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ABOUT THE EDITOR

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He is currently a distinguished professor of pharmaceutical sciences. He received his Ph.D. MS and bachelor degree in Pharmacy from the Hebrew University. He has more than 200 peer-reviewed manuscripts and books; 150 of them were published in the recent 10 years. He is currently an editor and an editorial board member of 50 international journals in the area of pharmaceutical sciences. His research includes: design and synthesis of anti-cancer prodrugs having targeted properties determined on the linker's type, design and synthesis of prodrugs having inefficient bioavailability (Dopamine), design and synthesis of prodrugs for masking bitter sensation of commonly used drugs. 4-Removal of pharmaceuticals from wastewater by novel adsorbents. He has special interest in Allied Health Science, Infectious Diseases, Pharmacy, Environmental Chemistry, Medicinal Chemistry. Organic Chemistry, Quantum Computing. His skills and expertise includes synthesis, water Treatment, Medicinal Chemistry, Water Treatment, Quantum Mechanics, Enzymes, Adsorption, Kinetics, Density Theory, Computational Chemistry, Therapeutic Outcomes, Electronic Structure, Pharmaceutical Technology, Drug Discovery, Molecular Simulation, Molecular Dynamics, Molecular Modeling, Infectious Diseases, Organic Chemistry, Catalysis, Quantum Chemistry, Environmental Chemistry, Bioavailability, Stability, Antibacterials, Pharmacy, Medicinal Chemistry, Chemical Physics, DFT Calculations.

PREFACE

This book covers key areas of Medicine and Medical Research. The contributions by the authors include reproductive Age, method of sterilisation, internal carotid arteries, left vertebral artery, left subclavian artery, diagnostic & surgical procedures, vertebral arteries arch of aorta, menopause, relapsed clubfoot, demographic factors, ofluorescence, automated microperimetry, myopic foveoretinal detachment, myopic foveoschisis, myopic macular hole, myopic traction maculopathy, posterior staphyloma, choroidal vascularity index, macular hole retinal detachment, family planning, sexually transmitted diseases, retinitis pigmentosa, oxidative stress, reactive oxygen species, photoreceptor degeneration, visual impairment, conventional laparotomy, laparoscopy, gynecological malignancies, physiological vital parameters, ambulation, hysterectomy women, musculoskeletal pain, cardiac rehabilitation programme, heart failure, cervicothoracic Junction, thoracic Spine, hematological malignancies, chronic myeloid leukemias, malignant lymphomas, reverse transcriptase quantitative polymerase chain reaction, abdominal-perineal amputation, posterior colpectomy, melanoma, rectal cancer and modern methods of contraceptive use. This book contains various materials suitable for students, researchers and academicians in the field of Medicine and Medical Research.

Chapter 1
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Study of Contraceptive Use and Its Determinants in Married Women of Reproductive Age Group in Urban Slum Area of Maharashtra, India

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ABSTRACT

This chapter aimed to determined the contraceptive use and its determinants in married women of reproductive age group in urban slum area of maharashtra, India. The contraceptive behaviour of the population in reproductive age group has got an important role to play in deciding the population size of a particular country. There are many factors which decides the contraceptive behaviour of males and females. A community-based cross-sectional study was conducted in slum area catered by Urban Health Training centre under Dept of Community Medicine of Solapur city, Maharashtra, India. Total 420 married women aged between 15 to 45 years participated in the study. Information was collected by pre-designed, pretested proforma by interview method. The use of contraceptives in married women is higher as compared to the findings of NFHS-3. Use of spacing methods are low. There is huge knowledge application gap between awareness and use of contraception.

Keywords: Contraceptives use; slums; married women of 15 -45 yrs; urban area; awareness; demographic factors.

1. INTRODUCTION

The factors that influence contraceptive practice are multifaceted and challenging. Several studies evident that most women's knowledge and use of contraception is associated with socio-demographic, socio-cultural, socio economic, source of information and family planning factors. According to the

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National Family Health Survey (NFHS)-3 and 4, the prevalence of modern methods of contraceptive use is 48.5% and 47.8% and by all methods 56%, which is still below the expected rate of 60% which is required to have a stable population [1]. The population of the world is growing at the rate of about 200 births per minute or 10,000 per hour or 2.5 lakhs per day or 10 crores per year. Three most populous countries in the world today are China, India and USA [2,3]. Globally, contraceptives help to prevent an estimated 2.7 million infant deaths and the loss of 60 million of healthy life in a year. At least 22,500 women died from unsafe abortion complications, 74 million unplanned pregnancies occur every year in the developing world [4]. The census of 2011 indicated that there were 1210.2 million people living in India. It contributes 17.31% of the global population, with an 18.1%2 growth rate. With 1,364 million people, India is the second-most populous nation in the world after China, but it ranks seventh in terms of land area. Having only 2.4% of the world's land. India contributes about 17.5%. Though contraceptive utilization has a comprehensive benefit for women, it was one of underutilized public intervention in the least developed countries particularly low in Africa (33%), in Central and Southeast Asia with only 47%, whereas in Ethiopia, according to EDHS 2016 report, only 35% are using a modern contraceptive method [4].

However the provisional population in 2011 is higher by about 110 million compared to the target set for the year 2010 [5]. It crossed 1 billion mark on 11 May 2000, and is projected to reach 1.53 billion by the year 2050. This will then make India most populous country in the world, surpassing China [6]. This alarming rise in population is slowing socioeconomic progress, lowering quality of life, harming the environment, and placing additional demands on our already overburdened resources. India is the first country to start family planning programme at national level, in 1951 [7]. National family planning programme was started way back in 1952 and in spite of political commitment for central government funded national family programme, birth rate has not come down as desired [8]. There will be at least 150 to 180 eligible couples per 1000 population in India. During year 2011, 40% of eligible couples in the reproductive age group 15-44yr were protected against conception and 60% of eligible couples were still unprotected against conception [6].

The urbanization of different parts of the world constitutes a major demographic issue of the twenty-first century. Maharashtra has the highest urban population of 50.83 million (13.48%) of the country's urban population [6]. In urban field, most of population (60%) resides in urban slum area. Urban slum is having deprived and vulnerable population as poverty, illiteracy and ignorance is more common [2]. So the study in urban slum area is aimed to know the – contraceptive use and to find the factors for non-acceptance of family planning methods.

Objectives:

1) To determine the extent of contraceptive use.
2) To study association of contraceptive use with various socio–demographic factors.

3) To study the sources of information, place of availability and awareness of contraceptives.
4) To find out reasons for not using contraceptives in married woman of reproductive age group.

2. MATERIALS AND METHODS

The community based cross-sectional was carried out in the slum area, catered by Urban Health Training Centre of the Department of Community Medicine, Solapur, Maharashtra from August 2016 to July 2017. Married woman of reproductive age group (15 – 45 years) participated & interviewed by pre designed pretested proforma. Informed consent was obtained from the study participants prior to data collection. A complete list of married women in reproductive age group 15-45 years was obtained from family survey register maintained in Anganwadi Centre. A team of ten internee doctors was trained for the data collection. Information was collected by pre-designed and pretested proforma by interviewing married women aged between 15 and 45 years.

The total population under the field practice of urban health centre is, approximately, 30,000 out of which 16,600 are residing in slum area. There are 2906 married women of reproductive age group (15–45 years) which constitute 17.50% of the total population residing in the slum area. According to NFHS-3 data, prevalence of modern contraceptive use in India is 49% [9]. With precision level of 10% and level of significance set at 5% with 95% confidence interval, a sample of 420 women was calculated. Simple random sampling method was used for collection of the data.

2.1 Statistical Analysis

The data was entered into excel sheet and analyzed by using SPSS software, trial version 17. Percentages were calculated, and χ^2 test was used to find any significant association between qualitative variables. A value of $p < 0.05$ was considered as significant.

3. RESULTS

A total of 420 married women between 15 and 45 years of age were interviewed. Table 1 shows maximum number of women 246 (58.57%) were between the age group of 20 and 29 years, 265 (63.09%) belonged to the Hindu religion, 202 (72.35%) were educated up to secondary school, 310 (73.81%) were housewives, and 208 (49.53%) belonged to joint family; 324 (77.14%) were from Class IV and V socio economic group as per modified B. G. Prasad classification. For calculation of chi-square test the temporary contraceptives were clubbed together and 2 groups (temporary and permanent method of contraception) were analysed.

Table 2 shows out of 420 married women 52.14% are currently using some method of contraception. Out of the total 219 users, 152 (36.19%) using limiting

method and 67(15.95%) spacing method. The most preferred spacing method was condom (5.47%) followed by OC pills (5.24%), IUD (2.86%) and injectables (2.38%) for contraception. No male partner used the method of sterilisation.

Table 3 shows that use of contraception was maximum (29.68%) in women age 25 – 29 years, educated up to secondary education (46.58%). (Spacing method most commonly used in women educated up to graduation and above (66.66%), maximum women were Hindu (64.38%), doing household work (69.86%), from nuclear family (45.66%), from class IV socio economic status (48.86%). In our study the women from upper socio economic class (class I) were only 3 and all were using some method of contraception, those having 3 or more children had maximum use (46.58%), women married in the age group of 18 – 24 years showed maximum use (57.07%), women having a 1 – 10 years of duration of marriage showed maximum use(54.35%) and spacing was the choice of contraception, women with 1 male child had shown maximum use of contraception. The observed difference among the women using contraceptives according to their age group, education, religion, type of family, SE status, number of children, age at time of marriage, duration of marriage, and number of male child was statistically significant ($p < 0.0001$).

Fig. 1 shows the awareness regarding contraceptive, maximum women were aware about OC pills (74.69%) and least aware about intrauterine device (31.48%) and injectable contraceptives (10.49%). In our study out of 420 women 324 (77.14%) women were aware of at least one method of contraception.

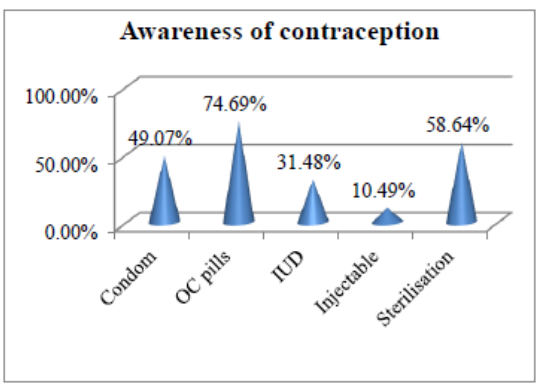

Fig. 1. Distribution of married women of reproductive age group according to awareness of contraception

Fig. 2 shows the source of information of contraceptive method. The major source of information was Doctors (46.29%), followed by Anganwadi worker (37.35%), relatives (14.81%), visiting nurse (0.93%) and pharmacist (0.62%).

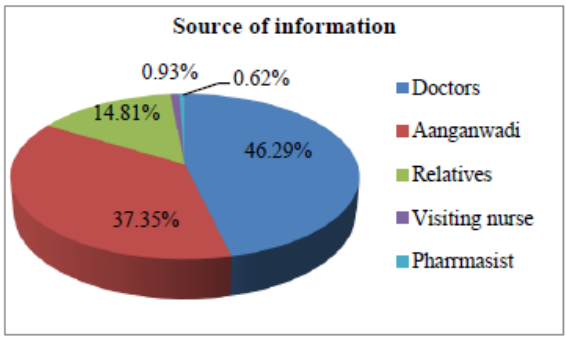

Fig. 2. Distribution of method of contraception used among contraceptive users according to source of information

Fig. 3 shows reason for non use of contraception, out of 201 women, 96(47.76%) felt that they were not at risk of pregnancy, 37(18.41%) want to became pregnant, 21(10.45%) didn't have any information, 13(6.47%) had difficulty in access and availability of contraceptives, 12 (5.97%) had opposition from husband and family members, 12(5.97%) had fear about side effects of contraception, 10 (4.97%) had other reasons i.e (care about little child, don't trust on contraceptives, infrequent sex).

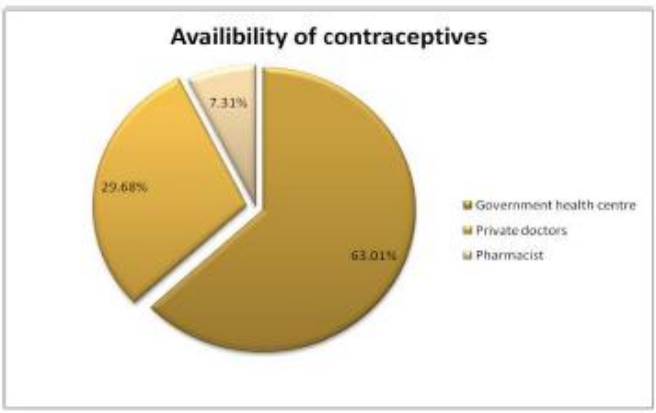

Fig. 3. Distribution of method of contraception used among contraceptive users according to place of availability of contraceptives

Fig. 4 showed availability of contraceptives among users, maximum (63.01%) number of users obtained contraceptive services from Government Health Centres followed by private doctors (29.68%) and Pharmacist (7.31%).

Table 1. Socio–demographic characteristic of married women of reproductive age group

Characteristics	Number	Percentage
Age group in years		
15-19	12	2.87
20-24	136	32.38
25-29	110	26.19
30-34	80	19.04
35-39	38	9.05
40-44	44	10.47
Education		
Illiterate	76	18.09
Primary	64	15.24
Secondary	202	48.09
Higher secondary	52	12.4
Graduation and above	26	6.18
Religion		
Hindu	265	63.09
Muslim	141	33.57
Christian	14	3.34
Occupation		
House work	310	73.81
Work productively	110	26.19
Type of family		
Joint	208	49.53
Nuclear	162	38.57
Three generation	60	11.90

Table 2. Distribution of married women of reproductive age according to current contraceptive use

Type of contraceptive method	Total (%)
Spacing method	
Condom	23 (5.47)
OC pills	22 (5.24)
Cu–T	12 (2.86)
Injectable	10 (2.38)
Total spacing method	67 (15.95)
Limiting method	
Male sterilisation	0
Female sterilisation	152 (36.19)
Total contraceptive method	219 (52.14)

Table 3. Association of contraceptive use and socio-demographic factors

Characteristics	Contraceptives used					Total	DF	P value
	Spacing				Limiting			
	Condoms	OC pills	IUD	Injectable	Sterilisation			
Age group in years								
20-24	9 (4.11)	11 (5.02)	8 (3.65)	6 (2.74)	22 (10.05)	56 (25.57)	4 56.4	P<0.001
25-29	12 (5.48)	8 (3.20)	4 (1.82)	4 (1.82)	38 (17.35)	65 (29.68)		
30-34	0	2 (0.91)	0	0	46(21)	48 (21.92)		
35-39	2 (0.91)	2 (0.91)	0	0	26 (11.87)	30 (13.70)		
40-44	0	0	0	0	20 (9.13)	20 (9.13)		
Educational status								
Illiterate	0	2 (0.91)	0	0	44 (20.09)	46 (21)	3 37.3	P<0.001
Primary school	3 (1.37)	0	0	0	26 (11.87)	29 (13.24)		
Secondary	10 (4.57)	12 (5.48)	6 (2.74)	10 (4.57)	64 (29.22)	102 (46.58)		
Higher secondary *	6 (2.74)	4 (1.82)	6 (2.74)	0	14 (6.39)	30 (13.70)		
Graduation and above*	4 (1.82)	4 (1.82)	0	0	4 (1.82)	12 (5.48)		
Religion								
Hindu	11 (5.02)	16 (7.31)	6 (2.74)	0	108 (49.31)	141 (64.38)	1 9.72	P<0.008
Muslim*	12 (5.48)	6 (2.74)	4 (1.82)	10 (4.57)	42 (19.17)	74 (33.8)		
Christian*	0	0	2 (0.91)	0	2 (0.91)	4 (1.82)		
Occupation								
House work	19 (8.68)	16 (7.31)	12 (5.48)	10 (4.57)	96 (43.83)	153 (69.86)	1 10.6	P<0.001
Working productively	4 (1.82)	6 (2.74)	0	0	56 (25.57)	66 (30.14)		
Type of family								
Nuclear	5 (2.28)	11 (5.02)	2 (0.91)	0	82 (37.44)	100 (45.66)	2 14.8	P<0.001
Joint	10 (4.57)	9 (4.11)	10 (4.57)	8 (3.65)	58 (26.48)	95 (43.38)		
Three generation	8 (3.65)	2 (0.91)	0	2 (0.91)	12 (5.48)	24 (10.96)		
Socio–economic status								
Class I*	0	2 (0.91)	0	0	1 (0.45)	3 (1.37)	2 22.6	P<0.001
Class II*	2 (0.91)	0	0	0	1 (0.45)	3 (1.37)		
Class III*	6 (2.74)	12 (5.48)	4 (1.82)	0	19 (8.67)	41 (18.72)		
Class IV	12 (5.48)	8 (3.65)	6 (2.74)	6 (2.74)	75 (34.25)	107 (48.86)		
Class V	3 (1.37)	0	2 (0.91)	4 (1.82)	56 (25.57)	65 (29.68)		

Continued.

Characteristics	Contraceptives used					Total	DF	P value
	Spacing			Limiting				
	Condoms	OC pills	IUD	Injectable	Sterilisation			
Number of living children								
1	10 (4.57)	8 (3.65)	0	4 (1.82)	6 (2.74)	28 (12.78)	2 56.3	P<0.001
2	10 (4.57)	12 (5.48)	10 (4.57)	4 (1.82)	53 (24.2)	89 (40.64)		
3 or more	3 (1.37)	2 (0.91)	2 (0.91)	2 (0.91)	93 (42.46)	102 (46.58)		
Age at time of marriage								
<18	1 (0.45)	8 (3.65)	5 (2.28)	1 (0.45)	69 (31.50)	84 (38.36)	1 12.2	P<0.01
18-24*	22 (10.04)	12 (5.47)	7 (3.19)	9 (4.10)	75 (34.25)	125 (57.07)		
>24*	0	2 (0.91)	0	0	8 (3.65)	10 (4.57)		
Duration of marriage in years								
1-10	21 (9.59)	16 (7.30)	12 (5.47)	10 (4.57)	60 (27.39)	119 (54.35)	2 45	P<0.001
11-20	2 (0.91)	6 (2.74)	0	0	71 (32.42)	79 (36.06)		
21-30	0	0	0	0	21 (9.59)	21 (9.59)		
Number of male children								
0	10 (4.57)	8 (3.65)	0	4 (1.82)	10 (4.57)	32 (14.61)	3 34.8	P<0.001
1	10 (4.57)	8 (3.65)	10 (4.57)	6 (2.74)	74 (33.79)	108 (49.31)		
2	3 (1.37)	6 (2.74)	2 (0.91)	0	48 (21.92)	59 (26.94)		
3	0	0	0	0	20 (9.13)	20 (9.14)		

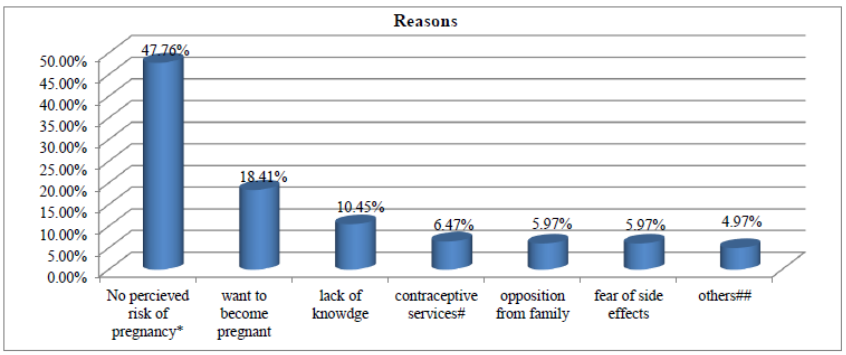

Fig. 4. Reasons for not using contraception in married woman of reproductive age group

4. DISCUSSION

Out of 420 married women of reproductive age group, 52.14% of married women are currently using any method of contraception. Out of the total 219 users, 152 (36.19%) women were using limiting method and 67(15.95%) women using spacing method of contraception. Among sterilisation female sterilisation was preferred method for permanent contraception, there was not a single male partner adopted the method of sterilisation. In the study, contraceptive use in urban slum was 52.14 which is higher than NFHS-4 study which was 47.8% [10], this may be due to implementation of Anganwadi Centre in slum area. Similar findings were seen in study done by Gayatri Bandhi et al [11], where the prevalence of contraception 53.02%, (among those 49.23% were used permanent and 3.8% used temporary methods) in urban slums of Raipur city, Chhattisgarh. Similar findings are seen in study conducted by Rajinder Singh Balgir et al. [12] and Avisek Gupta et al. [13]. According to age group, contraception use was maximum (29.68%) in women age 25 – 29 years, followed by 20 – 24 years (25.57%), minimum use of contraception was seen in age group of 40 – 44 years (9.13%) which is statistically highly significant (P<0.001). While contrary results were seen in Rajinder Singh Balgir et al. [12], that contraceptive use were maximum by couple aged between 30 -34 years (71.79%) followed by 65% in age group of 35-39 years. As per education profile of women it shows that the use was maximum in women educated upto secondary education (46.58%). Similar findings given by Relwani Nisha Ram et al. [14] in slum of Nagpur, that contraception use maximum (73.4%) among literate compared to illiterate (48.8%) and it is significant. Use of contraception by religion shows that maximum (64.38%) women using contraception were Hindu, the difference was statistically significant. Similar results shown by Padma Mohanan et al. [15] that majority (37.4%) acceptors of Contraception were from Hindu religion compared to Muslim (18.5%) and by SS prateek et al. [16], that the percentage of women using contraceptive was higher in Hindu. In our study women doing household work (69.86%) had more use of

contraception than women working productively (30.14%) and the difference was significant. Similar findings were seen by Sanku Dey et al. [17] in urban slums of Shillong city and Bratati Banergee et al. [18], that contraceptive prevalence rate was higher among the nonworking women than working. According to type of family, maximum women using contraceptives were from nuclear family (45.66%) and difference was statistically significant. Similar distribution seen in study by Avisek Gupta et al. [13] that women of nuclear families have more (70%) use of contraception. According to socioeconomic status, the maximum women belongs to class IV socio economic status (48.86%) and difference was significant. As per number of living children shows that maximum women using contraceptives having 3 or more children (46.58%) and difference was significant. Similar results seen by Nirankar Singh et al. [19] that majority (88.3%) of the women with 3 or more living sons were using contraception. As per, age at time of marriage shows that maximum (57.07%) women using contraceptives were married at age group of 18 – 24 years, the difference was significant. Similar findings showed by Avisek Gupta et al. [13], that 64% of contraceptive users belonged to 20–24 years of married age. According to duration of marriage it showed that maximum use of contraceptives done by women having 1 – 10 years of marriage (54.35%) and spacing method as choice of contraception. According to number of male child, maximum use of contraceptives done by women having one male child (49.31%). Similar findings seen by A. Kansal et al. [20] in rural population of Dehradun District, acceptance of family planning methods after delivery of at least one male child was significantly higher (53.25%) than those with no male child (6.18%). According to awareness of contraception maximum women (77.14%) were aware of at least one method of contraception. Similar findings was seen by Mitali and Girija et al. [21], that 73.5% of the participants were aware about the contraceptive methods. Study by Pandey S and Thitame S et al. [22] at tribal area of Ahmednagar District showed same result as 85.50% of married women had knowledge about one or other methods of family planning. According to source of information the major source of information was doctors (46.29%). Similar finding of source of information was found by Mamata Rani Giri et al. [23] and Suman Basu et al. [24] that main source of information about contraception were health workers. Study by Vashisht S, Prakash R et al. [25] showed that source of information mainly obtained by media (53.8%) followed by friends/relatives (36.3%). Maximum number of contraceptive users in our study obtained contraceptive services from Government Health Centres (63.01%). Similar finding of availability of contraceptive was found by Rubina Sarmad et al. [26] in urban slums of Jauharabad city. The most common reason for not using contraception was not at risk of pregnancy, want to became pregnant, lack of information, difficulty in access and availability, opposition from husband and family, fear of side effects and other reasons.

5. CONCLUSION

In our study contraceptive use was higher than the findings of NFHS-3 and NFHS-4. The preferred method of contraception is limiting method. Use of spacing methods was low. The government centres are a major source of

availability of contraceptives. There is huge knowledge application gap between awareness and use of contraception.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Chapter 2
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Triage, Risk Concept and Prehospital Emergencies in Psychiatric Ambulance: Proposal for Implementation in the City of Buenos Aires

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ABSTRACT

This chapter describe a Triage proposal to be applied in prehospital interventions by the psychiatric ambulance dependent on the Alvear Hospital and under current legal regulations. Psychiatric emergencies are severe behavioral changes secondary to worsening mental illness. Such situations present a risk to the patient and other people, so they need immediate therapeutic intervention. They are associated with feelings of fear, anger, prejudice, and even exclusion. The study of prehospital emergency interventions with the psychiatric ambulance of our hospital was carried out through the evolutions carried out in the "Ambulance Duty Book". The triage proposal included the internationally used criteria related to time, the reason for the intervention, the clinical presentation and the proposed approach modality. The triage system is a tool that allows for the systematisation of approaches against the variety of causes for consultation and presentation of mental pathologies in the emergency room, in addition to

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fostering greater interventional effectiveness, system homogeneity, and consensus among the health effectors. The application of triage in mental pathologies is based not only on the response time, but also on the resources that a device has to respond to them. In the particular case of prehospital ambulance emergencies, we consider it useful and that the scenarios (of the pathology and the environment) are propitious for the implementation of this type of strategy. It is concluded that the implementation of this proposal is useful for the clinical detection and risk management of psychiatric pathologies in the prehospital context, since it allows systematizing the interventions according to the resources of each health system.

Keywords: Psychiatry; ambulance; emergencies; triage.

1. INTRODUCTION

The heterogeneity of clinical presentations in psychiatric emergencies creates difficulties in the response by interdisciplinary Mental Health teams. This is aggravated and difficult when the care is carried out on public roads or the patient's home, that is, it is a pre-hospital context. In most cases, they represent extreme severity in mental illness, they are associated with feelings of fear, anger, prejudice, and even exclusion. Among the most prevalent psychiatric emergencies are suicidal behavior, severe depressive or manic episodes, self-mutilation, severely impaired judgment, severe self-neglect, substance intoxication or abstinence crises, and aggressive agitatio. Previously, we outlined the proposal for a classification system (triage) to be applied in the clinical, social context and under the current ethical-legal standards of our practice for the management of hospital emergencies. Mental illness-related stigma, including that which exists in the healthcare system and among healthcare providers, has been identified as a major barrier to treatment and recovery, resulting in poorer care quality for mentally ill people [1].

Argentina, the second largest country in South America, is a federation of 23 provinces and its capital, the autonomous city of Buenos Aires. Its population is a little over 40 million, 50% of whom reside in its five largest metropolitan areas. The rural areas are extensively underpopulated. The city of Buenos Aires and its suburbs contain 15.5 million inhabitants, making it one of the largest urban areas in the world [2]. The hospital specialises in mental health and is a part of the government of the City of Buenos Aires' network of health facilities, is situated in the Agronoma neighbourhood. Since it concentrates on providing psychiatric emergency care, its organisational structure and specificity set it apart from other programmes in Argentina (and Latin America). Although in its beginnings it was a general hospital, with the restitution of democracy in 1983, it was transformed into a specialized hospital designed exclusively for patients with acute mental illness who require an interdisciplinary approach with the aim of stabilizing their condition quickly and effectively; or failing that, referral to another effector. This position applied to the assistance of patients with mental pathologies since its origin in the 80's was consistent with the spirit and the postulates of the National Mental Health Law 26657/10, which in its articles specifies the need for

interdisciplinary treatments, with hospitalization times. As brief as possible and only in cases of certain and imminent risk the use of hospitalization.

One of the particularities that the hospital has is the work on public roads or other effectors through the psychiatric ambulance. In this, a psychiatrist and the driver attend the locations coordinated by the Emergency Medical Care System to perform psychiatric emergency services. The wide heterogeneity of cases that motivate ambulance interventions makes it difficult to systematize procedures, however, having the guidelines in interventions will generate efficiency in them and reduce the chances of errors due to partial approaches or without a scientific foundation.

The difficulties raised in relation to the systematization of the approaches cause a multiplicity of approach options that can alter their effectiveness, increase response times with the possibility of aggravation of psychopathological symptoms and increase the possibilities of medical error with the consequent associated litigation. For this reason, we consider it necessary and clinically useful for prehospital care management in psychiatric ambulances to implement a triage system based on risk assessment of the conditions that prompt assistance.

The objective of this proposed article is to describe a Triage proposal to be applied in prehospital interventions by the psychiatric ambulance dependent on the Alvear Hospital and under current legal regulations.

2. MATERIALS AND METHODS

For the realization of this proposal to be applied in the psychiatric ambulance:

1) global triage models were analyzed as a theoretical framework, which were described in a previous publication by our team [3],
2) the paradigm under which each triage model was carried out and its possible adaptation to that of our country based on the concept of risk in accordance with the National Mental Health Law 26657/10 was critically analyzed,
3) those factors or criteria with possible application for the proposal in the psychiatric ambulance were detected and extracted.
4) cases of prehospital emergency interventions with psychiatric ambulance carried out by psychiatric medical professionals from our "Torcuato de Alvear" Psychiatric Emergency Hospital in the period between January 2018 and December 2021 were randomly studied.

The bibliographic review of Triage models published worldwide with high reliability were: the Australian [Australian Triage Scale -ATS- and the specific Mental Health Australian Mental HealthTriage Scale -AMHTS-] [4-8], Canadian [Canadian Emergency Department Triage & Acuity Scale -CEDT&AS-] [9-11], Spanish [Sistema Español de Triage-Modelo Andorrano -SET-] [12-15], Manchester [Manchester Triage System -MTS-] [16] and from the USA

[Emergency Severy Index -ESI-, Pre hospital Training Life Support -PHTLS- and Advance Training Life Support -ATLS-] [17-21]. To access an updated review, a search was performed using the terms "triage", "emergency" and "psychiatry "or"mental health "or" ambulance".

The study of prehospital emergency interventions with the psychiatric ambulance of our hospital was carried out through the evolutions carried out in the "Ambulance Duty Book". They were analyzed by 2 psychiatrists with experience in prehospital emergencies and a systematization grid was put together to standardize the most prevalent and significant characteristics of clinical presentations, the approach modalities carried out, and the effectiveness of the interventions. Based on these emerging clinical data in the emergency, the construction of a triage for this context began.

The triage proposal included the internationally used criteria related to time, the reason for the intervention, the clinical presentation and the proposed approach modality. Given the prehospital context in a psychiatric ambulance, the division into 3 levels was agreed upon and the risk paradigm was taken into account for its preparation in accordance with the National Mental Health Law 26657/10.

3. RESULTS

For the preparation of the present Mental Health Guard Triage proposal, 3 severity levels were implemented with the colors of the same name as a traffic light, which gives the image of severity or alert in the maximum range of severity.

Three criteria were applied: risk, reason for consultation with clinical presentation, and suggested modality of intervention to be carried out in the prehospital context of a psychiatric ambulance [Fig. 1].

All the criteria maintained correlation and concatenation with each other based on different clinical presentations of the patients in said context, which, although it is heterogeneous and subjective to each individual and the environment where it is located, the risk-based assessment makes possible its structuring.

The "risk" criterion was divided according to its severity and attentive to Law 26657 as well as to the factors that make up the risk (risky condition and vulnerability) in (from highest to lowest risk): certain and imminent for oneself and third parties, true, and without evident or insignificant risk for the last level.

In the criterion "reason for consultation / clinical presentation" the main pictures and their characteristic signology were nominated in a general way and as a guideline to be taken as a framework.

The "intervention modality" criterion was based on interdisciplinary strategies that, according to the evaluation of the team and according to the level, contemplate the application of specific protocols (psychomotor agitation and/or physical and mechanical restraint), the requirement of other effectors (police,

firefighters), call an ambulance from a medical clinic when there may be a decompensated basic clinical picture that has psychiatric manifestations and eventual transfer to a general hospital for interdisciplinary evaluation with involuntary hospitalization (level 1) or other strategies.

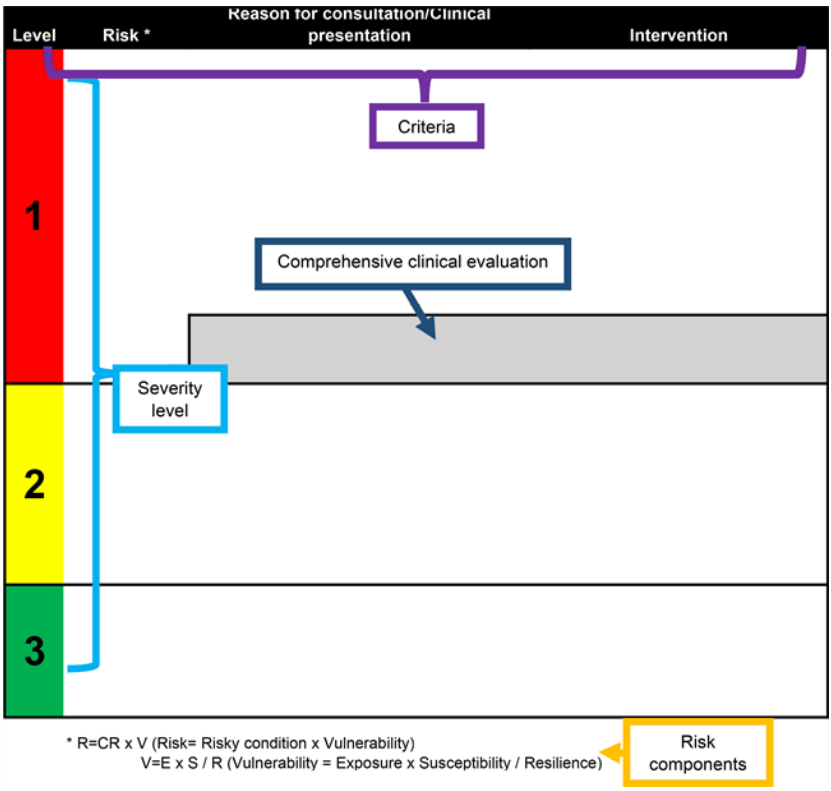


Fig. 1. Structure of the proposal triage

It was highlighted that, given the significant prevalence of comorbid substance use in patients with mental pathology that can trigger mental illness or in cases of chronic use of substances (at the level of use, abuse or dependence), for level 1 included a clinical and biochemical evaluation for those confusional pictures in order to rule out the toxicological cause, as well as metabolic or other organic causes that could alter clinical and pharmacological interventions. In these cases, it will be necessary to carry out biochemical, electrocardiographic and imaging studies, if necessary, in addition to a complete clinical evaluation.

Fig. 2 includes the Triage proposal for prehospital emergencies in a psychiatric ambulance.

Level	Risk *	Reason for consultation/Clinical presentation	Intervention
1	**Certain and imminent risk for oneself and third parties [↑↑ risky condition and ↑ vulnerability]**	Violent behavior, self-destructive or self-injurious behaviors, extreme agitation, and bizarre behavior. Endogenous Acute Psychotic Episode or due to substance use, psychomotor inhibition with catatonic risk. Autolysis attempts with high lethality. Suicidal ideation (with plan) Low or no ability to reflect on the problem in which he finds himself. Low or no recognition of the morbid nature of the behavior. Uncooperative patient.	1. If there is agitation or psychomotor excitement, comply with the "*Psychomotor Agitation Protocol* " and apply the "*Physical and mechanical Restraint Protocol* " if applicable. 2. Request Police and Fire Intervention if necessary 3. Request support from a medical clinic ambulance if applicable 4. **Referral to General Hospital** for interdisciplinary evaluation and hospitalization.
		Confusional and/or endogenous or exogenous pathologies related to metabolic and toxicological causes or other organic etiologies can explain the behavioral symptoms. **Referral to the General Hospital and assess the need for ambulance transfer from the Medical Clinic.**	
2	**Certain risk [risky condition or vulnerability]**	Ideas of death, references and manipulative demands, references to the death of relatives. Manipulative or low lethality self-injurious behaviors. Moderate capacity to reflect on the problem in which he finds himself. Moderate recognition of the morbid nature of the behavior. Uncooperative patient.	1. If there is agitation or psychomotor excitement, comply with the "*Psychomotor Agitation Protocol* ". 2. Request Police and Fire Intervention if necessary. 3. Referral to General Hospital for Interdisciplinary evaluation and to evaluate possible hospitalization.
3	**Non-significant or non-evident risk (no risk)**	Administrative issues. Orders for medication or prescription reinforcements. Judgment preserved. Lawsuits without risk. High capacity to reflect on the problem in which he finds himself. High recognition of the morbid nature of the behavior.	1.Give alarm and psychoeducation guidelines. 2. Referral at the discretion of the attending physician.

* R=CR x V (Risk= Risky condition x Vulnerability)
V=E x S / R (Vulnerability = Exposure x Susceptibility / Resilience)

Fig. 2. Triage proposal for pre-hospital emergencies in a psychiatric ambulance

We believe that in level 1 cases, and according to the assessment of the ambulance psychiatrist or the receiving interdisciplinary team in level 2 cases, they should be addressed by the general practitioner and the studies should be carried out as soon as the treatment ceases risk.

At all levels, a mixed assessment was included in the criterion "reason for consultation/clinical presentation": both objective and subjective. The objective one included the semiological description of behavioral alterations, while the subjective one is aimed at the evaluation by the professional team of the ability to reflect on the problem in which it is found and the recognition of the morbid nature of the behavior.

