have high mortality.[4]

The above misconceptions and theories portray the fact that there was a need to disseminate correct knowledge and encourage practices based on evidence, which can successfully prevent spread of this deadly outbreak worldwide. Therefore, this study was designed to explore the myths and misconceptions related to CoVID-19 pandemics in a pre and post health awareness workshop among the future health care professionals.

Methods

A quasi-experimental study was carried out in the beginning of March, 2020 over a period of two weeks at Shifa Tameer-e-Millat University, Islamabad after taking approval from IRB Ethics Committee. Simple random sampling was used to select participants of the study after forming a sampling frame. The participants included undergraduate medical, nursing and pharmaceutical sciences students. The sample size of 315 was calculated using online Raosoft sample size calculator, keeping 95% confidence level, population size 1500, anticipated response 50% (being a novel virus), and margin of error 5%. The data collection was done in three different settings of STMU.

Informed Consent was taken from the participants regarding the data collection pre- and post-intervention, following which a pilot tested self-designed, self-administered questionnaire comprising of variables focusing on the myths and misconceptions related to source, transmission, prevention, treatment and outcome were distributed to them. They were asked to fill out the questionnaire which took on an average seven minutes.

The filled questionnaires were collected by the researchers. Following this, a power point presentation by two of the investigators was given to them in 20 minutes regarding the epidemiology, myths and misconceptions related to CoVID-19 pandemic. The entire activity was carried out in English language as this is the medium of instruction. The audience came up with an interactive discussion after the presentation and found it very useful as it was very early in the CoVID-19 before the locked down was implemented. Table 1 represents the myths, facts and health education messages given to study participants. The questionnaire was distributed to all participants after the intervention and collected.

Data was entered and analyzed using SPSS version 23.0. Descriptive statistics were calculated for both qualitative and quantitative variables. Inferential statistics using McNemar's test was applied to determine the understanding of the facts related to the myths following health education, keeping p-value <0.05.

Table 1: Myths, Facts and Health Education regarding CoVID-19 given to participants

Myths	Facts	Health Education
Deliberately created for /by China	Analysis of genome sequence data showed no evidence that the virus can be created in a lab.	No evidence that the virus is man made in laboratory by Chinese to disrupt economy of other countries.
Common Signs & Symptoms (S/S)	Resemble those of common flu and pneumonia, SARs-CoV and MERs-CoV infection from same family	Sore throat, sneezing, dry cough, anosmia are considered easy to observe by the public
Non-Vegetarian/ omission of meat are not infected	No such evidence	Both vegetarians and meat eaters have been infected.
Elderly with comorbid are susceptible as much as any age	With increasing age immunity decreases, and hypertension diabetes mellitus, cancers, bronchial asthma, immune-compromised persons are more susceptible.	Cannot be associated with old age only, however with ageing immune system weakens along with increase in comorbidities and mortality
Eating Chinese food increases risk	No evidence has been found	If eating Chinese food can cause this infection than eating in Italian, Korean, Japanese and Iranian restaurants may also cause infection but this is not the case.
Imports from China increases the risk	The virus has different life span on different surfaces e.g. metal, glass and plastic :3-hours-3 days Cardboard: 24 hours	For the virus to stay viable it needs specific environmental conditions e.g. temperature, UV exposure and humidity that are not usually available in shipping packages.
Transfer from pets to humans	No evidence has been found	Cats have been found to have developed this infection after being exposed with high doses of the virus.
Most dangerous virus so far	It has a mortality rate of 2% which is much less as compared to other viruses.	As pandemic and due to non- availability of drugs and vaccines for disease, people got scared and started fearing as most dangerous.
Regular hand washing does not reduce the risk of transmission	Hand washing with soap for 20 seconds inactivates microorganisms the virus and temporarily suppresses the growth	Hand washing is one of the most important preventive measure
Closing borders will stop transmission	Travel restrictions in its have been beneficial	Entry of foreigners into every country was bringing more cases of CoVID-19, so travel ban and travel quarantine is important.
Use of Napkins while sneezing does not prevent	Covering mouth while sneezing prevents the spread of virus present in the form of droplets in the air	Use of all types of disposable mask is an essential step in the prevention
Regular mouth gargles with salt or saline water is preventive	Gargling with salt water in common cold does help to soothe throat but it does not kill the virus microorganisms.	Regular mouth rinsing or gargling with salt water or saline water does not kill the virus. It can only help to temporarily relief cough or sore throat.
Eating garlic, home remedies is protective	Garlic, turmeric & onions have antimicrobial properties.	There is no evidence
Pneumonia vaccine is protective	There is no vaccine for CoVID-19 till date. It is a vaccine against bacteria	Several researches and trials are ongoing on to develop a vaccine

Results

The total sample size in this study was 315; mean age was 22.15 ± 1.3 years. Majority of them were females 57.1% while 42.86% were males. The participants belonged to different undergraduate disciplines in STMU which included medical, nursing and pharmaceutical sciences, as is presented in Figure 1.

Pre and Post Workshop Comparison of the frequency and proportions of Myths & Misconceptions regarding the source, transmission, prevention, treatment and outcome of CoVID-19 Infection. Though a change in the frequency of concepts related to the myths and misconceptions was observed following the health awareness session, the results were statistically significant in most myths and misconceptions, p-value < 0.05. These are presented in Table 2, 3 and 4.

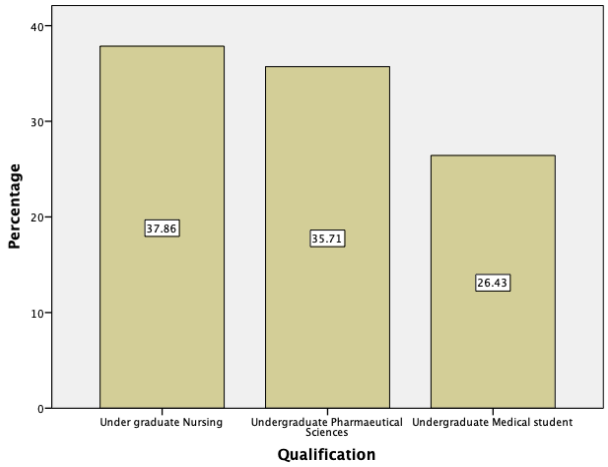

Figure 1: Undergraduate students belonging to different disciplines in STMU, Islamabad.

Table 2: Pre and Post Workshop Comparison of Percentage of Myths & Misconceptions regarding the source and transmission of CoVID-19 Infection.

Myths & Misconceptions	Pre- Workshop (%)			Post-Workshop (%)			p Value
	Yes	No	Don't Know	Yes	No	Don't Know	
Deliberately created for China	40	40	20	11.4	87.1	1.4	< 0.01
Infection is limited to China	9.3	87.9	2.9	2.9	95.0	2.1	> 0.05
Common signs & symptoms known	95.7	2.9	1.4	97.1	2.9	-	> 0.05
Emerged with direct contact with Bats & Snakes	28.6	44.3	27.1	3.6	92.9	3.6	< 0.01
Non-Vegetarian are not infected	10	77.9	12.1	99.3	-	0.7	> 0.05
Consumption of non-halal food is risky	40	47.1	12.9	3.6	95.7	0.7	< 0.01
Elderly with comorbid are more susceptible	67.1	22.9	10.0	88.6	10.7	0.7	< 0.01
Eating Chinese food increases risk	31.4	52.9	15.7	2.1	97.9	-	> 0.05
Imports from China increases risk	61.4	27.1	11.4	9.3	90	0.7	> 0.01
Omission of meat in diet reduces risk	13.6	70.7	15.7	0.7	99.3	-	> 0.05
Transfer from pets to humans	39.3	30.0	30.7	7.1	91.4	1.4	< 0.01
Most dangerous	33.6	52.9	13.6	15.0	85.0	-	> 0.05

Table 3: Pre and Post Workshop Comparison of Percentage of Myths & Misconceptions regarding the prevention against CoVID-19 Infection.

Myths & Misconceptions	Pre-Workshop (%)			Post-Workshop (%)			p-value
	Yes	No	Don't Know	Yes	No	Don't Know	
Regular hand washing reduces the risk	91.4	7.1	1.4.0	95.7	4.3	-	> 0.05
Closing borders will stop transmission	65.7	19.3	15.0	52.9	45	2.1	< 0.01
Meeting Chinese people with flu should be avoided	82.1	14.3	3.6	80.0	20.0	-	> 0.05
Use of napkins while sneezing prevents	71.4	15.7	12.9	73.6	26.4	-	> 0.05
Covering mouth while sneezing protects	63.6	30.0	6.4	35.0	62.9	2.1	< 0.01
Regular moth rinsing with salt water is protective	37.1	35.7	27.1	11.4	85.7	2.9	< 0.01
Eating garlic is protective	11.4	52.9	35.7	2.9	97.1	-	> 0.05
Role of gargles in prevention	11.4	42.1	46.4	6.4	93.6	-	> 0.05
Combination of turmeric, onion & honey water is protective	42.9	32.9	24.3	46.4	52.9	0.7	< 0.01
Screening of travelers is preventive	87.9	10.0	2.1	35.0	65.0	-	> 0.05
Mass burial of infected patients is preventive	18.6	54.3	27.1	4.3	92.1	3.6	< 0.01
Pneumonia vaccine is protective	11.4	66.4	22.1	1.4	97.1	1.4	< 0.01

Table 4: Pre and Post Workshop Comparison of Percentage of Myths & Misconceptions regarding the treatment and outcome of CoVID-19 Infection.

Myths & Misconceptions	Pre-Workshop (%)			Post-Workshop (%)			p-value
	Yes	No	Don't Know	Yes	No	Don't Know	
Wearing mask protects	42.9	46.4	10.7	16.4	83.6	-	> 0.05
3rd Generation Antibiotics are effective	8.6	67.9	23.6	2.9	96.4	0.7	< 0.01
Homeopathy & Ayurveda provide cure	11.4	50.7	37.9	0.7	99.3	-	> 0.05
All patient ultimately die	13.6	67.9	18.6	2.9	93.6	3.6	<0.01
No cure	27.9	42.9	29.3	97.1	2.9	-	> 0.05
No vaccine	57.9	29.3	12.9	97.9	2.1	-	> 0.05

Discussion

CoVID-19 is a global pandemic now with more than 200 countries being affected. When the novel Coronavirus outbreak happened, a lot of misconceptions took birth alongside the global pandemic rapidly spreading via social media. Since the virus was completely new, no

specific treatment, vaccine or drug was available for it. So, all these factors together created chaos among the general population. As it was first recognized in Wuhan city of China, majority of these myths were related to either meat market of Wuhan or Chinese people.

Studies carried out in Nigeria, United States of America, Pakistan and multiple other countries showed that participants strongly believed that the virus was either deliberately created for China or by China in a laboratory located close to Wuhan.[7-9] This is in accordance with these studies possibly because the respondents believed that this has been done in order to bring down China's growing economy.

Racheal in her study showed that the signs and symptoms of CoVID-19 resemble those of common flu and that the infected individual knows when he gets the infection.[10, 11] our study showed the same findings because the participants believed that the signs and symptoms of CoVID-19 are common as in any viral Upper respiratory tract infection. Majority of the participants of our study agreed with the myth believing that CoVID-19 shares close resemblance with SARS-CoV and MERS-CoV, which seem to have originated in bats and from snakes.[12, 13]

In a study carried out by Swapnajeet Saho among general population showed that eating non-vegetarian food (meat/eggs/fish/chicken) can lead to this infection based on the assumption that the virus first started from meat market of Wuhan, besides India with more than 4.85 million cases, is globally on second place after USA and their diet is predominately non-vegetarian.[1] These results were not in accordance with our results as our study focused on the absence of infection in non-vegetarians having properly cooked meat. In other studies, omission of meat from the diet in view of reducing risk of the infection has been focused which again showed no similarity with our results.[6]

Multiple studies carried out in different countries showed that majority of the participants believed in the fact that CoVID-19 affected the elderly more or elderly with comorbidities which include hypertension, diabetes mellitus, asthma, etc. were more vulnerable to the infection.[14-15] In our study, majority of the participants agreed with this fact owing to the possibility of weak or compromised immune system at older age. Zumama Khalid in her study at the Aga Khan University (AKU), Karachi showed that the virus cannot survive for long in unfavorable environment and it has a variable life span on different surfaces. However, in the light of this myth, majority of the population started believing that receiving packages from china or eating at Chinese restaurants increased the risk of infection.[16, 17] the results of these studies showed similarity with our survey study.

Many studies have shown that the respondents strongly believed in transmission of the infection by pets, however, scientists have carried out multiple experiments and finally concluded that the replication of this virus in cats, dogs, pigs and chicken is poor, provided adequate laboratory environment is available. So, no concrete evidence has been found on this myth and the results of these studies stayed in line with our study. [18, 19]

As soon as CoVID-19 infection was declared a pandemic by WHO, it created chaos world over. People started fearing the virus, considering it deadly and one of the most dangerous of kind because of the non-availability of vaccine or specific treatment.[16, 17] increased media reports on the increasing number of deaths further fueled similar misinformation. Multiple studies carried out in different countries had similar results. Zumama and Gurmeet found that the regular handwashing with soap and water for 20 seconds plays an essential role in the prevention of CoVID-19 to temporarily suppress the growth of virus.[15,16] Our study showed similar results and this could be perhaps because of the extensive health education program carried out both by WHO and social media.

Research carried out in Karachi, Pakistan showed that the effect of travel restrictions in the spread of CoVID-19 indicated that these were beneficial. However, the airlines have violated these restrictions which increased the likelihood of developing CoVID-19.[19, 20] our study agreed with these travel restrictions. Gurmeet Singh in his study showed that covering mouth with a napkin or disposable tissue while sneezing prevents the spread of CoVID-19.[6] our study also showed similar findings as covering mouth can prevent the spread of droplets in air.

A study done in Lahore, Pakistan showed that a good respiratory hygiene is very important to prevent the

spread of CoVID-19.[19] If an infected person sneezes and does not cover his mouth, he will be the source of infection to everyone who is around him. Our study showed similar findings. Studies done in the UK, India and by WHO have elucidated the misconceptions about rinsing mouth with salt water or saline solution to kill the virus present in nose or throat.[16,17] This strategy may help to soothe a sore throat or common cold, but this practice will not prevent anybody from developing CoVID-19, as responded by our participants.

Studies carried out locally as well as in the USA and India have discussed about the consumption of garlic, turmeric & onion used as home remedy to help common flu as it has antimicrobial properties. However, the myths have been snapped by WHO and Michael Abiola Okunlola.[17] Our study has shown similar results as most of the people disagree with this myth. WHO explained the most common symptoms of CoVID-19 as dry cough and tiredness which somehow mimicked the symptoms of pneumonia.[15] a study done in India has discussed a myth that vaccines against pneumonia can protect you against CoVID-19, but the evidence says that pneumococcal vaccine and Heamophilus influenza Type B vaccine do not protect against CoVID-19.[14]

Health education among the future health care professional needs to be addressed for adequate control of the Pandemic. In the absence of any post intervention data available, our study stands as light house for future studies to be held in this regard. It is recommended that during the times of pandemic, health education session is a useful means of spreading the facts related to different myths. It should be assessed and done periodically for the spread of corrective measures in order to ensure the protection and prevention against a disease.

Conclusion

Health education has a very significant role in public health especially in times when the health problem is novel.

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JSTMU Journal of Shifa Tameer-e-Millat University

https://j.stmu.edu.pk

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ORIGINAL ARTICLE

General disease awareness among parents of thalassemic children visiting government versus private care centers of Rawalpindi and Islamabad

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Author`s Contribution

[1-5] Conception, Data analysis, Design, interpretation, drafting, critical revising, import contents, final approval.

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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A B S T R A C T

Introduction: Thalassemia Major is a hemolytic anemia which is prevalent in developing countries and is preventable by promoting awareness among the masses.

Objectives: To assess the current general disease awareness and compare the level of understanding between parents attending government versus private thalassemia care facilities.

Methods: This cross-sectional study was conducted in four thalassemia centers of Rawalpindi and Islamabad from December 2017 to January 2019. Parents/caregivers of Thalassemia Major Patients were included by non-probability purposive sampling and those having children having other blood disorders, were excluded. After taking informed consent, a pretested structured questionnaire was given to participants and awareness level was classified into 'unaware', 'aware' and 'well-aware' categories, based on the score achieved. Data was evaluated using SPSS version 23.0. Chi-square test was used for analysis.

Results: A total of 277 parents were included. Parents who took their children to government and private centers were 161 (58.1%) vs 116 (41.9%) respectively. There was a statistically significant difference in the know-how about mode of disease transmission (p value=0.02), blood-borne diseases (p value=0.00), method of complete cure (p value= 0.05) and harmful effects of repetitive blood transfusions (p value=0.05) among parents visiting the two different facilities. While 80.2% parents in private centers were 'well-aware', the corresponding percentage in government centers was 57.1%.

Conclusion: General disease awareness was average. Parents visiting private institutes have shown much better awareness. Funding and dedicated education, with focus on government organizations, which are accessible for the common man, is required.

Keywords: *Thalassemia major, awareness, Pakistan*

Cite this article as: Raja MB, Sharif MK, Shahid J, Junaid A, Zulfqar R. General disease awareness among parents of thalassemic children visiting government versus private care centers of Rawalpindi and Islamabad. JSTMU. 2020; 3(2):88-92.

Introduction

Thalassemia is a hereditary, hemolytic anemia of varying severity where patients' lives are dependent on repetitive blood transfusions in the 'Major' subtype.[1] the prevalence of the disease is high in developing countries, particularly in Asian and Mediterranean countries. In Pakistan, every 1–4 per 1000 infants suffer from

Thalassemia, which makes it one of the high risk countries for Thalassemia in the world.[2] the average life expectancy of affected children is stated to be 10 years in Pakistan, which is quite lower than the global average of 10-50 years.[3]

Consanguineous marriages are a major risk factor and they are quite common in Pakistan due to the cultural beliefs prevalent in the country.[4] Pre-marital screening is not a known concept, especially in the rural areas. Majority people learn first about the disease when their own child or a close family member is affected.[5] prenatal screening is also lacking. A study done in Peshawar showed that even though 74% couples have knowledge of prenatal screening, only 11% opted for it.[6]

While blood transfusion is an essential part of management, the concept of safe blood transfusion is lacking in affected families and hence, Hepatitis C is quite prevalent in Thalassemia children. Acquisition of Hepatitis C adds to the morbidity and mortality of affected children. It has been reported as one of the top two causes of death in Thalassemia children- the second being cardiac complications, secondary to iron overload.[3]

In Pakistan, the average annual expenditure for managing disease in a child with thalassemia is US $ 4500, which is much more than the per capita revenue in Pakistan. Thalassemia contributes to an annual loss of 1.46–2.92 million disability adjusted life years (DALYs), leading to massive economic burden worldwide.[3]

Majority population finds government-based facilities more affordable and accessible. In the past, awareness assessment studies similar to this have been conducted but comparison of the level of understanding between private and government sector hospitals has not been done previously. The objective of this study was to assess the current general disease awareness and to compare the level of understanding between parents attending government versus private care facilities.

Methods

After taking IRB approval from SIH and various thalassemia centers of Rawalpindi and Islamabad, this cross-sectional study was conducted in Holy Family Hospital (HFH) Thalassemia Centre, Rawalpindi, Pakistan Institute of Medical Sciences (PIMS) Thalassemia Centre, Islamabad, Jamila Sultana Foundation (JSF), Rawalpindi and Thalassemia House, Rawalpindi from Dec 2017 to January 2019.

The sample size was calculated as 256 using the WHO sample size calculator taking 95% confidence level, 0.06% precision and approximate population size was taken as 6000. Parents/caregivers of thalassemia major patients were included, while those of children with hemolytic anemias like thalassemia minor, thalassemia intermedia, sickle cell anemia, hereditary spherocytosis and G6PD deficiency were excluded. Recruitment was done through non-probability purposive sampling after informed consent.

The pretested structured questionnaire was filled by the authors through small interview with parents/guardians in Urdu language. Later, the correct answers were communicated to all parents individually. The questionnaire consisted of 07 questions related to basic knowledge of Thalassemia and total score was calculated out of 07 depending upon number of correct answers. Participants were classified into three categories: unaware; having total score of 01 to 02. Aware; having total score of 03 to 05 and Well aware; having total score of 06 to 07. Scores of parents visiting government and private centers were compared.

Data was entered in SPSS software version 23 and analyzed. Chi-square test was applied and P-value ≤ 0.05 was considered significant.

Results

A total of 277 caregivers were included in this study. Parents who took their children to government and private centers were 161 (58.1%) vs 116 (41.9%) respectively. The responses of parents to the awareness questions about Thalassemia are shown in Table 1. Correct responses and statistically significant p-values have been highlighted in bold.

There was a statistically significant difference among government and private institutes, in the knowledge of mode of disease transmission (p value=0.02), blood-borne diseases (p value=0.00), method of complete cure (p value= 0.05) and harmful effects of repetitive blood transfusions (p value=0.05). Awareness levels of the participants are presented in Figure 1.

Table 1: Responses of parents to the awareness questions

Questions	Public sector participants	Private sector participants	P-value
Mode of Transmission: Genetic Sexually transmitted Unhealthy diet Not sure	 108 (67.1%) 7 (4.3%) 3 (1.9%) 43 (26.7%)	 95 (81.9%) 0 (0%) 2 (1.7%) 19 (16.4%)	0.02
Diagnostic test: Blood test Urine test Not sure	 152 (94.4%) 0 (0%) 9 (5.6%)	 109 (94.0%) 1 (0.9%) 6 (5.2%)	0.49
Should Pre-marital screening be done? Yes No Not sure	 151 (93.8%) 4 (2.5%) 6 (3.7%)	 114 (98.3%) 0 (0%) 2 (1.7%)	0.14
Is Prenatal diagnosis possible? Yes No Not sure	 138 (85.7%) 1 (0.6%) 22 (13.7%)	 107 (92.2%) 2 (1.7%) 7 (6.0%)	0.09
Diseases transmitted via repetitive blood transfusions: AIDS and Hepatitis C Cancer Not sure	 87 (54.0%) 14 (8.7%) 60 (37.3%)	 91 (78.4%) 3 (2.6%) 22 (19.0%)	0.00
Complete cure: Blood Transfusions Healthy Diet Bone marrow transplant Medication	 41 (25.5%) 11 (6.8%) 100 (62.1%) 9 (5.6%)	 18 (15.5%) 13 (11.2%) 83 (71.6%) 2 (1.7%)	0.05
Harmful effect of repetitive transfusions? Iron overload Calcium overload Not sure	 133 (82.6%) 7 (4.3%) 21 (13.0%)	 104 (89.7%) 0 (0%) 12 (10.3%)	0.05

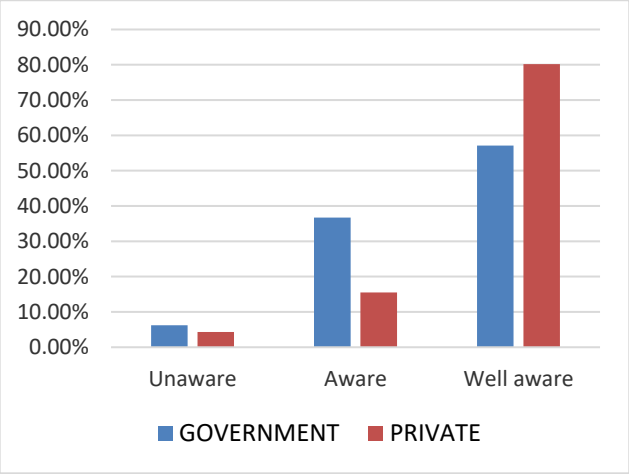

Figure 1: Awareness level of caregivers

Discussion

In our study, among government sector caregivers, 67.1% appropriately responded to the question on mode of disease transmission compared to 81.9% from the private sector, showing statistically significant difference (P-value=0.02). Knowledge was 82.6% in a 2018 study carried out in a government hospital of Rawalpindi/Islamabad.[5] Previous government hospital based studies carried out in other areas showed 47.6, 35 and 50% mindfulness sequentially.[7-9] Another study carried out in both government and private centers of the twin cities of Rawalpindi/Islamabad in 2017 reported 81.2% correct responses.[10] The previous work done in these twin cities is comparable to our work. Lastly, a study done in Rajasthan showed results of 43.3%, which is significantly lower compared to our study.[11]

When we tested the familiarity of the guardians about the diagnostic test for Thalassemia, 94.4% versus 94.0% responded correctly in government and private centers respectively and answered 'Blood test'. Awareness was almost the same in the two groups and with inconsequential difference. A study done in a private center in Karachi showed that 93% of parents knew that Thalassemia can be identified by a blood test, which is analogous to our finding.[2] In government and private centers, subjects in favor of pre-marital screening were 93.8% versus 98.3% respectively. The comparison was statistically insignificant. The cognizance was better relative to 29% and 89% reported in former Pakistani studies, done in the years 2017 and 2016 respectively.[10,8] This shows a temporal improvement.

Regarding the possibility of prenatal diagnosis, correct response was given by 85.7% versus 92.2% interviewees in our study- again with no significant difference. Other government sector researches from India and Rahim Yar Khan, Pakistan showed 50.9 and 39% awareness in order. [7,8] Knowledge similar to ours-88.3%, was noted in a previous twin cities-based study.[10] A study done in Punjab, India showed 76% of the population were aware of it.[12] A research based in another city of India showed that 60% of the population knew the benefits of it.[13]

When the caregivers in this study were asked about the diseases transmitted by blood transfusions, 54% from government versus 78.4% from private setting replied

correctly by answering AIDS &Hepatitis C. This was the most noteworthy difference in knowledge (P-value= 0.00). In the study by Mutar et al in Iraq, 37.3% and 56.9% gave correct response of AIDS and hepatitis C correspondingly.[14] Assessing awareness about the curative option for thalassemia, knowledge of bone marrow transplant was seen in 62.1% vs 71.6% government and private caregivers respectively. It was a statistically significant difference (P-value=0.05). Awareness of this aspect was much lower 2.7 and 25%, in former 2018 and 2016 studies based in India and Rahim Yar Khan, Pakistan sequentially.[7,8] Yet in a study done in Iraq, 80.1% had knowledge about it as a treatment option, but only 39.2% were cognizant of it being a complete cure.[14] However, in one more study from India (2020), only 6.78% of participants knew BMT as a treatment option and over 77.2% considered blood transfusions as the only treatment option.[15] From our results, consciousness of this aspect seems to be on the rise.

When asked about the harmful effect of multiple blood transfusions, correct response was 82.6% against 89.7% from the two groups respectively. The difference was statistically significant (p value= 0.05). This aspect was not assessed from this viewpoint in similar studies. With time, awareness is improving. The likely explanation of greater awareness level in private hospital participants is the higher doctor: patient ratio and better availability of resources. Monetary investment along with devoted education of the population needs to be done, especially in government centers, which are accessible and affordable for majority people. These measures can draw us closer to the target of a Thalassemia-free Pakistan in future.

The objectives of this study were achieved. The researchers also spent time and energy in communicating the correct answers to the study participants, once assessment was complete. However, the study has some limitations. A larger sample size may have provided a better representation of the actual disease statistics. Also, we did not inquire about factors like thalassemia screening behavior among family members and know-how about management of disease complications.

Conclusion

Overall, awareness about the disease was average, but seems to be improving. Private institutes have shown much better perception among parents as compared with government institutes. Funding along with dedicated teaching of the masses is required, especially in government organizations, for a future Thalassemia-free Pakistan.

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ORIGINAL ARTICLE

Impact of online learning; experiences and attitudes of faculty and students from two medical colleges

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Article Info.

Conflict of interest: Nil

Funding Sources: Nil

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Cite this article as: Ahmed S, Niaz M, Seemaab Z, Nadeem R. Impact of online learning; Experiences and attitudes of faculty and students from two medical colleges. JSTMU. 2020; 3(2):93-98.

A B S T R A C T

Introduction: In this changing paradigm of flipped classrooms, online learning is becoming center of focus. The spread of CoVID-19 pandemic has prompted medical institutions to quickly adopt online curriculum delivery to avoid any breaks. This transition seems to adequately serve the needs of medical education. As this new technology is rapidly being implemented, the students' and teachers' perspectives need to be evaluated to assess the outcome of these changes and to design effective strategies.

Objectives: To assess the impact of online learning by recording experiences and attitudes of faculty members and students from two medical institutions.

Materials & Methods: The study was conducted at SCM and FUMC, Islamabad. 275 3rd year MBBS students from both medical colleges along with 40 faculty members were enrolled after taking consent. Their perspectives were taken by a questionnaire. They were asked about familiarity of e-learning, its advantages, disadvantages, credibility of online assessments and whether e-learning should be part of future medical education. The data was analyzed using SPSS23.

Results: 34 faculty members and 214 students from both institutes completed the questionnaire. Majority of the faculty members and students believed that e-learning can only serve as complementary role to traditional teaching.

Conclusion: E-learning provided us the needed mode to continue delivering the course in the need of the hour. Both faculty and students deemed that online learning is not as proficient as face-to-face teaching however, hybrid model combining both modalities can achieve better results.

Keywords: *Medical education, online learning*

Introduction

In this changing paradigm of learner centered approach and flipped classrooms, online interactive learning is becoming center of focus. E-learning is an effective learning tool. Currently, the spread of the COVID-19 pandemic has prompted medical institutions to quick transition to online curriculum delivery to avoid any breaks in the education. It has proved to be fruitful in keeping students engaged with their studies in this unfortunate time. This shift to E-learning will have significant impact on the future learning trends and attitudes.[1, 2]

E-learning is considered by students a complement to instructor-led teaching rather than its replacement. It provides the students control over content of curriculum and pace of learning. Students can modify their schedules

and tailor the content according to their personal learning objectives. They get opportunity to interact with teachers at other institutes. It also provides numerous research opportunities to the teachers. E-learning has transformed the role of teachers from providers of knowledge to facilitators of learning.[3-5] The transition from on-campus activities to distant learning seems to adequately serve the needs of medical curriculum delivery, however, it has compromised annual academic calendars and caused deferring of many practical sessions/clinical rotations. Virtual distant learning has also resulted in social isolation and blurring of boundaries between work and personal life which may affect students as well as teachers.[3-5]

Most medical colleges have adapted various modes to continue their learning process. Medicine is a skill-based profession; therefore, impact of online learning must be distinct from other fields. As this new technology is rapidly being implemented and deployed in medical education, the students' and teachers' perspectives need to be evaluated to assess the outcome of these changes and to design effective E-learning strategies.[3-5] The aim of present study is to assess the experiences and attitudes of teachers as well as students from two medical institutes.

Objectives

To assess the impact of online learning by recording experiences and attitudes of faculty members and students from two medical institutions.

Methodology

The study was conducted by faculty members of pathology department of Shifa College of Medicine (SCM) and Foundation University Medical College, Islamabad (FUMC) teaching 3rd year MBBS. 111 3rd year MBBS students from SCM and 164 students from FUMC along with 40 faculty members of pathology department of both colleges were enrolled after taking consent. 34 faculty members and 214 students from both institutes completed the questionnaire. Personal information of the participants was kept confidential. They were asked about familiarity of e-learning, its advantages, disadvantages, credibility of online assessments and whether e-learning should be part of future medical education. The participants were asked to answer each question on five-point scale. The data was analyzed using SPSS 23. The analyses included descriptive statistics and chi-square test.

Results

Majority of the faculty members from FUMC (66%) believed that e-learning does not make students more active or self-learners and it is less comfortable and interactive as compared to on-campus teaching, however, most members of SCM had different opinion asserting that online learning makes students better self-learners (Figure 1). Less students' participation is seen in online classes according to the faculty members (55.8%). Majority of the teachers (58%) believed that online learning makes the daily routine more cumbersome and they do face household distractions during online classes. Internet connectivity issues is another problem confronted by half (50%) of the faculty population. When asked about online examinations, most of the faculty members (76%) believed that high stake examinations should not be conducted online, and these are not credible for grading the students. Majority of the faculty members (55%) think that e-learning can be used in combination with face to face teaching for better understanding of the students (Figure 2.)

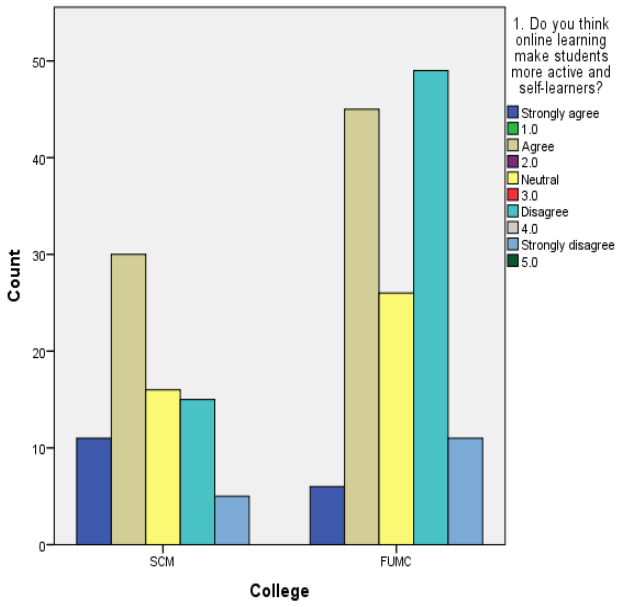

Figure **1: SCM and FUMC faculty's perceptions about** online learning making students more active and self-learners.

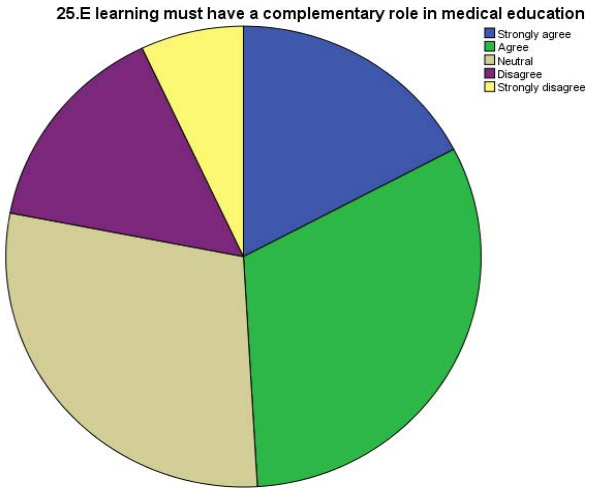

Figure **2: SCM and FUMC faculty's perceptions of e**-learning having a complementary role in medical education

In response to the question asked whether more students participate in online classes, majority of the students either disagreed (35%) or were neutral (24%) in the opinion. Students of SCM (53%) agreed that e-learning is more comfortable and promotes active learning. On the contrary, FUMC students had divided opinion, some agreed, and others disagreed (Figure-03). Pearson Chi-Square value was calculated on this question, which was significant (0.024). 82.7% of the students believed that uploaded lectures help in easy revision of the content. They (46.2%) also preferred case-based activities over simple lectures as it helps them to build better concepts. Students (61%) agreed that they suffer from household distractions while studying online and face internet connectivity issues. They feel that communication and interaction with teachers during online activities is not sufficient (50.5%).

About 60% students from both colleges disagreed with the concept of online examination; however, when asked about the credibility of exams, students had different opinions. Regarding easy cheating opportunity during online examinations, students of SCM and FUMC mostly disagreed (50.4%), however, 27% FUMC students remained neutral. 52.3% of the students think that curriculum can be delivered in less time through online classes as compared to on-campus delivery. Most of the students (75.2%) also believed that teachers were very helpful during online teaching and around 49.06% suggested that e-learning can play a complementary role in medical education.

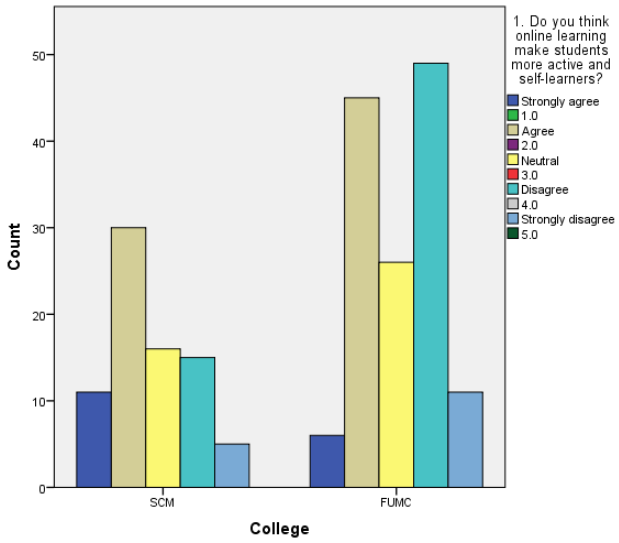

Figure 3: Perceptions of students from both medical colleges regarding online learning making them active and self-learners.