We emphasize that our triage proposal is not related to the triage models published in terms of the number of levels or the specificity of prehospital application in a psychiatric ambulance.

4. DISCUSSION

4.1 Triage Systems: Generalities, Proposals and Specificities

Triage is a French term applied by the medical sciences to classify, especially in emergency contexts. Triage implies "prioritizing", "classifying", "selecting" or "filtering", which is why it covers different behaviors tending to screen according to clinical needs, possibilities of approach and effectiveness of interventions, as well as organizing resources (material and human ones) in emergency contexts to achieve greater efficiency.

The actions included in the triage seek to direct care and resources towards those individuals who require immediate treatment due to the condition they present and clinical indicators of favorable response based on their clinical status, favoring them over those who suffer from symptoms of less serious or that due to their clinical and evolutionary state will not have benefits with the interventions.

The classification process can be carried out in a hospital or out-of-hospital setting. In both contexts, the same and vital importance is given, they complement and synergize in the cases of health systems with effectors from different levels of care [21,22] as is our case. In the particularity of our proposal, applying a pre-hospital triage carried out by a psychiatrist who performs her functions in the psychiatric ambulance will enhance and synergize the quality of the interventions.

The principles that support this procedure are the following:

- That the patient receives the level and quality of care according to the risk presented by the clinical picture.
- That the referral hospital be the appropriate one, attentive to the material and human resources necessary to address the patient's pathology, with less loss of time and resources,
- It supports the bioethical principle of Clinical Justice, whereby clinical efficiency must be based on appropriate care at the right time,
- Facilitate continuity of coordinated assessment and treatment,
- It falls within the legal regulatory framework and the ethical principles of the country of application.

Extra-hospital emergency triage begins with a telephone call to an Emergency Coordination or Regulatory Center, such as 107 or 911 in our City of Buenos Aires. There the urgency is assessed by sending a mobile with the relevant equipment, depending on the waiting time provided to the requirement and type of resource necessary to be used. Once the mobile arrives at home, the health team (driver and doctor) of pre-hospital care will carry out a new classification, being able to resolve the assistance on the spot or request a second on-site evaluation by specialized professionals (in the case of patients with mental disorders who attend a ambulance with a psychiatrist) or decide, based on the

degree of complexity assessed, referral to a care center. The destination of the referral is coordinated with the operating table, being in most cases the hospital in the area of the patient's residence (except in the case of need for specific assistance that exists only in certain centers). Once again at the hospital, the urgency will be reassessed and the procedure will be followed accordingly.

Although triage was generated and implemented in scenarios of massive demand secondary to catastrophes, wars or multiple emergencies, many work groups have applied it and use it in On-Call contexts that due to the increase in demand cannot be responded to for reasons of security. infrastructure or human or material resources. Triage models are generally designed in a classification of 5 levels of different severity that imply different clinical episodes (from mild to severe) and are related to the specification of a maximum clinical response time necessary to be treated, since otherwise the complications can be irreversible or life threatening. Usually colors are established for the 5 severity levels according to the possible delay: red, orange, yellow, green and blue level. This choice of colors is arbitrary and by consensus, its good symbolizes gravity very easily and clearly.

The application of triage in mental pathologies is based not only on the response time, but also on the resources that a device has to respond to them. In the particular case of prehospital ambulance emergencies, we consider it useful and that the scenarios (of the pathology and the environment) are propitious for the implementation of this type of strategy. Precisely because of the need for an operative and effective response, we consider the need for a triage based on 3 levels instead of 5, to operationalize its implementation and mindful that acute clinical presentations can be framed and classified in these 3 levels.

From the comparison with the triage models published worldwide, we found no relationship or association with them, given the specificity of the prehospital approach to mental pathology by a psychiatrist in an ambulance. In addition, its application is aimed at a technical or general medicine human resource and only two models (MTS and ATSMH) categorize and measure the risk of the condition (and not only strictly for life due to clinical-surgical issues), a concept of vital importance for our legal construct in the urgency that will determine conducts to follow in the case of the voluntary or not of the possible hospitalization. It is noteworthy that only one of the models was adapted for patients with mental pathology (the AMHTS); while the MTS, the CEDT&AS and the SET Andorran Model mention psychiatric symptoms but focus on the reason for consultation and not on the risk that this condition may entail. For these reasons, it is that the comparison of our triage proposal with that of the triage models analyzed would be wrong since their construction frameworks, and especially the means of application, are different and the comparison would generate biased results.

4.2 Risk: Concept and Assessment

One of the fundamental tasks in different fields (clinical care, work, education, forensic) is the prediction of human behavior [23]. The predictive task of being

able to see if a person may be at risk and contributes to making clinical decisions with legal impact.

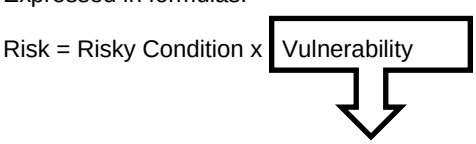
The previous legal paradigm that prevailed in our country was the evaluation of dangerousness (legal term that refers to the possibility, contingency or feasibility of generating or suffering damage that "has support over the existing one, implies "being" and has implications segregation [5,24,25]. In some countries, the term dangerousness was changed to “risk of violence” or “dangerous state”, which have no clinical logic or care applicability [26,27].

The risk refers to the proximity of damage, being exposed to a harmful event either actively or passively, as well as vulnerability to it, in this case it represents "being" and therefore constitutes an assessment situational according to Law 26657/10 on Mental Health.

According to the risk theory, risk has components that must be evaluated in the here and now, together with its previous and constitutional issues and factors (modifiable and non-modifiable) [7]. Risk is the combination of the probability that an event will occur and its negative consequences, and is subject to two variables: the risky condition and vulnerability.

For its part, the risky condition is a conduct or condition that can cause injury or some deleterious impact on health or material or other damage. Instead, vulnerability depends on the subjective characteristics of a person and the circumstances that may make him susceptible to harm. It is directly related to the exposure to it and the susceptibility of each person, and inversely with the resilience of the subject.

Expressed in formulas:



Vulnerability = Exposure x Susceptibility / Resilience

The risk assessment must also specify the nature of the hazard and the probability of its occurrence, as well as its frequency or duration, its severity and its consequences. In the same way, it should be taken into account that this is dynamic and contextual, that is, it can vary depending on the circumstances (24), so it is pertinent to reassess the risk with a certain periodicity to record these possible changes.

There are multiple factors that make evaluations more complex: biological, psychological, and social or environmental. These factors will not be determined in situ given the context of the emergency assisted by a psychiatric ambulance, but they will determine the place of referral of the patient. For example, among the biological factors are neurological and endocrinological alterations and

intoxications; the psychological ones are based on defensive and coping mechanisms, and the social ones are linked to the environment or cultural.

Among the factors, they can be divided into risk factors or protective factors. Risk factors are a variable that is positively and directly proportionally related to the certain and imminent risk of a person; protective factors refer to variables negatively linked to the risk situation, that is, inversely proportional to risk.

Together with the assessment, measures must be applied for its management, that is, the actions that are carried out to control a situation, contain or reduce the risk [24]. These management measures can be of 4 types: surveillance, supervision, treatment and planning for the safety of the victim.

The complete risk assessment in prehospital psychiatric emergencies by a psychiatrist in a psychiatric ambulance in situ where the behavior takes place in their environment should take into account all the factors described. The implementation of a triage for prehospital interventions by the psychiatric ambulance in accordance with current legal regulations will be of clinical utility, in the management of resources and in the prognosis of the condition in the emergency room.

This proposal for a triage system to be used in prehospital emergencies with a psychiatric ambulance constitutes a significant contribution since similar proposals have not been described or published. We emphasize that the present proposal in this scientific article arises from the clinical aspects experienced by psychiatric professionals from the only hospital specialized in psychiatric emergencies in Latin America, which also presents the characteristic of performing prehospital psychiatric care with a specific ambulance (in its equipment characteristics and professionals who work in it) on public roads, patients' homes or other institutions (health or not). These described characteristics constitute a limitation for its full implementation in other contexts or health networks as well as institutions, but it allows its adaptation in other contexts depending on the human or material factors available.

5. CONCLUSIONS

Mental pathology in emergencies is constantly growing, but its forms and methodologies of approach have not presented innovations to achieve greater effectiveness in interventions. The heterogeneity of the clinical presentations, added to the multiple contexts where it develops, provides a difficulty for the psychiatrist who attends to evaluate emergency cases at the prehospital level.

The classification by level of severity is scarce with the use of triage is scarce worldwide for these conditions, and in our country there are no proposals of this type.

We consider very useful the implementation of a triage model for the context of prehospital psychiatric emergency with ambulance that is framed in current legislation and in its spirit based on risk assessment.

This type of clinical management interventions will allow greater uniformity, criteria and homogeneity in the professional response, as well as systematize the interventions in order to improve the quality of care.

From the implementation of this proposal, a systematic evaluation every 6 months will be necessary to assess its usefulness in the context of the prehospital emergency clinic with a psychiatric ambulance.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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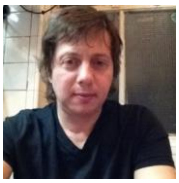

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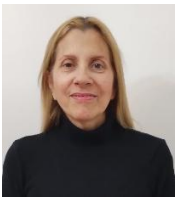

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Chapter 3
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Knowledge and Awarness of Use of Contraceptives among the Population in Rural Area of District Bareilly, Uttar Pradesh, India

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ABSTRACT

This chapter assess knowledge and practice of modern contraception in rural area of district Bareilly, Uttar Pradesh, India. The acceptance of contraceptive methods varies within societies and also among different castes and religious groups. The factors responsible operate at the individual, family and community level with their roots in the socio-economic and cultural milieu of Indian society. An important indicator for lowering maternal and neonatal morbidity and mortality is family planning awareness and proper contraceptive use. It is crucial for promoting the reproductive health of women in underdeveloped nations. This was a community based cross-sectional study conducted on 458 randomly selected eligible couples in a rural area of Bareilly.

A pre- structured questionnaire was used to collect information about knowledge of family planning methods, source of knowledge and current practices along with reasons of nonuse of contraception. Present study showed that main source of knowledge of contraceptive among study participant was health worker i.e. 90.83%, followed by mass media 75.33%, followed by doctors in multiple response answers. The appropriate statistical analysis was done to present the results.

It was observed that 48.03% eligible couples had adopted one or the other modern contraceptive measure. Female sterilization was the most common method used.

Women with less education need ongoing instruction and frequent communication about the significance of contraception. The results of this study will aid in the creation of programmes that will enhance knowledge and services while lowering negative effects and unintended pregnancies.

Keywords: Eligible couples; modern contraception; prevalence; family planning.

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1. INTRODUCTION

Knowledge as well as practice of contraceptives in women is used by the health organizations to assess family planning worldwide. Because of the lack of effective contraceptive options for men (only condoms, withdrawal methods and vasectomy), women nearly have all the responsibility for fertility regulation. Family planning deals with reproductive health of the mother, having adequate birth spacing, avoiding undesired pregnancies and abortions, preventing sexually transmitted diseases and improving the quality of life of mother, fetus and family as a whole [1,2]. India was one of the first countries to launch a national program on family planning. However, today, India is the second most populous country in the world, ranking next only to China, with a population of 1.21 billion according to the year 2011 census. The population of India is estimated to overtake that of China by the year 2050. Use of contraception prevents pregnancy-related health risks for women and children. When births are separated by less than 2 years, the infant mortality rate is 45% higher than it is when births are 2–3 years and 60% higher than it is when births are four or more years apart. Family planning offers a range of potential non-health benefits that encompass expanded educational opportunities and empowerment for women and sustainable population growth and economic development for countries [3]. Even though India has nearly 2.4% of the world's surface, it is home for more than 17.5% of the world's population. Family planning is the main strategy for prevention of unwanted pregnancies and thousands of maternal deaths and also offers a host of additional health, social and economic benefits. If these services were more widely available, up to 42 percent of maternal deaths could be prevented in developing countries. The mean proportion of maternal deaths that could have been averted was 24% as per study [4]. The contraceptive effect can be obtained through temporary or permanent means. Temporary methods include periodic abstinence during the fertile period, coitus interrupts (withdrawal), using the naturally occurring periods of infertility (e.g., during breastfeeding and postpartum amenorrhea), through the use of reproductive hormones (e.g., oral pills and long-acting injections and implants), placement of a device in the uterus (e.g. ,copper-bearing and hormone-releasing intrauterine devices), and interposing a barrier that prevents the ascension of the sperm into the upper female genital tract (e.g., condoms, diaphragms, and spermicides). Permanent methods of contraception include male and female sterilization [5].

2. STUDY METHODOLOGY

This was a community based cross-sectional study conducted on 458 randomly selected eligible couples in a rural area of Bareilly. Block Bhojipura was randomly selected from 15 blocks of district Bareilly. The data were collected for a period of one year from December 2016 to December 2018. After taking informed consent 458 enrolled eligible couples in the study were interviewed at their home after build up rapport and confidence. Their answer were noted in proforma of pre structured pretested questionnaire. These couples were asked questions to know about their knowledge and practice about contraception and the various methods

available thereof. They were counseled about various methods of family planning accordingly.

2.1 Sample Size Calculation

The contraceptive prevalence rate in western Uttar Pradesh was found to be 54.9 (SIFSA 2016) and taking this the sample size was calculated from the following formula [6]:

$$N = \frac{4pq}{L^2}$$

Where P is prevalence, for calculating sample size for our study P is taken as 54.9%,

Q is (100-P) = 100 - 54.9=45.1

L (absolute precision) as 5%,

$$N = \frac{4pq}{L^2}$$

$$= \frac{4 \times 54.9 \times 45.1}{5^2}$$

$$=396$$

Sample size after putting these values came out to be 396 after addition of 10% more for non-respondent, final figure was 436. After rounding of the figure, a sample size of 450 was taken for our study.

Sampling technique: Multistage random sampling method was used to select the requisite sample size.

2.2 Inclusion Criteria

Married couples whose wives were in the age group 15- 49 years residing in area more than 6 months and gave informed consent to participate in the study.

2.3 Exclusion Criteria

Married couples who refused to give consent to participate in study, divorced women/men, widows/widowers, guest residing in the family, women who had undergone hysterectomy, critically ill patient and bed ridden patients were excluded from study.

2.4 Data Analysis

The data collected were entered in Microsoft Excel and checked for any inconsistency. Data entered in the Excel spread sheet were statistically analyzed

by using IBM SPSS v 24.0.0. Categorical variables were analyzed using frequency with proportions and percentages.

3. RESULTS

In this study it was found that majority of women i.e. 150 (32.75%) were in age group of 25-29 years followed by 115 (25.11%) in the age group of 30-34 years. Mean age of women was 30.93 years in this study. It was found that 372 (81.22%) of participants were Hindus and remaining 82 (18.78%) were Muslims. Caste wise distribution of study participants revealed that majority 287 (62.66%) belonged to OBC category. 251 (54.80%) participants belonged to joint family and 207 (45.20%) to nuclear family. 169 (36.90%) women were illiterate and 173 (37.77%) women were educated up to Primary class.

Majority of women i.e. 79.26% were housewives, followed by unskilled workers (15.50%). Majority of husbands were unskilled worker i.e. 213 (46.51%) followed by skilled worker 105 (22.93%). 53.71% participants belonged to lower class i.e. about half of the participants followed by middle class i.e. 143 (31.22%) as per modified B.G. Prasad classification 2020.

Maximum numbers of women 440 (96.07%) knew about contraception. Female sterilization was the most common known method i.e. 414 (90.39%), followed by male condom 382 (84.50%). 346 (74.55%) study subjects knew about OCP while IUCD was known to 325 (70.96%) participants. Knowledge of traditional methods (LAM, rhythm, and withdrawal) was in 213 (46.51%) study subjects. Very few 18 (3.93%) participants had never heard about any contraceptive measures (Table 1).

Table 1. Distribution of participants according to knowledge of contraceptive methods

Contraceptive method	Number of respondents	Percentage
Oral pills	346	75.55
Male sterilization	343	74.89
Female sterilization	414	90.39
Injectables	209	45.63
Male condom	382	83.50
Female condom	0	0.00
IUCD	325	70.96
Traditional (LAM, rhythm, withdrawal)	213	46.51
Knowledge of any method	440	96.07
No knowledge of any method	18	3.93

In this study, the health workers contributed to 416 (90.83%) as the main source of knowledge for contraception followed by the mass media 345 (75.33%). The percentage for contribution by the doctors was 57.21% (Table 2).

Table 3 shows that out of total 458 participants, 251 (54.80%) were using both traditional and modern contraceptive methods and 220 (48.03%) were using only modern methods. Out of 251 (48.03%) current users, female sterilization was the most common method practiced 83 (37.73%) followed by male condom 72 (32.73%). 49 (22.27%) study subjects were using IUCD and 6.36% were using OCP. Very few of them preferred to use male sterilization method (0.91%). None of participants or their spouse was using injectables and female condom. Traditional methods were used by 6.77% of respondents at the time of study.

Out of 238 non contraceptive users, it was found that majority of the study subjects were not using any modern contraceptive methods due to fear of side effects (68.90%), 33.19% faced opposition from the family members. Husband opposition and breast feeding 33.19% and 22.69% respectively were the reasons for nonuse of contraception (Table 4).

Table 2. Distribution of participants according to source of knowledge regarding contraceptive methods*

Source of knowledge	Number	Percentage
TV/mass media	345	75.33
Magazine/newspaper	261	59.99
Friend/relative	24	5.24
Spouse	51	11.14
Health worker	416	90.83
Doctors	262	57.21

**(Multiple responses)*

Table 3. Distribution of study participants according to current uses of contraceptive methods

Contraceptive method	Current user	
	Number	Percentage
Oral pills	14	6.36
Male sterilization	2	0.91
Female sterilization	83	37.73
Injectables	0	0
Male condom	72	32.73
Female condom	0	0
IUCD	49	22.27
Total (modern contraception)	220	48.03
Traditional (LAM/rhythm/withdrawal)	31	6.77
Contraceptive (modern and traditional)	251	54.80

Table 4. Distribution of participants according to Reasons of non-use of contraception (n=238)*

Reasons	Number	Percentage
Fear of side effects	164	68.90
Want more children	46	19.33
Feel no need to use	39	16.39
Husband opposed	63	26.47
Family members opposed	79	33.19
Religious reasons	53	22.27
Health reasons	8	3.36
Economic reasons	0	0
Infertility	6	2.52
Breast feeding	54	22.69

**Multiple responses*

4. DISCUSSION

In present study knowledge of contraceptive methods was 96.07%. Female sterilization (90.39%) was most heard about method followed by male condom (84.50%), which is comparable to study by Jahan et al. where knowledge of contraceptive methods was 93.1% and OCP were most commonly heard methods (74.8%), condom (68.8%) and female sterilization (36.4%) [7]. According to NFHS III survey 2005-06, 98% of women knew one or more methods of contraception [8]. Female sterilization was the most widely known method among women (97%). A similar study done by Nair in where knowledge of contraceptive methods was 100% and knowledge about female sterilization was 94% followed by knowledge for barrier methods (70.2%), these differences may be due to demographic changes and characteristics of study participants [9]. Kripa et al. found that about 88% of the women knew that there are methods to prevent pregnancy whereas the rest were unaware of the idea of contraception, 79% of the patients were aware of Cu-T followed by female sterilization by 26% [10]. Dhupdale found that Knowledge of modern contraceptive was 95% [11]. 95% of the subjects were aware of condoms, 59% about oral pills, 53% about both CuT and sterilization and 22% about the injectable contraceptives. Srivastava et al. reported that 71.22% females had awareness regarding any method of contraception [12]. Most of women (95.8%) had knowledge about contraceptive methods in study by Wasnik et al. 2013 and Singh et al. who stated that more than 99% women in Varanasi city have heard about contraceptives and knew at least one method of contraception [13,14].

Present study showed that main source of knowledge of contraceptive among study participant was health worker i.e. 90.83%, followed by mass media 75.33%, followed by doctors in multiple response answers. Similar study was conducted by Nair where awareness was 100% regarding any method of contraception and the main source of information was health personnel [9]. Another study by Upadhayay reported that source of information were health worker (55%), hospital (48%), friends (44%) and newspaper (25%) [15]. Pegu et

al. found that knowledge about contraceptive methods was mainly obtained from health workers (58.6%) followed by media (24.1%) and social circle (15.5%) [16].

In contrast to study by Murugesan et al. social circle (49%) and health care providers (42%) played a major role as source of knowledge [17]. Ramaiah et al. found 64.1% of women got information from mass media, 20.9% from health personnel and 14.8% from social circle [18]. Shukla found that 91% had displayed an awareness of family planning method [19]. Out of 91%, about 78% had procured the information from family and friends and 13% got their information through mass media. Only 9% of women had been counseled in detail by health personnel. Jahan et al. observed that the most common source of information was mass media (53.2%) [7]. Chaudhary et al. observed that most common source of knowledge was the exposure to family planning messages (72.0%), followed by discussion with doctors and other health care staff [20]. Srivastava et al. reported that the most common source of information on contraception was mass media [12].

In presents study showed that 251 (54.80%) participant or their partners were using any form of contraceptive methods, out of which 48.03% were using modern methods of contraceptive and main reasons of use was completion of family. According NHFS-5 (2019-21) data contraceptive prevalence rate of India is 67% and for modern methods was 47.8% [7]. Another study by Jesha showed contraceptive prevalence rate of 48.95% [21].

In contrast to study by Gupta et al. contraceptive prevalence was higher than our study i.e. 70.6% [22]. Shukla et al. observed that 62.5% were using contraception [19]. In a study conducted by Jahan et al. showed the higher contraceptive prevalence rate 62.9% as compared to our study [7]. Kaushal et al. observed that 45.4% were current users of contraceptive methods [23].

It was seen in present study that use of contraception increases with age from 15-19 group (33.33%) to 20-24 year (50%) that is same up to 39 years and decreases by 40-49 age group (26%). Most preferred type of contraceptive use was female sterilization (37.73%) followed by male condom (32.73%), IUCD (22.27%), OCP (6.36%) and male sterilization 0.9%.

Male condom was preferred in Muslim communities in our study. In NHFS-4, total contraceptive use was 47.8% and female sterilization was (36%) that is near similar to our study and use of IUCD was 1.7%, which is higher in our study because in the year 2016-18 IUCD use rate increased and used as a long term effective methods and is also a results of PPIUCD promotion and target of GOI in hospital deliveries and incentive to ASHA and other trained provider [8].

In a study in Jammu, Gupta et al. found that 36.79% of females had chosen tubectomy as a contraceptive method followed by other methods of contraception like oral contraceptive pill and condom [22]. In contrast to study by Balgir et al. contraceptive prevalence was 53.84% where temporary methods were mostly used among user followed by 41.6% for condoms, 28.4% for OCPs and 8.0%

for IUDs, while permanent methods use was very low. Tubectomy and vasectomy which accounted for 4.23% and 1% respectively [24]. Jahan et al. observed that 62.9% had used at least one contraceptive method, three prevailing methods used were condom (65.1%), OCPs (31.8%) and IUCD (9.09) [7]. Jesha et al. observed that among 48.94% contraceptive users 26.9% had undergone sterilization, 47.5% were using Copper T, 13.5% used condoms and 11.9% used oral pills [21]. Pegu et al. observed that 38% of women were using any of the contraceptive methods, such as condom (38.2%) followed by oral contraceptive pills (27.6%), intra uterine contraceptive device (15.8%) [16]. Wasnik et al. found that 72.3% of the respondents were using contraceptives. Most commonly used contraceptive methods were oral contraceptive pills 43% and condom 31% [13]. Prateek found that contraceptive use rate was only 32.2%, out of these 89.66% women used temporary methods and 10.34% used permanent methods [25]. Chaudhary et al. observed that the tubectomy was the most commonly used method i.e. 32% followed by condom 30.5%, OCP 5.8% and IUD 4.3% [20]. Kumar et al. observed that about 53.40% adopted IUCD, 38.83% OC pills and only 7.77% of their partners used condoms [26].

In present study reasons for not using modern contraceptive was fear of side effect (68.90%). Other reasons were want of more children (19.33%), oppose of husband and family member was 26.47% and 33.19% respectively. Religious reason was 22.27%, 16.39% felt no need to use and health related issue was 3.36%.

Sudha et al. stated the most common reason for nonuse for contraception was fear of side effects, and others were infrequent sex, insisted by family members [4]. Another researcher Jahan et al. observed that reasons precluding women from practicing contraception were desire to have a child (60.5%), lack of knowledge (42.4%), and unbearable side effects (25.5%) [7]. Chaudhary et al. observed fertility related reasons (45.1%) were the main cause [7]. Murugesan et al. found that major reason of nonuse of contraception was desire of child (41%) and fear of side effects [17]. Lekshmi observed that majority i.e. 55.7% were not using family planning because of fertility related reasons. Top most reason for non-use of contraceptives responded was “husband out of home” (79.3 percent) [27]. Prateek et al. found that 21.3% participants were not using any contraceptive because they were afraid of the side effects of contraceptives [25]. Mahmood SE et al. 2019 observed that Respondents who were aware of EC (emergency contraception) first heard about EC from television (68.6%). Nearly a quarter of females had knowledge about EC. EC awareness was significantly lower among rural females (9.3%) than the urban (17.3%) females [28,29].

5. CONCLUSION

This study imparted an acceptable level of knowledge and positive practices among women seeking health care respect to birth control methods but overall usage of contraception was low need to focus at every step to contact with health facility or health workers. Because contraception and family-planning decision-making are almost always the responsibility of both partners, the involvement of

men in contraception knowledge issues is important. Females with lower levels of education require continued education and regular communication about the importance of fertility control. The findings from this study will help to develop programs that can improve knowledge and services and reduce adverse effect and unplanned pregnancies.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Chapter 4
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Fovea Saving Internal Limiting Membrane Surgical Approach to Safely Treat Myopic Foveoretinal Detachment

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ABSTRACT

This chapter describes the microstructural and functional results of three highly myopic eyes that underwent macular surgery for myopic foveoretinal detachment (FRD).

High myopia is a major cause of legal blindness in industrialized countries. In the United States, it affects nearly 2% of the general population aged 12 to 54 years. Up to 34% of patients with pathologic myopia (PM) have myopic foveoschisis (MF), the first stage of myopic traction maculopathy (MTM), which naturally progresses to form FRD or macular holes (MHs) with or without macular hole retinal detachment (MHRD) in highly myopic eyes.

Three highly myopic patients (age = 52.3 ± 11 years) with significant vision loss were evaluated by an ophthalmologist and underwent preoperative examinations. We retrospectively reviewed symptomatic eyes that underwent successful fovea-saving internal limiting membrane peeling (FSIP) macular surgery for chronic myopic FRD at the Retina Department of Oftalmologia Integral ABC, Mexico City, Mexico. We performed postoperative multimodal microstructural and functional evaluations including spectral domain (SD) and swept source (SS) optical coherence tomography (OCT), autofluorescence evaluation, and automated microperimetric macular examination.

In this report, despite surgical reattachment of the FRD within the first months, chronic separation of the photoreceptors and the presence of stagnant SRF in contact with the retinal pigment epithelium (RPE) were considered causes of photoreceptor damage. There was a substantial difference between the best-corrected visual acuity (BCVA) before and after surgery in all three cases. Surgery was associated with significant improvement in visual acuity, as confirmed using a paired-sample permutation test. The mean presurgical BCVA value (LogMAR; mean ± SE) was 0.83 ± 0.15, and the postsurgical value was

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0.43 ± 0.52 (p = 0.00065). The MF/FRD evaluation was 7.3 ± 3.5 months, with a mean postoperative follow-up time of 14 ± 4.08 months. At postoperative follow-up, postoperative multimodal imaging revealed an abnormal microstructural foveal SS-OCT pattern without signs of MH development. Using a stable central foveal fixation site and an anomalous retinal sensitivity analysis map, macular microperimetry confirmed subclinical reduced macular threshold sensitivity. Suble atrophic changes in the retinal pigment epithelium (RPE) were detected using autofluorescence imaging. Despite the successful microstructural disappearance of the myopic macular detachment, the last multidisciplinary functional and structural assessment demonstrated different subclinical macular alterations.

Keywords: Autofluorescence; automated microperimetry; myopic foveoretinal detachment; myopic foveoschisis; myopic macular hole; myopic traction maculopathy; posterior staphyloma; choroidal vascularity index; macular hole retinal detachment.

ABBREVIATIONS

3-D : Three-dimensional;
ATN : Classification system for myopic maculopathy including atrophic (A), tractional (T) and neovascular (N) components;
BBG : Brilliant Blue G;
BCVA : Best-corrected visual acuity;
ELM : External limiting membrane;
CVI : Choroidal vascularity index;
ERM : Epiretinal membrane;
FSIP : Foveal saving internal limiting membrane peeling;
FRD : Foveoretinal detachment;
ILM : Internal limiting membrane;
LA : luminal area;
LogMAR : Logarithm of the minimum angle of resolution;
ME : Myopic eye;
MF : myopic foveoschisis;
MH : Macular holes;
MHRD : Macular hole retinal detachment;
MTM : Myopic traction maculopathy;
OCT : Optical coherence tomography;
PM : Pathological myopia;
PS : Posterior staphyloma;
RPE : Retinal pigment epithelium;
RS : Retinoschisis;
SCA : Stromal choroidal area;
SD : Standard deviation;
SD : Spectral domain;
SS : Swept-source;
TCA : Total choroidal area;
VD : Vessel density;

1. INTRODUCTION

Pathological myopia (PM) is the fifth leading cause of low vision or blindness in Japan, and the second leading cause among people aged > 40 years in China. A progressive increase in axial length due to alterations in scleral connective tissue, together with the presence of epiretinal membranes (ERMs) and vascular rigidity, gives rise to early tractional changes, resulting in myopic foveoschisis (MF) followed by an advanced and progressive form of myopic foveoretinal detachment [1]. It is estimated that 50% of the world's population will develop myopia by 2050 (approximately 10% of high myopia cases) [2,3]. Myopic macular degeneration is a vision-threatening condition generally associated with high myopia, comprising diffuse or patchy macular atrophy, with or without lacquer cracks and Bruch's membrane defects. High myopia, a common cause of visual loss, can lead to blindness. High myopia is linked to PM, which is characterized by gradual deterioration of chorioretinal tissue caused by the development of posterior staphyloma (PS) and scleral elongation. These pathological myopia symptoms are in line with chorioretinal atrophy, choroidal neovascularization, and slow-moving tractional schisis-like foveomacular thickening [2,4]. Highly myopic eyes with macular myopic foveoschisis (MF) and myopic foveoretinal detachment (FRD) naturally develop partial- or full-thickness myopic macular holes (MHs) and myopic macular hole retinal detachment (MHRD) in the advanced stages of this condition [5].

Currently, an anteroposterior axial length ≥ 26.5 mm or more is considered indicative of high myopia. Other macular changes are associated with highly myopic eyes (MEs), such as ruptures in the Bruch's membrane and macular atrophy in the absence of macular pigments. PM can be complicated by PS [2]. Earliest-stage myopic traction maculopathy (MTM) has recently been reported as tractional elongation of the Henle fiber layer, also known as MF, which remains connected by Muller cells rather than splitting the retinal layers [3] (indicated by white asterisks in Figs. 1(a)–(c)), has a thin foveal center inner wall (roof) (Fig. 1(a), white arrow), and involves structural schisis-like thickening around the inner and outer layers of the retina (Fig. 1(a) and Fig. 1(c), red arrows). The vitreoretinal relationship is shown in Fig. 1(c) with green arrows. This phenomenon has a 66.12% prevalence in women [6,7]. Reduced thickness of individual collagen fibers, scleral thinning, and localized ectasia have been observed in postmortem MEs [8]. This entity was described by Panozzo and Mercanti in 2004 [6] as MTM, and optical coherence tomography (OCT), a noninvasive optical imaging technique, was used to characterize the elusive full spectrum of macular changes, including vitreomacular traction or ERMs, retinal thickening, retinoschisis (RS), and partial- or full-thickness MHs, which cause rhegmatogenous retinal detachment (RD). Posterior cortex remnants, rigidity of retinal vessels, and choroidal thinning have been identified as contributors to traction and degenerative changes [3]. Although the cause of foveoschisis is not completely understood, tractional forces might play a crucial role in its pathogenesis, particularly when combined with the progressive development of PS and subsequent stretching of the posterior retina [9,10]. Shimada et al. [11] classified and structurally defined MF using the spectral domain (SD-OCT). The

slow evolution of MF progresses to foveoretinal detachment (FRD) and MH, with or without RD in more severe cases, resulting in vision reduction. MF can be detected in up to 34% of eyes with PS and PM [3,6,7,8,10-16]. Pathologic scleral thinning [17], combined with subsequent progressive scleral ectasia formation, contributes to the stretching of critical retinal tissue in the macula [15-17]. There are few long-term functional results for foveoschisis; therefore, we mainly used visual insight to evaluate the changes in postoperative vision. Furthermore, vision quality is also affected by central retinal sensitivity, that is, we aimed to determine the structural swept-source (SS-OCT) and functional outcomes in FRD that were successfully surgically treated with the fovea-saving internal limiting membrane peeling (FSIP) technique.

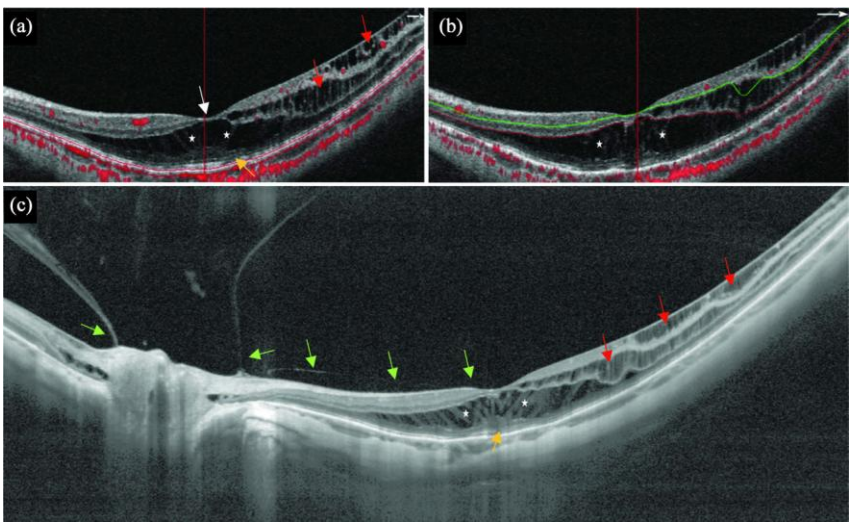

Fig. 1. Myopic foveoschisis in a highly myopic eye

(a) High-definition (HD) image showing a 9 mm horizontal B- scan of myopic foveoschisis (MF) and a very thin foveal roof (white arrow). Inner and outer macular schisis-like thickening temporal to the fovea (red arrows), tractional elongation of Henle's fiber layer (white asterisks). Subfoveal outer retina layer biomarkers show discontinuities and reflectance alterations (dark yellow arrow), and the red dots indicate the corresponding choroidal and retinal vessels. (b) Panel with image of the same MF with tractional elongation of Henle's fiber layer (white asterisks); inner and outer schisis-like thickening sublayers are well identified by the segmentation red and green lines, and red dots correspond to choroidal vessels. (c) Enhanced HD Line 12 mm image of avery elevated stage 1 myopic foveoschisis-related myopic tractional maculopathy (white asterisks). Inner and outer retinalayer macular foveoschisis (red arrows) is clearly shown temporal to the central thin fovea. Posterior cortical hyaloidal condensation is seen nasally and running toward the fovea, still attached to the peripapillary region (green arrows); the subfoveal outer retina layer shows ellipsoid zone discontinuities and hyporeflectance alterations (dark yellow arrow)

This chapter expands on previous related publications that include eyes with FRD and elaborates on the final anatomical and functional outcomes in operated eyes, in which FRD was completely resolved after macular surgery. Because of the significance of timely detection of visual changes in patients in the early stages of this condition, we consider writing a complete chapter dedicated to the early stages of this myopic tractional pathology of utmost importance [5].

2. CASE-SERIES REPORT/CASE PRESENTATION

2.1 Examination

Three patients (age = 52.3 ± 11 years) with significant vision loss were evaluated by an ophthalmologist and underwent preoperative examinations. Preoperative microperimetry was not performed because of the presence of submacular fluid in the patients with symptomatic myopic FRD. Preoperative horizontal microstructural imaging of the macular region was performed using SD-OCT (Ret-vue-3.4 OCT; Optovue Inc., Fremont, CA, USA). Coherence laser interferometry was used to measure axial lengths (Zeiss IOL Master 700; Carl Zeiss Meditec AG, Oberkochen, Germany). Ultrasonography (Ultrasound Unit; Quantel Medical, Du Bois Loli, Auvergne, France) was used to perform scleral and vitreoretinal relationship mapping to confirm the diagnosis of PS in all the eyes. SD- OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) and SS-OCT Triton equipment (Topcon Medical Systems, Inc., Oakland, NJ 07436) were used to perform postoperative microstructural evaluation and autofluorescence imaging testing.