Table 1**: Faculty and student's perception**s about online learning

	College	Strong Agree	Agree	Neutral	Disagree	Strong disagree	Total
FACULTY							
Q1	Do you think online teaching make students more active and self-learner?						
	SCM	0	6	3	3	1	13
	FUMC	0	5	2	12	2	21
	Total	0 (0%)	11 (32%)	5 (15%)	15 (44%)	3 (9%)	34
Q2	Online platform adequate to deliver knowledge						
	SCM	0	5	4	3	1	13
	FUMC	0	2	6	11	2	21
	Total	0	7 (21%)	10 (29%)	14 (41%)	3 (9%)	34
Q3	Online assignments facilitate in building concept						
	SCM	0	5	3	4	1	13
	FUMC	0	5	7	7	2	21
	Total	0	10 (30%)	10 (30%)	11 (32%)	3 (9%)	34
Q4	Case-based learning						
	SCM	0	8	1	4	0	13
	FUMC	0	12	7	1	1	21
	Total	0	20 (59%)	8 (23%)	5 (15%)	1 (3%)	34
STUDENTS							
Q1	Do you think online teaching make students more active and self-learners?						
	SCM	11	30	16	15	5	77
	FUMC	6	45	26	49	11	137
	Total	17 (8%)	75 (35%)	42 (20%)	64 (30%)	16 (8%)	214

Q2	Online platform adequate to grasp knowledge						
	SCM	9	32	19	14	3	77
	FUMC	9	38	35	39	16	137
	Total	18 (8%)	70 (33%)	54 (25%)	53 (25%)	19 (9%)	214
Q3	Online assignments facilitate in building concepts						
	SCM	12	29	21	13	2	77
	FUMC	7	29	32	44	25	137
	Total	19 (9%)	58 (27%)	53 (24%)	57 (27%)	27 (13%)	214
Q4	Case-based learning						
	SCM	8	33	25	6	5	77
	FUMC	9	49	33	36	10	137
	Total	17 (8%)	82 (38%)	58 (27%)	42 (20%)	15 (7%)	214

Table 2: **Faculty and student's perceptions about** online learning Assessments

	College	Strongly Agree	Agree	Neutral	Disagree	Strongly disagree	Total
FACULTY							
Q5	High-stakes exams should be conducted online						
	SCM	0	2	1	8	2	13
	FUMC	0	2	3	13	3	21
	Total	0	4 (12%)	4 (12%)	21 (62%)	5 (14%)	34
Q6	Household distractions						
	SCM	0	5	2	6	0	13
	FUMC	1	11	2	7	0	21
	Total	1 (3%)	16 (47%)	4 (12%)	13 (38%)	0	34
Q7	E-learning can replace conventional modes						
	SCM	1	2	2	6	2	13
	FUMC	0	1	1	7	12	21
	Total	1 (3%)	3 (9%)	3 (9%)	13 (38%)	14 (41%)	34
Q8	E-learning have complementary role						
.	SCM	3	7	1	1	1	13
	FUMC	0	9	8	4	0	21
	Total	3 (9%)	16 (47%)	9 (26%)	5 (15%)	1 (3%)	34
STUDENTS							
Q5	High-stakes exams should be conducted online						
	SC	10	8	14	20	25	77
	FUMC	8	30	2	45	33	137
	Total	18 (8%)	38 (18%)	35 (16%)	65 (30%)	58 (27%)	214
Q6	Household distractions						
	SCM	17	20	13	21	6	77
	FUMC	35	60	13	23	6	137
	Total	52 (24%)	80 (37%)	26 (12%)	44 (21%)	12 (6%)	214
Q7	E-learning can replace conventional modes						
	SCM	11	25	11	18	12	77
	FUMC	13	26	18	39	41	137
	Total	24 (11%)	51 (24%)	29 (14%)	57 (27%)	53 (25%)	214
Q8	E-learning have complementary role.						
	SCM	17	20	13	21	6	77
	FUMC	35	60	13	23	6	137
	Total	52 (24%)	80 (37%)	26 (12%)	44 (21%)	12 (6%)	214

Discussion

Pandemic has caused closure of schools and colleges throughout the world. Online learning even though was being utilized by medical colleges, but exclusive E-learning was unchartered territory for both the students and the teachers. This research draws attention to the experiences faced by students and their teachers to predict the future of online learning in the field of medicine post quarantine.

E-learning has had an important role in medicine for a very long time. But this global pandemic shifted the whole burden to online teaching. Multiple studies have shown good participation when attendance was made mandatory in these lectures or attendance was a part of course-grade; ensuring student participation [6-8] When asked students and faculty both presented a united front that 'exclusive online learning' did not ensure expected participation by the students. Interaction and communication are vital to know if the knowledge is being adequately grasped by the students. An Indian study concluded that interaction among teachers and students was less effective in e- learning compared to the face to face classroom learning.[6-8]

Students believe that they have become more responsible regarding their curriculum while studying online. The e-learning has made them active learners and changed their approach from teacher-centered learning to self-learning. Students with different learning styles are aided by this enabling them to study more efficiently.[5] However, views of SCM and FUMC students differ slightly (Table-01). A study conducted by Masic I, also discusses benefits of distance learning; stating that they are given the opportunity to learn how to work independently.[5] Even though online learning has proved to be flexible and accessible making distant learning exultantly easy to administer, there were still many kinks to evaluate. Online assignments and lectures were the main modes of delivering and assessing the knowledge. Faculty considered these to be inadequate for building the concepts amongst the students. While students gave a very neutral response to both these techniques. A study was published by Robert M. Bernard from Concordia University in 2004 presenting how Distant Education can be extremely efficacious at times and can work poorly.

Therefore, it is important to firstly know and then work out the problematic areas to make E-learning more efficient.[10]

Medicine is a skill- based profession, medical students must examine the patient, take history, and build a case to diagnose and manage the disease. Going to wards and visiting the patients was not possible during quarantine so case-based learning was the best alternative. A study done by Susan F Mclean in USA suggested CBL as an important tool for imparting practical relevance to the theory. Our students and faculty (46.2% and 58.8% respectively) also exhibited the pertinence of CBL during CoVID-19 era as a source of corelating theoretical knowledge. Inculcating cases and learning objectives in study guidelines have been appreciated by the teachers and the pupils (Table-01).[9-12]

Online assessments were imperative to evaluate the progress of students. Multiple examinations were conducted via online platforms; some were routine while others were high-stake assessments. Overall, faculty and students were dissatisfied by the credibility of online grading of such exams specifically for the important tests. Generally, any assessment brings about a concern for cheating, precautions were taken to make invigilation as cautious as possible[13] Thus, making it difficult for the students to attain outside aid to complete their evaluations. Newer and better technologies can help to improve reliability of online examinations, as stated in a previous study.[3]

Transition to online learning, though drastic, was seamlessly adopted by all. Online instructions being the sole way to transfer the knowledge led to myriads of problems faced by the administrations and the students. For instance, Lack of decorum during online lectures. Internet can make anonymity easy to use, to disrupt the discipline of the classes. Strict measures were taken to set examples for the rest of the students to convey that such behavior will not be tolerated in the future. Internet connectivity issues or technical difficulties have always caused some problems even before this outbreak. This remained as a problem during this time as well. In addition to this, home environment is contrasting to the workplace discipline. Many faced household distractions mingling with their working hours making home a less conducive learning environment. College managements were available during office hours to take care of any such issue and provided online assistance. Faculty was properly trained to deliver the content online. Their issues and suggestions were welcomed by the seniors and certain changes were made to make the process easier for all. Perhaps this quarantine has highlighted the issues to facilitate the learning to get the maximum benefits.[14,15]

Plethora of researches have been done in the past to see if network aided tools were reliable enough to be utilized in the curriculum delivery. A research done in Riyadh, suggested it to be innovative way to achieve course delivery goals.[16] During lockdown, this became an utmost necessity. Exclusive virtual learning for an extended period wanted us to see its future implications. We concurred that digital teaching could have a blended role in the future to save time and effort as previously studied. It cannot completely take over the conventional face to face teaching methods as it lac) ks teacher-student bonding and skill-based activities.[17,18]

Conclusion

E-learning provided us the needed mode to continue delivering the course in the need of the hour. Both faculty and students deemed that online learning is not as proficient as face-to-face teaching however, hybrid model combining both modalities can achieve better results.

Recommendations of study

Online-learning helped us to deliver curriculum during CoVID-19 pandemic. Now, we are more experienced and well equipped to deal with such crisis. We need to develop permanent systems to deal with any such adversity. Using our knowledge of the problems faced by us we can devise an effective mode of delivering the curriculum in case of an unfortunate event. Moreover, it has been highlighted that we need to redesign our educational systems to use the advantages of digital learning and apply it to our conventional teaching methods making learning easier to grasp and accessible.

Limitation of study

This study was done with 3rd year students and with faculty members of pathology department of both medical colleges. It can be done on a larger scale including all faculty members and all MBBS students from1st year to final year of both medical colleges.

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ORIGINAL ARTICLE

Post-wash total motile sperm count a useful predictor in the decision to perform IVF/ICSI in patients with non-male factor infertility

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[3] Data collection
[4] Manuscript preview and proofreading

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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Cite this article as: Qureshi SM, Kafeel S,Bibi R, Mohmand J. Post-wash total motile sperm count a useful predictor in the decision to perform IVF/ICSI in patients with non-male factor infertility. JSTMU. 2020; 3(2):99-106.

A B S T R A C T

Introduction: The unrestricted use of intracytoplasmic sperm injection (ICSI) for non-male factor infertility is associated with adverse outcomes. Post-wash total motile sperm count (PW-TMSC) offers prognostic value to assess sperm quality and aid in the decision to perform in vitro fertilization (IVF) or ICSI.

Objectives: The aim of this study was to identify the effect of PW-TMSC on fertilization rates in patients undergoing IVF cycles exclusively with non-male factor infertility. It also aimed to identify whether unnecessary ICSI could be avoided in such cases, thus maximizing optimal outcomes.

Materials & Methods: We retrospectively analyzed age, semen volume, prewash TMSC, and PW-TMSC in 68 conventional IVF cycles of infertile couples with non-male factor infertility. Clinical characteristics including female age, number of follicles, level of estradiol on trigger day, mature cumulus-oocyte complexes (COCs) collected, were also included.

Results: Incidence of <30% fertilization was significantly higher in the 4-<10 Million group compared with the ≥20 Million post-wash TMSC group (P<0.001). Furthermore, Receiver operating characteristics (ROC) analysis revealed post-wash TMSC as a significant predictor (P<0.05) of total failed fertilization (TFF) and of ≥30% fertilization (P<0.05) with area under curve (AUC) of 0. 79 and 0.77, respectively, with a deemed cutoff of 10.89 Million.

Conclusion: Post-wash TMSC is a good predictor of fertilization; it can help in avoiding potentially low or even total fertilization failure (TFF). A cut-off point of 10.89 Million or less should warrant the use of ICSI.

Keywords: *In vitro fertilization, fertilization rate, post wash sperm, total motile sperm count*

Introduction

Intracytoplasmic sperm injection (ICSI) procedure was a breakthrough technique introduced in 1992, in order to overcome male factor infertility and to improve fertilization outcomes in couples with fertilization failure in prior In Vitro Fertilization (IVF) cycles.[1,2] The benefits of utilizing ICSI for male factor infertility is well established.[3] In recent years ICSI has become increasingly popular, being encouraged by practitioners. Its use has broadened to include indications other than male factor infertility, such as poor oocyte quality, low oocyte yield, advanced maternal age, unexplained infertility, and even for routine use in all assisted reproductive technology (ART) cycles,

regardless of etiology.[4] The basis for utilizing ICSI for non-male factor indications is to prevent TFF and to maximize fertilization rates. However, there are potential risks associated with ICSI such as asynchrony in sperm chromosome decondensation,[5] oocyte degeneration, which is particularly higher in patients with fragile oocytes, the plausibility of injecting sperm with DNA anomalies,[6] lower implantation rates than conventional insemination in cases of non-male factor infertility,[7] risk of fetal malformations and chromosomal abnormalities.[5] Although the safety and efficacy of ICSI for male factor infertility has been evaluated.[8] Yet, the impact of unrestricted use of ICSI and associated risks for non-male factor infertility is still not fully understood. A recent study highlighted a strong association of ICSI with autism when used in the absence of male factor infertility.[9]

Currently, the decision to perform IVF or ICSI is mostly experience-based.[10] The total motile sperm count (TMSC) has been identified as a useful way to express semen quality; it is a combination of the ejaculate volume, sperm concentration (million sperm per ml), and motility percentage.[11] The use of TMSC in the native semen specimen has been proven to be of prognostic value in couples undergoing intrauterine insemination (IUI) cycles.[12] And according to 2010 classification of the World Health Organization (WHO), TMSC is considered of superior value in predicting the success of IVF cycles.[13] Several studies have suggested that TMSC following sperm preparation or post-wash, essentially by density gradient centrifugation method offers a more robust selection parameter for assessing semen quality. It reflects spermatozoa with high motility moreover, bearing normal morphology which fundamentally is associated with fertilization capacity.[14,15] The use of post-wash TMSC has been identified as a useful parameter to predict pregnancy in IUI cycles.[16] Moreover, post-wash TMSC parameter is a reproducible predictor of total failed fertilization (TFF) in conventional IVF cycles.[17] It is also used as a tool to assess sperm quality and aid in the decision to perform either IVF or ICSI.[10] However, the prognostic value of post-wash TMSC on fertilization rates in couples particularly of non-male factor infertility, undergoing IVF cycles is not yet well established. This study aimed to identify the effect of post-wash TMSC on fertilization rates in patients undergoing IVF cycles exclusively with non-male factor infertility. It is also intended to identify whether unnecessary ICSI could be avoided in such cases while ensuring that the simplest, most cost-effective and most successful treatment is offered to the patient.

Methods

Patient Selection

We retrospectively evaluated all cycles of IVF conducted during a 22-month period of time at a local fertility clinic for patients with no apparent indication for ICSI. This was confirmed by two prior semen analysis conducted as part of an initial workup. Semen was diagnosed as normozoospermic when having a sperm concentration of ≥20 Million /ml, motility ≥50%, and normal morphology ≥14%, as per the criteria of WHO 1999.[18] Sperm concentration was determined by Neubauer hemocytometer. The motility was evaluated by assessing at least 200 spermatozoa and expressed as a percent of motile sperms. Sperm morphology was assessed by Papanicolaou stain, following an assessment of at least 200 sperms. Male factor was diagnosed if any of the semen parameters were out of the reference range as per WHO 1999 criteria, hence not included in this study.

Only couples undergoing their first conventional IVF cycle, having normal semen parameters, and at least two mature cumulus-oocyte complexes (COC) retrieved were included. A total of 68 cycles met this criterion with the male partner's prewash and post-wash semen parameters on the day of oocyte pick up (OPU), evaluated along with the respective female partner's baseline characteristics of age, number of follicles, level of estradiol on day of trigger, and number of mature COC's retrieved.

Semen Assessment & Preparation

On the day of OPU, the semen sample was produced, usually before oocyte collection. Following liquefaction, the volume, sperm concentration, and motility were assessed in order to calculate TMSC in the neat sample. Semen was subjected to density gradient centrifugation using 90% spermgrad (Vitrolife, Sweden). Following centrifugation for 10 minutes at 450g, the pellet was resuspended in 02-03 ml of pre-equilibrated GIVF+ media

for washing (Vitrolife, Sweden). It was further centrifuged for 10 minutes at 350g. Lastly, the pellet was suspended in a final volume of 1 ml GIVF+. The post-wash TMSC was evaluated in the final suspension. The post-wash TMSC was categorized into three groups of 4 to <10 Million, ≥10 to 19.99 Million, and ≥20 Million or Higher.

IVF Protocol

Female partners were subjected to a standard long stimulation regime using GnRH agonist Buserelin acetate (Suprefact, Aventis Pharma) at a standard dose of 0.5 mg starting in the mid-luteal phase of the preceding cycle or subjected to a short antagonist IVF protocol using 0.25 mg Cetrorelix (Cetrotide® Merck Serono SA, Aubunne, Switzerland) commencing on day 6 of stimulation. Ovarian Stimulation was started using human menopausal gonadotrophin (Menogon Ferring SA, Sainet Prex, Switzerland) or recombinant follicle-stimulating hormone (rFSH), (Gonal F Merck Serono SA, Aubunne, Switzerland). OPU was performed 36-38 hours after a 10,000 IU hCG trigger (Pregnyl Organon, Oss, the Netherlands). Mature COC's were group cultured (2-6 COC's per well), in pre-equilibrated four-well dishes containing 0.5 ml GIVF+ and 0.5 ml oil overlay. Mature COC's were inseminated using 60,000 motile sperms per egg. Fertilization was assessed 16-20 hours post insemination, with two or more evident pronuclei considered as fertilized. Fertilization rates were categorized into three groups of <30%, ≥30 to 69.9 %, and ≥70% observed fertilization.

Ethical Approval

The research protocol was approved by Salma Kafeel Medical Services No.010-2016. Informed oral consent was obtained from each participant included in this study.

Statistical Analysis

Categorical data were analyzed using Fisher's exact test with pairwise post hoc analysis using Bonferroni adjustment. Continuous data variables with normality and homogeneous variance were tested using ANOVA with post hoc analysis using the Scheffé test. For non-parametric data or data with non-homogenous variance, Kruskal Wallis was used. To assess the capacity of prewash and post-wash TMSC to predict fertilization receiver operating characteristic (ROC) analysis was conducted. P value <0.05 was considered statistically significant unless stated otherwise. All tests were performed using SPSS 22.0 (Chicago, IL, USA) statistical package. Due to the limited number of subjects in this study post hoc power and effect size analyses were performed, with results presented for significant differences. Power analysis was conducted using G*Power.

Results

There was no significant difference between any parameters of the female clinical characteristic among the three different post-wash TMSC groups. These characteristics included female age, number of follicles, level of estradiol on trigger day, mature COC's collected The calculated prewash TMSC on the day of OPU, the prewash motile sperm count/mL and prewash TMSC varied significantly across all the three groups of 04 to <10 Million, ≥10 to 19.99 Million and ≥20 Million or higher post-wash TMSC (P<0.001), as presented in Table 1.

The incidence of fertilization classified into groups of <30%, 30 to 69.99%, and 70% or higher, in relation to the three post-wash TMSC groups of 04 to <10 Million, ≥10 to 19.99 Million and ≥20 Million. The incidence of lower than 30% fertilization was significantly higher in the post-wash TMSC group of 04 to <10 Million (N=38 P-value <0.005 statistically significant with Bonferroni adjustment.) compared with ≥20 Million group. Moreover, a significantly lower trend of 70% or greater fertilization was observed in this respective group in comparison with ≥20 Million, post-wash TMSC group (Figure 1) [P=0.004, effect size=0.99 (large), observed power=0.99].

While a higher trend of 30% to 69.99% fertilization and ≥70% fertilization was evident in the ≥20 Million post-wash TMSC groups in comparison with ≥10 to 19.99 Million post-wash TMSC group, however, this finding was not statistically significant. (N=61, P-value=0.31). Moreover, ROC analysis of all cycles was conducted in the prediction of total failed fertilization (TFF). The analysis revealed post-wash TMSC as a statistically significant predictor of this outcome (P=0.046) with Area under curve (AUC)=0.79, a cut off value of 10.89 Million post- wash TMSC, having 96.9% sensitivity and 75% specificity (Figure 2B). On the contrary, prewash TMSC (Figure 2A) was not a significant predictor of TFF (P=0.34). Furthermore, ROC analysis in order to predict

30% or higher fertilization revealed post-wash TMSC to be a significant predictor (P=0.026) for this outcome with AUC=0.77 however, not the parameter of prewash TMSC (P=0.27). A cut-off value of 10.89 Million TMSC demarked the prediction of this outcome with 98.4% sensitivity and 67% specificity (Figure 3).

Table 01: Clinical characteristics of female and male partner according to post-wash TMSC groups.

Variables	4 to <10 Million Post-Wash TMSC (n=4)	≥10 to 19.99 Million Post-Wash TMSC (n=14)	≥20 Million Post-Wash TMSC (n=50)	p-value
Female Age	32.0 ± 2.42	30.6 ± 1.18	31.71 ± 0.81	0.79
Female Infertility Etiology	0.00 %	2.6 %	5.3 %	0.06
PCOS	2.6 %	26.4 %	23.7 %	
Tubal Factor	0.0 %	2.6 %	7.9 %	
Endometriosis				
Ovulatory Dysfunction	2.6 %	0.0 %	26.3 %	
Number of Follicles	7.3 ± 4.84	10.64 ± 1.58	9.34 ± 0.64	0.50
E2 Level on Trigger Day	257.5 ± 24.50	809.57 ± 224.68	1026.08 ± 126.58	0.43
Mature COC's Collected	8.25 ± 2.86	5.50 ± 1.63	7.54 ± 0.69	0.13
Male Age	40.3 ± 2.73	41.2 ± 4.27	36.4 ± 1.09	0.28
Semen Volume	1.86 ± 0.16	1.84 ± 0.08	1.9 ± 0.04	0.38
Pre-wash Motile Sperm Count/mL	22.01 ± 7.45	28.72 ± 3.7	51.54 ± 3.17	<0.001
Pre-wash TMSC	39.65 ± 12.25	54.02 ± 8.10	100.62 ± 6.53	<0.001

Values are represented as Mean ± standard error of mean (SEM). ANOVA test performed between groups for parameters of female age, number of follicles, pre-wash motile sperm count/ml and pre-wash TMSC. Fisher's exact test performed between groups to assess distribution of female infertility etiology. Kruskal Wallis test performed between groups for all remaining parameters. p<0.05 was considered as statistically significant.

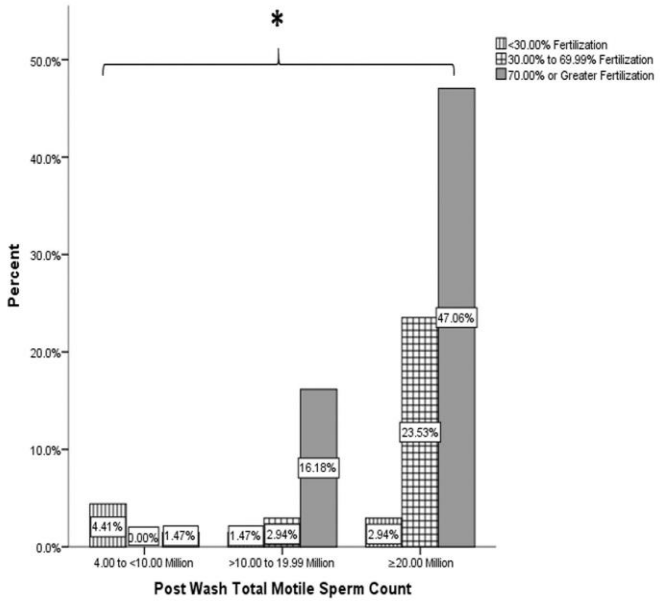

Figure 1. The incidence of fertilization classified into lower than 30%, 30% to 69.99% and 70% or higher, in relation with post-wash TMSC groups of 4.0 to <10 **Million, ≥10 to 19.99 Million and ≥20 Million post**-wash TMSC, respectively: presented as % of the total across all respective post- wash TMSC groups. **Fisher's** exact test performed with Bonferroni adjusted P-value between pairwise group comparisons. P<0.005 was considered statistically significant.

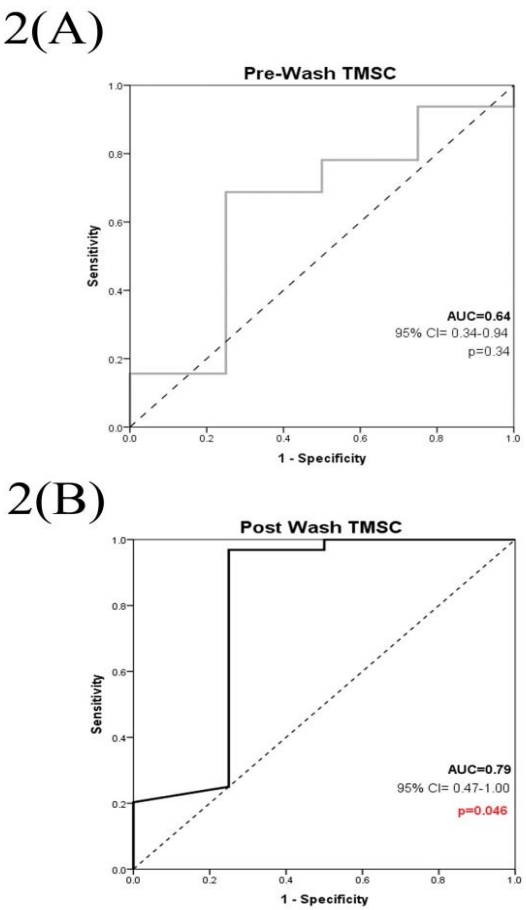

Figure 2. Receiver operating characteristic analysis for all cycles in the prediction of total failed fertilization by (A) Pre-wash TMSC and (B) Post wash TMSC. AUC= Area under curve, CI= Confidence Interval, dotted line represents reference line, bold p values indicate statistical significance.

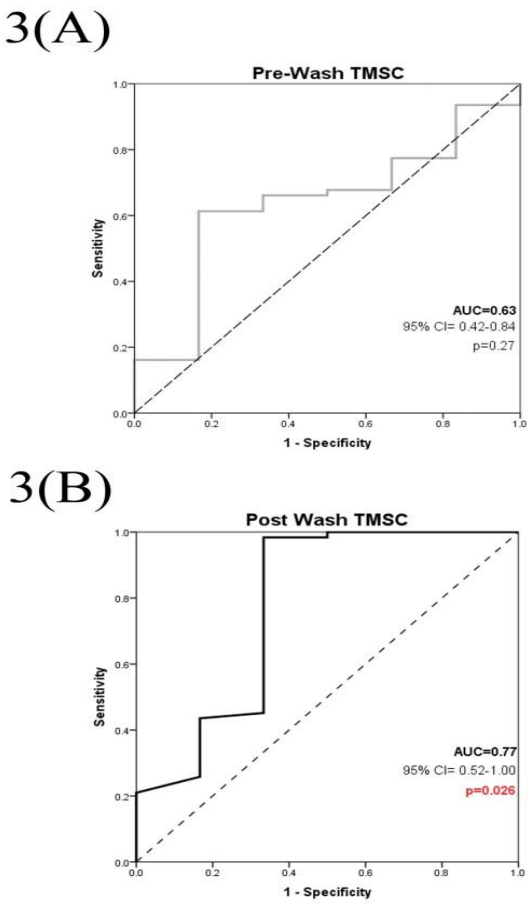

Figure 3. Receiver operating characteristic analysis for all cycles in the prediction of 30% or higher fertilization by (A) Pre-wash TMSC and (B) Post wash TMSC. AUC= Area under curve, CI= Confidence Interval, dotted line represents reference line, bold p values indicate statistical significance.

Discussion

Finding the most appropriate assisted reproductive treatment for a couple can prove to be challenging, essentially in terms of determining a modality that is least invasive, most cost-effective and offers the highest chance of achieving a healthy offspring.[17] For cases of non-male factor infertility, the use of ICSI as the default option is questionable.[3] Moreover, in such cases, the plausible negative effects associated with the use of ICSI include compromised embryonic development.[19] lower implantation and pregnancy rates per cycle.[7] increased risk of births defects.[4] None of these negative effects can be overlooked when compared with conventional IVF. Moreover, the selection of sperms in conventional IVF is extremely complex, dynamic, and rigorous in determining

spermatozoa possessing all the essential mechanisms of oocyte recognition, fusion and crucial intracellular factors.[19] Therefore, impacting fertilization and subsequent embryo development. All these intricate processes are bypassed in ICSI, and sperm selection is based on an embryologist's subjective assessment of sperm morphology.[20]

Thus, the aim of this study was to identify a practically useful parameter to predict fertilization in couples with non-male factor infertility that are undergoing IVF cycles. Furthermore, to enable a more robust selection of treatment modality, ensuring that unnecessary ICSI is avoided while still maximizing fertilization rates. This study considered only a single treatment cycle of each couple as multiple cycles of the same couple would be a source of bias. The study focused on post-wash TMSC as sperm preparation method of density gradient centrifugation was utilized, which essentially allows isolation of morphologically normal spermatozoa possessing a density of at least 1.10 g/ml.[21] Post-wash TMSC has been identified as a useful tool in the decision to perform conventional IVF or ICSI in cases of isolated teratozoospermia,[10] in the prediction of total fertilization failure including patients with male subfertility or unexplained infertility.[14] However, for couples with non-male factor infertility exclusively a criterion is not well established.

The results of this study showed that the incidence of <30% fertilization including total failed fertilization is significantly higher in 04 to the <10 Million post-wash TMSC group compared with the ≥20 Million post-wash TMSC group. Consequently, a significantly lower incidence of ≥70% fertilization was evident in the 04 to <10 Million group compared with the ≥20 Million post-wash TMSC group. This finding is consistent with that of an earlier study highlighting that 7.6 Million post-wash TMSC demarked IVF cycles showcasing no observed fertilization.[14] Furthermore, in order to identify a threshold of prewash TMSC and post-wash TMSC in predicting total failed fertilization, a ROC analysis was conducted in this study. The main finding of the ROC analysis in this study, revealed that post-wash TMSC but not the prewash TMSC is a significant predictor of successful fertilization. The rationale for this finding is also supported by previous studies. Supporting that while pre and post-wash TMSC fundamentally are highly associated. Nonetheless, post-wash TMSC obtained by density gradient sperm preparation method allows for isolation of motile, morphologically normal sperm and recovery of sperms with good DNA integrity in comparison with pre-wash specimens.[10, 22] Therefore, post-wash TMSC parameter reflects overall sperm quality, thus offers a higher predictive utility than pre-wash TMSC.[10] Additionally, another study investigated sperm anomalies/deformity indices assessed between pre and post-wash sperms. The grouped sperm anomalies indices of post-wash sperms were predictive of pregnancy outcomes in intrauterine insemination cycles, however not indices of pre-wash sperms.[23] Further, providing evidence for post-wash TMSC reflecting greater predictive utility in clinical practice and in demonstrating overall sperm quality.

In terms of identifying a cut-off point for the prediction of total failed fertilization, post-wash TMSC (AUC=0.79) demarked 10.89 Million bearing a sensitivity of 96.9% and specificity of 75% in the prediction of TFF. Below this threshold, ICSI would be beneficial in view of the potentially high risk of complete fertilization failure. While other studies propose a cut-off point of lower than 1.5[10] and 02 Million[14] post-wash TMSC as an indication for ICSI, which appears quite lower than the findings of this study. However, this is due to the selected patient population, as the findings presented here are specifically addressing non-male factor infertility couples and does not include patients with isolated teratozoospermia or with male factor subfertility.[14] Additionally, a threshold of 10.89 Million post-wash TMSC demarked a slightly reduced predictive capability of 98.4% sensitivity and 67% specificity in order to predict 30% or higher fertilization outcome (AUC=0.77). While the prognostic value for identifying a post-wash TMSC to predict 70% fertilization, would be clinically useful as it matches the average fertilization rates achieved by the ICSI technique. However, the small sample size in this study restricts the predictive utility for this outcome. Nonetheless, a higher trend of 30 to 69.99% fertilization and ≥70% fertilization was observed in ≥20 Million TMSC group as compared with 10.00 to 19.99 Million post-wash TMSC group. This finding did not prove to be statistically significant (P=0.31). Although, a recent study has showcased that a threshold of 25 Million post-wash TMSC can predict 70%

fertilization in conventional IVF cycles of couples with no apparent male factor infertility.[4] Therefore, providing evidence to support that post-wash TMSC threshold offers a robust treatment selection criterion for optimal fertilization rates.

Although sperm morphology has not been re-evaluated on the day of OPU and is a weakness of the study, yet all subjects had prior confirmed normal semen parameters including sperm concentration, motility, and normal sperm morphology as per WHO 1999.[18] A previous study has shown that normal and subnormal sperm morphology does not influence fertilization rates in conventional IVF cycles given that, the other semen parameters are normal.[24] Additionally, worth considering while additional assays such as sperm chromatin evaluation may offer value in deciding upon performing IVF or ICSI as the treatment modality. However, the variety of sperm chromatin/DNA assays lack standardized consensus, offers limited prognostic value, is expensive and essentially not part of the routine assessment in most ART laboratories.[25] Furthermore, it is known that sperm DNA/chromatin integrity is significantly improved following density gradient centrifugation however, its association with fertilization rates in IVF and ICSI still lacks significant correlation. Thus, post-wash TMSC offers a robust, simple and quick assessment to aid in the decision between IVF/ICSI.[10, 14, 17] Moreover, specifically for non-male factor infertility cases as highlighted in this study.

While the findings presented are of clinical significance, it is important to highlight a few limitations of this study. The retrospective nature, small sample size, and potential for selection bias due to lack of proper randomization are weaknesses of this study. However, corroboration of these observations with future studies could lead to definitive recommendations being proposed. In conclusion, our findings offer evidence-based strategies in the decision to perform IVF or ICSI for non-male factor infertility couples and suggests that post-wash TMSC is a good predictor for fertilization in such couples which should be measured routinely prior to conventional IVF inseminations. An identified threshold of 10.89 Million post-wash TMSC or lower is suggestive of increased risk of low fertilization and TFF in such couples and thus should warrant the use of ICSI procedure.

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JSTMU Journal of Shifa Tameer-e-Millat University

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ORIGINAL ARTICLE

Faculty development program: Way to excellence

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[1] Planning, data collection, article writing
[2] Data collection, critical review of manuscript
[3-5] Data Collection
[6] Planning of study, critical review of manuscript
[7] Critical review of manuscript

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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Cite this article as: Shafi R, Rauf A, Irshad K, Zaman I, Hussain A, Shah SS, Amir M. Faculty development program: Way to excellence. JSTMU. 2020; 3(2):107-112.

A B S T R A C T

Introduction: The importance of faculty development programs (FDP) to improve teaching effectiveness has been emphasized in recent years. Our endeavors to improve teaching ways at Shifa College of Medicine, include development of student feedback mechanisms, professional development programs, and research into teaching. New trends taking place in academic medicine were accommodated by modification of faculty development model.

Methods: With an aim to assess the perceptions of faculty about FDP at Shifa College of Medicine we gathered views of faculty, by administering questionnaire, conducting focus group and individual interviews.

Results: More than half of faculty (51%-83%) agreed with various items related to teaching and learning concepts, 79% believed that they learned assessment methods. 73% agreed that it was a source of introduction to new educational strategies. Sixty-eight percent agreed that FDP helped to improve skills in teaching of ethics and professionalism. Results of focus group discussion show that faculty found program helpful in their grooming and development and it made them more knowledgeable. Views from individual interviews stated that faculty development program has contributed towards learning.

Conclusion: In conclusion FDP at Shifa College of Medicine is valued by faculty. It has contributed towards excellence in teaching. This program should be continued with an endeavor to improve it further.

Keywords: *Faculty, teaching, learning*

Introduction

The importance of faculty development programs to improve the teaching effectiveness has been emphasized in recent years.[1] These programs are developed to improve the standard of teaching[2,3] and mostly focus on enhancing the abilities of medical faculty as teachers.[1] Faculty development is defined by Wilkerson and Irby "as a tool for improving the educational vitality of our institutions through attention to the competencies needed by individual teachers and to the institutional policies required to promote academic excellence".[4] An effective faculty development program improves the quality of teaching.[5] Training of faculty can positively impact the

teaching competencies leading to improved teaching practices[6,7,8] Faculty development programs help to enrich the knowledge and skills of teachers.[9] Clinical skills and knowledge alone do not necessarily make a good teacher, therefore more programs focusing on teaching skills are required for medical teachers.[10] Faculty development program must address the needs of the participants[11] to ensure faculty participation and interest.[12] The areas to be addressed may be identified through formal need assessment[13] or through informal encounters with the faculty, taking the institutional goals into consideration.[14] Shifa College of Medicine (SCM), a constituent college of Shifa Tameer-e-Millat University has always laid a great emphasis on acquiring able and committed faculty, and a continuing program for professional growth and development for its faculty has remained a top priority for the college.

SCM shifted from discipline based to system based integrated modular curriculum which required training of the faculty for skills and competence to adopt new strategies. The faculty development program was modified, keeping in view the curricular philosophy of SCM, which is student centered, constructivist, collaborative, lifelong learning, Integrated/ clinical relevance and critical thinking. This study was designed to describe the evolution of faculty development program at Shifa College of Medicine and assess the views of the faculty on effectiveness of this program.

Objectives

The objectives of this study are to:

1. Describe the evolution of faculty development program (FDP) at Shifa College of Medicine.
2. Assess the views of the faculty on effectiveness of faculty development program.

Methods

Study was approved by the Institutional Review Board and Ethics Committee of the institution. Mixed methods approach was used to increase validity of the findings.

Record of the faculty development program at Shifa College of Medicine was retrieved from Department of Health Professionals Education (DHPE). Faculty development program at SCM includes faculty development seminars, workshops, post graduate studies, and research and faculty participation in national and international conferences.

Data regarding perceptions of the faculty on faculty development sessions was collected through questionnaire, focus group and interviews. A feedback questionnaire using five point Likert scale was administered to the junior and senior faculty. Focus group discussion was also conducted with multidisciplinary group of faculty members, and in addition individual interviews were conducted with senior faculty members.

Results

Although faculty development program was initiated at Shifa College of Medicine in 1999, regular scheduling of the sessions was implemented in 2002. Last Saturday of every month is allocated for a two hours' duration faculty development seminar that is mandatory for all the faculty members. In the initial years of this program, most of the sessions included presentations on various professional and educational aspects. A move from subject based to system based integrated modular curriculum was directed towards interactive teaching and self-directed learning. The instructional approaches increased the emphasis on problem-solving, interpersonal skills and attitude. New trends and profound transformations taking place in academic medicine made remodeling of our faculty development program necessary. To accommodate these transitions major overall changes in faculty development were brought about and currently workshops and hands on activities have become predominant. Workshops are planned according to the needs identified during various sessions. Various faculty development seminars revolved around different themes which included teaching and learning concepts, needs assessment, technology, assessment (formative & summative), program evaluation, learning strategies, curriculum planning & development, quality in medical education, innovations (EBM, professionalism/ethics, humanities), medical research, community based education, learning environment, patient safety.

Table 1: Themes discussed in the faculty development seminars

FDP Themes	No of sessions under the identified themes
Teaching and learning concepts	27
Needs assessment	02
Technology	03
Assessment (formative & summative)	37
Program Evaluation	22
Learning Strategies	08
Curriculum Planning & Development	25
Quality in Medical Education	31
Innovations (EBM, Professionalism/Ethics, Humanities)	20
Medical Research	13
Community Based Education	04
Learning Environment	02
Patient safety	02

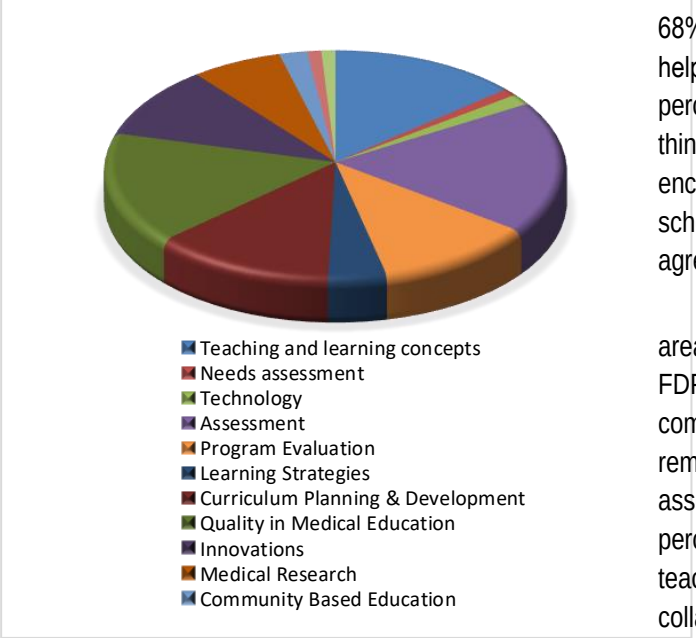

Figure 1: Seminars held under identified themes

Faculty was motivated to carry out research and this resulted in a significant number of scholarly publications in prestigious journals. Faculty was encouraged and supported to participate in various national and international conferences and to join postgraduate medical education programs. The evolution of faculty development program into a comprehensive, multilevel program helped in promoting excellence in teaching and research. These endeavors led to the development of a well-established department of health professions education, which functions to plan and organize the educational activities.