To perform automated macular microperimetry, a non-mydriatic confocal scanning laser ophthalmoscope (MAIA Confocal Microperimeter equipment from CenterVue, Fremont, Ca 94539 USA) fundus imaging examination device was used with 37 data measurement points over a 10° diameter area with a Goldman III size stimulus, low background luminance, and maximal light stimulus in the 36-decibel range (candela per square meter (cd/m^2)). Furthermore, the assessment of foveoretinal sensitivity (FRS), macular retinal sensitivity (MRS), fixation location pattern (FLP, also called preferred retinal loci (PRL)), and fixation stability pattern (FSP) was performed by tracking eye movements at 25 times/s. Eye movement distribution over the ophthalmoscope image was plotted using scanning laser vision. The site depicting PRL was assigned a dot for each movement.

2.2 Surgical Procedures

A three-port pars plana vitrectomy (PPV) technique was performed by an experienced retinal surgeon (MAQR) in three eyes under local anesthesia. A cannula with silicone tape (25-gauge and 2-mm soft tip) and active suction were used to remove the cortical vitreous from the retinal surface assisted with triamcinolone acetonide (Kenalog 40 mg/mL, Bristol-Myers, USA). Surgical macular evaluation was performed using an ophthalmic solution (0.15%) of

trypan blue (Membrane Blue TM 0.15%, Dutch Ophthalmic, USA) and 0.10 mL Brilliant Blue-G (BBG) at 0.25 mg/mL ($C_{47}H_{48}NaO_7S_2$) to facilitate the manipulation of the stained ILM, complemented with 25-G three-port PPV equipment (Constellation Vision System, Alcon Laboratories, Inc., USA) with a cut rate of 7000/CPM, fine grasping vitreoretinal Tano ILM forceps (24-G, Alcon Laboratories, Inc., USA), and a 25-G membrane scraper, assisted with a 25-G Finesse microinstrument (Grieshaber®. Alcon Laboratories, Inc., USA) with high surgical precision for ILM flap manipulation. At the end of the procedure, a bubble of perfluoropropane gas (15%) was used as long-lasting tamponade.

2.3 Clinical Case 1

In this case, a 65-year-old female patient suffered from aggravated symptomatic metamorphopsia, severe myopia, and progressive central vision loss in her right eye, and both eyes exhibited PS. Fig. 2a illustrates the right eye with an axial length of 28.92 mm, which underwent surgery due to a one-year history of structural FRD with distorted vision, depicted using yellow arrows in the figure. The patient's preoperative best-corrected visual acuity (BCVA) was 20/200 (1.00 logMAR). The eye underwent 25-gauge PPV using the FSIP surgical technique. Using perfluoropropane (15%), tamponade fluid–air–gas exchange was performed. After 19 months, SS-OCT imaging and longitudinal follow-up revealed a flat macula without evidence of FRD (Figs. 2(a1) and 2(a2)). Recovered outer retinal OCT biomarkers are depicted in Fig. 2(a1) and 2(a2) using a dark yellow arrow, and superficial retinal dimpling superior and temporal to the fovea are depicted in Fig. 2(a1) and 2(a2), respectively, using white arrows. The thin retinal pigment epithelium (RPE) over the macula did not show any postoperative deterioration on autofluorescence imaging (Fig. 2(a3)). The microperimetry control-examination images are shown in Fig. 3(control), 3(a), and 3(b).

Microperimetry showed a stable FSP, and the FLP was documented as foveocentral, as shown in Fig. 3(a1) and 3(a2). The final long-term postoperative SS-OCT image is shown in Fig. 3(d), showing no recurrence of FRD or progression to MH. postoperative BCVA was approximately 20/25 (0.01 logMAR).

2.4 Clinical Case 2

In this case, a 46-year-old woman with three months of persistent, disabling metamorphopsia, troublesome, and high myopia underwent standard 25-gauge three-port PPV followed by macular surgery on her phakic right eye for a very symptomatic focal and well-defined FRD, as indicated in Fig. 2(b) with a yellow arrow and persistent hyaloidal macular traction (green arrow). The inner retinal schisis-like thickening of the foveoschisis is depicted in Fig 2(b) by the red arrow. Her outer retinal layer biomarkers were distorted with localized subfoveal FRD, as depicted in Fig. 2(b) using a yellow arrow.

The patient underwent macular surgery using the BBG dye-assisted FSIP surgical technique and perfluoropropane long-acting non-expandable gas tamponade (15%). The preoperative BCVA was 20/100 (0.7 logMAR), with a shallow PS (data not shown) and an axial length of 27.7 mm. The final postoperative BCVA was 20/25 at the 14-month follow-up (0.10 logMAR). Postoperative structural OCT evaluation showed a resolved FRD, as depicted in Fig. 2(b1) and Fig. 2(b), released hyaloidal traction, a flat macula with a good foveal and macular profile, and evidence of superficial dimpling on en-face examination, as depicted in Fig. 2(b1) and Fig. 2(b2). The autofluorescence in this phakic eye showed some media lens-induced opacity and evidence of dissociated optic nerve fiber layer (DONFL) defects induced by ILM removal. The autofluorescence image shows only mild peripapillary pigment atrophy without evidence of foveal RPE alteration (Fig. 2(b3)). The microperimetric evaluation results were within the normal range, as shown in Figs. 3(b1) and 3(b2). The final SS-OCT image is shown in Fig. 3(e).

2.5 Clinical Case 3

In this case, a 49-year-old woman presented with aggravated symptomatic metamorphopsia in the right eye for more than seven months, accompanied by progressive vision loss. The myopic spherical equivalent was -22.90 diopters. The preoperative BCVA was approximately 20/120 (0.80 logMAR) with normal applanation intraocular tension (10 mmHg). An axial length of 30.76 mm and deep central PS were observed on fundus photography (data not shown), fundoscopy, and SS-OCT. Preoperative spectral-domain (SD)-OCT findings were consistent with ERM proliferation (Fig. 2(c), green arrows). Foveal detachment with a remarkable amount of central submacular fluid is depicted by yellow arrows in Fig. 2(c). Red arrows indicate schisis-like macular thickening. Macular surgery was performed using the FSIP. Owing to the patient's refractory FRD and increased foveal symptomatology, a second round of surgery was performed using BBG dye guidance to distinguish between epiretinal and ILM residues. Finally, air-fluid exchange with a mixture of octafluoropropane gas (15% non-expandable concentration) was safely performed. On crossline, vertical, and horizontal SS-OCT B-scan postoperative evaluations, no clinical evidence of residual macular ERM proliferation was observed on the superficial aspect of the macula (Fig. 2(c1) and 2(c2)). The foveomacular region remained attached at the 9-month last evaluation visit, with a BCVA of 20/40 (0.30 logMAR). Some vitreous cortical remnants inferior to the fovea were identified (Fig. 2(c1), green arrow) with localized DONFL defects temporal to the fovea (Fig. 2(c2), white arrow). Autofluorescence imaging revealed peripapillary and extrafoveal areas with well-defined hypoautofluorescence and faint foveal hypoautofluorescence with a mild surrounding halo of hyperautofluorescence (Fig. 2(c3)). Retinal sensitivity assessment confirmed abnormal macular sensitivity with a mild decrease in foveal threshold sensitivity, as shown in Fig. 3(c1) and 3(c2). The final long-term SS-OCT structural evaluation is shown in Fig. 3(f).

Table 1 summarizes the preoperative and postoperative structural and functional findings of the three eyes.

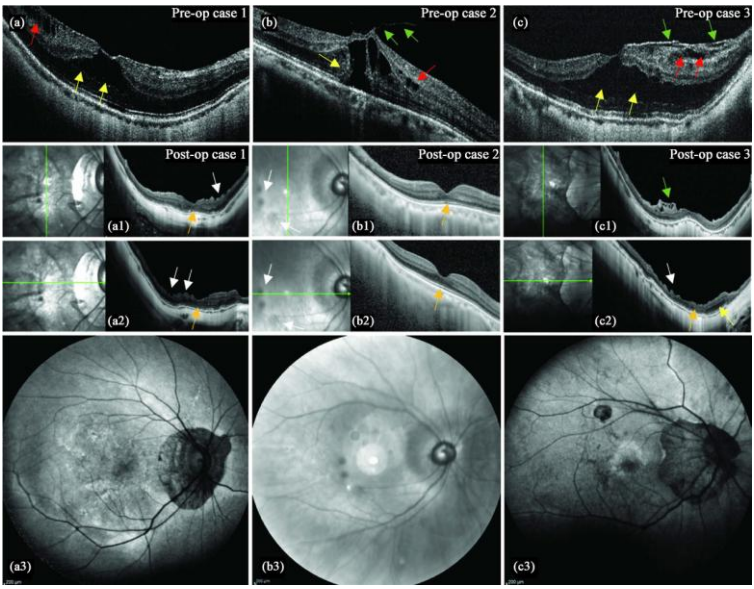

Fig. 2. Comparative preoperative and postoperative structural findings

The upper row shows the preoperative microstructural findings on the magnified SD-OCT horizontal B-scan image evaluation of the three highly myopic eyes.(a) Case 1 shows diffuse schisis-like inner retinal thickening (red arrow). There is some schisis-like outer retinal thickening nasally with extensive foveoretinal detachment (FRD) beneath the thinned fovea (yellow arrows) and a disrupted subfoveal EZ. (b) Case 2 shows vitreomacular traction (green arrows), schisis-like inner and outer foveal thickening of the fovea (red arrow), and localized tractional FRD with a disrupted subfoveal EZ (yellow arrow). A very shallow posterior staphyloma (PS) was detected in this patient's eye (not shown). (c) Case 3 shows an epiretinal macular membrane (ERM) (green arrows), with internal schisis-like thickening (red arrows), thinning of the foveal tissue, and deep FRD (yellow arrows). A disrupted ellipsoid zone (EZ) as well as a deep and irregular PS were detected in this case (partially shown). The postoperative swept-source OCT (SS-OCT) vertical and horizontal B- scans are displayed in the vertical columns. The left vertical column depicts Case 1 . (a1) The vertical B-scan through the fovea (green vertical line) depicts a recovered foveal contour, normal subfoveal EZ, thinning of the inferior retina, andlocalized DONFL defects superior to the fovea (white arrow). (a2) The horizontal B-scan (green horizontal line) depicts a residual ERM and localized DONFL defects temporal to the fovea (white arrows); the subfoveal EZ is preserved (dark yellow arrow). (a3) This panel image depicts very mild central hypoautofluorescence due to a thin RPE over the macula. The central vertical column shows Case 2. ((b1), (b2)) Crossline vertical and horizontal SS-OCT B-scans depicting a normal foveal contour, normal thickness of the sensorial macula, well-defined EZ, and some superficial retinal dimpling on the en face image (white arrow). (b3) Autofluorescence in this phakic eye shows only mild peripapillary pigment atrophy without evidence of foveal RPE alteration. The right column shows Case 3. (c1) The vertical B-scan depicts anirregular foveal contour, mild ERM, and hyaloid remnants inferior to the fovea (green arrow), with a well-preserved EZ. (c2) The horizontal B-scan shows an irregular foveal contour, residual schisis-like thickening nasalto the fovea (yellow arrow), mild ERM with a well-preserved EZ (dark yellow arrow), and localized DONFL defects temporal to the fovea (white arrow). (c3) This image depicts extrafoveal areas of well-defined hypoautofluorescence and mild foveal hypoautofluorescence with a mild surrounding halo of hyperautofluorescence. The images in this modified multipanel figure were originally published in Int J Ophthalmol Clin Res 8:132 and were used under the CreativeCommons Attribution 4.0 International License (https://creativecommons.org/b/4.0)

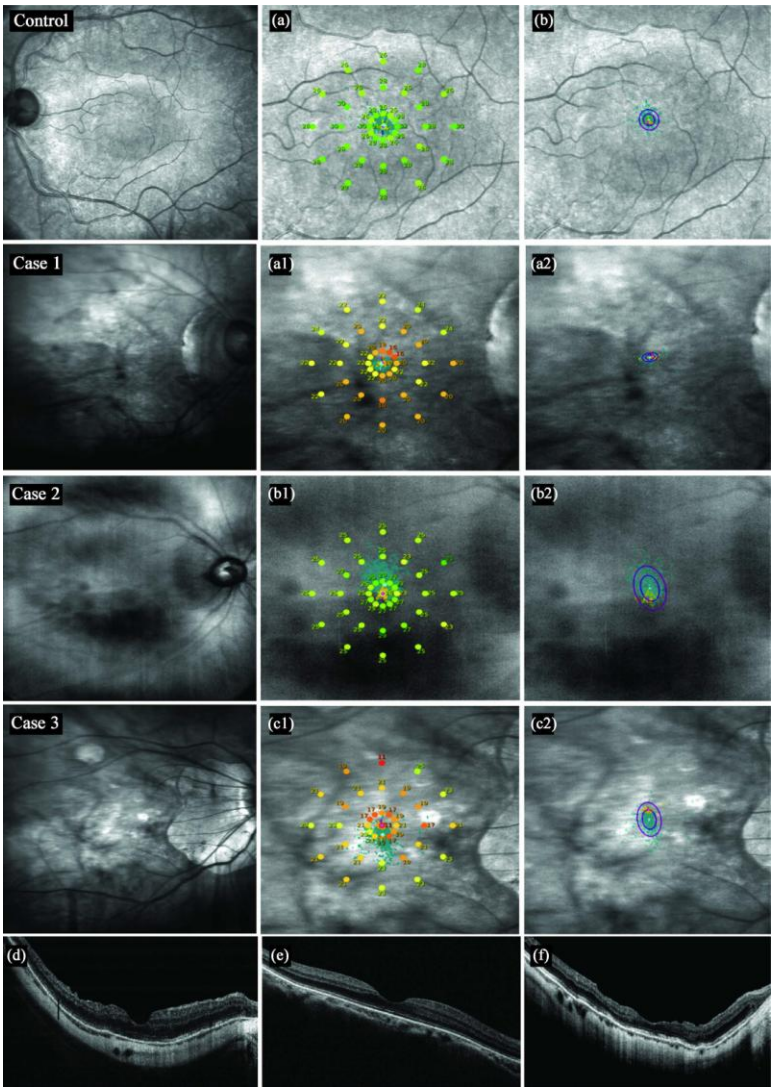

Fig. 3. Microperimetry and corresponding SD-OCT
(control, (a) and (b)) The microperimetry images in the upper row correspond to a healthy moderate myope patient. ((a1), (b1), (c1)) The retinal sensitivity analysis map indicates ill-defined macular integrity with a low macular threshold for all three patients ((a2), (b2), (c2)). In all three eyes, the fixation pattern was determined to be central, and the fixation stability pattern was stable. ((d)–(f)) Last SS-OCT structural evaluation of three cases. The images in this modified multipanel figure were originally published in Int J Ophthalmol Clin Res 8:132 and used under the Creative Commons Attribution 4.0 International License (https://creativecommons.org/b/4.0)

Table 1. Summary of preoperative and postoperative structural and functional findings

Findings	Case 1 (65 F)	Case 2 (46 F)	Case 3 (49 F)	Observations
Evolution of FRD	12 months	3 months	7 months	Mean = 7.3
Follow-up	19 months	14 months	9 months	months Mean = 14.0
Preoperative BCVA	LogMAR 1.00 (20/200)	LogMAR 0.70 (20/100)	LogMAR 0.90	months
Postoperative BCVA	LogMAR 0.10	LogMAR 0.10 (20/25)	(20/160) LogMAR	Snellen
Preoperative SD-OCT	(20/25) FRD+ERM	FRD	0.30 (20/40) FRD+ERM	equivalent
Axial length	28.92 mm	27.70 mm	30.76 mm	Mean 29.12 mm
CSFT Foveal contour	Less than 180 µm Disrupted	Up to 220 µm Recovered and preserved	Less than180 µm Disrupted	
ERM	No	No	Mild, inferotempo ral to the fovea	
Residual SRF	No	No	Residual nasal to fovea	
Residual foveoschisis	No	No	Nasal and extrafoveal	
Subfoveal EZ	Mild disruption	Preserved	Moderate disruption	
RPE changes	Faint central atrophy	Not detected	Mild central atrophy	
DONFL defects (dimples)	Isolated dimples	Mild dimples on En-face OCT	Not detected	
MRS	Reduced	Normal	Reduced	
FRS	Mild reduction	Normal	Deeply reduced	
FSP	Stable	Stable	Stable	
FLP (PRL)	Foveocentral	Foveocentral	Foveocentra l	
RSAM	Abnormal	Recovered to normal	Depressed abnormal	

BCVA, best-corrected visual acuity; SD-OCT, spectral-domain optical coherence tomography; SRF, subretinal fluid; CSFT, central subfoveal thickness; EZ, ellipsoid zone; ERM, epiretinal membrane; DONFL, dissociated optic nerve fiber layer; FRD, foveoretinal detachment; MRS, mean retinal sensitivity; FRS, foveoretinal sensitivity; FSP, fixation stability pattern; FLP, fixation location pattern; PRL, preferred retinal loci; RSAM, retinal sensitivity analysis map

3. DISCUSSION

We performed vitrectomy using the FSIP technique in three consecutive, symptomatic, and high MEs with FRD. Postoperative structural and functional evaluations were performed in all three cases. Although none of the patients developed MH, one patient demonstrated evidence of mild extrafoveal epiretinal membrane re-proliferation regardless of modified foveal-saved ILM removal in an updated manner. Evidence of a significant reduction in macular sensitivity was demonstrated by the results of functional evaluation. Automated microperimetry showed stable fixation and central location patterns in all three eyes. Two eyes showed subclinical evidence of reduced retinal sensitivity and abnormal retinal sensitivity in the analysis map, which correlated with postoperative BCVA.

Panozzo and Mercanti [6] concluded that macular reflattening can be facilitated by releasing epimacular and vitreous traction in the early stages of MTM, which prevents the development of MH orRD.

Shimada et al. [14] prospectively reported progressive macular thickening as a sign of the progression to foveomacular retinoschisis and FRD. Although the progression of foveomacular retinoschisis to MH formation has been reported recently, the myriad pathogenic properties, especially in the early stages of MTM, are still not well understood; therefore, we speculated that early stage detection of structural signs of the disorder in symptomatic eyes may improve surgical outcomes. Patients with early stage MTM, particularly MF, are among the least symptomatic when presented to retinal specialists. This kind of early stage might persist for a long time, with chronic subclinical progression before macular function is substantially impaired [13]. This observation confirms the proposal of Takano and Kishi in their classical study [12] and others [16,18] regarding MF occurrence at an earlier stage or as a direct precursor lesion followed by its development into FRD. Moreover, Uchida et al. [15] showed that during follow-up, 80% of eyes (n = 10) progressed to FRD, followed by the development of partial- or full-thickness MH. Hayashi et al. [19] evaluated 806 eyes of 429 patients (34% male and 66% female). It was confirmed that the progression of foveomacular retinoschisis to FRD occurred in approximately 41.0% of eyes, and progression into partial-thickness MH in approximately 20.70% of eyes. Initial findings, such as thickening of the outer retinal layers with tissue irregularities, were associated with the development of a partial-thickness macular defect associated with shallow focal FRD, which elevates the upper edge of the macula, leading to enlargement of the localized FRD [18,19].

Baba et al. [20] reported an incidence of up to 9% in eyes with high myopia and PS, which eventually developed FRD. According to previous studies, these malformations can be treated with vitrectomy, posterior hyaloidal removal, ILM stripping, or gas tamponade [13,16,21-23].

Currently, revised techniques, such as long-term gas with the FSIP surgical technique, are accessible for both primary and refractory cases, subsequently resulting in foveal reattachment and substantial visual improvement [24].

However, there are inherent risks associated with ILM removal, including thinning of superficial retinal layers, tiny superficial retinal holes, dissociated optic nerve fiber layer (DONFL) defects, and partial- or full-thickness MH formation.

Shimada et al. [25] attempted to avoid these risks in eyes with FRD using a modified technique called the foveal-sparing technique. They found that none of the eyes developed MH when this technique was used. Up to 16.7% of eyes progressed and finally developed full-thickness MH after total classical removal or non-sparing ILM removal [24,26]. Thus, progression to FRD may be indicative of poor prognosis leading to MH formation [13,18,21,24,16,27].

Herein, we report a case series of three eyes with symptomatic FRD. The best postoperative final logMAR vision was obtained using long-acting gas with the FSIP technique, with no MH development observed during the follow-up. An almost normal postoperative SS-OCT pattern was observed in only one eye, and the observed postoperative visual improvement in three eyes with FRD was substantial. One limitation of this report is that no standardization or correlation of the most important OCT biomarkers with functional results was available and postoperative multifocal electroretinography (mfERG) evaluation was lacking. Therefore, this study can only be empirically used to correlate functional results until an international and standardized SD-OCT biomarker classification is established. These biomarkers suggest that defects, including unusual foveal contours, ELM line disruptions, segmented RPE, DONFL defects observed on en face imaging, and subfoveal EZ disruptions, may be tomographic prognostic indicators of vision. However, the effect of these tomographic microstructures, their reactive recovery to surgical procedures, and their potential correlation with the final postoperative BCVA are unknown.

The appearance of DONFL defects may be a result of ILM removal, as discussed by Alkabes et al. [28]. However, in comparison with automated microperimetry and mfERG, its effect on macular function remains unclear. Huang et al. [29] considered myopic FRD one of the most crucial postsurgical risk factors for developing macular hole retinal detachment (MHRD) in MTM. In contrast to their findings, Al-Badawi et al. [27] recently reported a prospective study in which there was no difference in the development of MHRD when ILM was completely removed using the total classical technique, which was comparable to the results of theFSIP technique [16,25,26,29].

The FSIP technique inhibits the proliferation of epiretinal macular membranes and hypothetically halts the progression of RS and FRD to MH by reducing ILM rigidity [25,26,29]; However, other complications such as macular atrophy, lamellar holes (partial-thickness MH), and thinning of the inner layers of the retina have been previously described [29]. It is worth noting that the preoperative presence of FRD constitutes a risk factor for the development of MHRD [29]; However, a timely and uneventful surgical technique resolved macular traction, flattening the FRD without progression, as described in this chapter. Likewise, many novel surgical methods have recently been proposed for unexpected complications of postoperative MH, including autologous

neurosensory retinal-free patch transplantation [30], lens capsular flap transplantation [31], ILM repositioning with autologous blood [32], and inverted ILM insertion [33].

In this report, despite surgical reattachment of the FRD within the first months, chronic separation of the photoreceptors and the presence of stagnant SRF in contact with the RPE were considered the causes of photoreceptor damage. As shown in two eyes, abnormal structural SD-OCT findings correlated with macular regions that were abnormal on automated microperimetry. Thus, the retinal origin of the defect was highly certain. Eye movements and changes in retinal fixation can be overcome with microperimetry, which provides accurate retina-related sensitivity data. The strength of this study is that it is among the first to evaluate the functional and anatomical results in a series of three patients with high MEs who underwent the FSIP surgical technique using the best-known biomarkers to correlate functional results. However, this study has some limitations because the only functional evaluations available preoperatively were BCVA and Amsler tests. Additionally, when patients with FRD had profound vision loss and/or no clear central vision, preoperative microperimetry testing showed only false functional traces with no preoperative clinical relevance. Nevertheless, thorough microperimetry was performed during the final postoperative visit along with RPE evaluation using autofluorescence testing.

In summary, in the early stages of MTM (MF/FRD), there are several well-known major sources of traction on the retinal surface, including abnormal premacular tissues such as remnants of the vitreous cortex or ERMs, vitreomacular traction, and the ILM itself [34]. ILM inflexibility is a major cause of maculopathies. Furthermore, ILM peeling reduces rigidity, which allows the retina to conform better to PS [35]. In FSIP, the fovea is reattached in a manner comparable to that of classical total ILM removal. This suggests that tangential traction is likely to be released using the FSIP technique, similar to the classical technique. In terms of visual prognosis, both the FSIP and classical total ILM removal techniques showed improvement in BCVA after surgery. Such visual improvement with both types of surgical techniques might be attributed to foveoschisis restoration and the low occurrence of macular holes [20,25,26,27]. However, according to one meta-analysis [36], the FSIP eye group achieved better postoperative BCVA than the classical total ILM removal group.

In this case series, the anatomical outcomes were similar, with no evidence of residual RS or progression to MH or MHRD in either eye. The results favored the FSIP technique after assessing the structural results and changes in BCVA from the baseline. This result indicates that the FSIP technique achieved acceptable outcomes in terms of functional postoperative vision. Randomized clinical trials or MTM full-spectrum systematic reviews with meta-analyses should be conducted to investigate the best surgical approach for different MTM stages and postoperative MH and MHRD rates. We believe that a better pathogenic classification of MTM stages is an outcome of the broad application of OCT and vitrectomy [37], as the full spectrum of MTM is increasingly being considered as

a single clinical disorder with a wide range of clinical phenotypes, ranging from RS to MH, followed by FRD and RD [38].

Current developments in quantitative macular perfusional evaluation of vessel density (VD) and choriocapillaris flow area present a unique opportunity to fine-tune the approach to the evaluation and management of different MTM stages [39].

Early MTM stages are complex entities that are most commonly detected in the eyes with PM. However, current understanding of its pathophysiology and clinical behavior is limited. However, existing surgical approaches to the treatment of the early stages of MTM and its complications have been recently described but are constrained by the lack of data from randomized clinical trials and the limited number of reported case series published to date.

Quiroz-Reyes et al. [39] recently reported data from several saved ILM and ILM removal techniques; they did not observe statistically significant differences in the postoperative quantitative perfusion indices between the different ILM removal techniques. These results showed promise and highlight the clinical usefulness of quantitative perfusional markers.

This study found significantly decreased choroidal perfusion in myopic eyes, in accordance with an earlier study by Al-Sheikh et al. [40].

Quiroz-Reyes et al. [16,39,41] suggested an increased need for advanced surgical techniques at any stage of MTM, especially those related to ILM manipulation or foveal-saving ILM in the early stages of the disease, to maintain quantitative perfusion indices at normal values during and after surgery, to avoid microcirculatory alterations and, consequently, lower perfusion macular indices that could influence the final BCVA.

One more recently described vascular parameter is the choroidal vascularity index (CVI), which is derived from the technique of assessing the choroidal vasculature by quantifying vascular flow using enhanced optical coherence tomography (OCT) images. Several retinal and choroidal diseases have been characterized using this index. However, no study has established an association between CVI and different stages of MTM. In the processing to obtain binarized images to quantify this useful choroidal vascular marker, the total choroidal area (TCA, mm2), vascular luminal area (LA, mm2), and choroidal stromal area (SCA, mm2) are quantified using ImageJ software. CVI (%) was calculated as the ratio of LA to TCA. This parameter has been described in recent years; since CVI reflects vascular changes in the choroid, it provides a unique opportunity to obtain perfusion information about the choroid [42-46].

FRD, an early state of the MTM spectrum, a sight-threatening condition in individuals with high myopia, has received considerable attention for timely diagnosis and management, as it leads to multiple retinal pathologies if untreated on time [47]. MF and FRD are believed to be precursors of MTM. Identifying

these conditions early in their pathogenesis could potentially help to prevent vision loss. Monitoring the different stages of MTM and treatment outcomes longitudinally using non-invasive reproducible methods would be a significant achievement in managing this disease [18]. Previously, VD in the macular region was studied as a clinical measure in patients with high myopia; however, the findings were variable [48]. CVI may be a sensitive tool because it accounts for microcirculatory changes in the retina, [49-51] and there have been reports of a functional correlation between visual acuity and vessel density in the macula and choroid [52]. Therefore, we hypothesized that the CVI could predict the development of different stages of MTM in patients with high myopia. Recently, Tang et al. [53] assessed choroidal thickness and vascularity index in patients with high myopia after macular buckling surgery. They found that CVI increased at 1 and 3 months postoperatively and that the choroid thickened in the early post-operative period. Although many studies on high myopia have evaluated CVI in patient subgroups, comparative data between disease and control groups are lacking. The findings reported by Quiroz-Reyes et al. [40] imply that CVI may indicate the disease pathology in MTM at different stages. A lower CVI in diseased eyes suggests that choroidal vascular defects caused by pathological myopia or surgical procedures can influence functional outcomes at different stages of surgically resolved MTM. Significant developments have been made in imaging tools and assessment techniques for retinal diseases using objective and non-invasive techniques. CVI is an innovative tool that has recently been proposed as a novel marker for choroidal pathogenesis. Different studies [39-41] have shown that CVI might indicate MTM development in highly myopic eyes; the results are conclusive and strongly support this hypothesis. Further studies are warranted, especially to determine the range of CVI values for each stage of the disease, so that direct comparisons can be made for objective analysis of disease progression.

4. CONCLUSION

In conclusion, MTM-induced FRD should be treated as soon as possible to minimize damage to the photoreceptors and RPE. It is unclear whether the observed functional changes are associated with prolonged exposure to subretinal fluid or are secondary to mechanisms related to photoreceptor perfusion alterations, which in turn are consequences of vitrectomy. However, according to the current literature, different surgery-related ILM removal techniques do not significantly influence the choroidal perfusion values. Only subclinical damage permitted a successful early foveomacular anatomical reattachment. Thus, certain highly myopic eyes with PM, abnormal premacular tissues, and PS are at risk of developing MTM, which should be periodically monitored in the early stages, and timely, well-planned, and controlled perfusion updated with vitrectomy techniques should be performed.

STATEMENT OF ETHICS

The protocol for this study was approved by the Institutional Review Board (IRB) of Oftalmologia Integral ABC on May 10, 2022. All the protocols adhered to the

criteria of the Declaration of Helsinki of the World Medical Association. All three patients provided informed consent for the publication of this case report.

According to the Declaration of Helsinki, this report did not contain any personal information that could identify the patients.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration with all authors. Author MAQR conceptualized this work and drafted and reviewed the manuscript. Author EAQG was responsible for statistics and table generation. Author MAQG was responsible for the figures and artwork, and author VLG performed the final revision. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Oxidative Stress and Retinitis Pigmentosa: Mechanisms and Therapeutic Implications

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ABSTRACT

Retinitis pigmentosa (RP) represents a collection of hereditary retinal disorders typified by progressive photoreceptor cell degeneration, resulting in visual impairment and potential blindness in severe cases. Although RP pathogenesis has primarily been attributed to genetic mutations, emerging evidence indicates the significant role of oxidative stress in disease progression. Oxidative stress denotes an imbalance between reactive oxygen species (ROS) production and the retina's antioxidant defense mechanisms. This chapter endeavors to delve into the intricate involvement of oxidative stress in RP and its impact on disease etiology and progression. Gaining a comprehensive understanding of the complex interplay between oxidative stress and genetic mutations yields invaluable insights into disease mechanisms and paves the way for potential therapeutic interventions. Further research is imperative to elucidate the precise mechanisms underlying oxidative stress in RP and develop targeted antioxidant-based therapies to mitigate disease progression and safeguard vision in affected individuals.

Keywords: Retinitis pigmentosa; oxidative stress; Reactive Oxygen Species (ROS); photoreceptor degeneration; visual impairment.

1. INTRODUCTION

Retinitis pigmentosa (RP) refers to a group of retinal dysfunctions with a total incidence of about 1/3500 [1,2]. It is considered the largest class of inherited retinal dystrophies and has been linked with causal mutations in more than 70 distinct genes. Despite inflammation playing a minor role in the natural progression of the disease, the term "retinitis" is still used [2]. RP is a collection of diseases characterized by a progressive loss of vision. The most prevalent genetic disease of the retina, RP, also known as hereditary retinal dystrophy, affects one in every 3500 persons in the United States and almost one in 5000

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people globally [2,3]. Although typically affecting both eyes, cases of RP in only one eye have been reported. Nyctalopia, or night vision loss, is typically the first symptom of RP, followed by a gradual narrowing of the visual fields. However, it may appear and proceed with a range of clinical presentations. Depending on the degree and rate of the disease's progression, tunnel vision or total visual loss may develop over time. Other symptoms, such as loss of correct color discrimination and finally loss of visual acuity, may also appear as the condition worsens [3]. Most patients with late-stage RP retain some degree of light perception due to the macula's continued function. Photopsia, perception of flashes of light, is one of the most distressing late effects of RP and is believed to be caused by sensory deprivation,. About 70% to 80% of RP cases are not associated with any systemic symptoms and it is called non syndromic RP [3]. Another form of RP is syndromic RP, which occurs in conjunction with a systemic illness. Usher syndrome, the most common kind of syndromic RP, is characterized by neurosensory hearing loss coupled with visual loss [4].

2. ETIOLOGY

According to many studies, genetic abnormalities are the main cause of RP. These abnormalities lead to metabolic dysfunction, which directly affects the function of rod photoreceptors in the retina. Several pathways of injury, such as apoptosis, light damage, ciliary transport dysfunction, oxidative stress, and consequently endoplasmic reticulum stress, may be linked with these defects [3,5]. Apoptosis of the rod photoreceptors is a common outcome of all potential mechanisms.

The rods are crucial for low-light vision, and these cells are gradually lost, it results in night blindness, a hallmark of RP, along with a gradual loss of peripheral vision. Large-scale rod degeneration eventually negatively impacts the retinal pigment epithelium (RPE) and begins to affect cone photoreceptors as well [3].

Many published papers have described vulnerability of photoreceptors, particularly, to oxidative stress [6]. In this chapter, we will focus on oxidative stress and its direct role in the pathophysiology of RP.

3. THE ROLE OF OXIDATIVE STRESS IN THE PATHOLOGY OF RP

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize them using antioxidant defenses. ROS are normally produced as by-products of oxygen metabolism and serve various physiological functions, including cell signaling. Nevertheless, environmental stressors such as UV, ionizing radiation, pollutants, heavy metals and xenobiotics such as antiblastic drugs can significantly increase ROS production, creating an imbalance that damages to cellular structures including DNA, proteins, and lipids, resulting in cellular dysfunction and death [7]. Depending on the degree and nature of the insult, oxidative stress modifies cellular homeostasis and causes a variety of cell reactions. Below a certain

stress threshold, cells activate defense systems to ensure their survival. However, if stress levels exceed the threshold or protective mechanisms fail, alternate signaling pathways such as apoptosis, necrosis, proptosis, or autophagic cell death may be initiated [8].

An equilibrium between oxygen and antioxidant molecules is necessary for cell survival. The main class of ROS present at the cellular level includes superoxide anion (O2•), hydrogen peroxide (H_2O_2), hydroxyl radical (OH•), peroxy radical, and the second messenger nitric oxide (NO•), which can react with superoxide anion to generate peroxynitrate (ONOO) [6,7]. Normally, oxidative species and antioxidant defense systems coexist in equilibrium. These defense mechanisms are mediated by enzymes that metabolize or neutralize ROS, such as catalase, glutathione peroxidase, or superoxide dismutase [9].

In RP, the photoreceptor cells in the retina are particularly vulnerable to oxidative stress due to their constant exposure to light and oxygen, which can generate ROS. Moreover, mutations in genes involved in the antioxidant defense system can further impair the cells' ability to cope with oxidative stress. Many studies showed that oxidative stress triggers a cascade of events leading to the death of photoreceptor cells in RP, affecting both rod and cones [1,10]. In addition, oxidative stress can impair the function of mitochondria, which are the powerhouses of the cells that produce energy. Mitochondrial dysfunction can further exacerbate oxidative stress and contribute to photoreceptor cell death [11].

Recent studies have also revealed that RPE cells contain high levels of ROS, with phospholipids and fatty acids in the membrane being their molecular targets. The oxidation of these compounds can alter gene expression, intraretinal neurotransmission, and phototransduction pathways [9,12]. RPE cells and rods have a close structural and functional interaction. While the death of rods does not immediately lead to RPE cell demise, it initiates a series of changes that eventually cause RPE cells to migrate into the retina and surround retinal blood vessels after a considerable period, often several years [13].

Along with vascular and RPE cells, other cells are also affected by the loss of rods. Following the death of rods, cone photoreceptors begin to deteriorate. While the initial manifestation of RP, night blindness, is caused by the depletion of rods, the progressive reduction of visual fields and eventual blindness are primarily caused by the depletion of cones [3]. One of the most important unanswered questions in RP is the mechanism of cones' eventual demise. Although the rate of cone death can vary significantly, even among siblings with the same disease-causing mutation, it appears that cones rely on rods for survival, and once rods die, cone death becomes inevitable [3,11,14]. Furthermore, inflammation can also contribute to cone cell degeneration by inducing cell death and disrupting cellular signaling pathways. The abnormal presence of ROS can activate pro-inflammatory paths, leading to the release of cytokines and chemokines that recruit immune cells to the retina. These immune

cells can then release additional ROS and pro-inflammatory molecules, creating a detrimental cycle of damage and inflammation [15].

The role of oxidative stress in the pathology of RP is complex, involving a dynamic interplay between ROS, antioxidant defenses, inflammation, and mitochondrial function. A better understanding of the mechanisms of damage, such as oxidative stress pathways, is essential for exploring new therapeutic approaches aimed at preserving photoreceptors and rescuing vision. This represents a promising therapeutic strategy for treating RP. Some studies show that lowering the oxidative stress by exposing cones to hypoxia, decreases the oxidative stress on cones and rescues cone structure and function [16,17].

4. THE SOURCE OF THE FREE RADICALS IN THE EYE

Free radicals are highly reactive molecules that can cause cellular damage and maybe contribute to numerous pathological conditions affecting the eye directly. In the eye, free radicals are generated by several sources, including endogenous metabolic processes and environmental factors.

Endogenous sources of free radicals within the eye involve the normal metabolic processes occuring within cells, such as the production of energy in the mitochondria. ROS, a type of free radical, are generated as a byproduct of these processes. ROS can induce damage to cellular components, resulting to cellular dysfunction and death [18,19].