Questionnaire was administered to 92 faculty members which included both senior and junior faculty from multiple specialties using five point Likert scale. Strongly agree and agree were merged and strongly disagree and agree were also merged for the purpose of analysis.

More than half of the faculty (51%-83%) agreed with various items related to teaching and learning concept. Seventy-four per cent agreed that the FDP provided opportunities to improve basic facilitation skills. Fifty-five per cent said it was a source of motivation to improve academic qualifications. Eighty-three percent thought sharing of teaching experiences helped them learn and 68% agreed that discussions on student's feedback helped to reflect on one's performance. Seventy-four percent believed that it helped to reframe the traditional thinking of faculty. Fifty-one percent agreed that it encouraged change as an essential component for scholarship in teaching / learning process, and 68 % agreed that it helped to improve communication skills.

Fifty-eight percent thought it helped to identify their areas of improvement. Only 29% agreed with the fact that FDP improved skills in use of information technology and computer in education, 40% disagreed, whereas 32% remained neutral. Seventy-nine percent said they learned assessment methods through workshops. Sixty-seven percent agreed that it introduced learner centered teaching behavior, and helped to increase skills in collaborative teaching. Eighty percent and 73% respectively agreed that they learned various learning strategies and that they were introduced to new educational strategies. Only 32% said it helped to improve skills in teaching of bedside and clinical teaching, 33% remained neutral and 34% disagreed. Fifty-nine percent said it enhanced skills in curriculum planning and module design, 68% found it helpful in developing

educational objectives and blue printing. Seventy-four percent believed that it provides opportunities to learn recent advances, emerging trends and issues in the field of medical education, and 57% found it a source of sharing experiences of national/international exposure. Sixty-five percent said it introduced them to evidence based medicine. Forty-two percent believed it promoted personal growth of faculty through literature, poetry and religion, 68% agreed that FDP helped to improve teaching skills of ethics and professionalism and 53% thought it motivated for research. Forty-four percent found it to enhance medical writing skills, research methodology, scientific and medical education research. Sixty-eight percent thought it promoted learning environment.

Only 20% agreed, 35% were neutral and 25% disagreed, regarding the role of FDP in community based education. Focus group was conducted with multidisciplinary faculty members. The participants believed that faculty development program at SCM has been a useful experience for them. Sessions on learning strategies and assessment were appreciated. Some of the workshops clearly made a significant difference in performance. This program was said to have helped in grooming and development of faculty, and in making them more knowledgeable in the field of medical education. They thought that the faculty shared their experiences and innovative ideas through this program. It promoted team work and helped the faculty reflect on their performance. Sessions on arts and humanities were appreciated by the faculty. It was believed that FDP has definitely contributed towards the progress of faculty; it helped to improve their teaching skills and has helped the new teachers to learn various methods of teaching.

Individual interviews were conducted with four senior faculty members. They believed that the objective of FDP was to train the faculty to deliver curriculum optimally, it is organized to familiarize the faculty with learner centered approach, keep up with new trends and improve teaching and assessment.

"I was introduced to new learning strategies and assessment."

When asked if they see the objectives being fulfilled they responded that some of the objectives have been achieved like teaching strategies and assessment methods while other objectives like promotion of research have only been addressed partially. The faculty was able to learn and switch over from traditional to modular curriculum with the help of faculty development program.

"I have learned from these sessions most of the time."

Regarding the challenges faced when FDP was started, they said that it was a challenge to keep the faculty interested and engaged during sessions. Initially there was resistance for a change in the modality of curricular delivery, but over a period of time orientation through FDP helped in decreasing the resistance and now there is more acceptance. In response to a question about the contribution of FDP towards teaching excellence, they said that it has definitely contributed towards teaching excellence. This program should continue and should be further improved.

"It helps in grooming the faculty specially the new comers."

Discussion

Recently there has been a significant increase in number of medical colleges in the region, however maintaining the quality of medical education is a big challenge.[15] In addition to the implementation of measures for quality assurance in emerging medical schools, evaluation of the programs already adopted in established medical colleges is an essential component for maintaining the standard. We gathered views of the faculty about faculty development program at Shifa College of Medicine. The results show that the FDP was well received by our faculty. Similar findings were reported in a systematic review of faculty development initiatives designed to improve teaching effectiveness in medical education where faculty development programs were found to be rated high for satisfaction.[1] allies and Herman found a positive impact of educational development.[5] Traditionally the role of medical teacher has been to provide information to the students. The teacher of today is expected to be an efficient facilitator, curriculum and course planner, resource material creator, student assessor, mentor and program evaluator.[16]Harden and Crosby described roles of a teacher as information provider, resource developer, planner, assessor, facilitator and role model.[17] Our faculty development model helps to prepare the faculty for these

roles. Most of our faculty agreed that they were provided opportunities to improve their basic facilitation skills. More than half of the faculty said they learned curriculum planning and module design. Our faculty acknowledged learning of assessment strategies through FDP. It is important for the teacher to be aware of the new teaching methodologies that are being practiced in modern world, which include a shift from conventional teaching to small group teaching, problem based learning, innovative curriculum models and changes in assessment methods and tools.[18] The evolutionary change in FDP over the years with change in curricular delivery strategies was taken positively. Majority of our faculty felt that they learned various learning strategies through FDP. For successful implementation of curricular reforms, it is necessary to prepare the faculty for new teaching and assessment methodologies.[19] Our FDP focused on preparing the faculty for teaching in integrated modular curriculum, which ensured smooth transition and the faculty agreed with usefulness of the program in this respect. Our findings show that the faculty perceive FDP to have improved the teaching and research skills of the faculty. This is in consistence with the findings of a systematic review and meta-analysis which shows significant impact of faculty development programs on the knowledge and skills of the faculty.[9] Teaching in medical schools is an important responsibility and with changing trends in medical education good faculty development initiatives have become a need of the day.[20] Our FDP provided an opportunity to learn the recent advances, emerging trends and issues in the field of medical education. It is suggested that role modeling is the best way to inculcate professionalism in students.[21] Our FDP included seminars on professionalism and ethics.

Conclusion

Faculty development program at SCM is valued by the faculty. It has proved to be helpful in educating the faculty on innovative strategies and new trends in medical education, thus making them competent for efficient delivery of curriculum. It has contributed towards excellence in teaching. However constant improvement is an essential requirement to maintain high standards. This program should be continued with an endeavor to improve it further.

Acknowledgements: We acknowledge the efforts made by Dr. Mohammed Amin and his colleagues to start the faculty development program at Shifa College of Medicine and for providing their continued support and encouragement. We would also like to acknowledge the support and contributions made by present and former faculty of Shifa College of Medicine, in making the faculty development Program effective and successful.

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JSTMU Journal of Shifa Tameer-e-Millat University

https://j.stmu.edu.pk

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REVIEW ARTICLE

Immunologic aspect in diagnosis and treatment of SARS-COV-2 patients

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Author`s Contribution

[1] Article writing and data finding
[2] Article writing and reviewing
[3] Reviewing

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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Cite this article as: Yasin S, Bhatti T, Farooqi U, Mateen F. Immunologic Aspect in Diagnosis and Treatment of SARS-COV-2 patients; A Review Article. JSTMU. 2020; 3(2):113-121.

A B S T R A C T

Recent worldwide outbreak of novel coronavirus disease (CoVID-19) has affected massive human population including Pakistan, and has caused a huge number of mortalities in few months. CoVID-19 is an infectious disease caused by a virus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which is single stranded RNA enveloped beta coronavirus and affects lower respiratory tract. It transmits from human to human through respiratory droplets. It uses its S-protein to recognize ACE2 (Angiotensin Converting Enzyme-2) receptors in lung epithelial cells where it attaches and causes infection. The incubation period is 2-14 days. In pre-symptomatic phase, body's immune system starts antibodies production. Significant antibodies are IgM and IgG that produces within 03-06 days and 8-12 days respectively. This review provides the available information about immunological aspects in terms of diagnosis and screening of CoVID-19 and potential therapeutic targets for combating SARS-CoV-2 infection. Immunologic techniques to detect these antibodies are ELISA (Enzyme-linked Immunosorbent Assay), CMIA (Chemiluminescent Micro particle Immunoassay) and ICT (Immunochromatographic Test). Among these, ELISA and CMIA are found to be highly specific and sensitive in convalescent phase of infection. While the fundamental confirmatory test for SARS-CoV-2 infection is RT-PCR (Reverse Transcription Polymerase Chain Reaction) which detects the viral RNA in respiratory samples preferably nasopharyngeal swab. Serological assays are essential to find out rate of infection, and most importantly antibody titers in recovered patients to be used for therapeutic purpose. After some successful studies Convalescent Plasma is considered as a good therapeutic option in the absence of specific antiviral therapy.

Keywords: *Antibodies, ELISA, CMIA, convalescent plasma, COVID-19*

Introduction

The current rapid worldwide outbreak of a novel flu-like Coronavirus disease 2019 (CoVID 19) began in the city of Wuhan in China. Initially the causative agent was unknown and it was treated like pneumonia because of similar clinical characteristics.[1] Several such cases were reported by the Government of China on December 31st 2019.[2] Experts from Centers for Disease Control (CDC) performed analysis on respiratory samples and declared that this pneumonia is caused by the family of Coronavirus that belongs to the genus betacoronavirus.[3,4] Further, next generation sequencing revealed that this novel virus is RNA enveloped beta coronavirus having phylogenetic similarity to previously known beta coronaviruses that infected a massive human population in 2002-04 during SARS outbreak caused by SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and in

2012 during MERS outbreak caused by MERS-CoV (Middle East Respiratory Syndrome Coronavirus).[5] So, it was named as SARS-CoV-2 by international Committee on Taxonomy of viruses. Subsequently the disease was named as CoVID-19 by World Health Organization (WHO).[6, 7]

Within a month, cases reached up to 6065 globally in which 99% cases were from China but the virus spread to 15 other countries quickly. So on 30th January 2020, WHO declared the outbreak of CoVID-19 a "public health emergency of international concern".[6, 1] the number of cases were increasing exponentially worldwide. As of 11th February 2020, WHO data report has shown around 43000 confirmed cases from more than 28 countries. Hence, the CoVID-19 outbreak was declared a "Global pandemic" by WHO on 11th March 2020.[6] By June 18, 2020 CoVID-19 outbreak has affected almost 213 countries including Pakistan. According to WHO, total of 8,417,100 confirmed cases with 451,661 mortalities worldwide. While number of confirmed cases in Pakistan has reached up to 160,118 with 3,093 mortalities, currently these cases are increasing at an alarming rate and the situation is worst.8

Origin:

Novel coronavirus SARS-CoV-2 is of zoonotic origin like other betacoronaviruses.[6,9] Full genome sequencing of SARS-CoV-2 extracted from Broncho alveolar fluid sample that was taken from a patient who worked in seafood market revealed that there was 96.2% nucleotide sequence similarity to bat SARS-related-CoV (bat-SL-CoVZC45) and a low similarity of 79% and 50% to SARS-CoV and MERS-CoV respectively.[3] It is also suggested that in addition to bats, pangolin species are also natural reservoir of SARS-CoV-2.[7]

Bat (Rhinolophus affinis) is still the most probable species for the origin of novel SARS-CoV-2.[7] Tang, Xiaolu, et al. suggested that further research analysis is required to find out the intermediate animal host which is responsible for the transmission of SARS-CoV-2 from its original host to humans because the relative coronaviruses MERS-CoV and SARS-CoV do pass to their intermediate hosts before invading into human body such as civets or camels.[4]

Pathogenesis and genetic structure:

Single stranded RNA Coronavirus (CoV) is spherical to pleomorphic particle with diameter of 80-120nm. There are four different types of Coronavirus that are Alpha (α-CoV), Beta (β-CoV), Delta (δ-CoV), and Gamma Coronavirus (γ-CoV).[1, 7]

Six types of coronaviruses have previously infected human beings and have caused respiratory diseases. Two of them belong to the class of Alpha Coronavirus which includes 229E and NL63 while the rest belongs to the class of Beta Coronavirus named OC43, HKU1, SARS-CoV and MERS-CoV. SARS-CoV-2 is the seventh known Beta Coronavirus that has infected human population.[1, 7] SARS-CoV-2 uses ACE2 as a receptor for binding to enter into lung epithelial cells. S-Protein on the surface of SARS-CoV-2 helps recognize the corresponding receptor to get entry into the cell and cause infection. Structural analysis reveals that SARS-CoV-2 binds with ACE2 receptor with 10 time's higher affinity as compared to SARS-CoV.[1, 10]

There are four structural proteins in the virus, Spike (S-protein), Membrane (M-protein), Envelope (E-protein) and Nucleopsid (N-protein). Envelop of the virus is made up of Spike, Membrane and Envelop protein that gives shape to the virus.[10]

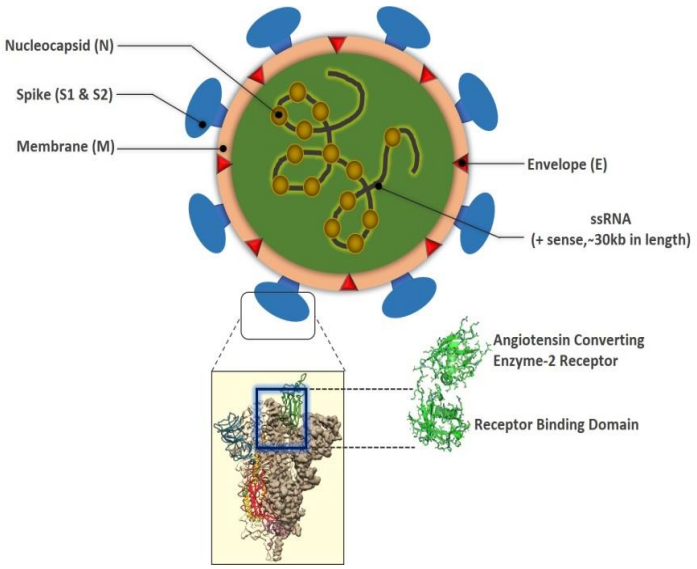

Figure 1. Genetic structure of SARS-CoV-2

The unique crown like appearance of the virus is due to the embedded polymers of S-protein in its envelop.[1] Spike glycoproteins in the viruses target the respiratory tract cells by binding to human ACE2 receptors having two subunits. The S1 subunit comprised of single peptide, an N-terminal domain and RBD (Receptor binding domain) that causes the direct interaction of Spike protein to the host receptor.[3, 7]

S2 subunit contains fusion peptides that makes it highly conserved. After the binding of Spike protein with target cells receptors, envelop of viruses fuses with the cell membrane and releases viral RNA into the target cell.[1,3,7] Mutations are observed in spike proteins that plays important role in differentiation mechanism and infectious capability of SARS-CoV-2.[5,10]

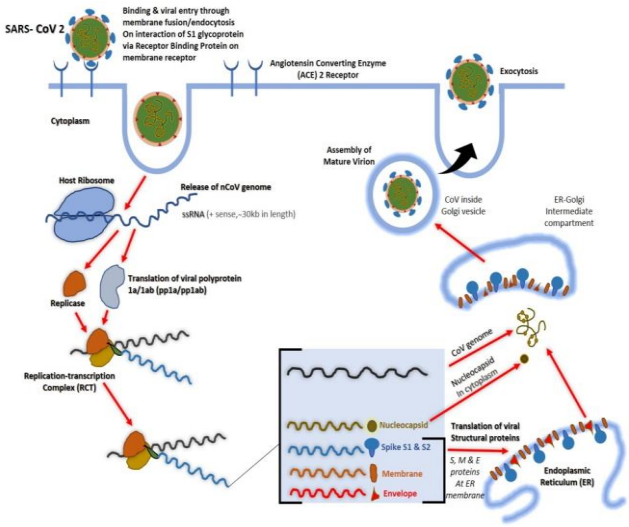

Figure 2. Entry and replication of SARS-CoV-2 inside the cell

Viral genome contains 12 functional open reading frames (ORFs), first ORF translates pp1a and pp1ab polypeptides that encodes for NSP (Non-structural proteins) namely NSP3 (papain-like protease), NSP5 (main protease), NSP12 (RNA dependent RNA polymerase), NSP13 (helicase) and other NSPs while remaining ORFs encodes for structural proteins.[3]

Mutations are observed in these NSPs, the NSP2 and NSP3 as well as in spike proteins that plays important role in differentiation mechanism and infectious capability of SARS-CoV-2.[5, 10]

Viral spread and transmission:

The respiratory droplets that come out of coughing and sneezing of an infected person are the source of the viral spread. When enter through inhaled air into another person's body, they stick to the mucosa of nasal cavity, mouth, eyes or in lungs where the viruses get the chance to invade into the cells.[2] in this context, WHO regarded CoVID-19 as airborne. Evidences have proved that its human to human transmission is not only from symptomatic patients but also occurs during asymptomatic phase when patient does not even know about his illness. Incubation period of SARS-CoV-2 is estimated to be 2-14 days.[11]

Humoral and cellular immunity:

ACE2 is expressed highly on apical side of lung epithelial cells in alveolar space, so this virus can likely enter those cells. It is also evident from the fact that early injury of lung was often seen in distal airway. Main components of innate immunity in airways are epithelial cells, alveolar macrophages and dendritic cells (DCs). DCs are located underneath the epithelium while macrophages are located at the apical side of epithelium.[4] Upon entry of the viruses, humoral and cellular immunity is stimulated when these viral antigens are presented to CD4+ helper T cells or CD8 cytotoxic T cells by macrophages and DCs in association with MHC class-2 and MHC class-1 molecules respectively.[12]

Two types of antibodies that have diagnostic significance are produced by the immune system named as IgM and IgG antibodies. IgM antibodies are produced earlier than IgG antibodies.[13] it takes about 03 to 06 days for IgM antibodies to be produced after the viral attack, giving seropositive results in current or recent infection. While IgG antibodies provide long term immunity having high affinity responses and are important for immunological memory. IgG takes longer to produce. It is detected after 8 days of infection.[13]

IgG antibodies are specific to Spike and Nucleopsid proteins and play a protective role against infections because they last longer while SARS-specific IgM remain in the blood for about 12 weeks then they degrade.[12]

The virus usually escapes the innate immune response and gets entry into the cell. Immune system first recognizes the unique molecular patterns of the

pathogens by PRRs (Pattern Recognition Receptors). The PRRs for respiratory viruses are TLRs (Toll-like Receptors) [3, 7, 8] present throughout the airway on different cells for defense mechanism.[4, 12] this recognition is led to signaling and to the production of pro-inflammatory cytokines. Unfortunately, by now, there is a little knowledge about antigen presentation of SARS-CoV-2. Studies described that the virus forms a double membrane vesicles during replicating in the cell that prevents it to be recognized by the host innate immunity. Additionally, activation of IFN (interferon) beta promoter and inhibition of nuclear transport of IFN regulating factor 3 by ORF4a, ORF4b, ORF5, and M-proteins also helps the virus to escape from innate immune system.[12]

Cytokine storm and viral sepsis:

Infection of SARS-CoV-2 in critical patients with symptoms of severe pneumonia, sometimes leads to overproduction of inflammatory cytokines, also termed as cytokine storm, which is uncontrollable. This leads to progression of disease, and to acute lung damage and acute respiratory distress syndrome (ARDS) that is a major contributing factor to mortality due to CoVID-19. The cytokines includes IFN-γ, IL (Interleukin)-1, IL-6, IL-12, and TGFβ (Transforming growth factor beta).[14,15,16] Cytokine storm may also lead to hyper activation of T cells, natural killer cells, macrophages, and different chemical mediators from immune cells in addition to excessive production of many cytokines. This impairs lung microvascular and alveolar barrier and it brings off vascular leakage, edema, and the conditions of hypoxia. Such conditions are potentially fatal.[14]

A very little published data has revealed that autopsy samples which included lungs, liver, kidney, and heart of elderly died patients had huge amount of inflammatory cell infiltrate, fibrosis, necrosis, and bleeding. Lymphatic organs and spleen also showed atrophy and other conditions of bacterial sepsis like disseminated intravascular coagulopathy (DIC). That's why a term 'viral sepsis' is coined in such condition. This undesired immune response and organ failure contributes to the mortality rate of the disease.[16]

Laboratory Diagnosis:

Two basic technologies for detection of the infection are molecular and serological methods of testing.

1. Molecular Methods:

A molecular method of testing is based upon isolation and detection of viral nucleic acid in the given specimen. Currently the most effective front line method for detection of viral load is RT-PCR (Reverse Transcription Polymerase Chain Reaction).[17]

Sample requirement:

RT-PCR detects the virus using respiratory samples. Broadly recommended samples are upper respiratory samples that include nasopharyngeal swabs (NPS), oropharyngeal swab and nasal aspirates while sputum, Broncho alveolar lavage (BAL) and aspirates of trachea are included in lower respiratory samples that are less likely to be collected. Viral loads detection in upper and lower respiratory samples depend upon the days after onset of illness. Low viral loads in the area sampled may lead to a false negative result.[18] Study showed that in the first week of onset of illness, high viral loads were observed that declined with time.[18]

i. RT-PCR

Viral RNA is detected by reverse transcription followed by amplification of targeted portion of cDNA using polymerase chain reaction (PCR). Following extraction of RNA by phenol-chloroform method, viral RNA is converted into cDNA through 'reverse transcription 'and then targeted portions of cDNA are amplified up to a detectable range using 'polymerase chain reaction'.[18]

Finding and analyzing SARS-CoV-2 related viral genome sequences for designing a set of primers was also a challenging task.[18] Those molecular targets include the genes that translate structural proteins like S (spike), E (Envelope), N (Nucleopsid), M (transmembrane) and Hel (helicase). Corman et al. discovered 3 regions for primer design. First one was RNA-dependent RNA polymerase gene or RdRp gene in the open reading frame (ORF). Second one is 'Envelope protein' gene or E gene and third one is 'Nucleopsid protein' or N gene.[18] To avoid cross-reaction with SARS-COV, different molecular targets are used for RT-PCR by different researchers in different countries.[19] Some of the viral genome sequence may not be constantly expressing and therefore the primers specific to that portion may not provide the real viral load information, although it may detect the presence of the virus. RT-PCR technology is high in specificity and

sensitivity but it is highly essential to collect the respiratory specimen at the right time from the right site for the accurate diagnosis because samples taken inappropriately or taken from the site with low viral load while missing the time window may lead to false negative results.[18] Many researchers found low sensitivity of RT-PCR because of this reason.[1,13,19] 83.3% sensitivity of RT-PCR was found in a study due to poor quality of nucleic acid in the specimen which led to false negative results.[20] However RT-PCR method remain highly specific and sensitive in early phase (within 2 weeks) of infection.[21]

2. Serological methods:

Serological methods are best to use not only for diagnosis purpose but also for analysis of epidemiological variables and prognosis of the disease by analyzing humoral response especially the detection and quantification of antibodies which are produced rapidly after infection.[22] Serological analysis against SARS-CoV-2 involves ELISA (Enzyme Linked Immunosorbent Assay), CMIA (Chemiluminescent Micro particle Immuno Assay), and ICT (Immunochromatographic Technique) with variations in their sensitivity, specificity, positive predictive value and negative predictive value.[21]

i. ELISA

Most important antibodies that can provide useful information about the course of infection are immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies. ELISA is a plate-based assay technique which is used for detection and quantification of proteins, peptides, antibodies, and hormones. In this technique, an immobilized antigen on a solid surface is attached with enzyme linked antibody. By adding conjugated enzyme, a measurable product is produced.[23]

In case of SARS-CoV-2, purified recombinant viral Nucleopsid proteins (rNPs) are used as coating antigens for the detection of IgM and IgG antibodies.[23] Mainly ELISA checks whether body's immune system has developed antibodies against SARS-CoV-2. It is also helpful after the recovery of the patients or in convalescent phase to check his immune status.[18] High levels of sensitivity and specificity were reported in studies but they didn't recommend ELISA as a backup of RT-PCR because antibodies might not be detected in asymptomatic phase and very early phase of disease onset.[17,18,23]

However, Guo L et al reported a higher detection rate (98.6%) of IgM ELISA as compared to PCR (51.9%) after 5 days of the disease onset.23 Study shows the median duration for IgM is 5 (03-06) days while for IgG, it is 14 (10-18) days. This study concludes that humoral response can be a reliable tool for the diagnosis of CoVID-19.[23]

ii. CMIA

Chemiluminescent Micro particle Immuno Assay (CMIA) is a quantitative measurement of immunoglobulins in patent's serum sample. It is intended to detect IgG as well as IgM antibodies production in a patient's serum against SARS-CoV-2.[24]

This test uses protein-coated micro particles. CMIA relies on mixing patient samples with a known viral protein, buffer reagents and specific enzyme labeled antibodies that allow a light based, luminescent read out. Antibodies present in the sample react to viral proteins followed by addition of enzyme labeled antibodies. A chemical reaction takes place that produces light, which is the measure of antibodies in the sample. This test can measure multiple types of antibodies including IgG, IgM and IgA.[24, 25]

There are few studies evident which use CMIA method of testing one of them was done by Mathur et al. Average sensitivity and specificity of general serological assays they reported were 84.90% and 98.63% respectively while CMIA turned out to be 89.36% sensitive and 99.63% specific in Convalescent phase.[25]

iii. ICT

Immunochromatographic Technique (ICT) is another serological method, also known as rapid chromatographic technique.[26] SARS-CoV-2 test device is newly developed colloidal gold based kit on which Nucleopsid protein (N-protein) of SARS-CoV-2 is used as an antigen. ICT contains a detection zone on top of a nitrocellulose strip. In this zone, IgG antibodies, IgM antibodies and SARS-CoV-2 N-protein have been immobilized onto a test line and control line separately. Colloidal gold particles are used where IgG/IgM antibodies and N-protein are to be coupled, it serves as a detector. Device contains two wells at the bottom for serum sample and buffer respectively.[26]

Shen et al. in their study evaluated the performance of colloidal gold immunochromatography assay for SARS-CoV-2 combined IgG/IgM. The method turned out to be sensitive and specific for CoVID-19 with noticeable increase in sensitivity of antibody assays with the course of disease.[26] in another experimental study researchers utilized antibody test using lateral flow immunoassay technique which takes less than 15 minutes to generate results. Results showed 88.66% and 90.62% sensitivity and specificity respectively. However, false negative and false positive results were also reported.13 ICT technique is still in use by many researchers and in hospital laboratories for rapid diagnosis but reliability of this technique is still is still questionable.[13]

Importance of serological data:

IgM antibodies specific to SARS-CoV-2 start to appear in the blood within 03 days of infection while stays in the body for approximately 42 days.[17] While IgG antibodies are detectable from day 05 and start increasing onwards. Studies showed that median time for seroconversion is 20 days. By that time about 60-75% of patients became immune to the infection and develops IgG antibodies against the virus.[17] following statements can be given using immune response timing.

1. Serological data gives some epidemiologically important variables such as rate of viral attack and spread essential for the assessment of community transmission.[22]
2. It has the prognostic importance by monitoring the effect of pharmacological and non-pharmacological treatment population wide. [22]
3. To detect immunologic response of recovered individuals and to make decision whether their antibody isolates can be used for the treatment purpose via Convalescent plasma therapy.[22]

Treatment and Management Strategies:

Corticosteroids:

Corticosteroid is a most commonly and traditionally used drug for its anti-inflammatory response. But it is also known for its immunosuppressive response. This two sided characteristic makes it controversial in its use.[14, 16] although it has been successfully used during SARS epidemic in resolving fever, and lung infiltrate but recent WHO guidelines do not recommend its use for SARS-CoV-2 patients for not showing significant results in patient's recovery.[14]

Interferon:

Use of interferon (IFN) in animal and human model showed mixed results. Early administration of IFN and ribavirin showed some beneficial results in lowering the viral load and improving patient's health. However, late application showed no beneficial results. [14]

Monoclonal antibodies:

Another potentially useful treatment strategy involves the utilization of anti-IL-6 monoclonal antibodies. It has been used in patients with Cytokine Release Syndrome (CRS) and found beneficial in the control of cytokine storm.[14] Studies have shown that besides lowering the cytokine storm, use of anti-IL-6 monoclonal antibodies results in increased expression of CD4+ and CD8+ T cells hence, improving the overall immune system for the wellbeing of the patient.[14,15]

Convalescent Plasma Therapy (CP therapy):

Convalescent Plasma Therapy is an adaptive immunotherapy. In this therapy, plasma of recovered patients of CoVID-19 is used because it carries enough titer of anti-SARS-CoV-2 antibodies and may improve clinical condition and survival of CoVID-19 patients.[27] Major problem whole world is facing in controlling CoVID-19 pandemic is not having approved specific antiviral agents for novel Coronavirus disease.[28] However, in addition to some pharmacological treatment options, an effective non-pharmacological treatment to improve the rate of survival is Convalescent Plasma Therapy.[28,29]

Donor Selection Criteria

Criteria for valuable donors for Convalescent plasma therapy recommended by 'New coronavirus pneumonia diagnosis and treatment program' (6th edition) published by National Health commission of China which is also followed by various successful experimental case studies. Recovered patients selected for plasma collection will be according to the following recovery criteria: [27, 28, and 29]

1. Body temperature normality for more than 3days.
2. Respiratory symptoms resolution.

3. Two consecutive RT-PCR assays of SARS-CoV-2 should be negative.
4. Blood should be collected after 3 weeks of onset of illness and 4days after discharge from the hospital.
5. Serology tests need to be performed for HIV, anti-HBV, HCV, donor need to be seronegative for all of them.
6. Enough anti-SARS-COV-2 antibody titer should be present in plasma (at least >1:640)
7. ABO-compatibility should be highly observed.
8. Written consent form of the donor.

Successful plasma therapy: evidences from case studies:

A study performed by Duan et al. in April, 2020 carried out in hospitals of China. Severely ill 10 patients were given Convalescent Plasma Therapy.[27] Results showed that a dose of convalescent plasma has significantly increased neutralizing antibodies in the patients. After 03 days of convalescent plasma therapy, patient's clinical symptoms were improved leading to virus elimination from the blood within 07 days. Decrease in lung lesions were also reported through radiological examination.[27]

In another study by Shen et al.[5] severely ill patients were administered convalescent plasma containing neutralizing antibodies.[28] Results turned out beneficial. In 04 out of 05 patients, body temperature normalized within 03 days. SOFA (sequential organ failure assessment) score (high SOFA score indicates severe illness, range 0-24) was successfully decreased along with decreasing viral loads. Within 12 days of Convalescent plasma transfusion viral loads of the patients became negative.[28] Moreover, above mentioned studies did not report any adverse event of convalescent plasma therapy. However, a donor selection criterion is recommended to be followed properly.[28]

Discussion

Various methods of diagnosis and their importance are already discussed in the article. Molecular testing and serological assays both are important. As CoVID-19 has strong infectivity, so a rapid and accurate diagnostic technique is required for identification, isolation and treatment of patients. Currently RT-PCR is acting as the fundamental test to detect exposure and infection. It has more specificity and accuracy than other serological testing techniques. However, expertise of the technologist performing the test is also really crucial, so a false negative test could not be reported.[20, 21, 23] Secondly, RT-PCR lacks the ability to find out who has developed the immunity before and after the onset of symptoms, here ELISA and/or CMIA comes into play and has the ability to quantify the amount of antibodies produced in the form of titers. Studies revealed that in very early days of infection the detection rate of the disease of PCR was 51.9% while that of ELISA and CMIA was 98.6%. For screening purpose among different serological techniques CMIA has found to be more reliable and more appropriate. ICT has comparatively low sensitivity and specificity than ELISA and CMIA. Average sensitivity and specificity of ELISA has been reported as 84.90% and 98.63% respectively while CMIA turned out to be 89.36% sensitive and 99.63% specific in Convalescent as well as asymptomatic phase.

Among different management strategies for CoVID-19 mentioned above, use of monoclonal antibodies and CP administration found out to be more suitable as compared to different immunomodulatory therapies i.e. use of corticosteroid and interferon. As mentioned above use of these immunomodulatory agents has not been approved by WHO as treatment agents as these are only useful if use in early stage of the infection. But compared to these, use of monoclonal antibodies and CP therapy is useful. Monoclonal antibodies are found out to be beneficial especially in controlling and minimizing the cytokine storm and lowering the adverse effects of over exaggerated immune response. Hence, cytokine storm and viral sepsis that tend to increase mortality rate of the disease are better to be treated with monoclonal antibodies than immunomodulatory therapies. Besides monoclonal antibodies, administrating convalescent plasma is also a very useful way in neutralizing viral antigen. Many successful studies revealed it to be one of the best ways in recovery of the patients.

For the purpose of administrating convalescent plasma to cure patients, CMIA and ELISA can be considered best techniques to detect immunity development in recovered individuals due to their higher specificity and sensitivity. The data helps doctors in finding suitable sources of convalescent plasma for

therapeutic purpose which is comparatively a better option in the absence of approved and specific antiviral therapy as of now.[28] The optimal dosage of convalescent plasma and criteria of donor selection were different in different studies which further needs to be clarified if this treatment strategy is to use in future.

Conclusion

Immunologic testing especially 'CMIA' and 'ELISA' are better options for screening individuals for CoVID-19 for being relatively cost effective and having more specificity and sensitivity, and it does not require any special skills. However, RT-PCR is still the gold standard in diagnosing SARS-CoV-2. The techniques are also useful in checking the level of antibodies in recovered patients so their plasma can be used for CP therapy. CP therapy and anti-IL-6 monoclonal antibodies can, so far, be considered better treatment options for CoVID-19 especially if there is no approved anti-viral drug is available.

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DOI: https://doi.org/10.1002/jmv.25882

JSTMU Journal of Shifa Tameer-e-Millat University

https://j.stmu.edu.pk

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REVIEW ARTICLE

Mental health issues during COVID-19 pandemic

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Author`s Contribution

[1] *Complication and critical review*
[2] *Literature search and literature review*
[3] *Literature searches*
[4] *Editing*
[5, 6] *Literature review*

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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Cite this article as: Naeem Z, Choudhry H, Bareach G, Naseem S, Rafi S, Mangrio S. Mental health issue during CoVID-19 pandemic. JSTMU. 2020; 3(2):122-127.

A B S T R A C T

Mental health issues due to the pandemic of CoVID-19 have not been properly addressed since the outbreak emerged. Numerous studies were conducted worldwide to highlight the importance of the effect of pandemic on mental health. A large number of researches were carried out to address the impacts of CoVID-19. In present times, when social distancing and isolation at home is the main preventive measure suggested by the WHO, mental health problems are surfacing which need to be timely addressed and treated. This review article focuses on the importance of mental health issues after the lockdown, social distancing, staying at home and other measures implemented due to the outbreak of CoVID-19.

Studies have also highlighted the effects of social media on the prevalence of mental health issues in people worldwide. Based on the findings of previous pandemics, mental health problems can leave long lasting and devastating effects on people. Therefore, adequate preventive measures must be taken to avoid such health problems. Studies have been carried out to emphasize the urgent need of research regarding the mental health issues due to CoVID-19. Many psychological problems like depression, anxiety, post-traumatic stress disorder, insomnia, fear of getting infected and death, lack of motivation is common during this perplexing period and the challenge is to remotely access such patients for early diagnosis and prompt treatment. Furthermore, the increase in the cases of domestic violence during this time has also been reported which should be addressed. In order to strengthen the mental health of a community, we must find ways to cope with stress and trauma in a better and healthy way in times of crisis.

Keywords: *COVID-19, mental health, psychosocial problems, depression, anxiety, stress*

Introduction

In January 2020, a new viral outbreak was declared by the World Health Organization (WHO), which began from the Wuhan City of China in December 2019 in a local fish market. The spread was rapid and thus, a strict lockdown was implemented in the month of March.[1] People were bound to stay at home, wear face masks and

gloves, wash their hands frequently, isolate themselves if they were exposed to the affected person and were advised to a maintain social distance which caused negative effects on the mental health of people worldwide.[1,3] People of all ages and races, belonging to different professions were affected due to the pandemic; be it medical health workers, adults, children or elderly. A lot of psychosocial problems arose; however, very little importance was given to mental health issues globally. As the past pandemics have suggested that these outbreaks leave a long lasting and profound impact on the mental health of people, therefore, serious and rapid steps must be taken to overcome the mental health issues expected in the future.[4-6] Such conditions must be addressed at the right time to provide early diagnosis with timely treatment.[7-9] Here we will discuss the major mental health issues and psychosocial problems among the health care workers and the people from all ages and professions.[10-12]

Methods

A literature search was conducted in the databases of PubMed, Google Scholar, Medline and PakMediNet published from Feb 2020 to Oct 2020. Ninety articles meeting the eligibility criteria regarding the mental health issues during the era of CoVID-19 were selected through the search. Out of these, 32 most relevant articles were finalized and included for the review which precisely talked about CoVID-19 pandemic causing mental health issues including depression, anxiety, Post Traumatic Stress Disorder, suicidal thoughts, insomnia, domestic violence and its impact on females.