Inflammation and immune system responses constitute additional endogenous sources of free radicals in the eye. Immune cells can produce ROS as part of their antimicrobial activity, while inflammation triggers the release of cytokines and other pro-inflammatory molecules, thereby elevating ROS production [15,20]. Environmental sources of free radicals in the eye include exposure to ultraviolet radiation, smoking, and air pollution. Ultraviolet radiation from sunlight can generate ROS in the retina, and chronic exposure can contribute to the development of age-related macular degeneration (AMD). Smoking is also a significant source of free radicals in the eye, and smoking-related oxidative stress constitutes a risk factor for AMD. Air pollution can generate ROS and other pollutants that can contribute to eye diseases [19].

5. MECHANISMS OF FREE RADICAL DAMAGE TO OCULAR TISSUES

As previously mentioned, numerous studies have demonstrated the direct involvement of free radicals in ocular tissue damage. Free radicals can damage ocular tissues through various mechanisms, including lipid peroxidation, protein oxidation, DNA damage, and inflammation. Consequently, these mechanisms can lead to cellular dysfunction, tissue damage, and ultimately vision loss.

Lipid peroxidation is a process in which free radicals attack and damage lipids, resulting in the production of toxic byproducts. In the eye, this process can

damage the lipids that compose the outer segments of photoreceptor cells in the retina, leading to their dysfunction and death. This process is particularly relevant in diseases such as AMD and RP, which are characterized by photoreceptor cell death [21].

Protein oxidation is another mechanism by which free radicals can cause damage to the ocular tissues. Free radicals can attack and modify amino acid residues in proteins, leading to protein misfolding, dysfunction and aggregation. In the eye, this process can result in the aggregation of abnormal proteins in the lens, contributing to the development of cataracts [22,23].

DNA damage is also considered one of the most important mechanisms through which free radicals can cause ocular tissue damage. Free radicals can attack and modify DNA, leading to peroxidation of nucleic acids, bases, lipids, proteins and carbohydrates. This process can induce mutations and chromosomal damage. It is particularly relevant in the development of ocular tumors, such as ocular melanoma and retinoblastoma [24].

Inflammation is a major cause of many ocular diseases, and numerous studies have shown its close association with excessive free radicals and oxidative stress. Free radicals can activate pro-inflammatory pathways, resulting in the release of cytokines and chemokines that recruit immune cells to the site of injury. These immune cells can then release additional free radicals and pro-inflammatory molecules, establishing a vicious cycle of damage and inflammation [15,25].

Overall, the mechanisms of free radical damage to ocular tissues are complex and multifactorial. Therapeutic plans aimed at reducing oxidative stress and inflammation in the eye, such as the use of antioxidants and anti-inflammatory agents, may help prevent or delay the onset and progression of ocular diseases.

6. IMPACT OF ANTIOXIDANTS ON RETINITIS PIGMENTOSA

As we stated before, the oxidative stress plays a major role in the pathology of RP. Based on this understanding, the use of antioxidants is expected to have an important effect in delaying the progression of the disease. Over the past 20 years, there has been an increase in the number of studies examining the impact of antioxidants on RP.

Antioxidants are compounds that can neutralize free radicals, which are highly reactive molecules that can cause damage to cellular components, including those in the retina. Numerous studies have explored the use of antioxidants in RP, yielding varying results. Some studies have suggested that antioxidants may slow the progression of the disease and improve visual function in RP patients [26,27]. Recently conducted clinical trials have shown that supplementation with a combination of antioxidants (vitamin C, vitamin E, and lutein/zeaxanthin) improved visual function in patients with RP [26].

However, the impact of antioxidants on RP is still a matter of debate, and further research is needed to fully comprehend their potential therapeutic effects. Some researchers propose that combined antioxidant therapy may have a greater effect in slowing the degeneration of rod photoreceptors [28]. Additionally, individual variations in antioxidant status and disease progression may contribute to the variability in treatment outcomes. Therefore, personalized approaches to antioxidant supplementation may be necessary to achieve optimal therapeutic benefit in RP patients [29].

7. CONCLUSION

RP is an inherited disease characterized by gene mutations that disrupt the balance between reactive oxygen species and antioxidant molecules, resulting in oxidative stress. This oxidative stress significantly impacts the photoreceptors, triggering a series of events that lead to photoreceptor death and vision loss. In some cases, the use of antioxidants in managing RP may play a role in delaying disease progression. A thorough understanding of the mechanisms underlying oxidative stress, such as oxidative stress pathways, is crucial for identifying new therapeutic targets aimed at preserving photoreceptors and restoring vision. Effective management of RP requires close collaboration among healthcare professionals in a focused and organized multidisciplinary approach.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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One notable achievement in Ehsan's career was his involvement in the development of a groundbreaking software for dosage tailoring, which was based on pharmacokinetics algorithms. His innovative work led to the successful patenting of this novel software, demonstrating his ability to apply scientific knowledge to practical solutions in the healthcare industry. Ehsan’s contributions to the field of pharmaceutical research extend beyond software development. He has also showcased his expertise as a first author in the publication of two articles and two book chapters. These publications highlight his commitment to advancing knowledge and sharing his research findings with the scientific community.
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He is a member of the Turkish Biochemical Society, where he actively engages with fellow researchers and contributes to the advancement of biochemistry in Turkey. His research interests encompass a wide range of topics, including molecular genetics, population genetics, bioinformatics, polymorphism, oxidative stress and antioxidant system, and protein chemistry. His diverse scientific pursuits demonstrate his interdisciplinary approach and his commitment to addressing crucial issues in human health and disease.

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Chapter 6
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Unusual Origin of Left Vertebral Artery from Arch of Aorta

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ABSTRACT

The brain requires constant oxygenation and nourishment. It requies high oxygen at rest almost one fifth of the body's total oxygen requirement. It is also very sensitive to oxygen and cell death can occure within minutes due to ischemia. The blood supply of brain is derived from the internal carotid arteries and the vertebral arteries. The vertebrobasilar system is formed by two vertebral arteries and one basilar artery. Both the vertebral arteries normally arise from the subclavian arteries and variations in the origin of vessels is important for all diagnostic and surgical procedures in the head and neck region. During our routine dissection on 70 years old donated embalmed male cadaver, we observed unusual origin of the left vertebral artery from the Arch of Aorta. No other associated congenital anomaly was observed. The photographs of the unusual origin of the vertebral artery were taken for proper documentation. This unusual branching pattern of the arch of aorta is of great significance for clinicians and mainly surgeons operating on the neck and thoracic region.

Keywords: Brain; oxygen; internal carotid arteries; vertebral arteries arch of aorta; left vertebral artery; left subclavian artery; diagnostic & surgical procedures.

1. INTRODUCTION

Aortic surgery procedures continue to be associated with high morbidity and mortality, and this disparate increase in risk to the patient is further realized in procedures involving the aortic arch [1,2]. Three branches emerge from the arch of the aorta: the left subclavian artery, the left common carotid artery, and the brachiocephalic (innominate) artery. In clinical angiography, these branches are important because they feed blood to the head, face, neck, and upper limb. The proximal portion of these branches and the arch of the aorta are frequently affected by atherosclerosis, which can limit the blood supply to the brain. The

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brain's hemodynamics can be changed by anomalies in these branches' sources of supply and growth. The vertebral artery (VA) is a significant branch of the subclavian artery in both its origin and distribution [3,4]. The supero-posterior aspect of the subclavian arteries gives rise to the first branch of the vertebral arteries, which start near the base of the neck. The scalenus anterior muscle is located medially to them. The two vertebral arteries are frequently unequal in size; the left being larger than the right. The vertebral arteries take a vertical posterior course to enter the foramina transversaria of the sixth cervical vertebrae on both sides, they then continue through the transverse foramina of the upper six cervical vertebrae. On emerging from the foramen transversarium of the atlas, they turn posteromedially on its posterior arch, then penetrate the posterior atlanto-occipital membrane and dura and enter the cranial cavity through the foramen magnum [5]. The segment of the VA from its origin at the subclavian artery to its entry into the respective transverse foramina is called the pretransverse or prevertebral segment [6]. The Vertebral arteries then join each other at the caudal border of the pons to form an unpaired basilar artery. This vessel courses along the ventral aspect of the pons and distributes blood to the brain.

2. CASE REPORT

During routine dissection, of the thoracic cavity of a 70 years old donated embalmed male cadaver in the Department of Anatomy, K.J. Somaiya Medical College, Sion, Mumbai, India, we observed four branches arising from the superior surface of the arch of aorta. First branch on the right side was the brachiocephalic trunk giving out its two branches – right common carotid artery and right subclavian artery. The second branch found was the left common carotid artery, the third branch was the left vertebral artery and the fourth branch was the left subclavian artery. The neck and thoracic cavity was opened and structures in the superior mediastinum were dissected. The branches of the arch of aorta were traced. The prevertebral segment of bilateral vertebral arteries were studied from the origin till the Foramen transversarium of the cervical vertebra. Arteries were assessed morphometrically using the following parameters:

Diameter was measured at the origin using sliding callipers:

Length of prevertebral segment was measured for each vertebral artery using a graduated measuring metered rule. The vertebral artery is vital to posterior cerebral circulation. The left vertebral artery of aortic origin was found to be narrower and longer as compared to the vertebral artery of subclavian origin. No other associated congenital anomaly was observed. The photographs of the variant origin of the vertebral artery were taken for proper documentation. The left vertebral artery was seen ascending behind the left common carotid artery with stellate ganglion and ventral rami of cervical spinal nerves posterior to it and thoracic duct arching anterior to it before it entered the foramen transversarium of C6 vertebra. Thereafter its course was normal. The Right VA originated from the posterosuperior

aspect first part of the Right subclavian artery. It traversed medially behind the common carotid artery to enter the foramen transversarium of C6 vertebra.

The diameters of the arteries were determined at their origin with the aid of sliding callipers. The lengths of the prevertebral segments of the arteries were also measured using a graduated measuring metered rule.

The left vertebral artery of aortic origin was found to be narrower and longer as compared to the vertebral artery of subclavian origin.

	Diameter at origin
Present case report Vertebral artery of aortic origin	3.7mm
Normal Vertebral arteries of subclavian origin	Between 5.5 - 6.9mm

	Length of Prevertebral segment
Present case report Vertebral artery of aortic origin	8.9 cm
Normal Vertebral arteries of subclavian origin	Between 3.8 cm - 4.3 cm

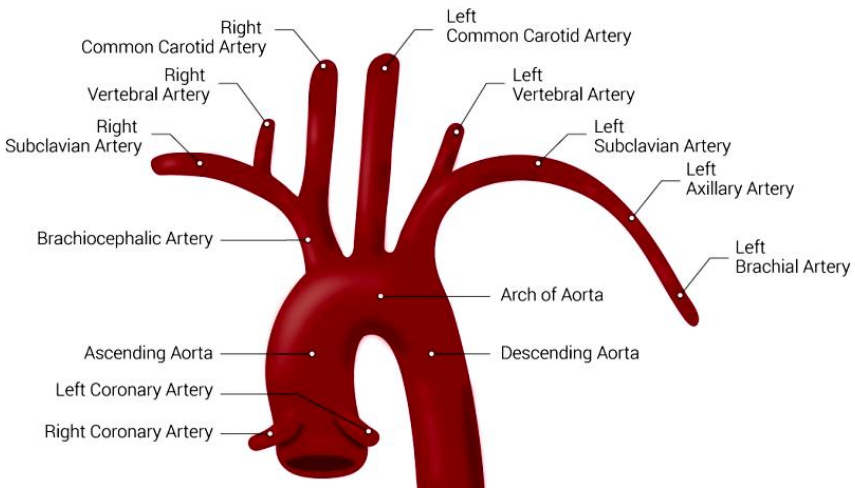

Fig. 1. Photographic presentation of the origin of Left Vertebral Artery from Arch of Aorta between Left Common Carotid and Left Subclavian Artery

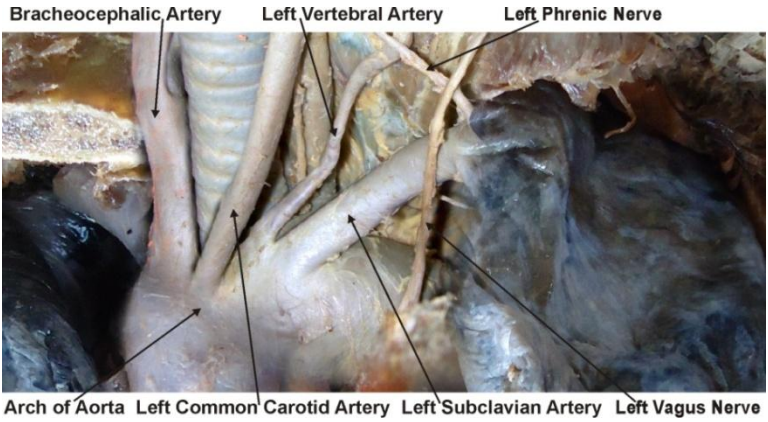

Fig. 2. Photographic presentation of the origin of Left Vertebral Artery from Arch of Aorta between Left Common Carotid and Left Subclavian Artery

3. DISCUSSION

In approximately 6% of the population the left vertebral artery arises from the arch of aorta, usually between left common carotid and left subclavian artery [7]. The left vertebral artery usually enters the sixth cervical foramina transversaria (88%), only in 5–7% cases the left vertebral artery will enter seventh or fifth cervical vertebra [8]. Nanthan & Seidal, 1993 had reported a left vertebral artery of aortic origin associated with retroesophageal right subclavian artery and thoracic duct terminating on right side, yet with normal origin of right vertebral artery [9]. Komiyana et al. [10] reported the incidence of arterial dissection of the vertebral artery of aortic origin and vertebral artery of subclavian origin. According to their studies left vertebral artery of aortic origin was associated with a significantly higher incidence of vertebral artery dissection than left or right vertebral artery of subclavian origin. In our observations the diameter of left vertebral artery was 3.7 mm at origin while it was 6.8 mm on right side. Earlier studies by Pasturet, 1958 had reported that left vertebral artery of <3.5 mm diameter may be considered hypoplastic [11].

Tracheobronchial arterial variants are predominantly left-sided variants (9 out of 11). They are linked to dominant paratracheal arterial connections, particularly the lateral longitudinal anastomosis. Unusual bronchial arteries of vertebral origin show a strong association with aberrant left vertebral arteries of aortic or proximal subclavian origin [12].

A vertebral artery of aortic arch origin has been earlier described by different authors in the range of 3.1-8.3% (Table 1). Nevertheless, most authors have stated that it is about 2.5-3%.

Table 1. Incidence of left vertebral artery of aortic arch origin

No.	Author (Year)	Incidence (%)
1	Bean (1905)	5.2%
2	Adachi (1928)	5.4%
3	Aso (1932)	3.2%
4	Mori (1941)	6.9%
5	Stein et al. (1962)	6%
6	Argenson et al. (1980)	5.8%
7	Lippert Pab (1985)	3.0%
8	Nizanowski et al. (1982)	3.1%
10	Cavdar and Arisan (1989)	8.3%
11	Takafuji and Sato (1991)	6.9%
12	Vorster (1998)	3.0%
13	Komiyama (2001)	2.4%
14	Panicker et al. (2002)	5%
15	Yamaki (2006)	5.8%

Lippert Pabst's classified the LVA according to the origin from the aortic arch [13] as:

Type	Incidence	Site of Origin
Type A	3%	between the LCCA and LSA
Type B	<1%	between a common trunk formed by BT and LCCA and LSA
Type C	<1%	after the LSA
Type D	<0,1%	after the LSA as the third branch
Type E	<0,1%	after a common trunk as the second branch
Type F	<0,1%	RSA appears from descending aorta
Type G	<1%	one of two roots as a penultimate branch
Type H	<0,1%	both VA branch from the aortic arch

The variant origin of vertebral artery was documented in the present case report is Lippert Pabst's Type A.

Origin point of the VA has also been reported from the thyrocervical trunk, from the brachiocephalic trunk, from the common carotid artery, from the external carotid artery, from a trunk formed by LSA and LVA [14–18].

Gluncic reported the length of the prevertebral segment of the left vertebral artery originating from aortic arch as 87.3 mm and its diameter at the origin as 3.3 mm. Panicker reported the diameter of left vertebral artery at origin was 3.1 mm as compared to that of the right, which had a diameter of 6.5 mm at origin. The length of prevertebral segments of right vertebral artery was 38 mm and that of left vertebral artery was 92 mm [19]. Entry point of the LVA originating from the aortic arch, into the Foramen transversarium was also reported variable. Most common entry points were reported as C5 and C6, respectively Overall, the most common entrance for vertebral arteries was at C6 [20].

The lengths of the prevertebral segments of the left vertebral artery of aortic origin were 8.9 cm as compared to the vertebral artery of normal subclavian origin showing that the vertebral artery of aortic origin has a much longer course than normal which was between 3.8 cm - 4.3 cm.

The diameter at the origin of the left vertebral artery of aortic origin were 3.7 mm as compared to the diameter of the vertebral artery of normal subclavian origin showing that the vertebral artery of aortic origin has a much smaller diameter than normal which was between 5.5 - 6.9mm

4. EMBRYOLOGICAL BASIS

Thirty or more branches of the dorsal aorta form the dorsal intersegmental arteries. They originate from the branchial aortic system. In the neck, the cervical intersegmental arteries unite to form a longitudinal artery on each side which develops into the vertebral artery. Most of the original links of the intersegmental arteries to the dorsal aorta disappear. Mostly the first part of vertebral artery develops from proximal part of dorsal branch of seventh cervical intersegmental artery proximal to postcostal anastomosis. The second part is derived from longitudinal communications of the postcostal anastomosis. Third part is from spinal branch of the first cervical intersegmental artery and fourth part is a continuation of third part [21].

In the present case, the left sixth dorsal intersegmental artery may have persisted as the first part of vertebral artery hence left vertebral artery began from arch of aorta.

The left fourth aortic arch forms part of the arch of aorta. The proximal part of the arch develops from the aortic sac & the distal part from the left dorsal aorta. The left subclavian artery is not derived from aortic arch but from the left seventh intersegmental artery. As development proceeds, differential growth shifts the origin of the left subclavian artery cranially, subsequently it comes to be positioned in close proximity to the origin of the left common carotid artery [22].

According to Vorster et al, 1998, there are two factors that control the development of the branches of subclavian artery [23]. First, ability of the blood to follow the longitudinal channels offering the least resistance and second, the tension on the vessels; resulting from the caudal shifting of the heart and aorta. The proximal parts of the segmental arteries are exposed to longitudinal tension and bending due to caudal shifting of the aorta resulting in retarded blood flow and abnormal connections between longitudinal channels (vertebral artery) and subclavian artery or aorta. Panicker et al. conceded the views of Vorster et al. and opined that a left vertebral artery of aortic arch origin may be because of persistence of dorsal division of left 6th intersegmental artery becoming the first part of vertebral artery instead of that of left 7th dorsal intersegmental artery.

Arey is of the view that the anomalous blood vessels may be due to (i) the choice of unusual paths in the primitive vascular plexus, (ii) the persistence of vessels

normally obliterated, (iii) the disappearance of vessels normally retained, (iv) incomplete development, and (v) fusions and absorption of the parts usually distinct [24].

5. CLINICAL SIGNIFICANCE

A knowledge of a morphological variation of the left vertebral artery is considerably important for all diagnostic and surgical procedures such as vascular angiographies and arterial dissection as well as all non-invasive procedures in the head and neck region [25]. Anomalous Vertebral Artery origin also represents a potential pitfall in diagnostic cerebrovascular injury [26]. An incomplete knowledge can result in complications. The extracranial portion of Vertebral Artery is frequently affected from atherosclerosis [27] and according to Fischer et al the most common site of the resultant stenosis is at its origin from subclavian artery [28]. According to Bernardi and Detori, the unusual origin of the Vertebral Artery ‘‘may favor cerebral disorders because of alterations in the cerebral haemodynamics’’ [29]. According to the literature, most patients with morphological variation of the left vertebral artery are clinically asymptomatic. Though the overall occurrence of anomalous origin of prevertebral segment of vertebral artery is low, it is of clinical importance to identify the origin and course of the prevertebral segment of the vertebral artery in detail so as to prevent complications [19]. Preceding any medical procedures it is vital to gauge vascularisation of the region. The most significant benefit of detecting potential left vertebral artery origin variants is diagnostic improvements before vascular surgeries of supra aortic arteries. The knowledge is essential for planning aortic arch surgery or endovascular interventions [25]. The CT neck revealed a bovine aortic arch with an aberrant origin of bilateral vertebral arteries from the aortic arch. The right vertebral artery arose between the bovine trunk and the left subclavian artery, while the left vertebral artery was present distal to the left subclavian artery [30]. It is also of great consequence for assessing vertebro-basilar insufficiency thought to be due to atherosclerosis, and during cannulation of vertebral artery for endovascular procedures. Vitte et al. stressed to keep the variant origin of vertebral artery in mind during its manual compression which is used routinely for positional haemodynamic vertebro-basilar insufficiency [31].

6. CONCLUSION

In approximately 6% of the population the left vertebral artery arises from the arch of aorta, usually between left common carotid and left subclavian artery. The left vertebral artery usually enters the sixth cervical foramina transversaria (88%), It occurs due to persistence of the left sixth dorsal intersegmental artery as the first part of vertebral artery, hence the aortic origin. A variant origin of vertebral artery of this kind may favor cerebral disorders because of alterations in cerebral haemodynamics. It is important to be aware of this rare variation in the origin and course of left vertebral artery as it might have serious implication in surgical and angiographic procedures. The knowledge is necessary and beneficial for planning aortic arch surgery or endovascular interventions.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Chapter 7
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Preoperative Education and Its Impact on Short-term Postoperative Outcomes in Hysterectomy

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ABSTRACT

This chapter aimed to evaluate the effectiveness of preoperative education in improving short-term postoperative outcomes in hysterectomy women. Hysterectomy is the surgical removal of the uterus performed either through the abdomen or the vagina to treat a number of conditions, including heavy or painful periods, fibroids, and prolapse. A quasi-experimental study was conducted in the District Tertiary Care Hospital in Salem, Tamilnadu, India. Subjects were selected with convenience sampling technique for the experimental group (n1=200) and control group (n2=100) respectively. Demographic proforma and flow chart to note down physiological vital parameters and other parameters were tools used. Results showed there was no significant difference revealed in physiological vital parameters ($p>0.05$) except for inspiratory capacity. The experimental group ambulated earlier (30.33±8.594) as compared to the control group (41.56± 6.960) and these differences were statistically significant ($p<0.001$). The mean length of stay was more in the experimental group (17.65±3.587) as compared to the control group (14.31±3.349). There was a drastic improvement in inspiratory capacity in the postoperative period seen among subjects in the experimental group as compared to the control group. Women will be guided to understand postoperative care after hysterectomy, to facilitate participation in postoperative self-care activities, and to prevent potential complications by structured education about perioperative care and postoperative exercises in the preoperative period.

Keywords: Elective hysterectomy; preoperative education; physiological vital parameters; ambulation; demand for additional analgesics; total amount of analgesics received; length of stay.

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1. INTRODUCTION

The uterus is a symbol of womanhood. After a Caesarean section, hysterectomy is the second most prevalent operation performed on women. Hysterectomy is a major surgical procedure that has risks and benefits, and may be classified as abdominal and vaginal according to the route of access. The abdominal route may be through conventional laparotomy, laparoscopy or robotic surgery, or vaginal hysterectomy through the superior part of the vagina. Occasionally both routes are used in combination. It is a common operation carried out in women for problems associated with reproductive organs. The indications for hysterectomy include benign conditions such as dysfunctional uterine bleeding, uterine fibroids, endometriosis, adenomyosis and genital prolapse. In addition, it is indicated in cases of gynecological malignancies 0f the uterus, ovaries and cervix, and for future malignancy risk-reducing indications [1]. Global statistics reveal that around 50,000 hysterectomies are done in the United Kingdom every year. One in five women will undergo this surgery by the age of 65 years [2]; whereas in the United States around 60,000 hysterectomies are undertaken annually. For every 10 minutes, 12 hysterectomies are performed. Of these 75% of surgeries are done among women between the ages of 20 and 49 years and the remaining 25% will undergo them by the time they are 60 years [3]. In Australia, the incidence is 4.8 per 1000 women [4]. In India, there is no national registry maintained to report hysterectomies, so the majority of them go unreported. Studies in limited geographical areas have indicated prevalence rates of hysterectomy ranging from 4% to 10% [5-6]. At vaginal hysterectomy the uterus is excised through an incision at the vaginal vault, thus avoiding an abdominal incision. This procedure is preferred in cases of uterine prolapse, vaginal walls laxity, stress incontinence and deficient perineum. To be eligible for a vaginal hysterectomy, the uterus must be of a certain size as it is not very suitable in cases of large pelvic masses and suspected malignancies. The National Family Health Survey carried out in 2005-2006 reported that 12.7% of women in the age group of 30 to 45 years attained early menopause due to hysterectomy [7]. A standard of nursing practise in the surgical setting is preoperative teaching. Preoperative teaching typically includes important details about the procedure as well as problems that patients can expect to encounter both before and after the operation [8]. Preoperative education helps patients recover quickly from surgery, shortens hospital stays, increases patient satisfaction, reduces postoperative complications, and improves psychological health [9]. Effective preoperative teaching has a positive impact in the postoperative period especially on the first 24 hours. Several works of literature have reported preoperative teaching promoted early ambulation, decreased demand for additional analgesics, and total analgesics administered in general surgical patients. The present study aimed to evaluate the effectiveness of preoperative education in improving short-term postoperative outcomes in hysterectomy women.

2. METHODS AND MATERIALS

A quasi-experimental study was conducted in the District Tertiary Care Hospital in Salem, Tamilnadu, India. Subjects were selected with convenience sampling technique for the experimental group (n1=200) and control group (n2=100) respectively. Women between the age group of 30-60 years; those living with a partner; premenopausal/postmenopausal age; who undergo abdominal/vaginal hysterectomy with or without Salphingo-oophorectomy for nonmalignant reasons, were included in the study. Informed written consent was obtained from each subject after explaining the objectives of the study. Demographic proforma was used to collect the socio-demographic data of subjects. Physiological vital parameters (Temperature, Pulse, Respiration, Blood pressure, and Inspiratory capacity) were measured once in the preoperative period for baseline data (Pretest) followed by at 5 points in the postoperative period namely at 12 hours (Posttest-1), 24 hours (Posttest-2), Second postoperative day (Posttest-3), Fifth postoperative day (Posttest-4) and at discharge (Posttest- 5). Hours after surgery (Ambulation) the subjects initiated the first walk was noted by observation. Rest of the parameters like demand for additional analgesics, the total amount of analgesics received and length of stay were taken from the medical records and noted in the flow chart. The experimental group received perioperative information which includes general information about surgery, preoperative preparations, preparations on the day of surgery, intraoperative care, immediate postoperative care, and late postoperative care until discharge. Postoperative exercises mainly respiratory exercises, mobilizing exercises, and muscle strengthening exercises were taught and demonstrated to the subjects by the investigator in the preoperative period. Subjects showed the return demonstration followed by the time allotted to clarify their doubts. Incentive spirometry was given to each subject and instructed to practice it. The control group received routine hospital care. Collected data were coded and analyzed using SPSS software 17.0 based on the objectives of the study. After attrition, the total subject size became 279 of which, 184 belonged to experimental groups and 95 in the control group.

3. RESULTS

Demographic characteristics of subjects showed more than one-quarter of subjects, 33.7% belong 36-40 years in the experimental group and 34.7% of them fall between 41-45 years in the control group. Most of them were illiterate (53.3% in the experimental group and 46.3% in the control group). The majority were coolie workers in both groups (56% in the experimental group and 71.6% in the control group). 53.8% earned below Rs.2000 in both groups as family monthly income. The majority of them had 2 children in both groups (52.7% in the experimental group and 40% in the control group) respectively. Regarding the duration of complaints, most of them, 46.2% in the experimental group and 29.5% in the control group, had their complaints in less than 3 months. The majority of them were diagnosed with fibroid uterus and underwent total abdominal hysterectomy and Bilateral Salphingo-Oophorectomy.

Table 1. Physiological vital parameters in experimental group and control group (N= 279)

S.No	Physiological vital parameters	Pretest		Posttest -1		Posttest -2		Posttest -3		Posttest -4		Posttest -5	
		EG	CG	EG	CG	EG	CG	EG	CG	EG	CG	EG	CG
		%	%	%	%	%	%	%	%	%	%	%	%
1	Temperature												
	a) 98.1-99 °F	100	100	56.0	57.9	66.3	80	72.2	83.1	90.8	94.7	100	100
	b)99.1-100 °F	0	0	36.4	31.6	23.9	12.6	23.4	11.6	9.2	4.2	0	0
	c)100.1-101 °F	0	0	7.6	10.5	9.8	5.3	3.3	1.1	0	1.1	0	0
	d) 101.1-102 °F	0	0	0	0	0	2.1	1.1	4.2	0	0	0	0
2	Pulse												
	a) 61-70/minute	8.7	5.3	1.1	2.1	1.6	0	14.1	12.6	6.0	11.6	9.8	13.7
	b) 71-80/minute	84.2	87.3	82.1	73.7	78.3	70.5	71.3	74.8	87.5	77.9	87.5	86.3
	c) 81-90/ minute	7.1	7.4	16.8	24.2	16.3	21.0	13.0	9.5	6.5	10.5	2.7	0
	d) 91-100/minute	0	0	0	0	3.8	8.5	1.6	3.1	0	0	0	0
3	Respiration												
	a) 16-20/minute	71.7	66.3	50.6	45.3	50	35.8	63	63.2	72.8	64.2	82.6	73.7
	b) 21-24 /minute	28.3	33.7	46.7	51.6	46.2	62.1	37	36.8	27.2	35.8	17.4	26.3
	c) 25-28 /minute	0	0	2.7	3.1	3.8	2.1	0	0	0	0	0	0
4	Systolic BP												
	a) 90-100 mm of Hg	17.4	19.0	17.9	14.7	17.4	22.1	20.1	21.1	24.4	29.5	38	52.7
	b) 110-120mm of Hg	66.3	73.6	63.6	76.9	63	67.3	62	67.3	62.5	52.6	50.6	44.2
	c) 130-140mm of Hg	16.3	7.4	15.2	5.3	16.8	5.3	16.3	07.4	13.1	17.9	11.4	03.1
	d) 150-160mm of Hg	0	0	3.3	3.1	2.7	5.3	1.6	4.2	0	0	0	0
5	Diastolic BP												
	a) 70 mm of Hg	51.1	58.9	53.2	56.9	52.2	60	55.4	44.2	70.1	74.7	70.1	62.1
	b) 80 mm of Hg	32.6	33.7	28.3	34.7	28.3	29.4	26.6	37.9	16.3	18.9	28.3	34.8
	c) 90 mm of Hg	16.3	7.4	15.2	5.3	16.8	5.3	16.4	15.8	13.6	6.3	1.6	3.1
	d) 100 mm of Hg	0	0	3.3	3.1	2.7	5.3	1.6	2.1	0	0	0	0
6	Inspiratory capacity												
	a) 600 ml	11.9	14.7	82.1	84.2	77.2	82.1	61.9	81.1	8.1	54.7	3.8	30.5
	b) 900 ml	40.8	46.4	17.9	15.8	22.8	17.9	38.1	18.9	28.3	34.7	29.9	50.5
	c) 1200 ml	47.3	38.9	0	0	0	0	0	0	63.6	10.6	66.3	19.0

Table 2. Comparison of physiological vital parameters between experimental group and control group (N=279)

S.No	Physiological vital parameters	Pretest		Post-test 1		Post-test 2		Post-test 3		Post-test 4		Post-test 5	
		EG	CG	EG	CG	EG	CG	EG	CG	EG	CG	EG	CG
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
1.	Temperature	98.57	98.56	99.21	99.19	99.13	99.06	98.96	98.88	98.69	98.64	98.56	98.56
	t test/p value	0.137	0.137	0.589	0.643	0.601	0.615	0.568	0.673	0.352	0.33	0.137	0.136
		0.183/0.855		**0.182/0.856**		**0.824/0.411**		**1.084/0.279**		**1.268/0.206**		**0.183/0.855**	
2.	Pulse	75.26	75.73	76.91	77.60	77.65	79.33	75.79	76.23	75.97	75.18	74.64	73.77
		4.323	3.888	5.151	5.669	6.479	7.793	6.080	6.548	4.363	5.438	3.693	3.824
	t test/p value	**0.881/0.379**		**1.020/0.309**		**1.906/0.058**		**0.555/0.579**		**1.312/0.190**		**1.848/0.066**	
3.	Respiration	19.30	19.87	20.66	21.20	20.79	21.37	20.09	20.11	19.55	19.96	18.88	19.28
		2.652	2.590	2.824	2.758	2.758	2.514	2.757	2.742	2.636	2.783	2.435	2.575
	t test/p value	**1.713/0.088**		**1.517/0.130**		**1.699/0.090**		**0.053/0.958**		**1.189/0.235**		**1.287/0.199**	
4.	Systolic BP	113.97	111.58	114.57	112.95	114.89	113.05	113.91	112.53	110.98	112.11	110.00	107.89
		11.163	8.910	12.537	11.000	12.631	12.722	11.684	10.102	9.181	10.609	9.973	9.553
	t test/p value	**1.809/0.072**		**1.064/0.288**		**1.149/0.251**		**0.982/0.327**		**0.921/0.358**		**1.695/0.091**	
5.	Diastolic BP	76.52	74.84	76.85	75.47	77.01	75.58	76.41	77.58	74.35	73.16	75.16	74.11
		7.456	6.335	8.484	7.404	8.447	8.215	8.109	7.951	7.213	5.882	7.316	5.553
	t test/p value	**1.874/0.062**		**1.337/0.182**		**1.354/0.177**		**1.146/0.253**		**1.387/0.167**		**1.237/0.217**	
6.	Inspiratory capacity	1005.98	972.63	653.80	647.37	668.48	653.68	714.13	656.84	1066.30	767.37	1095.65	865.26
		205.703	208.563	115.407	109.973	126.257	115.603	146.046	118.189	192.639	203.920	149.982	209.238
	t test/p value	**1.277/0.203**		**0.448/0.654**		**0.954/0.341**		**3.304/0.001****		**12.039/0.000*****		**10.578/0.000*****	

***Significant at p<0.01 ***Significant at p<0.001*

Table 3. Distribution of other parameters in experimental group and control group. (N=279)

S.No	Other parameters	Experimental (n_1=184)		Control (n_2=95)	
		f	%	f	%
1.	**Ambulation**				
	a) 24 hours	111	60.30	04	04.20
	b) 36 hours	049	26.70	43	45.30
	c) 48hours	024	13.00	48	50.50
2.	**Demand for additional analgesic**				
	a) Yes	027	14.67	20	21.05
	b) No	157	85.33	75	78.95
3.	**Total amount of parenteral analgesics received**				
	a) 1 – 2 doses	016	08.70	15	15.80
	b) 3 - 4 doses	133	72.30	59	62.10
	c) 5 – 6 doses	029	15.80	12	12.60
	d) 7 – 8 doses	006	03.30	09	09.50
4.	**Length of stay(LOS)**				
	a) 5-10 days	09	04.90	18	18.90
	b) 11 – 15 days	49	26.60	46	48.40
	c) 16 -20 days	91	49.40	29	30.60
	d) 21 -25 days	35	19.10	02	02.10

Table 4. Comparison of other parameters between experimental group and control group

S.No	Other parameters	Experimental (n_1=184)		Control (n_2=95)		t-test	p value
		Mean	SD	Mean	SD		
1.	Ambulation	30.33	8.594	41.56	6.960	11.007	0.000***
2.	Demand for additional analgesic	0.15	0.366	0.21	0.410	1.349	0.179
3.	Total amount of parenteral analgesics received	3.81	1.132	3.91	1.509	0.594	0.796
4.	Length of stay(LOS)	17.65	3.587	14.31	3.349	7.540	0.000***

****Significant at p<0.001*

Table 1 describes the distribution of physiological vital parameters in experimental group and control group at different points of measurement.

Table 2 describes there was a significant difference ($p<0.05$) noted in inspiratory capacity during post-test 3, post- test 4 and post-test 5 between experimental group and control group. Rest of the parameters, it was not significant.

4. DISCUSSION

Measurement of physiological vital parameters revealed majority had normal vital signs among subjects in both groups. There was no significant difference found between subjects except for inspiratory capacity. There was a drastic improvement in inspiratory capacity in the postoperative period seen among subjects in the experimental group as compared to the control group. Effective practice of deep breathing-controlled coughing exercises and the use of an incentive spirometer in the postoperative period helped the experimental group to achieve positive results. Above findings were supported in a study conducted by Naz, Siddiqui, and Ikram (2014) among patients who underwent laparotomy. The experimental group that received incentive spirometry and breathing exercises had an improved BORG scale and FEV1/FVC ratio significantly ($P=0.0001$, $p=0.0001$) as compared to the control group which practiced only deep breathing exercises [10]. A similar study conducted by Sanjeev Kumar (2013) also revealed that the patients in the incentive spirometry group had better pulmonary functions as compared to the deep breathing exercise group after three days and five days of surgery [11]. The experimental group ambulated earlier (30.33 ± 8.594) as compared to the control group (41.56 ± 6.960) which had statistical significance ($p<0.001$). These findings were consistent with another studies [12-13]. Oetker-black, Jones, Estok, Ryan, Gale, and Parker (2003) reported in their study that efficacy enhancing group ambulated for a mean of 330 seconds (SD=615) than the usual care group ambulated for a mean of 156 seconds (SD=97) and the differences were statistically significant ($p<0.05$) [14].

Most of the subjects in both groups did not demand additional analgesic and received only 3-4 doses of parenteral analgesia in the postoperative period. Similar findings were seen in other studies conducted by Chumbley et al. [15], Sjoling et al. [16] and Patrick Callaghan and Ho Cheung Li [17]. Length of stay was more in the experimental group which is 17 days as compared to the control group which stayed only for 14 days. In government settings, it was noted that there was a lack of policy on the total length of stay after gynecological surgery. Many times, it was left to the women's preferences. Once they felt physically better, they decided to go home. However, most of them preferred to stay in the hospital for a longer duration in order to take more rest than in home settings. These factors contributed to the increase in the length of stay for the present study. These findings are also supported by another study conducted by Shuldham et al. [18] among three hundred and fifty-six patients to assess the preoperative education on postoperative pain, anxiety, depression, and well-being following coronary artery bypass surgery. These findings contradicted

other studies [19-21] as all of them revealed the intervention group had a lesser LOS as compared to the usual group.

5. CONCLUSION

Administering preoperative education was found to be effective in improving short-term postoperative outcomes mainly inspiratory capacity and ambulation among women undergone hysterectomy. Providing education about perioperative care and postoperative exercises in the preoperative period in a structured manner will guide women to understand postoperative care after hysterectomy, to facilitate participation in postoperative self-care activities, and prevent potential complications.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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Chapter 8
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Timed Online Exposure and Musculoskeletal Health during COVID Pandemic: A Closer Look

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ABSTRACT

Background: During the COVID epidemic, musculoskeletal disorders have steadily increased for students of allied health sciences taking online classes.
Objectives: To investigate the association between timed internet exposure and musculoskeletal health in allied health sciences students who have just a basic understanding of the etiology and prevention.
Methods: Students in allied health science institutions who took online programs were given an online questionnaire, and those who consented to participate were included. The standardized Nordic questionnaire was utilized, along with a demographic section and the number of hours spent in online classes.
Result: The Nordic questionnaire for cervical spine and upper extremity in 7 days of exposure was statistically significant, with 66.3% reporting discomfort.
Conclusion: Musculoskeletal disorders grew as students spent more time in front of computers/mobile phones for long periods of time for their lessons. It is caused by further initial exposure.

Keywords: Musculoskeletal pain; nordic questionnaire; pain.

1. INTRODUCTION

1.1 SAR-COV

SAR-COV initially appeared around the end of December 2019, and the virus's spread caused numerous serious illnesses in several nations by the beginning of 2020, when it was formally declared a pandemic by the World Health Organisation (WHO) [1]. The virus struck India hard since it is a developing country with a large population. The second wave arrived in March 2021 and had a significant impact on people's lives. As the number of persons affected increased, some states were forced to put new limitations on people's public and private life. To regulate the transmission and prevent the spread, a set of criteria

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were mandated to be followed by each individual, such as social separation, sanitization, and the wearing of masks.

1.2 SAR-COV, Education System and its effect on Musculoskeletal Health

The new restrictions embraced all aspects of life, including social life and the education system [2]. The first online lessons were held during the first outbreak, but with the second wave's impact, it wreaked havoc on people's mental and physical characteristics of life, raising concerns about examinations as the time of online instruction increased. Online education makes greater use of digital content, including both audio and video instruction [3]. During this period of change in online education, the use of computers and mobile phones as online education instruments became more important than it had been in the traditional education system.

The alterations in schooling occurred as a result of a sudden shift in the demand of the circumstances, which was when living with numerous uncertainties had a significant impact on a student's physical and emotional well-being [4,5,6]. There have been few research on the impact of online classes.

Musculoskeletal discomfort has a negative impact on their ability to grasp subjects and even impacts performance during regular tasks [7]. Workers are more prone to musculoskeletal pain as a result of exposure to many types of stress, such as physical, mental, and environmental stress [8,9]. Because it is part of their curriculum, allied health sciences students are more aware of the anatomy and physiology of pain. They are also exposed to physical and psychological factors that trigger the occurrence of musculoskeletal pain, both in the academic setting and in the workplace [10]. The new educational system shift has increased the time of computer exposure, which is accompanied by an unsuitable chair and sitting location, resulting in stress overload on numerous musculoskeletal tissues [6,11]. They routinely use laptops and cell phones to expand their education and for enjoyment, during which they exhibit improper posture, resulting in pain and other changes in musculoskeletal areas, particularly the spine and upper extremity [12]. Increased timed exposure to devices is causing an increase in musculoskeletal difficulties, which is affecting their general health and well-being. As a result, the study's goal was to discover the association between timed online exposure and musculoskeletal health in allied health sciences students despite their lack of awareness regarding the cause and preventive.

1.3 Objective

Identify the relationship between timed exposures to laptops/phone to its effect on musculoskeletal health.

1.4 Research Question

Which musculoskeletal areas are more affected and does time of exposure plays a role in determining it.

1.5 Research Hypothesis

There is no significant relationship between time of exposure and areas of musculoskeletal issues acquired by the beneficiaries and their gender.

1.6 Population of the Study

The target population for this study comprised 132 allied health students of Bhubaneswar, Odisha

2. METHODOLOGY

A cross-sectional study was carried out in allied health science students randomly in Bhubaneswar, Odisha. A total of 200 students were sent with the questionnaire out of which only 172 responses were recorded. The sample size was calculated using 95% confidence interval with 5% margin of error, therefore it was necessary to get a response of 132 number of students as participant in the survey.

2.1 Inclusion Criteria

Students enrolled under Utkal University in allied health science course in which only two courses were included i.e BASLP and BPT. The students who had online classes during the COVID pandemic conducted by Institutes located at Bhubaneswar (that is, between 20th March to 11th May 2021 and April 2021 to 10th May 2021). To respond to all of the questions included in the evaluation survey and who provided their consent to participate in thissurvey.

The data collection was carried out in online mode during the months of April and May 2021, using Google forms which had two sections, Section A comprising of socio- demographic information like age, gender, duration of online education, pain before pandemic(COVID) and duration of daily use of computers and other technological devices and attention to body alignment. Section B consisted of the standardized Nordic Questionnaire (SNQ), The SNQ is divided into two parts, the general, and the specific. The part used asked focused 27 questions with Yes/No answers about any musculoskeletal symptoms experienced during the previous 12 months or the previous seven days in regards to the impact on activities during the 12 months. All of the questions were focused on nine areas: neck, shoulders, elbows, wrists/hands, the upper part of the back, the lower part of the back, hips/thighs, knees, and ankles/feet [13,14].

The statistical analysis was done using IBM Statistical package for social sciences (SPSS) 20. A descriptive analysis of section A variables was done by calculating average values (to determine the central tendency) and standard deviation (as a measure of dispersion). The 2 way ANOVA test was done to find out the impact of musculoskeletal pain in the nine areas with duration of exposure of altered posture, each segment was analyzed for.

3. RESULTS

This study showed out of 172 responded 88 were women i.e 52% (Table 1). A descriptive statistics showed the female population had a more exposure and consistency in attending classes.

Table 1. Descriptive statistics of sample

		Age of participants	How long do you seat infront of computers to attend your classes	Gender	Do u have any pain
N	Valid	172	172	86	172
	Missing	0	0	88	0
Mean		20.35	4.02	1.49	1.66
Median		20.50	3.00	1.00	2.00
Std. Deviation		2.068	1.402	.503	.474
Variance		4.275	1.964	.253	.225

Difference between timed exposure and pain was found to be significant i.e students exposed to more than 4 hrs had a high prevalence rate of musculoskeletal pain (Tables 2 and 3).

Table 2. Prevalence of pain in students due to online classes

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	NO	58	33.7	33.7	33.7
	Yes	114	66.3	66.3	100.0
	Total	172	100.0	100.0	

Table 3. Timed exposure of both gender for online classes

		How long do you seat in front of computers to attend your classes		Total
		1-3	4-6	
Gender	Female	38	50	88
	Male	34	50	84
Total		72	100	172

Two way ANOVA analyses were carried out to find out impact in different areas and its chronicity. Pain areas showed consistency from 7 days to 12 months with neck, shoulder and wrist showing higher significance and no significance was found in alteration of activities during last 12 months. With increase in duration (12 months) showed a consistent result for upper extremity but for lower spine and extremity showed increase in incidence.

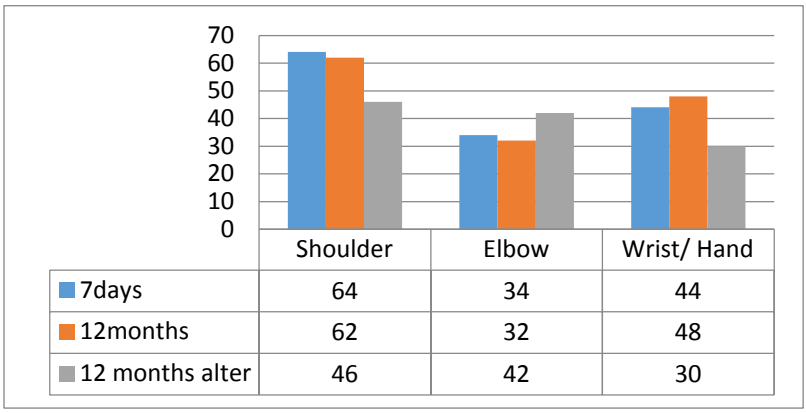


Fig. 1. Relationship between upper extremity ,duration and activities alteration in 12 months

Table 4. A two way ANOVA analysis of upper extremity pain in 7 days &12months/alteration in activities in relation to duration of exposure

Anova: Two-Factor With Replication						
Source of Variation	**SS**	**df**	**MS**	**F**	**P-value**	**F crit**
Duration	0.744186	2	0.37209302	1.96976242	0.139842	3.001571
Areas of impact	4.3875969	2	2.19379845	11.6133909	0.000010	3.001571
Interaction	1.751938	4	0.4379845	2.31857451	0.05509	2.37771
Within	290.72093	1539	0.18890249			
Total	297.60465	1547				

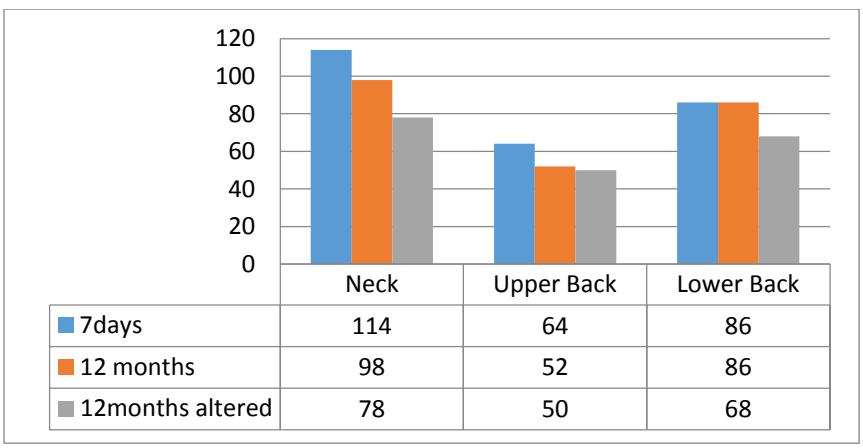


Fig. 2. Relationship between spine ,duration and activities alteration in 12 months

Table 5. A two way ANOVA analysis of spine pain/alteration in activities in relation to duration of exposure

Anova: Two-Factor With Replication						
Source of Variation	**SS**	**df**	**MS**	**F**	**P-value**	**F crit**
Duration	4.52713	2	2.2636	9.62	0.000071	3.002
Areas of impact	15.0853	2	7.5426	32	0.000000	3.002
Interaction	1.17829	4	0.2946	1.25	0.287231	2.378
Within	362.279	1539	0.2354			
Total	383.07	1547				

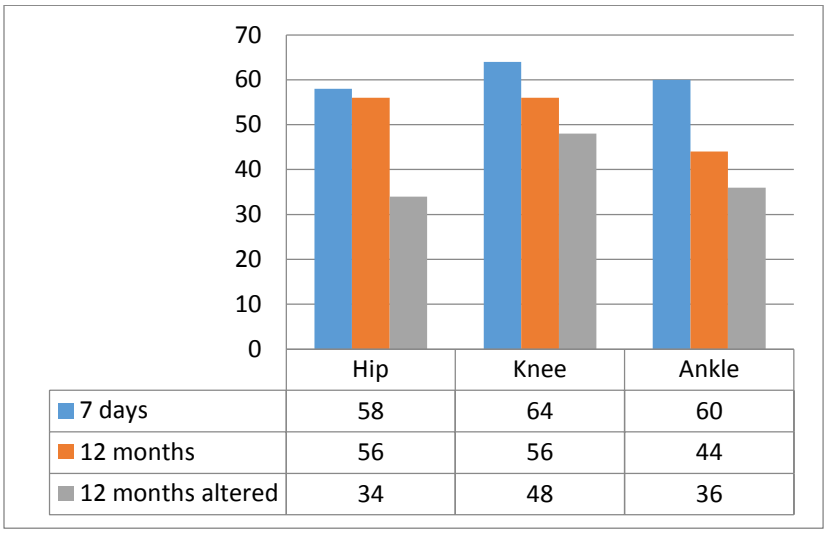
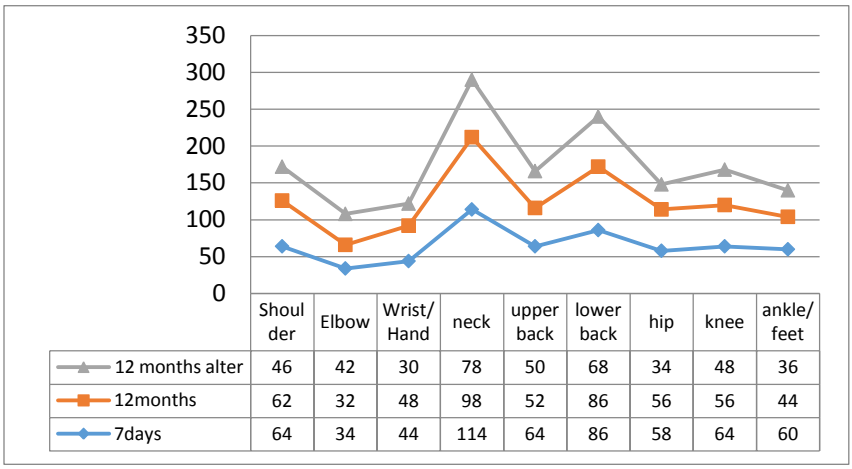


Fig. 3. Relationship between lower extremity , duration and activities alteration in 12 months

Table 6. A two way ANOVA analysis of lower extremity pain/alteration in activities in relation to duration of exposure

Anova: Two-Factor With Replication						
Source of Variation	**SS**	**df**	**MS**	**F**	**P-value**	**F crit**
Duration	4.0155039	2	2.007752	9.7682	0.000061	3.001571
Areas of Impact	0.8062016	2	0.403101	1.9612	0.141043	3.001571
Interaction	0.5271318	4	0.131783	0.6412	0.633186	2.37771
Within	316.32558	1539	0.20554			
Total	321.67442	1547				



	Shoulder	Elbow	Wrist/ Hand	neck	upper back	lower back	hip	knee	ankle/ feet
12 months alter	46	42	30	78	50	68	34	48	36
12months	62	32	48	98	52	86	56	56	44
7days	64	34	44	114	64	86	58	64	60

Fig. 4. Relationship between all nine areas of pain/discomfort /numbness due to timed exposure

Table 7. A two way ANOVA analysis of 9 areas of pain in 7 days & 12 months/alteration in activities in relation to duration of exposure

ANOVA: Two-Factor With Replication						
Source of Variation	**SS**	**df**	**MS**	**F**	**P-value**	**F crit**
Duration	5442.667	2	2721.333333	11.99804	0.000488	3.554557
Areas of impact	1394.667	2	697.3333333	3.074461	0.051019	3.554557
Interaction	202.6667	4	50.66666667	0.223383	0.921813	2.927744
Within	4082.667	18	226.8148148			
Total	11122.67	26				

4. DISCUSSION

The COVID pandemic has taken a toll on every individual's life, making him inactive and staying at home due to government guidelines, causing a shift in balance, and with the advent of online classes, students are exposed to phones/laptops for long periods of time in faulty ergonomic and unfamiliar environments, resulting in poor musculoskeletal health.

The purpose of this research study was to determine the prevalence of musculoskeletal difficulties in allied health science students with the emergence of online education as a necessity of the hour, with one year of lockdown and shutdown in a on and off phase. These pupils are aware of improper postures and their impact on numerous soft tissues, but they also demonstrated substantial musculoskeletal difficulties. This study sought to demonstrate that, even with understanding, there is a lack of self-awareness for maintaining one's health. Because health is at stake during COVID, all students should focus on instilling good habits and proper ergonomic care during online classes or online exposure for other purposes.

The nine regions of musculoskeletal pain analysed show that both genders suffered from areas of pain (cervical spine and upper extremity) in 7 days and 12 months, while neither gender predicted any major loss in activities for the same. Various research investigations have discovered a link between improper ergonomics and timed exposure in females and males, but this study shows that both genders are at equal risk for musculoskeletal pain [15-16]. Timed exposure and musculoskeletal health have been linked in studies, but the association in the first and second decades of life has yet to be studied, but lumbar spine pain has been identified as a frequent and persistent complaint in young women [17,18].

In addition to the rise in the prevalence of pain in the neck, shoulder, and wrist, previous studies established a link between long-term exposure to mobile phones/laptops and increased discomfort in the aforementioned locations [19-22]. Proper ergonomic adjustments, such as adjusting the keyboard height to be at or below elbow level, arm support for complex chairs, and ambient modifications, can reduce the risk of musculoskeletal difficulties [23]. The shift to an online education platform exposes students to electronic gadgets without sufficient ergonomic correction and stretches/breaks further lack of self-awareness [24,25].

Finally, the population being researched is made up entirely of allied health science students, which is a limitation of the study. Despite modest limitations, there are substantial strengths. This is a broad relational study that represents young health care professionals in India and demonstrates that both genders are at danger with continuous exposure for a day for classes.

5. CONCLUSION

With COVID new strains and variants, the lockdown shutdown phase has become a part of our life, and education, as an intrinsic aspect, has modified its techniques and teaching platform. Musculoskeletal difficulties grew as students spent more time in front of computers/mobile phones for long periods of time for their classes due to a change in platform teaching as the need of the hour. This research investigation shows that it is caused by the initial encounter. It can be kept at bay with a concentrated method of instruction, ongoing self-realization, and academic professional contributions. The purpose of this study is to make allied health workers aware. Furthermore, health institutions should put in place various methods to enforce health regulations, promote good health, and improve quality of life.

ETHICAL APPROVAL

The study was approved by theInstitutional Ethics Committee.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Chapter 9
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A Systematic Review and Meta-Analysis of Randomized Clinical Trials on the Benefits of Exercise in Heart Failure Patients

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ABSTRACT

Objective: To update Sagar et al. systematic review and meta-analysis on exercise-based rehabilitation in heart failure.
Methods: MEDLINE, OVID and cross references were searched for randomized clinical trials published between February 2013 to August 2018 on exercised-based cardiac rehabilitation. Trials with at least 6 months follow up were included if with exercise training program alone or as a component of comprehensive cardiac rehabilitation program compared with groups without exercise prescription.
Results: A total of 43 randomized clinical trials involving 11,989 patients predominantly with reduced EF and NYHA class ll-lll were included in the study. Exercise training program prescription in heart failure patients was shown to reduced the all-cause mortality (RR=0.76; 95%CI= 0.66, 0.87; P= 0.001), all cause hospitalization after 12 months (RR=0.70; 95% CI= 0.52, 0.96; P= 0.02) rehospitalization due to heart failure (RR= 0.49; 95% CI= 0.44, 0.55; P= <0.0001) and improvement in quality-of-life scores (RR= -0.36; 95% CI= -0.58, -0.14; P= 0.002). All-cause mortality and hospitalization admission after 12 months follow up showed significant benefits with exercise therapy program, particularly on exercise setting(p=0.026) and exercise dose (p=0.013), respectively, as revealed by the univariate meta-regression results.
Conclusion: Exercise therapy either in center or home based has been shown to benefit heart failure patients in reducing the risk of all-cause mortality up to 12 months, hospital admission up 12 months, and gave better quality of life. The new studies included have further strengthened the findings of previous studies that an exercise therapy program provides benefit to heart failure patients, either as an “alone” intervention or together with a cardiac rehabilitation program; and that the setting and dose of an exercise therapy program provide significant

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impact in reducing the risk of all-cause mortality and hospitalization after 12 months follow up, respectively.

Keywords: Clinical trials; heart failure patients; therapy; cardiac rehabilitation programme

1. INTRODUCTION

A progressive heart disease leading to chronic heart failure, regardless of its etiology can lead to poor quality of life and depression to a previously active person. Dyspnea, fatigue, and inability to do activities of daily living worst outcomes [1] would include decrease mobility, low quality of life, frequent hospital readmissions and eventually increase in mortality [2]. Exercise and cardiac rehabilitation studies in heart failure patients have revealed effectiveness of an exercise program in improving the functional capacity, quality of life, clinical outcomes and cost effectiveness. Thus, exercise training has been recommended by different guidelines as a reasonable adjunctive therapy in chronic heart failure. Moderate continuous endurance exercise has been demonstrated to be effective and safe for this subset of patients [3].

Published studies on exercise benefits in heart failure, both in preserved and reduced EF with follow up of at least 6 months was done using different search engines to update the findings of a systematic and meta-analysis published in 2014 by Sagar et al with objective of updating the 2010 Cochrane systematic review on exercised-based rehabilitation for heart failure, focusing on the effectiveness of exercise on mortality, readmission and health related quality of life. Three studies included elderly patients aged >70 years old [4,5,6], women [7], critically ill patients [4] and patients with atrial fibrillation [8]. Two studies reevaluated the cost effectiveness of the intervention [9,10].

The aim of this update is to reassess the effectiveness of exercise therapy/cardiac rehabilitation, either in center- or home- based, in improving quality of life of heart failure patients.

2. METHODS

2.1 Protocol and Registration

The protocol followed the PRISMA statement, and the methods done by Viral Sagar et al. in their systemic review (http://dx. Doi.org/10.1136/openhrt- 2014-000163). Database (Medline and OVID) was searched from January 2013 (the searching end date of the previous Cochrane review) to present date using the following search terms: exercise, physical exertion, heart failure, HFpEF, HFrEF and rehabilitation. References of journals were also reviewed for potential studies.

2.2 Eligibility Criteria

All randomized clinical trials from February 2013 to August 2018 that included subjects with heart failure (both HFrEF and HFpEF) who are at least 18 years old

and had follow up period of 6 months or more were included in the analysis. Studies with patients with previous exercise therapy/cardiac rehabilitation program were excluded. Studies included were those that have control groups that did not receive any form of exercise intervention but on optimal medical treatment and intervention groups have received exercise therapy or a programmed cardiac rehabilitation. Further, the studies have findings on four outcomes, namely: (1) death (all-cause, HF-related and sudden death); (2) hospital readmission (all-cause or HF-related); (3) quality of life assessed using validated outcomes questionnaires and (4) treatment cost-effectiveness. Investigators screened the titles, abstract and full text journals for eligibility. Some of the authors were contacted for information not found or clarifications of data in the manuscripts.

2.3 Data Extraction

In every study included, the design, patients' characteristics, intervention group details (including type frequency, duration, and intensity of the exercise), nature of control group, length of follow-up and outcomes were extracted manually and through RevMan 5.3 (Table 7). Trial quality was also assessed based on Cochrane risk of bias tool.

2.4 Statistical Analysis

Cochrane Handbook for Systematic Reviews of Interventions was followed to analyze all data. Nominal or binary variables are reported as the number of patients with events and without events in both the control and intervention groups and quality of life. Continuous variables are reported as standard deviations or mean for the different variables and when these are not available median was used (also a measure of central tendency). The absolute mean and standard deviation at follow up for both groups were used. Heterogeneity was assessed qualitatively by comparing the characteristics of the studies (Table 2) and I^2 statistics for quantitative data. Funnel plot was used to identify small study bias and publication bias. Data on the three outcomes from the studies published February 2013 to present were incorporated in the previous data to increase the number of studies and patients to obtain accurate results. All data were analyzed using the Stata/SE 15 and RevMan 5.3. To further the analysis, the F-test for equality of variances and the t-test for pooled-variances based on the result of the F-test for equality of variances were also used.

3. RESULTS

3.1 Descriptive Summary of Included Studies

The searches yielded 1065 studies. After the review of the abstracts, 41 full papers were included. However, 31 papers were excluded and only 10 full papers (RCTs) fulfilled the review inclusion criteria. The 2014 updated Cochrane review conducted by Sagar et al provided 33 RCTs resulting to a total of 43 studies. This is summarized in Fig. 1.

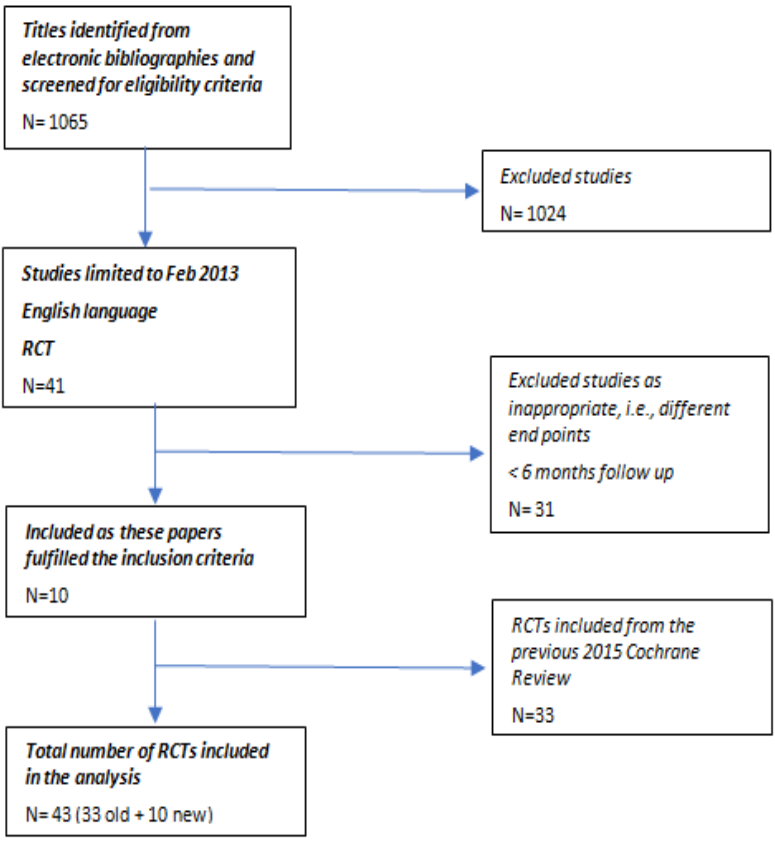

Fig. 1. Summary of study inclusion/exclusion process

From the 43 studies, as shown in Table 1, a total of 11,989 (4740 old and 7249 new) patients were included, predominantly with reduced EF and NYHA class ll - lll. Selected characteristics of the 33 RCTs (old) were found in the previous Cochrane review [11]. These are also found in the 10 new RCTs included in the update review. The study by I. Pina et al. (2013), which is a sub-study of the HF ACTION, contributed 2331 patients in the new RCTs included. The mean age of patients ranged from 58 to 76 years (51 to 81 years for the old studies). Both sexes were recruited in the new RCTs in contrast to more females in the previous review. There are six trials with more than 12 months follow period. Details of the interventions done in the new RCTs vary from marching in place to walking, resistance/strength and aerobic exercises for both center- and home-based settings. Majority of the exercise sessions were done first in exercise

centers/hospital rehabilitation sections followed by exercises done at home. The duration of the exercise training varied widely with sessions duration of 20 to 250 minutes per week with intensity of up to 70% of maximal heart rate or Borg rating of 12-15 and delivered from six months to more than 36 months.

Table 1. Selected characteristics of the new included RCTs

Characteristics	Number
Exercise only	0
Setting	
Center based	0
Home based	3
Both	7
Sample size	37 to 2331
Publication date	
Feb 2013 to present	10
Single center	4
Multi center	6
Study Locations	
Europe	4
America	3
Others	3
Sex	
Men only	0
Women only	1
Both	9
Age (years)	58.5 to 76.9
Diagnosis	
HFREF	8
HFPEF	0
Both	2
Left ventricular ejection fraction (%0	25% to 50%
Included NYHA IV	3

Legend: HFREF, heart failure with reduced ejection fraction; HFPEF, heart failure with preserved ejection fraction Risk of bias

Table 2 shows that several clinical trials did not give sufficient data to allow complete assessment of risk of bias. The overall risk of bias was moderate. Majority [5] of the trials did not elaborate on how randomization was done [12,13,14,5,7,6,8] and 2 trials did not mention randomization in the methodology [4,15]. All studies had group balanced at baseline and only two studies [5,7] had an intention to do a treat analysis. Given the nature of intervention, it was impossible to blind the caregivers and participants and not all participants were accounted for at the end of the study.

Table 2. Summary didactic categorical description of risk of bias assessment of new studies by author

Author (year)	Adequate sequence generation	Allocation concealment	Outcome blinding	Intention to treat analysis	Group balanced at baseline	Complete outcome report
Hollriegel (2016)	yes	yes	?	?	yes	yes
Chen (2017	yes	yes	yes	?	yes	no
Hagglund (2017)	yes	?	?	no	yes	yes
Denehy (2013)	yes	yes	yes	?	yes	yes
Krainer (2013)	no	no	no	?	?	?
Mudge (2018)	yes	yes	no	yes	yes	yes
Pina (2014)	yes	yes	yes	yes	yes	No
Antonicelli (2016)	yes	yes	yes	no	no	no
Lou (2017)	yes	yes	yes	yes	yes	yes
Doukky [16]	no	no	no	?	?	?

3.2 Outcomes

Mortality: There was significant difference in pooled mortality of up to 12 months follow up between the control and exercise training groups (28 trials, RR=0.76; 95% CI= 0.66,0.87; P= <0.00001). There was a reduction in all-cause mortality in heart failure patients in favor of exercise training program. This was driven by the study of Pina (2014) which contributed to 54.0% and Doukky (2016) 24.4% of the effect.

Old and new studies have statistically the same RRs (F-prob $_{(0.05)}$ = 0.098; t-prob $_{(0.05)}$ = 0.179). However, it has to be noted that the new studies revealed a reduced risk in mortality in the exercise groups than those in old studies (Mean$_{(new)}$ = 0.54 < Mean$_{(old)}$ = 1.27). They also have less varied composition of RRs than the old studies included in this updated review (CV $_{(new)}$ = 54.06% < CV $_{(old)}$ = 70.74%). These risk ratios retrieved from the new studies signify the benefit of exercise training program in reducing mortality among heart failure patients and strengthen the findings of previous studies.

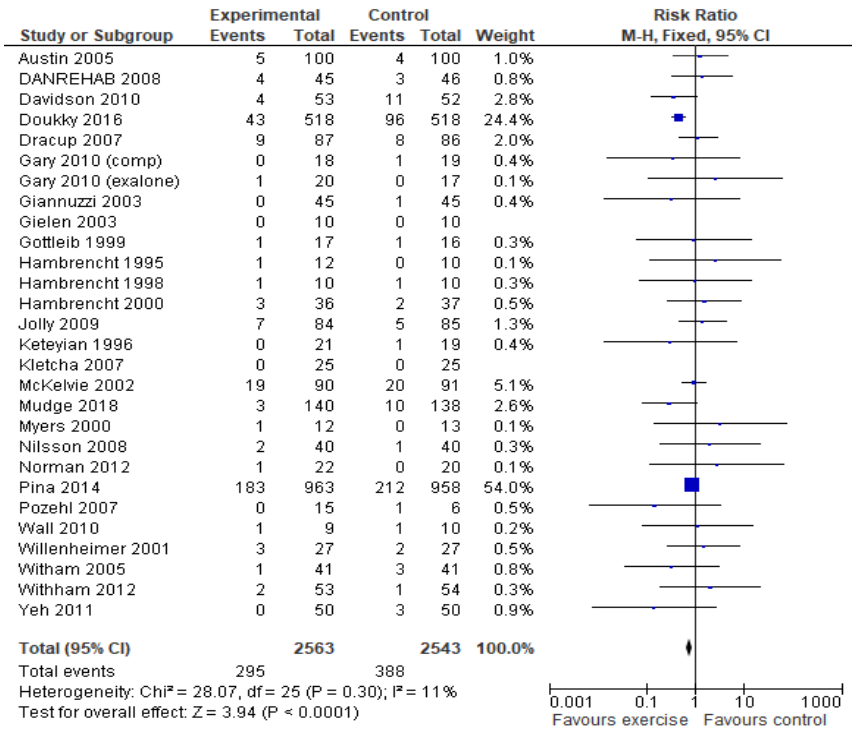

Fig. 2. Pooled all-cause mortality of all trials (old and new) up to 12 months follow up

Table 3. Comparative summary of all-cause mortality risk ratios

Studies Included	Mean	SD	CV	F-prob $_{(0.05)}$	t-prob $_{(0.05)}$
Old	1.27	0.90	70.74%	0.098	0.179
New	0.54	0.29	54.06%		

3.3 Hospital Admissions

A significant reduction in hospital admissions after 12 months (8 trials, RR= 0.70; 95% CI= 0.52,0.96; P=0.02) and heart failure rehospitalizations (18 trials, RR=0.49; 95% CI= 0.44,0.55; P=<0.00001) were observed in the exercise training groups compared to the no exercise (usual care) group (Figs. 3 and 4).

Findings on hospitalization outcomes have further revealed that old studies and new studies have statistically the same RRs (Hospitalization Admission after 12 months follow-up: F-prob $_{(0.05)}$ = 0.297; t-prob $_{(0.05)}$ = 0.717; Hospitalization Admission Due to Heart Failure rehospitalization: F-prob $_{(0.05)}$ = 0.083; t-prob $_{(0.05)}$ = 0.535). Though the new studies revealed reduce risk in hospital admission after 12 months follow up in the exercise training groups than those in old studies, this is not the case in hospitalization readmission due to heart failure (Hospitalization Admission after 12 months follow-up: Mean$_{(new)}$ = 0.69 < Mean$_{(old)}$ = 0.81; Hospitalization Admission Due to Heart Failure Rehospitalization: Mean$_{(new)}$ = 0.86 > Mean$_{(old)}$ = 0.66). Nevertheless, these results still signified the benefit of exercise training program in heart failure patients.

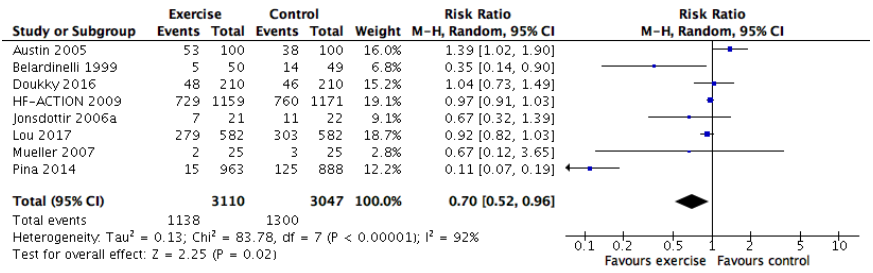

Fig. 3. Hospital admission outcomes after 12 months of follow up

Table 4. Comparative summary of hospital admission outcomes (After 12 Months Follow up) risk ratios

Studies Included	Mean	SD	CV	F-prob $_{(0.05)}$	t-prob $_{(0.05)}$
Old	0.81	0.39	48.32%	0.297	0.717
New	0.69	0.51	73.31%		

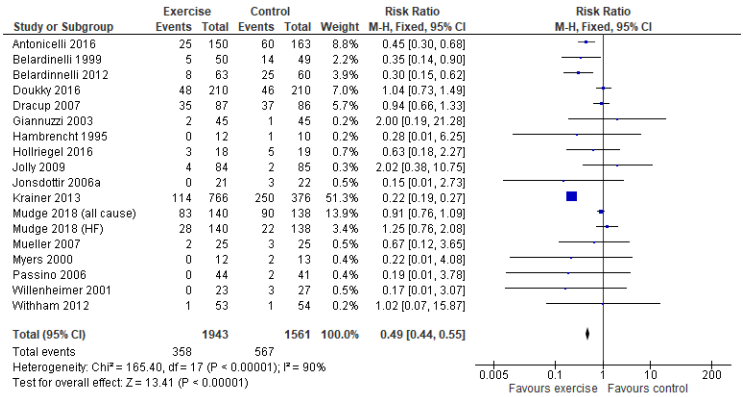

Fig. 4. Hospital admissions outcomes due heart failure rehospitalization

Table 5. Comparative Summary of Hospital Admission Outcomes (Due to HF Rehospitalization) risk ratios

Studies Included	Mean	SD	CV	F-prob (0.05)	t-prob (0.05)
Old	0.66	0.67	101.58%	0.083	0.535
New	0.86	0.32	37.31%		

Health-related Quality of Life: There are 24 trials (18 old and 4 new) that reported a validated health related quality of life measures. Majority of the trials used the Minnesota Living with Heart Failure questionnaire. Lou (2017) and the HF-ACTION trial, however, used the Kansas City Cardiomyopathy questionnaire. Fig. 5 shows that there was an improvement in all quality-of-life scores of up to 12 months follow up in the trials included in the analysis (24 trials: SMD=-0.36; 95% CI= -0.58-0.14; P=0.002). However, a favorable significant improvement is detected in the exercise training groups. The new studies included gave more weight on this finding than the old studies (Mean $_{(\text{weight new})}$ = 4.10 > Mean $_{(\text{weight old})}$ = 3.67). This is further strengthened by the size of the intervention effect of the new studies than the old studies (Mean $_{(\text{SMD new})}$ = -0.22 > Mean $_{(\text{SMDold})}$ = -0.61).