Depression:

Depression is most common in situations like current pandemic i.e. CoVID-19.[8] the implementation of lockdown and social distancing has left a negative impact on the mental health of people. Most importantly, misconceptions about CoVID-19 being spread on social media lead to a greater number of cases of depression worldwide.[13,15] A number of studies were done during the outbreak of CoVID-19 to compare the effect of pandemic on the mental health of healthcare workers versus non-healthcare workers which revealed that depression and burnout were more prevailing among the healthcare workers due to increased workload and prolonged stress.[10-12] Previously, pandemics like MERS, SARS and Ebola could have left a long-term negative effect on the mental health of people due to social distancing and less support from the family and friends in times when everyone is worried about their own health.[4-9,16] Some studies showed that depression was more common in young adults due to unemployment, uncertainty and low market for jobs after graduating from universities.[17-19]

A study carried out in Iran found that generally depression is more common in females as compared to males due to the hormonal changes which causes hyper activation of the greater limbic system leading to increased response to the negative stimuli which increases the risk of developing mental health problems like depression.[20] The common clinical manifestations of depression were found to be dull looking skin, loss of appetite, weight loss, loss of interest, irritability etc. due to the negative effects of CoVID-19 pandemic, which can leave profound and prolonged effects on the mental health of people.[21,22] A study by Christoph Pieh showed that physical activity plays an important role in coping with stress during challenging times as the people who were more physically active had less signs of depression.[23]

In order to prevent such problems, awareness programmes to cope with stress during the pandemics must be designed and implemented. There is a need to practice and deliver more effective ways to identify and treat the patients of depression who need more attention during this pandemic.[10, 24]

Anxiety:

In times of a pandemic, it is common for the people to be stressed as they are socially isolated with few friends and limited family support. In such situations, anxiety is likely to occur especially in children and in young adults due to unemployment and hopelessness.[25] Evidence from a large number of publications indicate that mass tragedies particularly the ones which involve infectious diseases bring a lot of distress and negative impact on the mental health of people worldwide.[26]

One study highlights the prevalence of negative effects on the mental health of people due to the large-scale disasters like mass shooting, infectious diseases, 9/11 world trade Centre USA attack and deep-water horizon oil spill.[27] Some studies showed that social media exposure played a major role in affecting the mental

health of people through the misconceptions and anxiety provoking news about CoVID-19. This resulted in a lot of distress among people in terms of being more scared of getting infected and dying due to CoVID-19.[22] Moreover self-isolation, social distancing and having no access to medical care for psychological problems can also cause increased anxiety and fear of death among people.[20] People who were not aware of the pandemic spent more time on social media and became more susceptible to developing depression and anxiety symptoms.[18] Many studies focused on the prevalence of anxiety in healthcare workers as mental health problems like panic, distress and anxiety can result in reduced performance at work. Moreover, Young doctors were more susceptible to developing anxiety due to the fear of getting infected, being stigmatized, worried about their families getting infected and above all because of the number of fatalities in the healthcare facilities due to CoVID-19.[15,21]

Another study by Pieh C showed that anxiety was common in children as they experienced lack of concentration, nervousness, and feeling of loneliness at home, also because they were unable to go out and meet friends. It was suggested that increase in the physical activity can prevent symptoms of anxiety disorder.[16] a report by Elisabeth Mahase suggested that interventions should be done to prevent wrong and fake news reaching through social media by promoting right ways to deal with the perplexed situation of CoVID-19 pandemic. Furthermore, it was suggested that health education system must be strengthened, adequate psychological services should be provided and comfortable environment must be given in hospitals and isolation centers to prevent mental health issues during the time of CoVID-19 pandemic.[8]

Suicidal tendencies:

Social distancing and isolation have led to increase in the number of suicide cases.[10] Most common risk factors were testing positive for CoVID-19, stigmatizing the people who were positive, pressure to be self-isolated, loneliness, work related stress, being unable to visit family due to CoVID-19, conflict of families, depression and anxiety due to postponed examinations.[15] A number of studies showed that there was a strong association between economic decline and increase in the number of suicidal attempts worldwide.[20] Statistics of suicide in Pakistan show a rise resulting in extreme stress and anxiety among communities, raising concerns for all the developing and third-world countries .[18]

Furthermore, another study by Mamun MA showed that people who suddenly experienced poverty and economic crisis faced severe situations due to distress and inability to cope with uncertainty. Some suicide attempts were done due to stigmatization and misinformation imposed by other people for example; boycotting people who were suspected of CoVID-19, only to discover later that they were CoVID negative on autopsy. Such inhuman behavior from society can trigger more suicide cases in future.[12] a case of infanticide was reported in Saudi Arabia where a nurse killed her infant and then committed suicide as she feared facing economic crisis and getting infected from her sick husband who was hospitalized due to CoVID-19 infection. The uncertainty and fear can lead to devastating incidents worldwide. These problems need to be addressed and fixed by screening the people who are at the risk of developing serious mental health problems.[5]

Post-traumatic stress disorder (PTSD):

Literature reveals that whenever people were exposed to any such situation, be it mass trauma or pandemics, post-traumatic stress disorder was a global issue. Social media exposure has manifested a major role in increasing depression and anxiety in people in such overwhelming times, which ultimately results in post-traumatic stress disorder.[28] One study indicated that people who survived severe and critical illnesses in the past were at a higher risk of developing depression and PTSD.[29] During the Severe Acute Respiratory Syndrome (SARS) epidemic which was also first identified in China, a number of moderate to severe cases of PTSD were reported among the most affected. Most of the reported cases were females as they are at a higher risk of developing mental health problems in such severe situations.[30] several studies have highlighted the importance of early diagnosis and prompt treatment of mental health problems to avoid severe PTSD symptoms in CoVID-19 pandemic.[28]

Insomnia:

As CoVID-19 was declared a pandemic by WHO, mental health problems like stress, depression and anxiety became more common among healthcare workers

due to panic and increased workload in the hospital. There was a rise in the number of severe insomnia cases reported among the healthcare workers.[29] A study carried out among healthcare workers in China showed that more than one third of the healthcare workers experienced severe symptoms of insomnia during CoVID-19 pandemic. The risk factors included lower level of education, an isolated environment, psychosocial problems and concerns regarding CoVID-19. Above all, there was a pressure and panic situation at work every day. It was suggested that interventions must be done within the healthcare facility to avoid burnout situations and symptoms related to severe anxiety and insomnia.[19]

A case was presented in China who was negative for CoVID-19, yet showed symptoms of insomnia, restlessness, irritability and bulimia related to stress due to the fear of getting infected and he was diagnosed with early symptoms of mental health issues. He was advised to carry out self-psychological treatment by doing daily workouts, increased physical activity, listening to music, scheduled eating and sleeping habits and by maintaining a healthy lifestyle. Such cases can develop severe symptoms of mental health illnesses with the passage of time. Early diagnosis and prompt treatment can prevent lifelong mental health problems. So, these problems need to be addressed at the right time.[24]

Abusive behavior leading to domestic violence:

During the CoVID-19 pandemic, there was a rise in the number of cases of domestic violence all over the world. It is unacceptable at any time and efforts should be made to put an end to such abusive behaviors in our society.[24] such behaviors have a negative impact on the whole family, especially children. In the United Kingdom, a leading domestic abuse organization reported that there was a massive increase in the number of distress calls following the lockdown and strict social distancing measures.[27] Home is a place where one seeks peace and solace, but when people live in an abusive environment, mental health problems are very common. In CoVID-19 pandemic, people who were living in an already abusive environment had to stay at home due to the strict lockdown. This resulted in an increase in the number of domestic violence cases worldwide.[30] multiple reports have surfaced due to a noticeable increase in the number of domestic homicides worldwide. A country like Spain, which was severely affected by the CoVID-19 pandemic, reported its first case of domestic violence within the first week of lockdown where a woman was murdered by her husband in front of their children in the city of Valencia.[27]

Domestic violence is quite common in countries like Pakistan, India and Bangladesh where such cases are not brought to attention due to under reporting and complexities of the reporting process. In order to overcome such problems, it is important to establish an efficient surveillance followed by interventional programmes for domestic violence and child abuse. There should also be an acceptance of the fact that females and children have limited availability to report such cases as some victims are bound to stay at home. Domestic violence and child abuse may have a negative impact on the mental health of a society.[28]

Impact on women and girls:

In developing countries like Pakistan, ranking at the second lowest for gender equality as described by the Global Gender Gap Index (UNFPA), gender discrimination remains a major concern even during CoVID-19 Pandemic. Women, who have limited access to education, information and health care, remained most vulnerable during the lockdown as they were the ones taking care of the ill at home as well as doing all the household chores for their families. A study conducted in Pakistan showed that many educated women had to step down from their jobs to carry out their household errands to an extent beyond retrieval.[31] A country like Italy also reported more anxiety in pregnant women during their antenatal period due to social distancing and isolation during the CoVID-19 pandemic.[32]

Due to isolation in the lockdown, domestic violence was increased, placing many women and children at risk.[30] In Pakistan, helpline is commenced for help and facilitation of women when and if required, by the Ministry of Human Rights. Such initiatives should be taken by the governments to prevent the long-term psychological impacts of CoVID-19 on women and children and to protect them.

Conclusion

The increase in mental health issues during pandemics is alarming as less or no importance was

given to it during previous pandemics. Therefore, with limited literature available, we cannot address these issues effectively. It is evident that pandemics cause mental health issues and we require more research to develop profound measures for early diagnosis of problems like depression, anxiety, insomnia, PTSD to improve the present treatments accordingly.

Furthermore, early diagnosis and intervention through efficient surveillance and screening would be helpful to deal with this impending epidemic of mental health illnesses. In addition, counselling services should also be provided remotely by qualified psychiatrists and clinical psychologists to reach out to the patients who are isolated or quarantined at their homes.

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SHORT COMMUNICATION

Pathogenesis of COVID-19 associated with organ-based comorbidities

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Article Info.

Conflict of interest: Nil

Funding Sources: Nil

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Cite this article as: Naseer F, Bibi H. Pathogenesis of COVID-19 associated with organ-based comorbidities. JSTMU. 2020; 3(2):128-131.

A B S T R A C T

The coronavirus disease of 2019 outburst remains progressing promptly, worldwide. It is associated with many comorbidities which in turn is related to patient survival. The goal of this review is to identify prevalence of comorbidities associated to CoVID-19. Comorbidities associated with CoVID-19 are mostly hypertension, cerebro-vascular disease, cardiovascular diseases, diabetes, hepatitis C & B, kidney diseases, immunodeficiency, cancer, coronary artery disease, congestive heart failure, asthma, COPD, obstructive sleep apnea, immunosuppression HIV, malignancy history of solid organ transplant, liver disease, obesity. The method used was search through Google Scholar and PubMed using the key terms 'CoVID-19', 'co-morbidities' up to October 31, 2020.

Keywords: *COVID-19; organ comorbidities*

Introduction

Coronaviruses cause illness extending from the general cold to more serious diseases. Coronavirus disease of 2019 (CoVID-19) is caused by a coronavirus well-known as Severe Acute Respiratory Syndrome Coronavirus 2.[1] CoVID-19 is a major concern for health, and it can be devastating, especially for the elder people. There are seven strains of human coronavirus. Coronaviruses are single stranded RNA viruses, and they are susceptible to mutation and recombination. The life cycle of the virus consists of attachment, penetration, biosynthesis, maturation, and release. The virus perhaps affects the cell by attaching its virion protein to the ACE-2 receptor, which is normally present on epithelium alveolar cells of the lung.[2] The incubation time for CoVID-19 is between 14 to 2 days.[3] There are many identification tests for CoVID-19 but generally used is R*everse transcription polymerase chain reaction* (RT-PCR).

CoVID-19 transmits from human-to-human through respiratory droplets and interaction with contaminated secretions from an infected person coughs, sneezes, or exhales.[4] some preventive measures include; hand hygiene, medical mask and social distancing [5]. There is no specific antiviral treatment, and no vaccine is currently available for treatment of CoVID-19. The treatment is symptomatic. It includes breathing support, steroids, and blood plasma transfusions, plenty of rest.

CoVID-19 with Comorbidities:

Medical symptoms of CoVID-19 are, heterogeneous, as in correspondence to the most recent studies.[6,15] A study conducted in December 2019 to January 2020 in China showed that the highest occurrence of comorbidities were cardio-vascular illnesses (53.7%) and high blood pressure (16.9%). Patients with minimum one comorbidity were 399 (25.1%) and were older with a mean age of 60.8 vs. 44.8 years whereas patients with two or more comorbidities were older with mean age of 66.2 vs. 58.2 years. Out of total 1590 patients 16.9% reported of hypertension, 3.7% of cardiovascular diseases, 1.9% cerebrovascular disease, 8.2% diabetes, 1.8% hepatitis B, 1.5% COPD, 1.3% chronic kidney

diseases, 1.1% malignancy, 0.2% immunodeficiency. It showed that mostly reports were of hypertension and diabetes. When a comparison with severe cases to non-severe cases were performed, comorbidities were more likely to be hypertension 32.7% *vs* 12.6%, cardiovascular diseases 33.9% *vs* 15.3%, cerebrovascular diseases 50.0% *vs* 15.3%, diabetes 34.6% *vs* 14.3%, hepatitis B infections 32.1% *vs* 15.7%, COPD 62.5% *vs* 15.3%, chronic kidney diseases 38.1% *vs* 15.7% and malignancy 50.0% *vs* 15.6%. So, it explained that severe cases have more chances of the prevalence of these comorbidities.[16]

In March 2020 seven studies were performed to evaluate the occurrence of comorbidities in SARS-CoV 2, comprising of 1576 diseased patients and results exposed that maximum predominant co-morbidities were hypertension (21.1%), diabetes (9.7%), cardio-vascular (8.4%) and respiratory diseases (1.5%).[17] Another study was conducted in a hospital of Zhongnan (Wuhan, China) from 11 January 2020 to 16 March 2020 to review the involvement of vital organ-centered comorbidities in the prediction of the likely course of CoVID-19 patients. A total of 212 CoVID-19 patients were involved in this retrospective cohort research. CoVID-19 diseased patients with liver, heart and kidney comorbidity were linked to patients without these comorbidities, were more expected to have liver injuries, cardiac injuries, kidney injury, and there percentage was [13.0% (3/23) vs 3.2% (6/189)], [9.1% (3/33) vs 2.2% (4/179)] and [54.5%(6/11) vs 2.0% (4/201)] respectively with higher risk of mortality.[18]

In another research of CoVID-19 in New-York on April 2020 included 5700 patients with median age of 63 years with an interquartile range of 52-75 and a range of 0-107 years. It showed that normally occurring comorbidities were high blood pressure (3026; 56.6%), obesity (increase weight) (1737; 41.7%), and diabetes (1808; 33.8%). Other comorbidities existed as cancer 320 (6%), hypertension 3026 (56.6%), coronary artery disease 595 (11.1%), congestive heart failure 371 (6.9%), asthma 479 (9%), chronic obstructive pulmonary disease 287 (5.4%), obstructive sleep apnea 154 (2.9%), immunosuppression HIV 43 (0.8%), history of solid organ transplant 55 (1%), Kidney disease chronic 268 (5%), end-stage 186 (3.5%), liver disease Cirrhosis 19 (0.4%), chronic hepatitis B 8 (0.1%), hepatitis C 3 (0.1%), metabolic disease as obesity (BMI ≥30) 1737 (41.7%), morbid obesity (BMI ≥35) 791 (19.0%) and diabetes 1808 (33.8%).[19]

And another study showed evidence of diabetes association with poorer outcomes in CoVID-19 with increased incidence and severity as well. Blood-glucose management is essential for patients who are afflicted with CoVID-19.[20]

In another study of Wuhan University from 1 January to 10 February 2020 uncovered that frequent symptoms of elder patients with CoVID-19 included fever (94.5%), chest distress (63.6%) and dry cough (69.1%). When matched with young patients, older patients had more laboratory irregularities and comorbidities.[21] A research showed that older age (SMD: 1.25 [0.78-1.72]), pre-existing comorbidity (RR = 1.69 [1.48-1.94]) and being male (RR = 1.32 [1.13-1.54]) were identified as risk factors of in-hospital mortality.[22]

Recent progress:

Currently, there are no anti-viral treatments for CoVID-19, however, Remdesivir, Lopinavir, Ritonavir, Interferon-α Nebulization, Ribavirin, Chloroquine, and Umifenovir may be effective against CoVID-19.[23,24] A research suggests protective effects of aspirin against CoVID-19 because it hinders the replication of the virus by interfering with viral protein increase and viral RNA synthesis and weaken formation of viral replication transcription complexes in vitro.[25] Statins may also offer protection against the growth of CoVID-19.[19]

Recommendations:

Diseases such as high blood pressure, diabetes, respiratory disease, cardio-vascular disease, and their vulnerability may be related to the possible consequences of CoVID-19. A larger figure of comorbidities correlates with more disease seriousness. The people with these comorbidities should be included in future CoVID-19 vaccination proposals. More studies should be performed to verify the association. There is a lot of diversity in initial symptoms still many patients have fever and respiratory issues so people with flu like symptoms should be screened properly. Since CoVID-19 is an evolving virus, no specific treatment is currently available. So, we can control this epidemic by following some rules and regulations by WHO. The health policymakers should

implement comprehensive protective measures since medical staff is at risk. It is recommended that a fiber optic bronchoscope and conservative fluid treatment strategy be used for sputum suction and for fluid resuscitation respectively, if needed. To reduce the load of these comorbidity infections affecting deaths in CoVID-19 patients there is a requirement for a worldwide public health campaign to raise awareness.

Conclusion

Patients with any comorbidity and increase in the figure of comorbidities, is associated with worse clinical consequences. Common comorbidities include hypertension, cerebro-vascular disease, cardio-vascular diseases, diabetes, hepatitis C & B, kidney diseases, coronary artery disease, immunodeficiency, cancer, COPD, congestive heart failure, asthma, obstructive sleep apnea, immunosuppression HIV, malignancy history of solid organ transplant, liver disease cirrhosis, obesity. Age is also a risk factor for CoVID-19.

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SHORT COMMENTARY

Overlooked hepatotoxicity with Clopidogrel

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Article Info.

Conflict of interest: Nil

Funding Sources: Nil

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Cite this article as: Malik J. Overlooked hepatotoxicity with clopidogrel. JSTMU. 2020; 3(2):132-133.

A B S T R A C T

Clopidogrel is an adenosine diphosphate receptor blocker. It is widely used as a part of dual antiplatelet therapy (DAPT) in patients with ischemic heart disease (IHD), regardless of the acute coronary syndrome (ACS). Although a rarely reported entity, clopidogrel-induced liver injury is commonly seen in clinical practice. It is widely overlooked by clinicians and is thus a potential hazard to patients with IHD.

Keywords: *Drug-induced liver injury, clopidogrel-induced hepatotoxicity, p2y12 inhibitor side effects*

Clopidogrel is an inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation. It acts by direct inhibition of ADP on its receptor and the subsequent ADP-mediated activation of glycoprotein GPIIb/IIIa complex. It is a pro-drug, which metabolizes into an active form in the liver cytochrome complex (CYP1A2, CYP2C19, CYP3A4) leading to the inhibition of platelet aggregation.[1] The association between the liver metabolism and pharmacokinetics of Clopidogrel was studied in two sub-studies of clinical trials (Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY-TIMI 28) and Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndrome (TRITON-TIMI 38).[2,3] The active metabolites of Clopidogrel inhibit the binding of ADP selectively to its P2Y12 receptor, thereby inhibiting platelet aggregation. All the steps in this metabolism are irreversible. As a consequence, platelets exposed to the drug's active metabolite are affected for their life span in the body.