Table 6. Comparative summary of old and new studies

	Mean	SD	CV	F-prob (0.05)	t-prob (0.05)
Weight					
Old	3.67	0.62	16.72%	0.265	0.373
New	4.10	0.71	12.19%		
Std. Mean Difference					
Old	-0.61	0.40	66.55%	0.055	0.201
New	-0.22	0.03	12.86%		

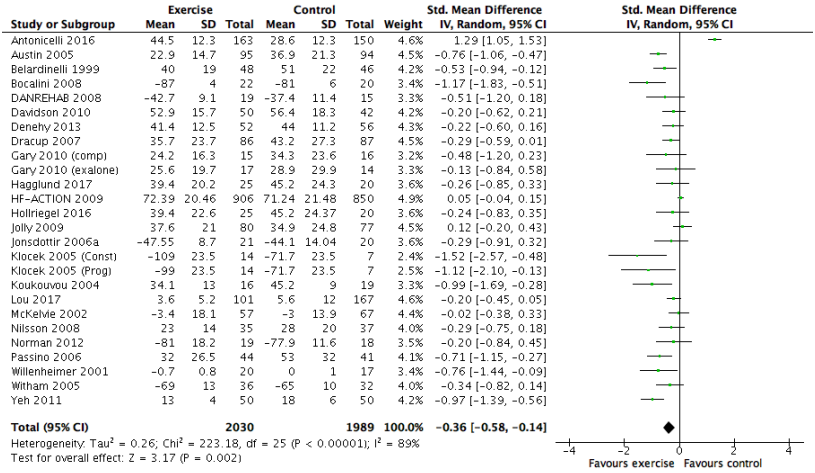

Fig. 5. Forrest plot of comparison: All Quality-of-Life scores up to 12 months follow up

Meta regression analysis: Among the health quality related outcomes, only the all-cause mortality and the hospitalization admission after 12 months follow up have significant association with exercise setting and exercise dose, respectively, as revealed by the univariate meta-regression results. The risk of bias is significantly associated with the MLWHF and the all HRQol. The risk of bias in the quality of life is significant because results of smaller studies are subject to greater variation in sampling hence are less precise [17] as reflected in the smaller weights each study contributed to the Forrest plot (Figs. 4, 5).

Low risk bias: absence of > 4/6 risk of bias items; high risk: absence of bias <4/6 risk of bias items; MLWHF: Minnesota Living with heart failure questionnaire: HRQol: health related quality of life

Cost and Cost effectiveness: In the previous Cochrane review [11], an additional healthcare cost of US$3227/patient is expected in the exercise training group with incremental life expectancy of 1.82 years/person. Recently, a cost analysis study in Columbia found that exercised-based cardiac rehabilitation in heart failure resulted in an ICER of US$3156 per life year gained and US$998 per QALY when compared with usual care [10]. The willingness-to-pay thresholds of US$7 000, US$14 000, and US$21 000 (which is equivalent to 1, 2, and 3 times the GDP per capita in Colombia in 2011), respectively was found to be cost effective [10]. Exercise training program has been found to be cost-effective if the willingness to pay is >$29,697 with ICERs of $31,624 per life year save, incremental life year saved of 0.81 and life year saved of 7.93 years per patient [16].

Table 7. Univariate meta-regression results

	All-cause mortality p Value	**All hospitalizations p Value**	**MLWHF P Value**	**All HRQoL outcomes p Value**
Type of rehabilitation (exercise only vs comprehensive)	0.199	0.328	0.236	0.283
Type of exercise (aerobic training alone vs aerobic plus resistance training	0.618	0.701	0.776	0.442
Exercise setting	0.026	0.770	0.068	0.100
Exercise dose	0.646	0.013	0.613	0.521
Single versus multicenter	0.072	0.909	0.432	0.321
Publication date	0.687	0.196	0.398	0.023
Risk of Bias	0.831	0.259	0.005	0.020

Small study bias: The hospital admission after 12 months follow-up (Egger test: estimated coefficient of 0.008; SE of 1.7 and P=0.996) and hospital admission due to heart failure (Egger test: estimated bias coefficient of -2.4; SE of 0.88 and P=0.01) did not show funnel plot asymmetry (Appendix Figs. 7,8,9). The test provides weak evidence for the presence of small-study effects and publication bias. However, funnel plot asymmetry was seen with all-cause mortality of up to 12 months (Egger test: estimated bias coefficient of 0.68; SE of 0.24 and P= 0.009) (Appendix Fig. 6) and all quality-of-life scores (Egger test: estimated coefficient of -2.41; SE of 0.88 and P=0.011).

4. DISCUSSION

This updated systematic review reveals benefit of exercise therapy/cardiac rehabilitation, either in center- or home- based, to heart failure patients, by meta-analyzing 43 studies with a total of 11,989 (4740 old and 7249 new) patients who were included in the randomized clinical trials, predominantly with reduced EF and NYHA class ll-lll. The analysis found that the exercise therapy has benefited the heart failure patients in reducing the risk of all-cause mortality up to 12 months, hospital admission up 12 months, and has resulted to a better quality of life including patients with heart failure and depression [18]. Though this finding is based on the 43 studies, where 33 are old published studies and 10 are new, the new studies included in this systematic review and meta-analysis have been shown to reduce the risks in all health-related outcomes covered in this study than those that were recorded by the old studies. The new studies included have further strengthened the findings of previous studies that an exercise therapy program provide benefit to heart failure patients, either as an “alone’ intervention or is together with a cardiac rehabilitation program. This is in contrast with the result of previous review by Sagar, et.al. [11], which showed no difference in pooled all-cause mortality between exercise CR with follow-up to 1 year (12 months) and the control group and Lewinter, et.al (24) with no difference in all-cause mortality after 6 months follow up but with increase in exercise capacity and reduced hospitalization. But, the improvement in health-related quality of life with exercise training in heart failure demonstrated in this updated review concurs with that of Sagar et al. [11] and Lewinter et al. [19]. The significant benefits of exercise therapy are specifically validated in the reduced risk in all-cause mortality and hospitalization after 12 months follow up based on exercise setting and exercise dose, respectively, using univariate meta-regression [20-24].

5. CONCLUSION

This updated review study, which aims to reassess the effectiveness of exercise therapy/cardiac rehabilitation, either in center- or home- based, to heart failure patients found out that the:

1. Exercise therapy has benefited the heart failure patients in reducing the risk of all-cause mortality up to 12 months, hospital admission up 12 months, and has given a better quality of life.

2. The new studies included have shown reduced risks in all health-related outcomes covered in this study than those that were recorded by the old studies. Thus, further strengthened the findings of previous studies that an exercise therapy program provide benefit to heart failure patients, either it is an "alone' intervention or is together with a cardiac rehabilitation program.
3. The setting and dose of an exercise therapy program provide significant contribution to a reduced risk in all-cause mortality and hospitalization after 12 months follow up, respectively.

All these could change the landscape of treating heart failure by including non-conventional mode of treatment like exercise training program to improve overall patients' outcome.

6. STUDY LIMITATIONS

Funnel plot asymmetry in the all-cause mortality and quality of life scores outcomes implied evidence of small study bias and probably publication bias, thus grey literature can be searched for other unpublished studies to reduce such biases. The review was limited to English-language articles, introducing a risk of bias. There were also studies included which details limited descriptions of the interventions and controls in accordance with Consolidated Standards of Reporting Trials (CONSORT). Adding heart failure patients with preserved ejection fraction can prevent small study bias and would give us incites on the benefits of exercise in this population.

DISCLAIMER REGARDING CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

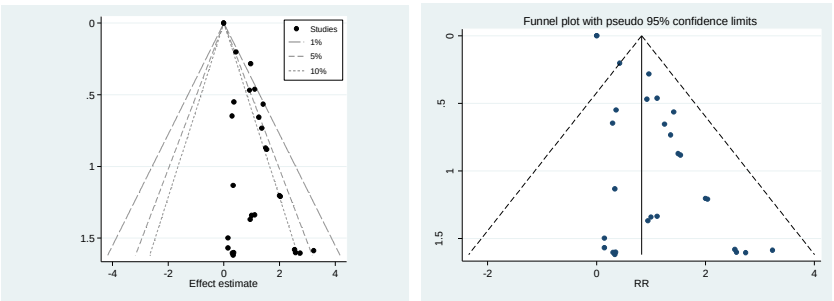

Fig. 6. Funnel plot of comparison: 1 All exercise interventions versus usual care, outcome: All-cause mortality up to 12 months' follow-up.

Egger's test for small-study effects:

Number of studies = 26 Root MSE = .7528

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.4946349	.1481874	3.34	0.003	.1887911	.8004787
bias	.6849844	.2413394	2.84	0.009	.1868844	1.183084

Test of H0: no small-study effects P = 0.009

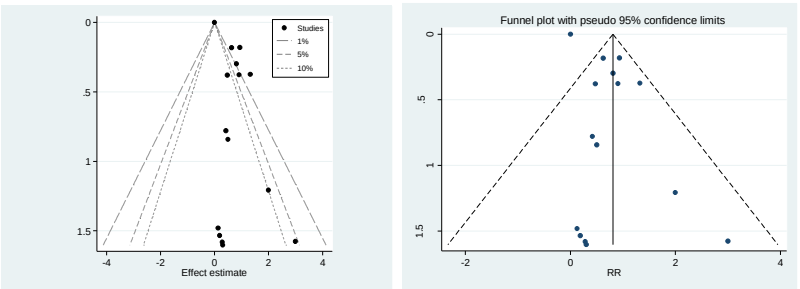

Fig. 7. Funnel plot of comparison: 1. All exercise interventions versus usual care, outcome: hospital admissions after 12 months' follow up

Egger's test for small-study effects:

Number of studies = 15 Root MSE = .8211

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
		.1304713	6.04	0.000	.5033527	1.071898
slope	.7876252					
bias	.0769059	.3472714	0.22	0.828	-.6797335	.8335452

Test of H0: no small-study effects P = 0.828

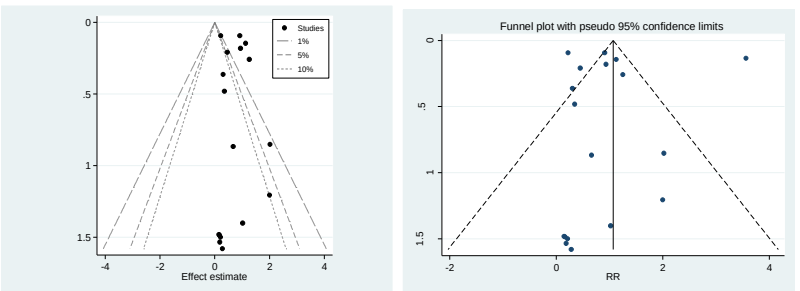

Fig. 8. Funnel plot of comparison: 1: All exercise interventions versus usual care, outcome: hospital admissions due to heart failure rehospitalizations

Egger's test for small-study effects:

Number of studies = 18 Root MSE = 5.271

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.067766	.368975	2.89	0.011	.285574	1.849958
bias	.0089696	1.774585	0.01	0.996	-3.752983	3.770922

Test of H0: no small-study effects P = 0.996

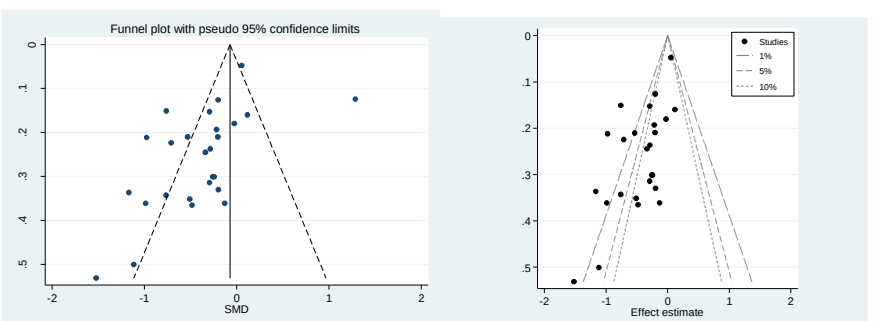

Fig. 9. Funnel plot of comparison: All quality of Life scores up to 12 months follow up

Egger's test for small-study effects:

Number of studies = 26 Root MSE = 2.661

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
slope	.2467116	.1442672	1.71	0.100	-.0510412	.5444643
bias	-2.414468	.8803689	-2.74	0.011	-4.23146	-.5974758

Test of H0: no small-study effects *P = 0.011*

Egger's Test Reference:
fmwww.bc.edu/RePEc/bocode/m/metabias

Syntax:
metabias EffectEstimate SE, egger
metafunnel EffectEstimate SE, xtitle("RR") ytitle("SE[log RR]")
metafunnel EffectEstimate SE, xtitle("MD") ytitle("SE[MD]")
confunnel EffectEstimate SE

Table 8. Characteristics of the trials included

Author	Year	Methods	Participants	Interventions	Outcome	Comparison	Country	Follow up
Lou	2017	RCT parallel group	HF <35% EF with atrial fibrillation Female:30%; Age: 58.6-63.1y	Aerobic(walking/biking) 90mins/week 60-70% HR reserve	QoL (KCCQ) All cause mortality All cause hospitalization Heart failure hospitalization	Usual care Medical tx	USA multicenter	36months
Doukky	2016	RCT multicenter Partially blinded	HF <40% EF Age: 63-65y Male:45-56%	Aerobic exercise 90 mins/week	All cause mortality HF hospitalization	Usual care No exercise Medical tx	USA	36 months
Pina	2014	RCT multicenter	HF <35% EF NYHA II-IV Age: 57-60y Men: 70%	Aerobic exercise 30-40 mins 5x/week 60-70% HR reserve	All cause mortality QoL (KCCQ) All cause hospitalization	Usual care Medical tx	USA	24 months
Mudge	2018	RCT Blinded outcome assesors	HF <31% EF Men: 70% Age: 61.9-62.9y	Aerobic exercise (treadmill/bike) 30mins 5x/week	All cause death readmission	Usual care Medical tx HF disease Mgt program	Australia	12 months
Krainer	2013	Prospective Cohort study	High risk subjects Age: 75-78 y Women: 64-66%	Any physical activity At work and home	Heart failure admission	Usual care No active physical activity	USA	120months
Hollriegel	2016	RCT Parallel group	HF <24% EF Age: 60 y	Exercise training (not specified) 5-20mins 3-6x/week	All cause death Heart failure hospitalization	Usual care Medical tx	Germany	12 months

Author	Year	Methods	Participants	Interventions	Outcome	Comparison	Country	Follow up
Antonicelli	2016	Prospective RCT	HF <50% EF Men: 56.9% Age: >70 y	Exercise training and telemonitoring Hospital Cardiac Rehab	All cause readmission QoL (MLHFH)	Usual care Medical tx	Italy	6 months
Denehy	2013	Stratified phase ll RCT Parallel group	HF Age: 60.4-61.4y Men: 58-68%	Exercise training (marching in place/standing and resistance exercises) 30-60mins 2x/week	All cause readmission All cause mortality	Usual care Medical tx Sit on bed	Australia	12 months
Hagglund	2017	Mixed method randomly assigned study	HF <50% EF Age 71-85y Men: 77%	Tai chi 60min/sesssion	Qol (MLHFQ)	Usual care Medical tx	Sweden	6 months
Chen	2017	Randomized prospective trial	HF <50% EF Age: 60-61y Men: 83%	Aerobic exercise Hospital to home 30mins 3x week 60-80%HR reserve	Qol (MLHFQ)	Usual care Medical tx	Taiwan	12 months

F-Test Two-Sample for Variances

	RR (On or Before 2013 Stuides)	RR (Beyond 2013 Studies)
Mean	1.2726087	0.53666667
Variance	0.81049289	0.08403333
Observations	23	3
df	22	2
F	9.64489749	
P(F<=f) one-tail	0.09804999	
F Critical one-tail	19.4503065	

F-test for Equality of Variances = p-rob 0.098 > a=0.05

Thus, the variances of the two studies are statistically the same.

The t-test for pooled-variance shall then be utilized for comparison of the RRs

t-Test: Two-Sample Assuming Equal Variances

	RR (On or Before 2013 Stuides)	RR (Beyond 2013 Studies)				
Mean	1.2726087	0.53666667	sd		cv (?2013 studies)	cv (>2013 studies)
Variance	0.81049289	0.08403333	0.90027378	0.28988504	70.7423882	54.015845
Observations	23	3				
Pooled Variance	0.74995459					
Hypothesized Mean Difference	0					
df	24					
t Stat	1.38440766					
P(T<=t) one-tail	0.08948588					
t Critical one-tail	1.71088208					
P(T<=t) two-tail	0.17897177					
t Critical two-tail	2.06389856					

DISCLAIMER
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Chapter 10
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Feasibility of Crossed Intralaminar Screws for Fusion of the Cervicothoracic Junction and the Thoracic Spine: Initial Experience and Surgical Technique Description in an Iberic Department

M. Şincari [a++*] and M. Conceição [a#]

DOI: 10.9734/bpi/cpmmr/v1/5825B

ABSTRACT

This chapter highlights the Feasibility of crossed Intralaminar Screws for fusion of the Cervicothoracic Junction and the Thoracic spine: Initial experience in an Iberic Department, surgical technique description. Intralaminar screws have been shown to be a biomechanically salvage technique in the thoracic spine, especially in long cervicothoracic, thoracic and thoracolumbar fixation. The goals of this article are to demonstrate our initial experience and the range of indications for thoracic crossed intralaminar screws. Pathologies affecting the cervicothoracic junction and thoracic spine have never been easy to treat. Finding a replacement for pedicle screws in thoracic spine surgery is necessary due to anatomical variations and the recurrent failure of pedicle screw insertion. The interlaminar crossed screws is a well-known and secure method for fusion in cervical spine, but in the thoracic spine and in the cervicothoracic junction there are insufficient clinical data to support this technique, until now. The use of crossed intralaminar screw in the thoracic region is an underestimated technique; this free hand technique is a fast, efficient and alternative method of transpedicular fixation and this technique at different thoracic levels appears to be a useful tool in the armamentarium of the spinal surgeon. The patients follow up is to be published in future articles.

Keywords: Crossed intralaminar; spinolaminar angle; thoracic; imaging; lamina screws; spinal fusion/instrumentation/methods; thoracic vertebrae.

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1. INTRODUCTION

The importance of the bridging of the cervicothoracic junction is strongly supported by different authors. Christoph Scholz et al. found that fewer revisions were necessary if the fusion had extended to the thoracic spine. They recommend bridging the cervicothoracic junction when fusion starts at C0–C3 [1]. Dissatisfaction with lateral mass fixation at C7 and T1 led T.J. Albert et al. to use lower cervical pedicle screw fixation for several cervical spine disorders. They used pedicle screws in C7 placed with laminoforaminotomy and palpation technique and concluded to be safe and efficacious and excellent fixation can be achieved [2]. Every time more authors defend cervicothoracic junction bridging, stating that patients with multisegmental posterior cervical fusions ending at C7 showed a greater rate of clinically symptomatic pathologies at the adjacent level below the instrumentation, advising to consider to bridge the cervicothoracic junction and to end the instrumentation at T1 or T2 in those cases [3]. These statements increase the importance of the development of accessible and easy methods of fixation of the cervicothoracic junction, due to difficult proper insertion of the transpedicular screws in this junctional region. On the other hand, there are reports that show that crossing the cervicothoracic junction was associated with increased surgical time, estimated blood loss and the rates of wound dehiscence. These tradeoffs should be considered in the planning of posterior cervical decompression and fusion procedures [4]. Also, there are opposite positions, like a meta-analysis that suggests similar clinical and radiographic outcomes in multilevel posterior cervical fusion, regardless of inclusion of the cervicothoracic junction, stating that the lowest instrumented level did not significantly affect revision rates or complications. The ideal stopping point must be tailored to each patient on an individualized basis [5]. The cervicothoracic junction represents a unique region in the spine because of its biomechanical properties and by different challenges put in front of spine surgeons. We demonstrate in an initial series of 10 cases treated with interlaminar crossed screws in association of other fusion techniques in the cervicothoracic junction and thoracic spine with good initial results. The development of new surgical techniques and new instrumentation will allow better access and fixation to the cervicothoracic junction and thoracic regions. In 2004, Wright described the C2 translaminar screw fixation, which involves the insertion of bilateral screws into the lamina of C2 in a crossing fashion that are then connected to C1 lateral mass screws.

Wright states that anatomic variability of the foramen transversarium in the body of the axis can preclude safe transarticular C1-C2 screw placement in up to 20% of patients and C2 screw fixation with pedicle screws remains a significant risk to the vertebral artery. So, he describes a novel technique of C2 rigid screw fixation using bilateral, crossing C2 laminar screws, which do not risk to lesion the vertebral artery during C2 fixation [6].

Other popular indication for use of laminar screws was on the C7 vertebra because the insertion of transpedicular screws at this level has a difficult feasibility due to shoulder shadowing seen in traditional fluoroscopy. Also, lateral

mass screws at this level have a disadvantage to exhibit low resistance to pull out. We present the use of laminar screws as a safe option, especially in long constructions involving cervico-thoracic junction.

The advantages of using laminar screws in C7, are:

- No risk of damage to the vertebral artery when it courses into transverse foramen;
- No need to use fluoroscopy or navigation systems;
- Direct visual placement of screws, using posterior laminar cortex as guide;
- Tactile feedback;
- Alternative method when anomalous anatomy of pedicles is present;
- Not very time-consuming procedure;
- Does not require extensive spine surgical skills.

McGuirt et al, in 2009, compared the transpedicular fixation in Th1 and Th2 versus intralaminar fixation in long subaxial cervical constructs on human cadaveric spines and found a minimal difference after cyclical loadings between translaminar and transpedicular screws. His studies concluded that upper thoracic translaminar screws are a biomechanically effective option to stabilize rigidly the cervicothoracic junction [7].

In 2010, Kretzer at al., conducted a study, in cadaveric models about biomechanical resistance comparing the laminar and transpedicular screws fixation involving Th1 and Th2 vertebrae. They found that translaminar screws in the upper thoracic spine offer similar stability to pedicle screw fixation for constructs bridging the cervicothoracic junction. Small difference in range of motion must be clinically weighed against the potential benefits of translaminar screws insertion at Th1-Th2 [8].

2. SURGICAL TECHNIQUE

As described by medical literature, the most important step is to identify the entry point. This point is always located at the spinolaminar junction, pointing to the junction between the lamina and the lateral mass [9,10].

The authors advice that both entry point and screw length must be calculated based on CT scan slices. Special attention must be taken when performing this technique to:

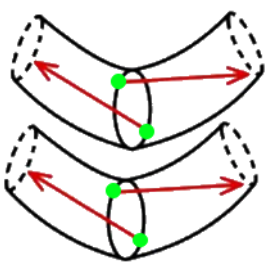
1) The screw diameter
2) The angulation during the insertion.
3) Level of screws insertion in the lamina

The diameter of laminar screws must be measured in the CT scan before the procedure. If the screw is too long, it may injure the facet joint or even the cervical nerve root. Also, angulation during the insertion must be calculated in order to prevent its penetration in the ventral surface of the lamina and injury to

the spinal cord. The direction is also important to avoid the collision of two screws against each other (in the case of bilateral screw insertion).
We strongly advise the accurate identification of the entry start point for the screws in order to reduce breaches of the dorsal lamina cortex.

For bilateral crossing intralaminar screws, the direction and the level of insertion must be taken in mind in order to prevent screw collision at the midline. This collision occurs when both screws have the same level entry point and as a result, they collide and the trajectory of the second screw can suffer a detour. To avoid this, the first screw's entry point should be close to the rostral margin of the spinolaminar junction and the other screw entry point is made is at the level of caudal margin of the spinolaminar junction. Identification of accurate screw entry start point can reduce possible complications [11].

The direction of the screw in the bilateral interlaminar fixation is also important in order to prevent the collision. The first rostral screw must point to the inferior angle between the lamina and the lateral mass and the second caudal screw goes up along the lamina (Drawing). Thus, the first (rostral) screw has an almost horizontal trajectory, and the second (caudal) screw has an ascending trajectory (Drawing) (Model 1).



Model 1. Drawing scheme of the thoracic laminas and screws trajectory. Green dots: entry points at spinolaminar angle, Red arrows: screws directions, almost horizontal for the rostral screw and ascending for the caudal screws

In Centro Hospitalar Tondela-Viseu, in Portugal, we started to use this technique since 2021 and this article is to demonstrate our initial series. The majority of the patients are still in follow-up. Our series has a wide range of ages, from 31 to 86 years old, male predominance and traumatic etiology.

Case 1: 81 years old skinny man with C6-C7 transdiscal fracture type C AO. He comes 3 months after the initial trauma. He was selected for circumferential cervicothoracic arthrodesis with interbody mesh C6-C7 and anterior plate with cemented screws and posterior fixation C5, C6 transpedicular screws C7, Th1,

Th2 intralaminar crossed screws and cross link (Figs. 1C, D) associated with posterior decompression (flavectomy C6-C7).

CT scan (Fig. 1A) and MRI (Fig. 1B) confirmed a transdiscal fracture with reabsorption of fracture margins.

During the post-operative period, he developed wound dehiscence which was treated with resection of spinous apophysis in the cervicodorsal region in order to release tissues tension and vacuum-assisted closure. Followed up more than 2 years. Serial CT demonstrates signs of fusion, noticed a very thin skin above posterior instrumentation (Fig. 1E).

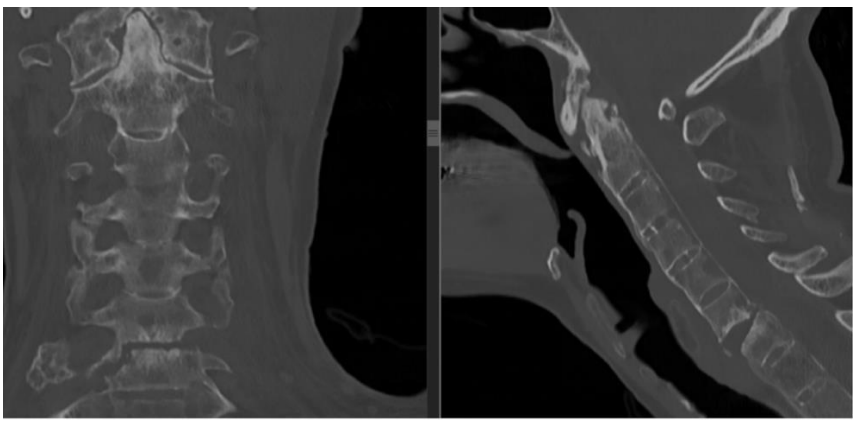


Fig. 1A. C6-C7 transdiscal fracture type C AO on CT scan

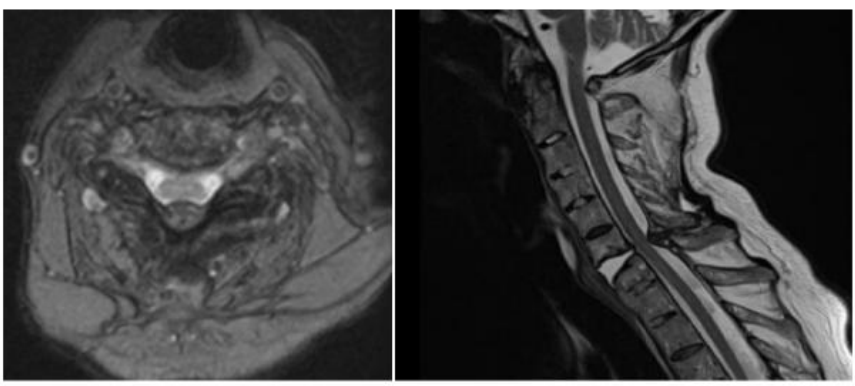


Fig. 1B. MRI confirmed a transdiscal fracture of three columns of stability with reabsorption of fracture margins, posterior slight spine cord compression by ligament

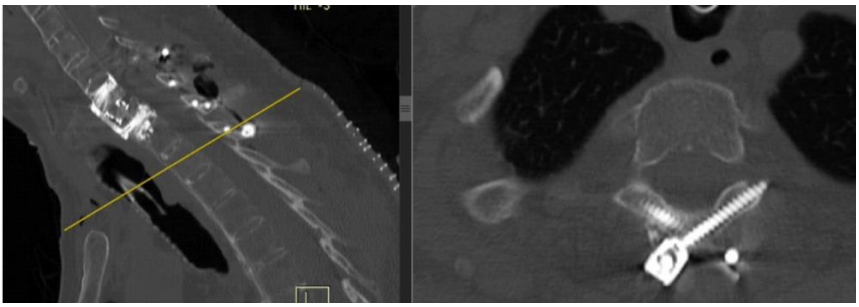


Fig. 1C. Mesh C6-C7 and anterior plate with cemented screws and posterior fixation C5, C6 transpedicular screws C7, Th1, Th2 intralaminar crossed screws and cross link, posterior decompression (yellow ligament removal C6-C7)

Fig. 1D. Mesh C6-C7 and anterior plate with cemented screws and posterior fixation C5, C6 transpedicular screws C7, Th1, Th2 intralaminar crossed screws and cross link, posterior decompression (yellow ligament removal C6-C7)

Case 2: 76 years old man with type B1 AO fracture at C7 level confirmed on CT and MRI (Figs. 2A, B). The patient presented bilateral distal weakness of hands. The surgery performed was: C6-C7 anterior arthrodesis with mesh, plate and cemented screws, posterior fixation C4-C6 lateral mass and C7 unilateral intralaminar screw, Th1, Th2 crossed intralaminar screws and cross link (Figs. 2C, D). In the postoperative period, showed slow improvement of hand dexterity. Half a year after surgery, X-Ray showed good positioning of the construct (Fig. 2E).

Fig. 1E. 1 year after surgery, wound picture

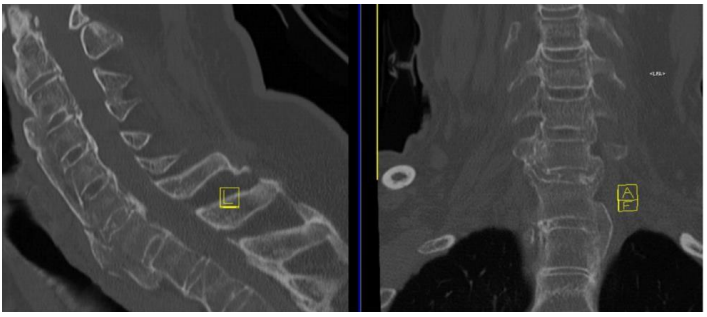


Fig. 2A. CT scan revealing B1 type AO C7 fracture

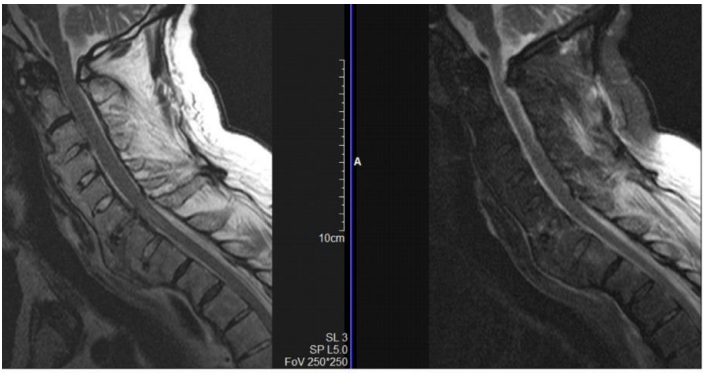


Fig. 2B. Same type of fracture confirmed on MRI

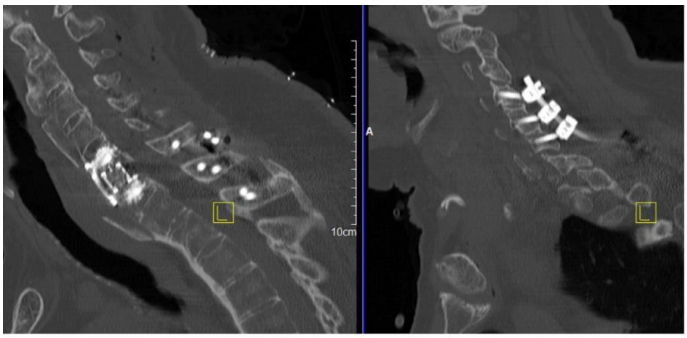


Fig. 2C. Postoperative CT scan: C6-C7 anterior arthrodesis with mesh, plate and cemented screws, posterior fixation C4-C6 lateral mass and C7 unilateral intralaminar screw, Th1, Th2 crossed intralaminar screws and cross link

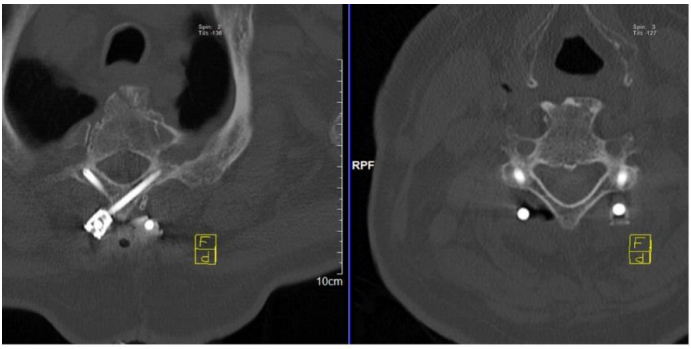


Fig. 2D. Th1, Th2 crossed intralaminar screws and cross link

Fig. 2E. 6 months postoperative X-Ray

Case 3: 78 years old man with fracture type C AO C6-C7 and posterior compression of the spinal cord with ligament fragments on MRI (Fig. 3A). He was operated as follows: anterior arthrodesis C6-C7 with cage with screws and plate with cemented crews and posterior fixation lateral mass C4-C6 and crossed intralaminar screws C7, Th1, Th2 and cross link. Postoperative CT scan showed adequate positioning of the screws (Fig. 3B).

Fig. 3A. MRI fracture type C AO C6-C7 and posterior compression of the spine cord with ligament fragments

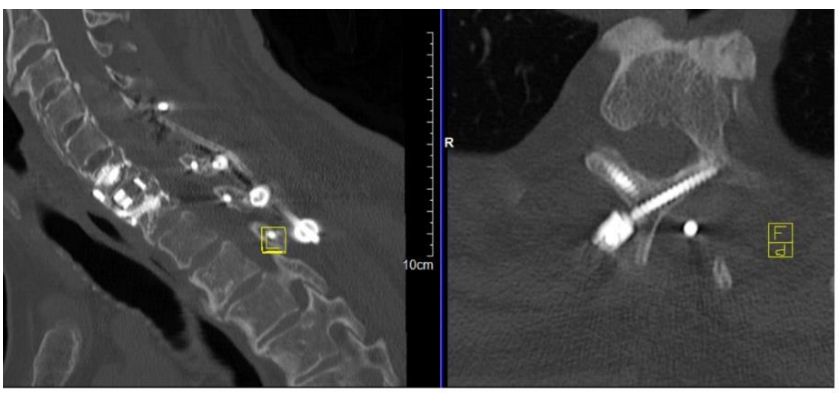


Fig. 3B. Postoperative CT scan arthrodesis C6-C7 with cage with screws and plate with cemented crews and posterior fixation lateral mass C4-C6 and crossed intralaminar screws C7, Th1, Th2 and cross link, adequate positioning of the screws

Case 4: 77 years old man with type B3 AO C6-C7 fracture (Fig. 4A) was selected for posterior fixation: lateral mass C5, C6 and crossed intralaminar screws C7, Th1, Th2 (Fig. 4B and Fig. 4C) with good postoperative evolution and good postoperative CT scan.

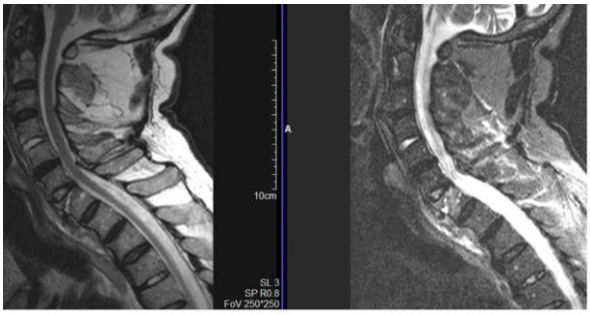


Fig. 4A. B3 AO C6-C7 fracture

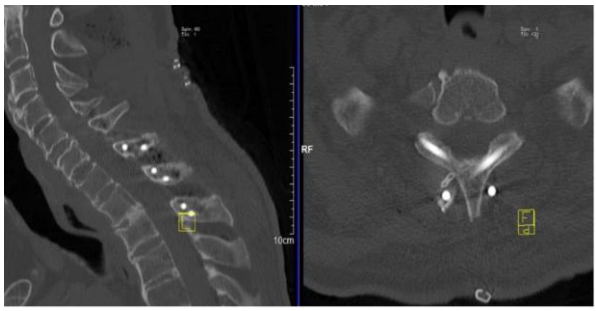


Fig. 4B. Postoperative CT scan: lateral mass C5, C6 and crossed intralaminar screws C7, Th1, Th2

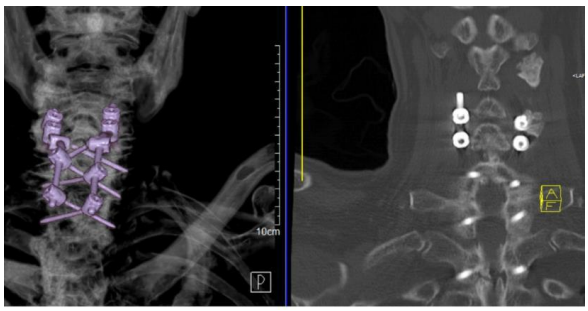


Fig. 4C. Postoperative CT scan: lateral mass C5, C6 and crossed intralaminar screws C7, Th1, Th2

Case 5: 31 years old obese, pregnant woman (6 weeks of pregnancy) with fracture type A2 AO Th8 and type A1 AO Th9 (Fig. 5A) was proposed for Th5-Th11 with intralaminar crossed screws using crossed intralaminar screws as salvage technique in order to avoid X-Ray due to the pregnancy (Fig. 5B). Unfortunately, one month after being discharged, she had a spontaneous abortion, postoperative X-Ray showed good screw positioning (Fig. 5C).

Fig. 5A. MRI fracture type A2 AO Th8 and type A1 AO Th9

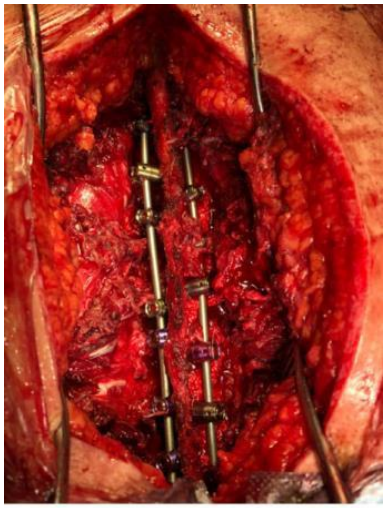


Fig. 5B. Intra-operative view

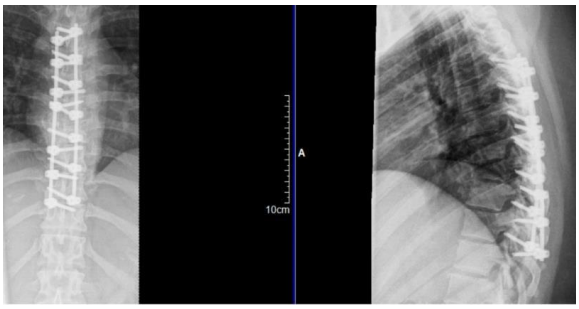


Fig. 5C. Postoperative X-Ray after spontaneous abortion

Case 6: 64 years old patient with Hangman fracture C2 and Th3, Th4 fracture type B2 AO (Figs. 6A, B) was operated as follows: C2 Hangman fracture fixation with bilateral transpedicular compressive screws and T1-Th5 crossed intralaminar screws (Fig. 6C). On postoperative CT scan all the screws are intralaminar, acceptable ligamentotaxis effect of the fixation (Fig. 6D).

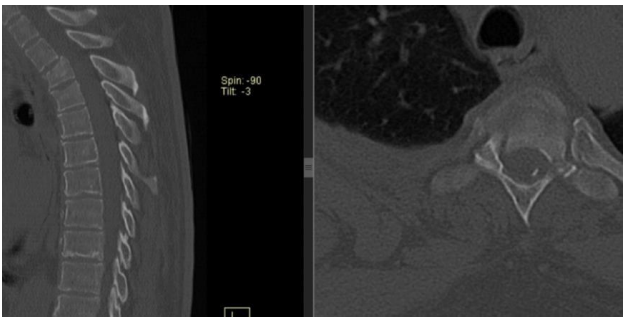


Fig. 6A. CT scan Th3, Th4 fracture type B2 AO

Fig. 6B. MRI Th3, Th4 fracture type B2 AO

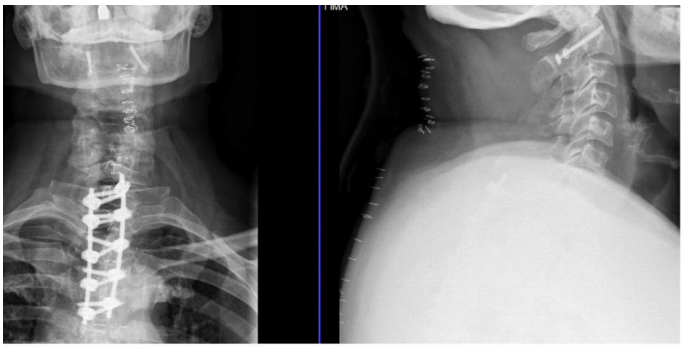


Fig. 6C. Postoperative X-Ray: T1-Th5 crossed intralaminar screws and C2 Hangman fracture fixation with bilateral transpedicular screws;

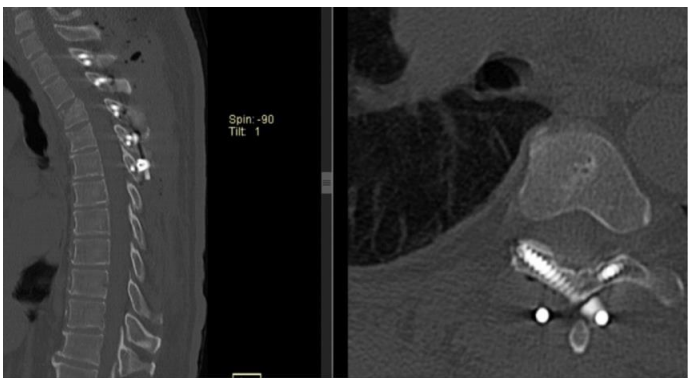


Fig. 6D. Postoperative CT scan all the screws are intralaminar, sufficient ligamentotaxis effect of the fixation

Case 7: 64 years old man, operated before L2-S1 arthrodesis and interbody cages in another service for multiple level lumbar stenosis, came due to pain and inferior paraparesis with adjacent level fracture L1 and regional kyphosis (Fig. 7A). He was operated as follows: extension of the fixation to S2 and Th10 (Fig. 7A) with good restoration of kyphosis. The patient recovered well, but 6 months later came back with severe paraparesis and Th10 screws pull out and regional kyphosis (Fig. 7B). He was submitted to extension of the fixation to Th3 with crossed intralaminar screws in Th4-Th8, in Th9 and Th3 we put transpedicular screws with double heads and double lateral rods (Figs. 7C, D). In the postoperative period, showed slow recuperation of motor deficit, no mention of pain.

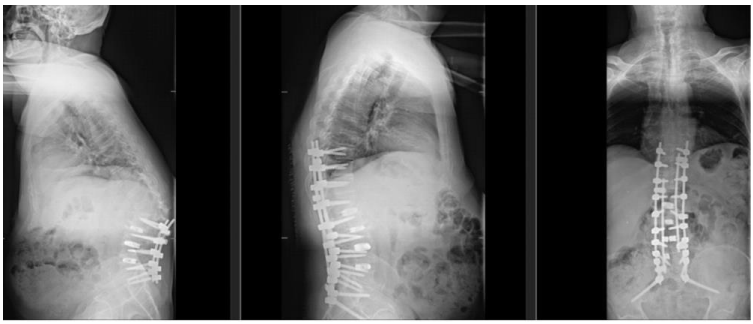


Fig. 7A. L2-S1 arthrodesis and interbody cages adjacent level fracture L1 and regional kyphosis

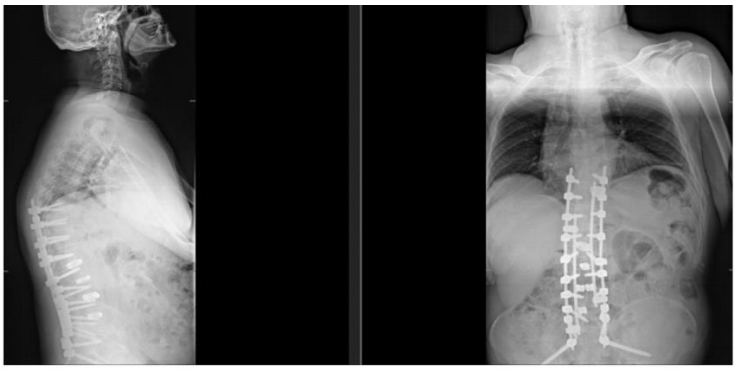


Fig. 7B. Extension of the fixation to S2 and Th10 with good restoration of kyphosis

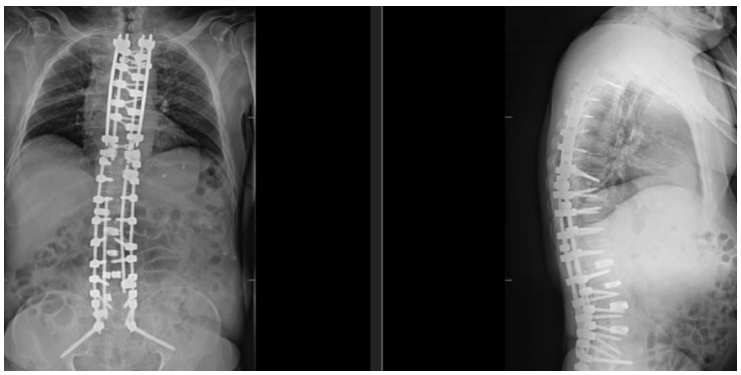


Fig. 7C. Th10 screws pull out and regional kyphosis

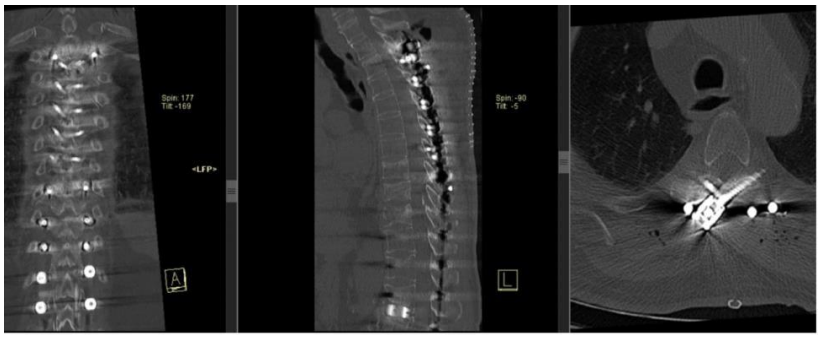


Fig. 7D. Extension of the fixation to Th3 with crossed intralaminar screws in Th4-Th8, in Th9 and Th3 transpedicular screws with double heads and double lateral rods

Case 8: 64 years old female, operated 12 years ago in another hospital. According to her, she had been operated three times during the hospitalization and does not know the specific pathology that had caused the hospitalization and the surgeries. Medical records were lost. Suffered poliomyelitis in child with severe neurologic sequels. At neurologic evaluation she had severe spastic tetra paresis, disabled and needs constant help, unable to walk on her own (Nurick grade 5). X-Ray reveals iatrogenic kyphosis, listesis C7, lower screws placed intradiscal (Fig. 8A). MRI and CT scan revealed kyphosis with severe spinal cord compression (Figs. 8B, C), caused by postoperative pseudarthrosis. She was operated on: cervicothoracic posterior fixation, lateral mass in the cervical region and crossed intralaminar screws in the thoracic region, decompressive laminectomy. In the postoperative period developed right C5 root palsy with gradual recuperation, good arthrodesis material positioning at on CT scan (Fig. 8D).

Fig. 8A. X-Ray revealing pseudarthrosis C7-Th1

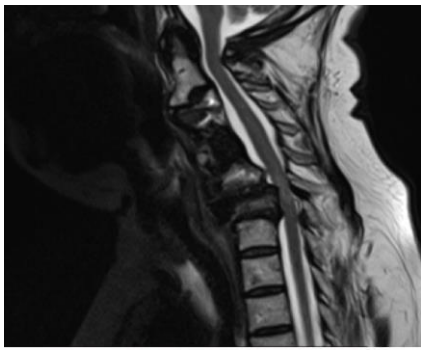


Fig. 8B. MRI revealed kyphosis with severe spinal cord compression

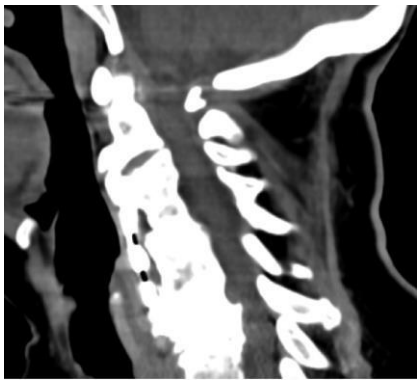


Fig. 8C. CT scan revealed kyphosis with severe spinal cord compression

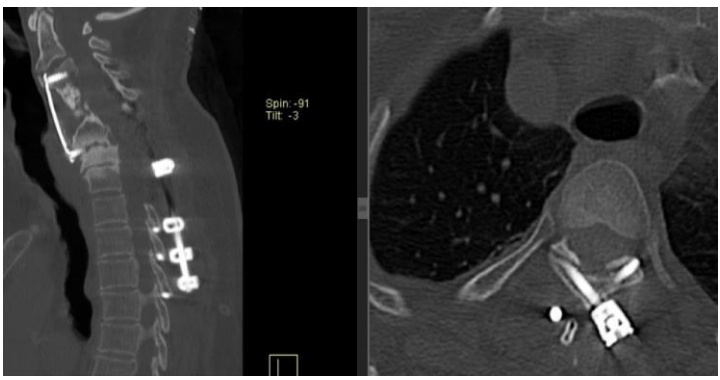


Fig. 8D. Postoperative CT scan

Fig. 8E. 6 months XR with whole constructions

Case 9: 82 years old man, fall from height with AO type C dorsal fracture at Th3 level (Fig. 9A) without neurological deficit. Was operated on: posterior fixation C7-Th2, Th4-Th6, Th3 laminectomy (Fig. 9B). After putting the lateral bars, we performed slight distraction and extension using in situ lateral bar molding tools with good ligamentotaxis effect, proven on postoperative CT and MRI (Fig. 9C).

Fig. 9A. Sagittal CT scan showing C type Th3 fracture

Fig. 9B. Postoperative CT scan picture

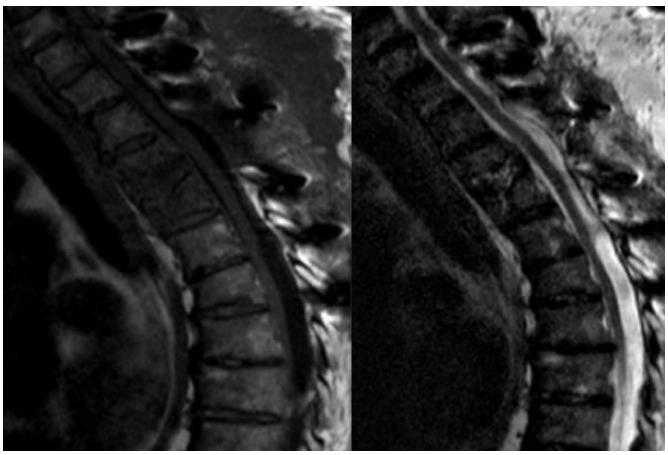


Fig. 9C. Post-op MRI

Case 10: 82 years old man, admitted for inferior paraparesis with installation within several weeks, no fever. MRI revealed spondylodiscitis Th3-Th4 with extensive epidural abscess and severe spinal cord compression (Fig. 10A). He was operated on: corpectomy Th3, Th4 through right side costotranseversectomy and arthrodesis with cylinder and posterior fixation with intralaminar crossed screws two level above and two below (Fig. 10B). Bacteriologic study showed no bacterial grow.

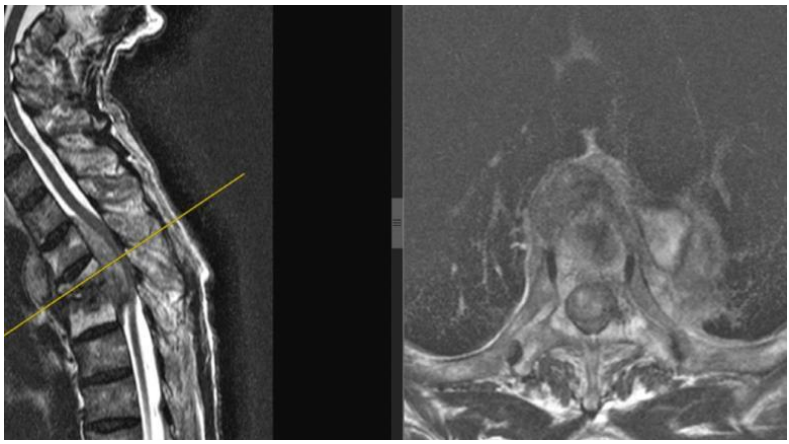


Fig. 10A. MRI revealed spondylodiscitis Th3-Th4 with extensive epidural abscess and severe spinal cord compression

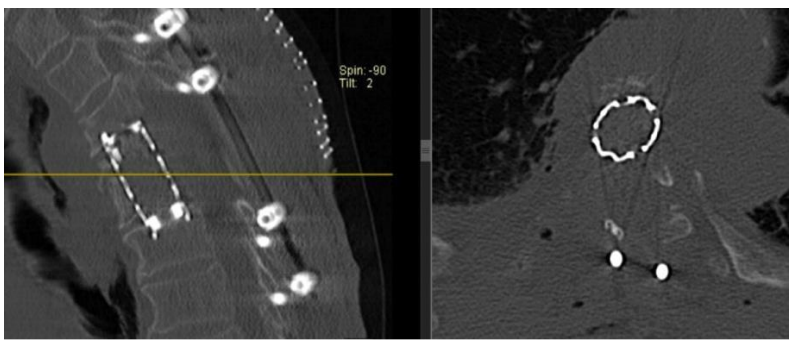


Fig. 10B. Post-op CT scan: corpectomy Th3, Th4 through right side costotranseversectomy and arthrodesis with cylinder and posterior fixation with intralaminar crossed screws two level above and two below

3. DISCUSSION

There are plenty of studies describing the feasibility of the C7 laminar screws. Most of the cadaveric study specimens demonstrate that:

1) Diameter of the lamina in C7 is suitable for 3,5 mm screw [12]
2) Equivalent pullout strength of C7 laminar screws and C7 pedicle screws, both being superior to lateral mass fixation [13]
3) Unilateral fixation is more feasible in women and bilateral fixation in men [14,15].

4) The majority of C7 levels would accept laminar screws based on width; all would accept bilateral screws based on height; and pullout strength was equivalent to C7 pedicle screws and greater than C2 laminar screw fixation [16,17].

Tae-Hyun Baek at al. based C7 vertebrae from 18 adult specimens performed morphometric measurements of laminar thickness, and found these anatomic measuments:

- the mean mid-laminar height was 13.7 mm,
- mean minimal laminar thickness was 6.6 mm,
- mean maximal screw length was 24.6 mm,
- mean spinolaminar angle was 50.8±4.7°.

Cross-sectional measurement results showed that the mean maximal thickness of upper, middle, and lower thirds was 5.0 mm, 7.5 mm, and 7.3 mm, respectively, and mean surface area for each part was 21.2 mm^2, 46.8 mm^2, and 34.7 mm^2, respectively. The vertical cross-sectioned area of the middle thirds at C7 spinolaminar junction was the largest area and the 3.5 mm screw can be accommodated with 77.8% of feasibility when lower thirds are the screw entry point. Thus, selection of middle and lower thirds for each side of the screw entry point in spinolaminar junction would be the safest way to place bilateral crossing laminar screw within the entire lamina [11].

Few references exist about the use of intralaminar screws in the thoracic region, except for upper thoracic vertebrae Th1, Th2 in the studies of McGirt [7] and Kretzer [8]. John Weaver et al. analyzed 112 T1 vertebrae. The placement of screws with widths of 3.5mm or 4mm and screws with lengths of 24mm or 26mm in the T1 lamina was feasible in all of the laminas measured with the exception of 2 outliers. Furthermore, relationships were found between T1 lamina size and patient height and between T1 lamina size and sex, but no relationship was found between T1 lamina size and race. The morphology of the T1 lamina allows for the simple and safe placement of common screw diameters and is a viable salvage or alternative to the traditional pedicle screw [18]. Müller evaluated 50 females and 50 males (age 20 to 60) CT with polytrauma CT from 2010 to 2012, randomly selected. Patients with injury in the thoracic spine, trauma-independent deformity, or dysplasia of the thoracic spine were excluded. A three-dimensional reconstruction of the thoracic spine was performed from the data set. The anatomical data of the lamina were measured under consideration of the potential trajectory of a laminar screw. The caliber of the corresponding pedicle was measured as well. The diameters of the lamina show a decline in superior-inferior direction (0.66cm in T1 to 0.60cm in T12 in males, 0.62 to 0.56cm in females). Diameters of pedicle and lamina show no correlation. Twenty percent of the pedicles have a hypoplasia with a diameter of less than 0.5cm. However, in these vertebrae, 62.3% of the laminae would be suitable for 0.4cm lamina screws. Only in 2.75% of the vertebral bodies there was no possibility for intralaminar or pedicle screws. This study shows that it is possible to use intralaminar screws in the thoracic spine in most of the patients [19].

4. CONCLUSION

The intralaminar screw insertion in the cervicothoracic junction and in the thoracic level can be used as an alternative or salvage technique to the use of pedicle screws. This technique is relatively safe and easy, but precise anatomic knowledge is required for safe insertion of bilateral crossing intralaminar screws. With a good preoperative planning of screw entry points, collision between the same lamina screw as well as the violation of laminar cortex can be both avoided. For bilateral crossing laminar screw insertion, rostral and caudal spinolaminar junctions can be chosen for each side, respectively, and different angles of screws, almost horizontal for the first screw pointing to the inferior angle of the lamina and lateral mass and ascendant for the second screw. Preoperative CT analysis helps to understand if the use of crossed screws is a feasible technique for each patient. The use of crossed intralaminar screw in the thoracic region is an underestimated technique; this free hand technique is a fast, efficient and alternative method of transpedicular fixation and this technique at different thoracic levels appears to be a useful tool in the armamentarium of the spinal surgeon. The patients follow up is to be published in future articles.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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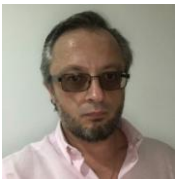

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Chapter 11
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Epidemiological Landscape of Hematological Malignancies: Global Trends and Health Estimations

Vasile Musteata [a,b*]

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ABSTRACT

This chapter evaluate the identification of the epidemiological patterns of HM in the Republic of Moldova and the evaluation of their global epidemiological trends and disease burden issues. Hematological malignancies (HM) are a public health problem. The pattern and distribution of diagnosed hematological cancers vary depending on age, sex, geography, and ethnicity suggesting the involvement of genetic and environmental factors for the development of these diseases.
This is an epidemiological, observational, cross-sectional and big data analytics study. The diagnosis was proved in all cases by histopathological, cytological, cytogenetic, molecular and immunophenotyping examinations. The qualitative type researches were performed and enriched by the narrative synthesis of the data from the specialized international bibliographic sources and official statistics concerning HM. The chapter summarized and systematized the primary studies, dedicated to the epidemiological landscape and global disease burden of HM. In order to obtain the scheduled objectives, the scientific medical publications were searched via GoogleSearch, PubMed, Z-library, NCIB, Medscape, Hinari database, by the keywords: “hematological malignancies”, “chronic leukemias”, “malignant lymphomas”, “epidemiological patterns”, “incidence”, “mortality”, “disability-adjusted life-years”, “disease burden”, “COVID-19 infection”, “management”. Forty-six relevant primary sources were identified and selected, according to the significance of the impact score under the scientific and reproducible approach to the disuted subject, with the subsequent data extraction, evaluation and interpretation. Intending to minimize the erratum, a copy of the data extraction sheet was initially formed, sharing all the elements to be extracted from the primary studies. The decrease of the incidence of HM in 2020 as compared to 2016 and 2017 can be explained by labor population migration and the impact of the COVID-19 pandemic on patients’ addressability. The average age of men was 54.7 years, of women – 57.9 years. In both gender groups, the patients aged between 50 and 79 years prevailed (males – 65%,

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females – 72.5%), partially fitting the category of a workable population. The gender analysis of morbidity showed that the male's rate was 51.5%, the female's rate – 48.5% in 2019. Within 2 years males were 50.4%, females – 49.6%. In the recent epidemiological context, the association of COVID-19 infection with HM proved to be of scientific and practical interest, taken into account an apparently immunocompromised status of patients with lymphoproliferative and myeloproliferative neoplasms.
The epidemiological study found that the Republic of Moldova had a slightly lower HM morbidity than countries in West Europe, primarily as a result of the migration of a workable population. The patients with chronic leukemias and malignant lymphomas, male gender and age categories of 50-79 years constituted the global epidemilological landscape. The narrative analysis of the literature has proved that patients with HM may experience a considerable disease burden with negative impact on their employment status, working productivity, annual household income and epidemiological susceptibility.

Keywords: Hematological malignancies; chronic leukemias; malignant lymphomas; epidemiological patterns; incidence; mortality; disability-adjusted life-years; disease burden; COVID-19 infection; management.

ABBREVIATIONS

HM : Hematological malignancies
NHL : Non-Hodgkin lymphomas
CML : Chronic myeloid leukemia
WHO : Word Health Organisation
BCR-ABL1 : Breakpoint cluster region-Abelson 1
JAK2 : Janus kinase 2
RT-QPCR : Reverse transcriptase quantitative polymerase chain reaction
GBD : Global burden of disease
DALYs : Disability-adjusted life-years
ASIR : Age-standardized incidence rate
EAPC : Estimated annual percentage changes
SDI : Social-demographic index

1. RATIONALE

Hematological malignancies (HM) are relatively frequent nosological entities within the structure of morbidity by malignant tumors, exhibiting a severe evolution, restrained prognosis and negative socio-economic impact in the advanced stages and phases. Several classification systems have been developed over the past several years to subdivide the HM by relevant clinical and biological means. These classifications facilitate the recognition of HM and therefore refine our ability to diagnose and treat these cancers [1,2]. Moreover, they enable the use of the same definition of a specific hematopoietic neoplasm, so that data comparison between studies is possible. In the economically developed nations and regions of the world, HM accounts for about 9% of all cancer cases and is the fourth most frequently diagnosed cancer in both males and females, behind prostate, lung, and colorectum [3]. HM may be considered

as an actual issue of the public health and oncology at the national, regional and global levels due to the severe relapsing evolution, restrained prognosis and unfavorable socio-economic impact in the advanced stages and phases. The Global Burden of Disease Study 2017 provided the incidence trends of leukemias; however, despite the major epidemiologic concerns about the quality of care and its components, comprehensive published data on the quality of care of HMs are scarce. Besides, the absence of a universal index to assess the quality of care in HMs is thought to be the principal problem in this journey [4]. Over the decades, there has been a growing trend in the incidence and prevalence of leukemias and malignant lymphomas both in the industrialized countries globally and in the majority of the administrative territorial units of the Republic of Moldova. Malignant lymphomas are malignant monoclonal proliferations of the lymphoid tissue cells [3,4]. Currently, NHL are a more frequent group of malignant hematological diseases, the incidence being continuously increasing [5,7,8]. The incidence of non-Hodgkin's lymphomas in USA and European countries is 14–19 new cases per 100000 population (4% of malignancies) [3,7]. The increased morbidity by extranodal B-cell lymphomas, follicular lymphomas, and T-cell lymphomas [8] is found in the majority specialty references. In 2016, there were 461000 newly diagnosed cases of NHL and 240,000 deaths due to the progression of these malignant lymphoproliferations. The incidence of NHL increased by 45% between 2006 and 2016, from 319078 to 461000 cases. Between 2006 and 2016, the incidence of leukemias increased by 26%, from 370000 to 467000 cases [5]. Chronic myeloproliferative neoplasms are the clonal leukemic neoplasms of the hematopoietic system, accounting for 40-50% of all leukemias in adults. These pathologies are characterized by the uncontrollable multiplication of myeloid, megakaryocyte and / or erythrocyte cell lineages, with the increase of the total and circulating cell pools. Morbidity due to CML varies between 0.6 – 1.6 cases per 100000 population [6,9,10]. The incidence of primary myelofibrosis is 0.5 – 1.5 cases per 100000 population [6,11,12]. The morbidity by polycythemia vera varies between 0.2 – 1.3 cases per 100000 population [6,11]. The morbidity by HM increases with age, with a maximum incidence between 45 and 65 years [7], the diseases thus affecting the working-age population. The increase in morbidity and disability in the working population, the weighted rate of late diagnosis of malignant hematological diseases argued the need to study their epidemiological aspects, indicating the priority of the topic under discussion for oncology hematology and public health.

2. OBJECTIVES OF THE STUDY

The aims of the study were the identification of the epidemiological patterns of HM in the Republic of Moldova and the evaluation of their global epidemiological trends and disease burden issues.

3. MATERIALS AND METHODS

The patients were followed-up between 2016-2022 at the comprehensive cancer center – Institute of Oncology from the Republic of Moldova. We applied the following research methods: epidemiological, observational, descriptive statistics, clinical-analytic, cross-sectional, big data analytics [13]. All patients from the

National Cancer Register were enrolled into the study. The epidemiological data about patients with HM were generated and processed in cooperation with the Medical Statistics unit. The diagnosis was proved by histopathological, immunohistochemical, cytological, cytogenetic, molecular and immune-phenotyping examinations of the bone marrow, peripheral blood, and biopsied lymph nodes. The type of HM was identified according to the criteria of the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue revised in 2017 [2,14,16]. Therefore, the diagnosis of acute leukemia was morphologically confirmed by complete blood count, bone marrow aspiration with cytological, cytochemical and cytogenetic examination, and determination of the percentage (≥ 20%) and type of blast cells. In cases of uncertain diagnosis, the type of acute leukemia was identified by performing immunophenotyping and cytogenetic examination of the venous blood and bone marrow aspirate [15]. RT-QPCR was applied in CML cases in order to determine the expression of p210 and p190 chimeric BCR-ABL1 gene transcripts at the step of diagnosis [9,10]. In cases with polycythemia vera and idiopathic myelofibrosis, the major diagnostic option was the bone marrow biopsy and the detection of JAK2 V617F mutation in the peripheral blood [11,16]. The diagnosis of multiple myeloma was proved by the bone marrow aspiration, which revealed the presence of malignant plasmacytic cells over 10% in cases of bone lesions. The relevant diagnostic percentage of myeloma cells should exceed 20% in cases of the absence of bone lesions [17]. Quantitative immunoglobulins and beta-2 microglobulin assay, M serum gradient and immunophenotyping were performed in the diagnostically uncertain cases. The qualitative type researches were performed and enriched by the narrative synthesis of the data. The accumulation of information for our researches was done by studying data from the specialized international bibliographic sources and official statistics concerning variables of HM. The chapter summarized and systematized the primary studies, dedicated to the epidemiological landscape and global disease burden of HM. In order to obtain the scheduled objectives, the scientific medical publications were searched via GoogleSearch, PubMed, Z-library, NCIB, Medscape, Hinari database, by the keywords: „hematological malignancies", „chronic leukemias", „malignant lymphomas", „epidemiological patterns", „incidence", „mortality", „disability-adjusted life-years", "disease burden", „COVID-19 infection", „management". Forty-six relevant primary sources were identified and selected, according to the significance of the impact score under the scientific and reproducible approach to the disuted subject, with the subsequent data extraction, evaluation and interpretation. With the aim to minimize the erratum, a copy of the data sheet was initially produced, listing the items to be extracted from the primary studies. The following indicators and variables related to HM were investigated: incidence and structure of morbidity, disease span from the onset to diagnosis, age-adjusted prevalence, GBD, age-standardized incidence rate, age-standardized rate, estimated annual percentage changes, DALYs.

4. RESULTS

The cooperation with the Medical Statistics unit allowed generation and processing the statistical data that revealed the epidemiological situation and

trend in the field of HM in the Republic of Moldova during the years 2016 – 2021. The number of newly diagnosed and followed-up patients with HM at the Institute of Oncology in 2016, 2017, 2018, 2019, 2020 and 2021 amounted respectively to 725, 802, 613, 628, 536 and 528, the incidence (new cases per 100000 population) being 17.6, 19.5, 14.9, 17.7, 15.1 and 20.3 per 100000 population (Fig. 1). After two intermittent years of decrease, the incidence of HM, thus, exhibited the slight increasing trend.

In 2020 Hodgkin lymphoma was diagnosed in 10.26% of all cases with HM, non-Hodgkin lymphomas – in 34.89%, multiple myeloma and plasma cells neoplasms – in 8.40%, lymphoid leukemias – in 18.28%, myeloid leukemias – in 9.51%, monocytic leukemias - in 2.24%, and other leukemias – in 15.86%. In 2021 HM constituted 6.2% of all newly-diagnosed cases with malignant tumors in the Republic of Moldova. In the same year Hodgkin lymphoma was diagnosed in 10.04% of cases, NHL – in 31.63%, multiple myeloma and plasma cells neoplasms – in 7.77%, lymphoid leukemias – in 17.42%, myeloid leukemias – in 12.31%, monocytic leukemias - in 0.95%, and other leukemias – in 16.29% (Fig. 2).

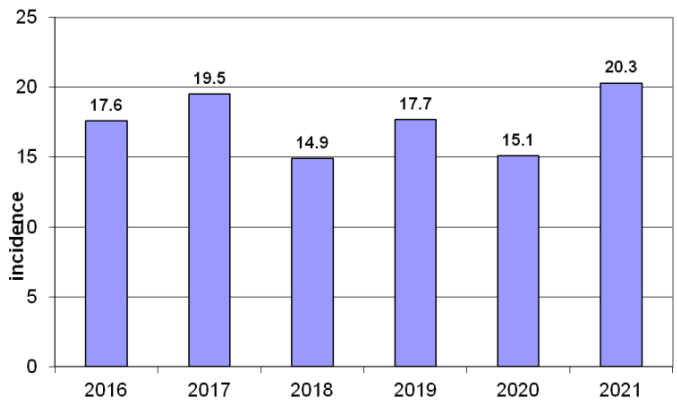

Fig. 1. The incidence trend of hematological malignancies per 100000 of population in the Republic of Moldova

In 2021, the incidence of Hodgkin's lymphoma (C81) was 2.0, NHL (C82-C85; C88, C96) – 6.4, multiple myeloma and plasma cell tumors (C90) – 1.6, lymphoid leukemias (C91) – 3.5, myeloid leukemias (C92) – 2.5, other leukemias (C93-C95) – 4.2 per 100000 (Fig. 3).

The decrease of the incidence of HM in 2020 as compared to 2016 and 2017 can be explained by labor population migration and the impact of the COVID-19 pandemic on patients' addressability. The average age of men was 54.7 years, of women – 57.9 years. In both gender groups, the patients aged between 50 and 79 years prevailed (males – 65%, females – 72.5%), partially fitting the category

of a workable population. The gender analysis of morbidity showed that the male's rate was 51.5%, the female's rate – 48.5% in 2019. Within 2 years males were 266 (50.4%), females – 262 (49.6%).The children constituted 4.0% of the newly diagnosed cases, 4.8% of those under the follow-up at the end of the year 2019 and 6.4% of the newly diagnosed cases in 2021.

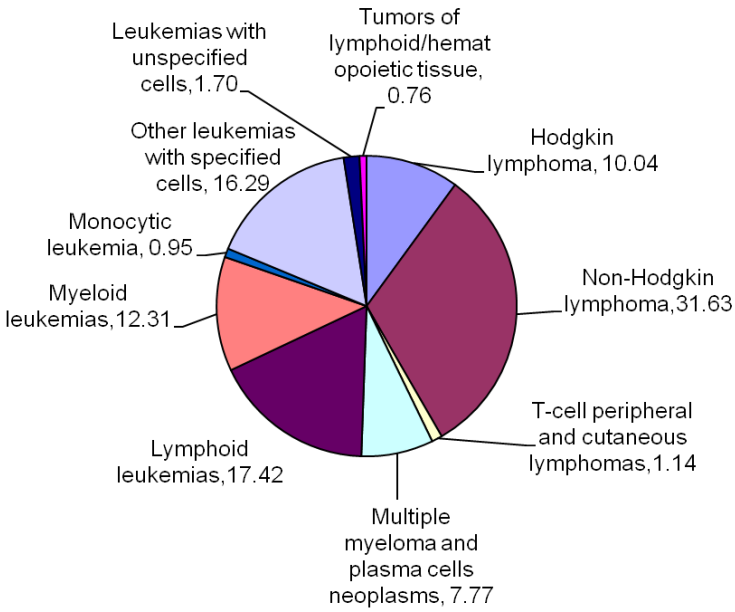

Fig. 2. The structure of morbidity by hematological malignancies in the Republic of Moldova in 2021

The study of the newly diagnosed advanced HM cases was performed for calendar years 2019 and 2021. In 2021 the disease span from the onset to diagnosis ranged between 1 – 24 months in the advanced cases and constituted on average 5.63 months, without significant difference as compared to 2019 (5.76 months). In the advanced cases, the diagnosis of HM was established within 1-6 months in 74.3%, within 7-12 months – in 20%, and within 12-24 months – 5.7% ($p > 0.05$). Indolent non-Hodgkin lymphoma, multiple myeloma and primary myelofibrosis cases were commonly associated with the delayed diagnosis.