Various large-scale trials have shown that clopidogrel decreases major adverse cardiovascular events (MACE) in patients with acute coronary syndromes. Its role is pivotal in medically treated subsets of ACS and it is considered to be an adjunct to aspirin after percutaneous coronary intervention (PCI). The clinical evidence of the efficacy of clopidogrel is demonstrated in four clinical trials involving 81,090 patients: The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE); Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE); The Clopidogrel and Metoprolol in Myocardial Infarction/Second Chinese Cardiac Study (COMMIT/CCS-2) and The CLARITY-TIMI 28.[4-6]

Food and drug administration (FDA) has deemed Clopidogrel as safe as aspirin due to its low-risk side-effect profile and positive clinical feedback for the past two decades. The most common adverse effects are gastrointestinal discomfort, easy bruisability, pruritus, and increased bleeding. Other more serious, but rare effects are immune thrombocytopenic purpura (ITP), aplastic anaemia, hemolytic-uremic syndrome (HUS), and severe hypersensitivity.[7]. Acute liver injury leading to liver failure is very rarely defined in the literature. It was added later in the post-marketing surveillance in the Plavix® (Clopidogrel) package insert. Clopidogrel is associated with elevation of liver enzymes in no less than 5% of the patients after initiating the treatment. It can take from 24 hours to 24 weeks (on average 6 weeks) for the liver injury to set in.[8] Although fulminant hepatic failure is only defined in two case reports, in clinical practice, it is more commonly seen than it is reported. The usual pattern of liver enzyme elevation is hepatocellular, but cases with cholestatic or mixed pictures of jaundice are also reported. The mechanism of injury is unknown but several

reviews have hypothesized an idiosyncratic immunologic reaction with the complex hepatic metabolism of the Clopidogrel molecule.[9] There is a susceptibility of drug-drug interaction of Clopidogrel with agents that exhibit an interplay with the cytochrome complex., specifically the CYP2C19 allele. Among various wild type alleles of CYP2C19, *17 allele is associated with increased activity while an allele which encodes two or more non-functional phenotypes are called poor metabolizers of the drug. This is hypothesized to cause the liver injury.[10]

In a routine cardiology clinic (Rawalpindi Institute of Cardiology), we see a multitude of cases with no apparent cause for elevated liver enzymes or jaundice other than drug-induced liver injury (DILI). They are only suspected of having an adverse response to initiation of clopidogrel but due to the non-progressive course of this hepatocellular damage, it is often overlooked by the clinicians. It usually acts like a 'scrub-sink' of learning at our institute but dissemination to the global audience is lacking. This conduct is partially due to the paucity of literature on this subject. To date, only 15 case reports have been documented on clopidogrel-induced hepatotoxicity. In the existing literature, it has been shown that the idiosyncratic liver injury is not related to the presence of pre-existing liver abnormalities.[8] This is usually a diagnosis of exclusion and there are no validated scores to label DILI. However, several case reports have used Maria and Victorino and/or Roussel Uclaf causality assessment method (RUCAM) scale successfully in diagnosing clopidogrel-induced liver injury.[11]

For clinicians and specialists working in cardiology, they must be updated regarding the DILI score systems. The importance of a review of the literature on this subject cannot be emphasized for every future and practising cardiologist. Apart from development of diagnostic biomarkers, it would be feasible to sensitize our fellow clinicians about the various DILI scales and refinement of the parameters to incorporate the relevant items for an acceptable level of diagnosis.

Conclusion

In conclusion, the RUCAM and Maria and Victorino scales should be adopted for the comprehensive assessment of the causal association of Clopidogrel and liver injury. Moreover, clinical trials must be initiated to scientifically prove the mechanisms behind clopidogrel-induced liver injury and degree of hepatocellular damage.

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LETTER TO EDITOR

Effects of COVID-19 on musculoskeletal system

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Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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Cite this article as: Sultan N, Khushnood K, and Awan A. Effects of COVID-19 on musculoskeletal system. JSTMU. 2020; 3(2):134-135.

Severe acute respiratory syndrome corona virus (SARS-CoV-2), also known as CoVID-19 has induced tremendous damage worldwide causing threat to the existence of human race. It primarily involves the respiratory system, compromises immune system, and exacerbates co – morbidities which ultimately leads to multiple system failure and death. Patients with deteriorated condition have to get hospitalized and the ones with mild symptoms need to self-quarantine themselves at home. Everyone has to be home bounded and opt for social distancing protocols, which has led to a huge change in lifestyle and mobility of people globally.[1]

In order to stay healthy, physical activity is necessary. Human body constantly sense the internal environment and responds accordingly. Contracting muscles during exercise need excessive amount of energy that challenges body's homeostasis and leads to multiple responses by body organs. Muscle activation can raise the metabolic demands up to 100 times as compared to the resting state. In order to meet the rising energy demands certain adaptations take place in the body that may lead to long term changes as a result of physical activity. These adaptive changes involve every contractile unit i.e. sarcomere. On the contrary, Immobilization and decline in physical activity will hamper the overall structure of skeletal muscles, causing muscle wasting thereby declining the overall strength in the human body.[2]

Researchers found that CoVID-19 causes weight loss and anorexia. The receptor for this virus is angiotensin converting enzyme 2 (ACE 2), which is found on skeletal muscles, so the one who is infected may have myalgia and weakness; and if combined with immobilization, bed rest or ventilator support it can lead to sarcopenia and cachexia.[3]

As literature shows that musculoskeletal dysfunction is one of the main consequences of CoVID-19. Sarcopenia is reduction in muscle function along with the loss of muscle fibers. Aging leads to primary sarcopenia, whereas sarcopenia due to underlying medical conditions is known as secondary sarcopenia, these underlying conditions could be chronic or acute. People affected with SARS-CoV-2 are likely to develop secondary sarcopenia due to several weeks of decreased physical activity and reduced functioning. Lung damage caused by CoVID-19 leads to hypoxemia that eventually results in decreased oxygen supply throughout the body including the muscle fibers and add up to destruction that is already being caused by the disease. Presence of ACE 2 receptor on muscles is the reason for causing theses effects.[3] after recovery, the patients who were critically ill and needed mechanical ventilation, reported with secondary complications such as weakness in the muscles and frailness of the bones. The other complication is cachexia; which is "complex metabolic syndrome associated with underlying illness causing muscle loss." Weight loss, anorexia, low albumin, inflammation and muscle protein breakdown are main features of cachexia.[3,4] Sarcopenia and cachexia are one of the main contributors to morbidity and mortality. People with sarcopenia may need

exercises prescribed by a physical therapist and nutritional supplements throughout their lives, while the survivors of cachexia often need extensive rehabilitation management.[5]

Provision of routine exercise plans to every individual, especially to the ones who are isolated, is the dire need of today. It has been found evident that exercises and physical activity improves the outcomes in the hospitalized patients by reducing the damage caused to musculoskeletal system, by CoVID-19. In order to acquire and improve the agility, strength and flexibility of musculoskeletal system, regular planned physical exercise regimes should also be opted by the patients who are in recovery phase.

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LETTER TO EDITOR

Joint Commission International Accreditation: A breakthrough in Pakistan

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[3] Critical analysis, final approval & accountable for all the work

Article Info.

Conflict of interest: Nil
Funding Sources: Nil

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Cite this article as: Awan A. Qureshi S. Khushnood K. Joint Commission International Accreditation: A breakthrough in Pakistan. JSTMU. 2020; 3(2):136-137.

Joint commission international (JCI) is model of excellence for healthcare all around the world. It determines the most effective pattern of working to rule out quality of treatment and steps taken in regard of patients' safety.[1] enhancing the quality of healthcare organizations started right after the beginning of 20th century. Initially Joint Commission on accreditation of Hospitals (JCAHO) was formed in 1951; it only accredited the healthcare setups and medical centers in the United States of America (USA). Afterwards, in 1991 with an increasing need for improving the quality standards of health care across the globe, JCI was founded. Now internationally JCI accredits the hospitals that are providing the quality medical services to the patients.[2] currently there are 1081 hospitals all over the world which are accredited by JCI. If we talk about South Asia a total of 47 hospitals are there that are commissioned or accredited by JCI and moving towards our country Pakistan, there are only 4 hospitals that are accredited by JCI.[3] As we see that most of the world is moving towards acquiring JCI accreditation, hospitals and healthcare setups all over the world are taking steps to assure patient's satisfaction by improving the quality of their medical services. If hospitals are accredited by JCI, both patients and hospitals will benefit in a way that the patients' health status will enhance as well as the reputation of healthcare system of Pakistan. The four hospitals that are JCI accredited in Pakistan are; Agha Khan University Hospital Karachi, Shifa International Hospitals Ltd. Islamabad, Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore and Shaukat Khanum Memorial Cancer Hospital and Research Centre Peshawar.[4] In our country it is the need of hour to improve quality of medical services and patients' satisfaction in both public and private sector hospitals, though the quality of medical services is improving in private hospitals but they are not cost-effective considering the fact that most people in our country are unable to afford them. To conclude, JCI accreditation is an important milestone in health care management system of Pakistan. The professionals working in JCI accredited health care organizations are aware of its significance and implications on the quality of health care in Pakistan. However, health professionals associated with organizations that are not JCI accredited are not aware of the standards that are used by it to ensure quality health care, infection control and patient safety. Furthermore, it has also shed a light on the fact that top notch health care is seldom available to the masses. Emphasis should be placed on the government to accredit the public sector hospitals with JCI in order to provide common man with premium quality of health care services.

Keeping in view all the benefits of JCI accreditation, it is highly recommended that government should seek

assistance of the hospitals that are already accredited by JCI in accrediting public sector hospitals.

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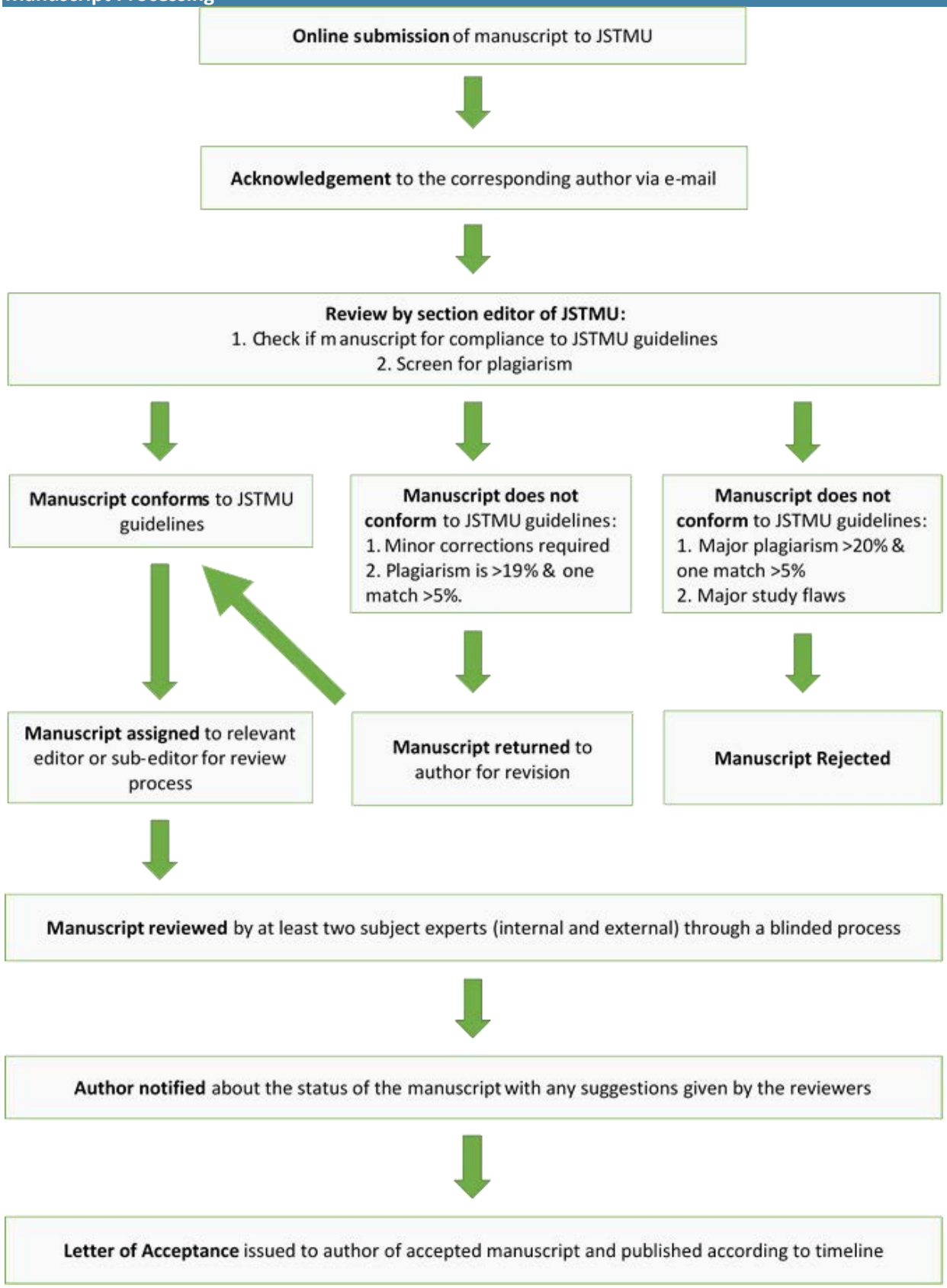

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Authors should not use an excessive number of citations to support one point.

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Initial decision to review	1-2 weeks after submission
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A. Original Research Articles

The Journal considers original articles that are, cohort study, case-control study, clinical trials, intervention study, epidemiological assessment, cross-sectional study, meta-analysis, cost-effective analysis, decision analysis, study of screening and diagnostic test, other observational studies, and qualitative studies such as focus group discussions, in-depth open-ended survey etc. Articles based on thesis maybe submitted provided the data is not more than three years old.

Each original article must contain:

Title page *

Title page should contain the following information:

1. Complete title of the article
2. Name(s) of author(s)
3. Department(s)
4. Institution(s) at which work was performed
5. Official phone/fax number, mobile phone number, personal e-mail address of the corresponding author, and institutions address.

Abstract

The abstract should be structured and NOT more than 250 words. The abstract must be written under the following subheadings:

1. Introduction
2. Objectives
3. Methodology
4. Results
5. Conclusion

Text

Text must be arranged under the following headings:

1. Introduction
2. Methods
3. Results
4. Discussion
5. Conclusion(s)
6. Acknowledgements (if any)

Introduction: Should provide brief review of relevant literature in such a way that it highlights the importance of the study and that the purpose of the study should be clearly stated. The articles used in the review of literature should be properly referenced by Vancouver Style.

Methods: Should include the setting(s), the subjects (participants), sampling methods and sample size, if used, type of study design used, and other procedures that were conducted. The Methods section should be brief, crisp and detailed enough to enable the reader to replicate the study in another setting. Commonly used procedures and methods need not be described but require a reference to the original source.

Results: Should include the factual findings of the research study done and, presented in the form tables or figures. Each table and figures should be properly labelled with headings and numbers (e.g. Table

No. 1, Figure No. 1) on separate pages. The write-up of results in the text should highlight the important findings without duplication of presentations displayed in the tables or figures. *Explanation of the findings should be reserved for the Discussion section.*

Discussion: Should highlight the important findings comparing and contrasting the study's results with that of other similar researches published and it should be appropriately referenced. Discussion should be concise and supported by the presented data.

Conclusion: Is restricted to the study and is drawn from the results and discussion.

Acknowledgements: If any, should be placed at the end of the text and before references.

References: *

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Citation Example:

Equal amounts of dietary carbohydrates have variable blood glucose response considerably as a function of specific food ingested.[1]

Bibliography/References Example:

1. Wolever TMS, Yang M, Zeng XY, Atkinson F, Brand-Miller JC. Food glycemic index, as given in Glycemic Index tables, is a significant determinant of glycemic responses elicited by composite breakfast meals. *Am J Clin Nutr* 2006; 83(6):1306–12.
   DOI: https://doi.org/10.1093/ajcn/83.6.1306

B. Meta -Analysis/ Systematic Reviews

Meta-analysis are systematic, critical assessments of literature and data sources pertaining to clinical topics, emphasizing factors such as cause, diagnosis, prognosis, therapy, or prevention, and that includes a statistical technique for quantitatively combining the results of multiple studies that measure the same outcome into a single pooled or summary estimate. All articles or data sources should be searched for and selected systematically for inclusion and critically evaluated, and the search and selection process should be described in the manuscript. Inclusion and exclusion criteria must be mentioned. Details of searching articles and search engines used should be clearly stated. The specific type of study or analysis, population, intervention, exposure, and tests or outcomes should be described for each article or data source. These should be described in the Method section. The data sources should be as current as possible, ideally with the search having been conducted within several months of manuscript submission. Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram and checklist. Authors of meta-analyses of observational studies should submit the MOOSE checklist. Follow EQUATOR Reporting Guidelines. The text **should NOT exceed 6000 words** excluding abstract, references, tables and figures.

Each of the sections of these articles should include specific sub-sections as follows:

Structured Abstract: (Not exceeding 250 words):

1. Objectives
2. Methodology
3. Results
4. Conclusion

Text should be organized under the following headings:

Introduction:

1. Rationale
2. Objectives
3. Research question

Methods:

1. Study design
2. Participants, interventions, comparators
3. Systematic review protocol
4. Search strategy
5. Data sources, studies sections and data extraction
6. Data analysis

Results:

1. Provide a flow diagram of the studies retrieved for the review
2. Study selection and characteristics
3. Synthesized findings

Discussion:

1. Summary of main findings
2. Risk of bias
3. Limitations
4. Conclusions

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C. Systematic Review (without meta-analysis): Review articles

Systematic Reviews/ review article are critical evaluation and assessments of scientific literature and other sources of data relating to health sciences topics, emphasizing factors such as cause, diagnosis, prognosis, therapy, or prevention. Systematic Reviews without meta-analysis are published as Review articles; those with meta-analysis are published as Original Investigations.

Systematic Reviews should include the following:

1. Abstract (Unstructured abstract of no more than 350 words)
2. Introduction (150-250 words)
3. Methods (150-250 words)
4. Results (1000-1250 words)
5. Discussion (1000 words)
6. Conclusions (2-3 sentences)

Maximum length: **Should NOT exceed 3500 words of text** (not including abstract, tables, figures, acknowledgments, references), with no more than a total of 5 tables and/or figures and no more than 50-75 references.

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D. Case Reports/Case Series

The journal will consider only those case report/series that represent very rare case(s), or epidemic diseases that are new or emerging, or first observation(s) of some emerging phenomenon or disease. They should have clinical significance and may also include observation of new adverse effect(s) of a drug, vaccine, or procedure or other unique observations, etc. Informed written consent of the patient or next of kin (if patient is not alive or comatose/disabled) should be obtained before submission of the manuscript. A covering letter from the authors that convincingly describe the merits of the case in the light of the mentioned criteria and it's educational or scientific merits should be sent along with the manuscript.

Case Report /case series should contain a single paragraph abstract and text **should NOT exceed 1000 words** (excluding abstract, references, tables and figures) with maximum 10 bibliographic references and either three figures or three tables. Each case report must contain:

1. Abstract (unstructured - should not exceed 120 words)
2. Introduction
3. Case Presentation
4. Discussion
5. Conclusion
6. Competing interest
7. Patient consent

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E. Rapid/Special /Short Communications

Rapid/Special/Short communication should be complete work, such as COMPLETE results of a short RESEARCH study, NOT a preliminary report and **should NOT exceed 1500 words** with one figure and/or one table. An editorial decision will be provided rapidly without reviews.

F. Letters to Editor

Letters should only be written on a specific article in the most recent publication of journal. The letter should be objective and provide constructive opinions offer some academic or clinical interest to the readers.
Letters **should NOT exceed 400 words** of text and 5 references, 1 of which should be to the recent article. It should not have more than 3 authors. The text should include the full name, academic degrees, and institutional affiliation for author and the email address for the corresponding author. Letters considered for publication shall be forwarded to the author of the cited article for possible response. The editor reserves the right to shorten these letters, delete objectionable comments, make other changes, or take any other suitable decision to comply with the style and policies of the journal. For writing and references style, follow the same instructions listed above.

Letter in Reply

Replies by authors should not exceed 500 words of text and 6 references. They should have no more than 3 authors.

G. Editorial

The topics of the editorial are decided by editorial board and/or Editor-in-Chief. Editorial is written either by one member of the editorial board or some expert on that topic invited by the Editor-in-Chief. As a convention, the editorial addresses relevant areas of interest that may pertain to a range of areas influencing health and health care sciences.

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