The research sample enrolled 121 (52.2%) male cases and 111 (47.8%) female cases with CML, with statistical representation. Unlike most hematological malignancies, there is currently no statistically significant gender predominance in CML, the male:female ratio being 1.1:1 ($p>0.05$). The average age of the patients at the time of diagnosis was 47.9 ± 0.94 years, ranging from 19 to 81 years. The distribution by age groups indicated an increased frequency of

subjects of the age category up to 60 years (75.0%). This phenomenon denotes the prevalence of the workable age patients, as well as the important share of the relatively young patients (up to 50 years) – 51.3% subjects. At the same time, most patients have been diagnosed in the age groups of 40-49 and 50-59 years, accounting respectively 53 (22.8%) and 55 (23.7%) cases ($p<0.05$). Nevertheless, we observed the CML trends to affect younger age groups of male gender (19-29 years = 14.0%, 30-39 years = 18.2%) and 60-69 years age group (22.5%) of the female gender. The study of the structure of the research sample according to the residence identified the higher rate of patients from the urban areas (58.2%) regardless of gender ($p<0.05$). According to the available data of the official statistics (2022) in the Republic of Moldova the rural resident population constituted 57.7%, and those urban residents – 42.3%.

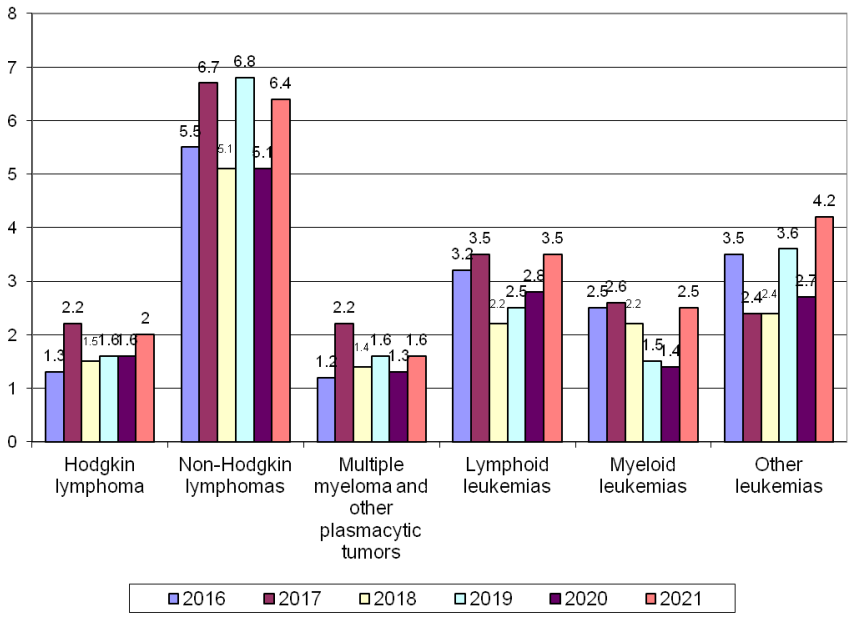

Fig. 3. The incidence trend of hematological malignancies per 100000 of population in the Republic of Moldova with regard to nosological entity

5. DISCUSSION

The narrative review of the published world experience was performed with the aim to assess the epidemiological trends, disease burden and financial impact of HM on public health. To perform the situational analysis, the global studies used the statistical indicators of the GLOBOCAN database, obtained for the year 2018 from 185 countries, as well as the incidence records from Cancer Incidence in Five Continents (CI5) in order to examine dynamic trends [18,19]. Currently, NHL

are considered the more common group of HM, the incidence being continuously increasing. The incidence of Western cancers is 14-19 new cases per 100000 inhabitants and equal to 4% of all cases with malignant tumors [3,5,7]. Increased morbidity in extra-ganglionic B-cell lymphomas, follicular lymphomas, and T-cell lymphoma lymphomas is found in the majority of specialty references. In 2016, there were 461000 (95% UI, 428000-482000) newly diagnosed cases of non-Hodgkin lymphoma and 240000 deaths (95% UI, 221000-248000) due to the progression of these lymphoproliferative malignancies [5]. The incidence of NHL increased by 45% between 2006 and 2016, from 319078 to 461000 cases. Globally, the newly diagnosed cases cases between 2006 and 2016 increased by 45% (95%UI, 38%-48%), of which 17% were due to the increasing age-specific incidence rates, 15% – to changing population age structure, and 12% – to population growth. Worldwide in 2018, NHL constituted the 5-9th most frequent group of malignant neoplasms, with nearly 509590 new cases and 248724 deaths [20]. Incidence rates at the beginning of the last decade varied significantly by geographical region, being higher in males, especially in Israeli Jews (age-standardized incidence of 17.6 per 100000 inhabitants), in white Americans (14.5 per 100000), in Australia (15.3 per 100000), Canada (13.7 per 100000) and Portugal (13.3 per 100000). The similar geographical pattern was also observed in females, with the highest incidence rates recorded in the population of Israel (13.0 per 100000), white Americans (10.4 per 100000), in Canada (10.0 per 100000), Australia (12.3 per 100000) and the lowest – in Middle Africa (2.8 per 100000), South Africa (1.6 per 100000), Vietnam (3.5 per 100 100000), India (3.6 per 100000). Higher incidence rates of non-Hodgkin's lymphomas were frequently found in countries classified as having a very high Human Development Index, while many countries rated as having a low and medium Human Development Index showed a lower incidence. The authors summarized that the relationship between the incidence rate of NHL and the level of the Human Development Index seemed to be determined by countries with a very high level of this composite statistical indicator. Compared with Western countries, Asian patients have an increased rate of marginal zone lymphoma and a decreased rate of follicular lymphoma and chronic lymphocytic leukemia/small cell lymphocytic lymphoma [21-23]. Those differences likely reflect known variations in genetic susceptibility to B-cell NHL between Asian and Western populations [24,25]. For some histopathological subtypes, the existence of certain molecular pathways or etiological factors is assumed, which may contribute to regional differences in incidence rates. For example, despite the low incidence of follicular lymphoma in Asia compared to Western populations, the frequency of the bcl-2 translocation, characteristic of this histopathological type, is similar in healthy populations from both regions, suggesting that the development of follicular lymphoma may be triggered in Asia and in western countries through different mechanisms [26]. However, the incidence of NHL is increasing both globally and regionally. The epidemiological study, performed in South Korea, demonstrated that the age-standardized incidence of B-cell NHL increased dynamically from 5.74 (95% CI, 5.51 to 5.98) per 100000 inhabitants in 2011 to 6.96 (95% CI, 6.72 to 7.20) per 100000 inhabitants in 2015. The age-standardized incidence rates of diffuse B-macrocell lymphoma, marginal zone lymphoma and of follicular lymphoma were significantly increased ($p<0.001$), with

similar increases seen in men and women [27]. Between 2011 and 2015, the incidence of diffuse large B-cell lymphoma increased by 11%, of marginal zone lymphoma – by 32%, and of follicular lymphoma – by 25%. The age-standardized incidences of mantle cell lymphoma and Waldenstrom's macroglobulinemia remained relatively stable between 2011 and 2015, although in Waldenstrom's macroglobulinemia there was some annual variation in morbidity in women and men. The crude and age-standardized prevalence of B-cell NHL increased steadily every year and was about 2.5 times higher in 2015 than in 2011. The South Korean epidemiological study shows that the prevalence indices of each subtype of B-cell NHL also increased. The age-adjusted prevalence of diffuse large B-cell lymphoma increased 1.8 times, of chronic lymphocytic leukemia/lymphocytic lymphoma – 1.7 times, of follicular lymphoma – 2.6 times, of mantle cell lymphoma – 4.0 times, marginal zone lymphoma – 11.3 times and Waldenstrom's macroglobulinemia – 1.6 times ($p<0001$). These increases are considererd to be similar in women and men across all B-cell NHL subtypes.

Despite the implementation of new antineoplastic agents, the available bibliographic sources reported about a dynamic increase of gross and age-standardized mortality rates. The recent researches revealed that the age-standardized mortality increased by 42% from 1.33 per 100000 inhabitants in 2011 to 1.89 per 100000 population in 2015. NHL mortality rate was also growing before this period, estimated at 143000 deaths in 1990 and 210000 deaths in 2010 [28]. The highest mortality rate from NHL was reported in New Zealand and Canada. The mortality rate in the USA was estimated at 1910 cases in 2018 [22] and at 3125 cases in Canada during the years 1984–2014 [29]. The similar trend from the mortality rate was observed in China, with 52,100 deaths caused by this malignant tumor (32700 men and 19400 women) in 2015 [30]. According to another publications, the death rate from NHL increased by 2.5% annually from 1975 to 1991, with a downward trend during 1991-1997 (1.6% annually). Subsequently, during the period 2006-2011, the mortality rate decreased annually by 3.1% [31,32]. In 2016, there were 467000 (95% UI, 423000-489000) new cases of leukemias worldwide and 310000 (95% UI, 286000-324000) deaths. Between 2006 and 2016, the newly diagnosed cases increased by 26% from 370000 (95% UI, 344 000-385000) to 467 000 (95% UI, 423 000-489 000). The main contributors to this increase were population growth by 12%, population aging by 10%, and an increase in age-specific incidence rates with 3% [5]. In 2011, an estimated 44600 patients were diagnosed with acute and chronic leukemia in the United States, and in 21780 cases death occurred due to the progression of these diseases. The growing interest is attributed to the epidemiological patterns and diseases burden of the BCL/ABL1-positive and BCL/ABL1-negative myeloproliferative neoplasms. The incidence and prevalence of these HM varies worldwide, but exhibit a trend of slow increase. Morbidity due to chronic myeloid leukemia varies between 0.6-1.6 cases per 100000 population. The incidence of primary myelofibrosis is 0.5-1.5 cases per 100000 population. Morbidity due to polycythemia vera varies between 0.2-1.3 cases per 100000 population. Morbidity due to malignant hematological diseases increases with age, with a maximum incidence between 45 and 65 years, the diseases thus affecting the working-age population.

In 2017 the study of the GBD analyzed and systematized data on the incidence and annual mortality of CML, DALYs, risk attributive factors, as well as information on age, geographical distribution and sex. Globally, NHL caused 6.8 million (95% CI, 6.2–7.1 million) DALYs in 2016, with 98% arising from years of life lost and 2% from years lived with disability [5], placing these lymphoproliferative malignancies in a favorable position as compared to leukemias. Worldwide in 2016 leukemias caused 10.2 million DALYs (95% UI, 9.3-10.8 million). The GBD 2017 study classified the countries of the world into 5 quintiles (high, high-medium, medium, low-medium, low) of the SDI. With regard to CML, the GBD has varied significantly from country to country due to different possibilities for early screening, accessibility of new antineoplastic agents and medical resources [33,34]. In order to describe the CML burden, annual incidence cases, death cases, DALYs and the corresponding ASR were analyzed. The EAPC were appreciated on the ASR base and used to quantify the ASR trend. In 1990, the ASIR was higher (1.34 per 100000 population) in quintiles with high SDI. By 2017, there was a significant upward trend of ASIR in low SDI quintiles (0.65 per 100000 population, 95% IU), which exceeded high SDI quintiles (0.53 per 100000 population, 95% IU). Regarding the geographical distribution, in 2017 Western Europe with an incidence of 61.62×10^2 (95% IU) of cases and South Asia with an incidence of 80.44×10^2 (95% IU) of cases remained in the top of the higher morbidities among regions of the world. In the same year in these geographical areas the highest number of deaths and DALYs was found – respectively 42.45×10^2 (95% IU) and 66.60×10^2 (95% IU), 68.46×10^3 (95% IU) and 207.79×10^3 (95% IU). In 1990 the age-standardized death rate (ASDR) (0.92 per 100000, 95% IU) and the ASR of DALYs (24.23 per 100000, 95% IU) proved to be superior in quintiles with high SDI. In 2017, the situation was considerably opposed, with a comparatively high level of ASDR (0.6 per 100000 population, 95% IU) and ASR of DALYs (16.71 per 100000 population, 95% IU) in quintiles with low SDI. The study found that ASIR ($\rho = -0.610$, $p<0.01$), ASDR ($\rho = -0.471$, $p<0.01$) and age-standardized DALYs rate ($\rho = -0.403$, $p<0.01$)) in 1990 exhibited negative correlation with the corresponding EAPC. The correlations between SDI and EAPC incidence ($\rho = -0.509$, $p<0.01$), deaths ($\rho = -0.620$, $p<0.01$) and DALYs ($\rho = -0.632$, $p<0.01$) were also negative. Herewith, the the referring study could demonstrate a faster decreasing trend of ASR in countries with weightier disease reservoir baseline in 1990 or with higher SDI in 2017. The trends in the CML burden revealed by the GBD study provided important information for the promotion of medical services and public health. Despite the declining overall trend of ASIR, ASDR, and age-standardized DALYs in quintiles with high SDI, the CML burden remains stable due to increased population growth in the emerging region countries and an aging population in the developed countries [5]. Between 1990-2017, the incidence decreased by 34.9% in quintiles with high SDI, increasing by over 60% in quintiles with low SDI, medium-small and medium SDI. Developing countries continue to bear the substantial burden of CML mainly due to the reduced access to the newest targeted antineoplastic therapy [35].

The issues of medical costs of HM treatment is a subject of regular concerns in the scientific literature, emerged especially in the realm of NHL. A retrospective

cohort analysis of direct costs was undertaken in patients primarily diagnosed with NHL and in the control group (subjects without oncologic diagnosis) using the MarketScan® medical and drug claims database from the eligible employers [36]. The analysis was carried out in order to demonstrate the dynamics of costs related to aggressive NHL by examining the costs associated with the remission induction, secondary and palliative phases of treatment, as well as to evaluate the economic consequences of treatment failure. Patients with aggressive (n = 356) and indolent (n = 698) NHL were found to receive health services with high associated costs compared to control group. The primary determinants of costs were hospitalizations (aggressive NHL – 44%, indolent NHL – 50% of total costs) and outpatient visits (aggressive non-Hodgkin's lymphomas – 39%, indolent non-Hodgkin's lymphomas – 34% of total costs).

A study of the USA working population [37] may be considered of scientific and practical values, which assessed the indirect costs and workplace productivity losses associated with NHL using The MarketScan® Commercial Claims and Encounters and Health and Productivity database Management Databases (2007–2013). As compared to the control group, patients with NHL sustained the most significant loss of workplace productivity (31.99 days; 95% CI: 25.24 days, 38.73 days; p<0001). After 12 months from diagnosis, indirect costs associated with non-Hodgkin's lymphomas were increased (6302.34$; 95% CI: 4973.40$, 7631.28$; p<0001). In aggressive NHL, the mean monthly costs of induction treatment (10970$) and palliative care (9836$) exceeded those related to the secondary phase of treatment (3302$). The average cost of treatment failure in the respective histopathological types was 14174$ per month and 85934$ over the entire study period. Therefore, the treatment-related expenses were higher in aggressive NHL compared to indolent ones, especially in the induction phase and palliative care. The authors concluded that treatment failure proved to be the most costly aspect of medical care.

The degree of utilization of health system resources was studied in cases of progression of NHL. Patients with tumor progression had 23% more frequent outpatient visits compared to patients in remission (p<0001). In the group of patients with progression, the frequency of referral for laboratory investigations was twice as higher (p<0001) in outpatient conditions. The proportion of patients who received chemotherapy increased significantly (72%) as compared to those without progression (29%; p<0001). In the group of patients with progression, the authors found the higher frequency of visits for combined infusional chemotherapy (1610.86) as compared to the group without progression (166.07; p<0001), suggesting the administration of more intensive chemotherapy regimens, since the majority of responded patients followed the maintenance therapy with Rituximab. Follicular NHL progression was associated with a higher frequency (18%) of hospitalizations and emergency departments visits as compared to cases with remissions or tumor stabilization (4%; p<0.001). The obtained results supported the authors' hypothesis, according to which the treatment strategies that postponed or prevented the progression of follicular NHL not only improved clinical balances, but also ensured the substantial economic benefits in terms of costs reduction of the provided medical services.

Another study [38] demonstrated that, based on the standard monthly cost for a patient, the mean costs of treatment failure in aggressive NHL were 14174$, being significantly higher than those estimated in follicular NHL. The improved survival rates indicate that more patients are living with the disease. The patients with progression of the tumor process and conventional treatment registered a relatively long life span [39].

An analysis of the Living with MPNs survey was conducted to assess the impact of chronic myeloproliferative neoplasias on employment, career potential and work productivity [40]. This cross-sectional survey included respondents between the ages of 18 and 70 living in the US. The survey included ~100 questions related to the diagnosis of chronic myeloproliferative neoplasia, medical history of the disease, symptoms and functional status determined by chronic myeloproliferative neoplasia, changes in employment and work productivity, impact on daily activities from the date of diagnosis. The Chronic Myeloproliferative Neoplasia Symptom Assessment Form Total Score (MPN-SAF TSS) was used to assess symptom burden. The Work Productivity and Activity Impaired by Specific Health Problem Questionnaire (WPAI-SHP) was used to assess the effects of chronic myeloproliferative neoplasia on work productivity and activity. Of the 904 respondents, 592 were employed at the time of diagnosis. About half (50.5%) of the 592 respondents reported ≥1 change in their employment status due to diagnosis, the most common being “left a job” (30.2%), “went on leave medical leave due to disability" (24.8%) and "had reduced working hours for at least 3 months" (21.8%). Among respondents who remained employed at the time of survey participation (n = 398), mean WPAI-SHP scores were as follows: absenteeism – 6.9%, presenteeism – 27.4%, total work impairment – 31.1 % and activity impairment – 32.8%. WPAI-SHP scores correlated positively with MPN-SAF TSS (correlation coefficients – 0.37-0.70; P <0.001). Analysis of the Living With MPNs study indicated that chronic myeloproliferative neoplasms exert a substantial negative impact on patients' employment, career potential and work productivity. The degree of work productivity impairment caused by chronic myeloproliferative neoplasia was comparable to that in other chronic pathologies. Patients with moderate to severe rheumatoid arthritis reported impairments regarding productivity and work activity (range of mean scores: absenteeism – 2.4-11.8; presenteeism – 13.7-39.7, total work impairment – 15.2-43.2 , activity impairment – 19.1-56.2), which were similar to values recorded from respondents in the Living with MPNs survey.

An extensive study of the financial burden of chronic myeloproliferative neoplasms on patients was conducted in the USA in 2014 [38]. For analysis, 369 subjects were eligible, with the diagnosis established until 2013 and the age between 16 – 65 years at the time of diagnosis (primary myelofibrosis – 85, polycythemia vera – 172, essential thrombocythemia – 112). Almost all patients (99%) had health insurance, including commercial insurance by an employer (primary myelofibrosis – 46%, polycythemia vera – 53%, essential thrombocythemia – 57%) and Medicare (primary myelofibrosis – 40%, polycythemia vera – 34%, essential thrombocythemia – 24%). The average household income in 2013 for patients with primary myelofibrosis, polycythemia

vera, and essential thrombocythemia was similar to each other (79,800 $, 80,200 $, and 80,400 $, respectively) and slightly higher than the total income per capita in 2013 (75,839 $). A significant proportion of patients in each group of chronic myeloproliferative neoplasms reported that their disease led to reduced working hours, interruption of activity and medical disability: primary myelofibrosis – 38%, 35%, 33%, polycythemia vera – 33%, 28% and 15%, essential thrombocythemia – 28%, 21% and 4%, respectively. The patient's medical and social aspects, such as age and health insurance status, were similar among patients who reported effects associated with chronic myeloproliferative neoplasms on employment and patients who were not related to each group of chronic myeloproliferative neoplasms. In each group of chronic myeloproliferative neoplasms, the average percentage of loss of household income in patients with reduced working hours, discontinuation of employment and medical disability were in primary myelofibrosis – 16%, 18%, 28%, polycythemia vera – 15%, 24%, 17% and essential thrombocythemia – 0%, 24%, 37%, respectively, compared to patients who did not have any impact of chronic myeloproliferative neoplasms on their employment status. Discontinuation of employment and medical disability tended to have a wider negative impact as compared to reduced working hours in all chronic myeloproliferative neoplasms [38,41]. Nevertheless, the degree of impairment of occupational productivity, caused by chronic myeloproliferative neoplasms, proved to be comparable to that in other chronic non-oncologic pathologies.

A relevant study of multiple myeloma related costs was performed by the university hematology centers from Italy [42]. The study enrolled 236 patients with this common and disabiliting HM. In 164 (69.5%) cases the period of disease monitoring and reporting did not exceed 5 years. Patients treated with autologous hematopoietic stem cell transplantation were younger (average age – 58.7 years) as compared to those managed with chemotherapy and immunomodulatory drugs (average age – 67.8 years). The total costs of the disease reached the value of 19267.1 € ± 25078.6 (asymptomatic patients – 959.3 € ± 1091.6; symptomatic patients receiving medication – 21707.8 € ± 21785.3; symptomatic patients treated with autologous transplantation of stem cells – 59243.7 € ± 4214.0; patients in plateau / remission – 8130.7 € ± 15092.5). The main determinants of the total costs of the disease were medication and hospitalizations (46.1% and 29.4%, respectively). Antineoplastic and immunomodulatory preparations constituted 21.6% and 21.1% of the total costs of the disease. The list of costs of antineoplastic drugs was led by bortezomib (97.4%), while lenalidomide (99.4%) served as the determining cost factor in immunomodulatory therapy. The cost of hospitalization ensured by the Italian National Health Service was mainly influenced by transplantation (94.6%), while chemotherapy and treatment of skeletal fractures did not exceed 1% and 2%, respectively. The financing of health care costs, pocket expenses and lost productivity accounted repectively for 83.8%, 3.1% and 13.1% of the total costs of the disease. The lowest and highest occupational productivity losses were reported by asymptomatic patients (21.9 € ± 95.3) and patients after autologous stem cell transplantation (9538.3 € ± 17612.4). These amounts were equal respectively to 2.3% and 16.1% of the total costs of the disease. The same

groups of patients required the lowest and highest costs for informal care: 51.3 € ± 147.7 (5.4% of the total cost of illness) and 1015.4 € ± 2100.1 (1.7% of the total cost of the disease), respectively.

Regional disparities are reported in patient characteristics and socio-economic impact of HM, which may reflect the differences of the ethno-racial identity and level of access to healthcare [43]. The Hemato-Oncology Latin America (HOLA) study described characteristics and treatment patterns of Latin American patients with multiple myeloma, chronic lymphocytic leukemia and NHL. Of 5,140 patients, 2,967 (57.7%) had NHL, 1,518 (29.5%) multiple myeloma, and 655 (12.7%) chronic lymphocytic leukemia. Median follow-up was 2.2 years for multiple myeloma, 3.0 years for chronic lymphocytic leukemia, and 2.2 years for NHL, and approximately 26% died during the study observation period. Most patients had at least one comorbidity at diagnosis. The most frequent induction regimen was thalidomide-based chemotherapy for multiple myeloma and chlorambucil with or without prednisone for chronic lymphocytic leukemia. Most patients with NHL had diffuse large B-cell lymphoma (49.1%) or follicular lymphoma (19.5%). The majority of patients with diffuse large B-cell lymphoma or follicular lymphoma received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. The HOLA study produced the high-quality and real-world evidence on patient characteristics, treatment patterns and impact of HM.

In the recent epidemiological context, the association of COVID-19 infection with HM proved to be of scientific and practical interest, taken into account an apparently immunocompromised status of patients with lymphoproliferative and myeloproliferative neoplasms. A study of 125 hospitalized patients with malignant hematological neoplasms revealed a 10 percentile rate (6, 17%) of COVID-19 infection in 2020, but none of the subjects were diagnosed with CML [44]. Despite the results of this study in the same year during the pandemic with SARS-CoV-2 infection, 530 cases of CML were studied in 29 medical centers of the Anti-Cancer Association of Hubei (China) [45,46]. Five patients developed COVID-19 infection, so the prevalence of this disease was 0.9% (95%, 0.1, 1.8% privacy interval), nine times exceeding that indicator (0,1% (0, 0,12%)) in the healthy population, but being lower than 10% (6, 17%) reported in the hospitalized patients with other HM and 7% (4, 12%) - in the healthy health care providers. The evolution of the infectious process in cases with CML has proven to be typical both in terms of the clinical picture and the imaging of the chest on computed tomography. Co-variations associated with an increased risk of developing COVID-19 among patients with CML were exposure to persons infected with SARS-CoV-2 (P = 0.037), lack of complete hematologic response (P = 0.003) and comorbidities (P = 0.024). At the same time, the increased risk of developing COVID-19 infection was observed in patients with advanced CML (P = 0.004) despite obtaining a complete cytogenetic response or major molecular response at the time of exposure to SARS-CoV-2. During the treatment with TKYs, COVID-19 infection developed in one of 21 patients under the 3rd generation medication, in 3 of 346 under the imatinib mesylate medication, and in none of the 162 who received the 2nd generation (P = 0.096). From these data it

can be suggested that generations 1 and 2 of TKIs are associated with a reduced risk of SARS-CoV-2 infection and emerged disability, which contends the corresponding evaluations from the previous study. Other co-variations such as age and duration of treatment with TKIs were not associated with an increased risk of developing COVID-19 infection. It can be recapitulated that patients with the identified risk factors should benefit from the increased surveillance in terms of SARS-CoV-2 infection under the management plan, with the possibility of protective isolation and testing.

The narrative analysis of the recently published studies revealed, that the socio-economic impact of HM depended on nosological entity, and was determined by the degree of emerged disability, level of access to healthcare, treatment complexity and the need for hospitalizations. Prevention or reversal of unfavorable medical and social patterns of HM can be considered as a factor of the improvement of patients' management, which reduces the negative impact on their employment status, working productivity, annual household income and epidemiological susceptibility.

6. CONCLUSIONS

The epidemiological study revealed the slightly lower morbidity by HM in the Republic of Moldova as compared to the West European countries mainly due to the migration of a workable population. Patients with chronic leukemias and malignant lymphomas, male gender and age categories of 50-79 years constituted the global epidemilological landscape of HM. Nevertheless, the epidemiological study of CML determined the prevalence of the workable age patients, as well as the important share of the relatively young patients (up to 50 years) and female gender. The narrative analysis of the literature has proved that patients with HM may experience a considerable disease burden with negative impact on their employment status, working productivity and annual household income. Asian patients had an increased rate of marginal zone lymphoma and a lower rate of follicular lymphoma and chronic lymphocytic leukemia/small cell lymphocytic lymphoma, as compared to the Western countries. The narrative analysis of the literature revealed that patients with HM, especially those with aggressive NHL, acute leukemias, multiple myeloma and chronic myeloproliferative neoplasms, may experience a considerable disease burden with negative impact on their employment status and working productivity, which in turn may be associated with low annual household income. The synthesis of bibliographic references showed the increase of expenses related to the treatment of aggressive NHL as compared to those indolent, especially in the induction phase and within the framework of the palliative service. Treatment failure proved to be the most costly issue of medical services provided to patients with NHL. The prevention or reversal of the unfavorable medical and social patterns of HM can be considered as an optimizing factor of patients' management, which reduces the negative impact on their employment status, working productivity, annual household income and epidemiological susceptibility.

AUTHOR'S CONTRIBUTION

The sole author designed, analysed and interpreted the data, prepared and revised the manuscript.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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DISCLAIMER
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Chapter 12
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Enhancing Healing and Psychological Comfort through Taylor Flap Reconstruction: Addressing Therapeutic Challenges in a Developing Country

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ABSTRACT

This chapter aimed to assess the feasibility and then report the short, medium and long-term results of Taylor flap reconstructions after abdomino-perineal amputation extended to the posterior wall of the vagina, taken by the tumor mass. The essential physical and psychosocial features of hospitals are studied in relationship to various hospital inhabitants' objective and perceptive health outcomes. These environmental features are interrelated and affect healing.

We describe and analyze below two cases of perineal reconstruction by modified Taylor flap.

Two of our patients underwent abdominoperineal amputations in 2020 due to malignant melanoma of the anal canal and lower rectum adenocarcinoma, respectively. These patients underwent rectus abdominis musculocutaneous flap reconstruction pedicled on the inferior epigastric vessels and with a transverse skin paddle. .

Our two patients underwent a posterior colpectomy associated with abdominoperineal amputation, which improved the quality of life of the patients, in particular an almost normal sexual activity in the medium and long term. the Taylor flap represents the reference technique for covering large pelvic-perineal losses of substance, particularly in enlarged APAs.

The postoperative follow-up was simple with an average hospital stay of 09 days. Abdominoperineal healing completed with a median of 19.5 days.

The implementation of modified Taylor flaps allowed for both patients' psychological comfort in connection with satisfying sexual activity as well as a complete and quick perineal healing.

Keywords: Taylor flap; abdominal-perineal amputation; posterior colpectomy; melanoma; rectal cancer; rectus abdominus.

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1. INTRODUCTION

The abdomino-perineal amputation is burdened with significant morbidity closely related to the inevitable large perineal defect due to wide excision.

Hence the importance of pelviperineal filling techniques to facilitate perineal healing and to ensure a better quality of life, especially sexual, in women after posterior colpectomy, instead of a mutilating posterior pelvic exenteration [1,2]. The **Abdomino Perineal Amputation** (APA) is the gold standard procedure for lower rectal cancers.

In the latest published series, postoperative complication rates without perineal reconstruction vary from 35 to 66% [3].

With the evolution of soft-tissue reconstruction, microsurgery, and free-tissue transfer, muscle and myocutaneous flaps have become established workhorse flaps for numerous types of reconstructive surgeries. Although perforator and fasciocutaneous flaps have recently grown in popularity, muscle and myocutaneous flaps have vascular supply from named vessels and have a consistent blood supply, and remain a good option for many different reconstructions [4]. Since 2002, we have turned to plastic surgery using musculocutaneous flaps to address the postoperative complications brought on by the extent of the excision and the challenge of closing the perineal defect. By preserving the lower genital tract, we are able to preserve sexual function, especially in women, which has a significant positive impact on the patients' quality of life.

We report two cases of perineal reconstruction using a modified Taylor flap. We analyzed the postoperative course, specific complications, and results of this surgery.

2. METHODS

We report two cases of lower rectal cancer treated during the year 2020. They were two women in their 50s with a WHO (world health organization) score of 0, preserved nutritional status, and no surgical history that could compromise vascular flow tributary to the lower epigastric vessels.

One of them had a malignant melanoma of the anal canal (Fig. 1), while the other patient had a well-differentiated adenocarcinoma of the lower rectum (Fig. 2), treated with APA after concomitant radio-chemotherapy.

In both patients, the abdominoperineal amputation extended to the lower 2/3 of the posterior vaginal wall to obtain an R0 resection and the reconstruction required an extension of the skin flap to ensure the plasticity of the posterior vaginal wall.

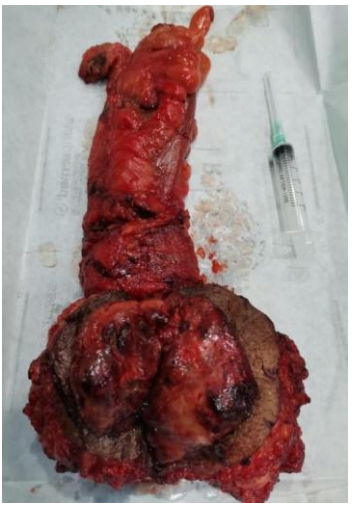

Fig. 1. Surgical specimen of a melanoma of the anal canal after APA

Fig. 2a. **Fig. 2b.**

Fig. 2a and 2b. Surgical specimen of an adenocarcinoma of the lower rectum infiltrating the posterior wall of the vagina after APA and posterior colpectomy

Thus, the reconstruction began with the removal of the musculocutaneous flap with an average size of eight centimeters in width and twenty-one centimeters in length, initially traced (Fig. 3) along a transverse axis at the height of the navel on the right side, giving way to the definitive colostomy on the left at the end of the operation.

Fig. 3. Incision of the skin paddle of the transverse Taylor flap

Once the flap has been mobilized (Fig. 4), it is tilted downwards by a 180° rotation intra-abdominally to fill in the perineum. The proximal musculocutaneous part is fixed in two planes to cover the perineal region and the distal part of the skin paddle fills the posterior aspect of the vagina, without having to open and section the broad and round ligament.

Fig. 4a.

Fig. 4b.

Fig. 4a and 4b. Mobilization of the Taylor flap

Reconstruction is performed as soon as the abdominoperineal amputation is completed. The distal colonic stump concerned by the stoma is left to stand, hemmed in to the skin at the last stage of the operation.

Finally, the flap will be fixed to the perineal floor by separate stitches going up the posterior surface of the vagina (Fig. 5).

Fig. 5. Cutaneous suture of the flap

Furthermore, the fascia is closed simply by bringing the fascial edges of the anterior rectus fascia together, without any prosthetic reinforcement, in order to reduce the risk of sepsis, which is increased by the proximity of the definitive left iliac colostomy, and taking care not to plicate or injure the feeder pedicle of the flap.

In performing the perineo-vaginal plasty, the objective is to evaluate the duration incurred for optimal healing and the quality of our patient's lifes, particularly sexual quality, by means of close clinical monitoring, initially weekly for one month, then every 15 days during the first trimester, and then monthly, with a current follow-up of 8 months.

Thus, healing is declared when the 2 sites; abdominal donor and perineo-vaginal receptor have completely healed.

The quality of sexual life will be judged by the extent of the period of coital arrest, relating the degree of vaginal dryness and dyspareunia.

3. RESULTS

In the hospital, the patient operated on a melanoma of the anal canal had presented phlyctenoid bullae on the proximal cutaneous side of the flap which have collapsed by application of fatty plaster changed daily. Apart from this, both patients progressed well without the emergence of any complication specific to the excision surgery or specific to the plastic surgery procedure.

The length of hospitalization for both patients was 10 days.

Complete perineal healing was obtained at the end of the 3rd week in both patients.

With an average follow-up of one year, no complications arose at either the donor or recipient sites.

Coital resumption started progressively from the second week, just after complete perineo-vaginal healing (Fig. 6); delayed by one week, following dyspareunia in the patient who underwent excision for anal melanoma.

Fig. 6. Healing status of the perineal site (last check at 18 weeks)

4. DISCUSION

Perineal healing and psychological ease, particularly sexual ease, represent the essential goal in patients who have undergone APA associated with posterior colpectomy [5,6].

In 1983, Taylor described a musculocutaneous flap of the rectus abdominis pedicled on the deep inferior epigastric vessels [7-10]. The skin racket was

initially traced along an oblique axis that follows a line from the umbilicus to the tip of the scapula.

The technical variant eventually adopted in our two patients consisted in harvesting a paddle with a large transverse axis. This transverse rectus abdominis myocutaneous flap (TRAM flap) with an inferior pedicle is mainly indicated in slim individuals.

This option is one of the safest and most effective solutions for the coverage and filling of pelvic-perineal tissue loss [11-12].

Direct closure with omentoplasty as one of the alternatives to the Taylor flap had a significantly higher complication rate, healing time and occurrence of perineal hernias (48.9% vs. 26.8% and 117 d vs. 18.7 d; 15.4% vs. 0% respectively in the series of Lefèvre et al.) than with a Taylor flap, with an almost identical incidence of occurrence of abdominal eventrations [13,14-15].

During pelvic-perineal plasties, we can also resort to the use of other flaps such as the Gracilis flap, at the cost of a questionable vascular reliability and a much smaller size compared to the Taylor flap, which most often results in samples being taken from both sides, or even by combining several at the same time, especially at the time of enlarged reconstructions (example: reconstruction by using petal flap of the lotus and the pudendal fascio-cutaneous flap) which are complex and difficult techniques, and which can be complicated by partial or total necrosis of the flaps, of ischemic or suppurative origin in 25% of the cases; elucidated during innumerable series of studies [16,17,18,19].

Thus, the Taylor flap represents the reference technique for covering large pelvic-perineal losses of substance, particularly in enlarged APAs. The other plasty techniques are considered as a second choice, or in case of impossibility of harvesting the pedicled rectus flap (anterior laparotomies complicated by wide parietal ventrations) [20,21].

5. CONCLUSION

Vascular reliability and the large volume of the musculocutaneous flap are key assets to ensure optimal filling of the pelvic-perineal defect associated with pelvic exenteration and abdomino-perineal amputations.

According to previous published series and our two reported cases [22], the Taylor flap is the technique of choice with a much reduced healing time, in all patients who have undergone PAA for anal or lower rectal cancer without worsening the morbidity figures, related to the radical surgery, with a benefit on psychological comfort and sexual quality of life [23].

CONSENT

As per international standard or university standard, patients written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

AUTHORS' CONTRIBUTIONS

All authors contributed to the study concept and design, data interpretation, drafting, fnal approval, and accountability for all aspects of the work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Chapter 13
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Adults with Neglected and Recurring Clubfoot: An Approach towards Acute Surgical Correction

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ABSTRACT

In this chapter, we ought to find out the functional outcome of Talipes Equinovarus in adults. Neglected clubfoot by definition is untreated equino-cavo-adducto-varus in older children, adolescents or even adults. Untreated severe clubfoot rarely exists today in developed countries, except in some migrants from low- and middle-income countries. The study was conducted at Bashaer University Hospital and Future Hospital in Khartoum, Sudan. All surgeries were done by the same foot and ankle surgery team in both hospitals. Data was collected using a questionnaire and the functional outcome has been assessed using the American Orthopedic Foot and Ankle Society Score (AOFAS). This score was measured before surgery and one year after surgery. Results: the mean age was 19.9 ± 4.7 years. Males were 25 (62.5%) and females were 15 (37.5%). The mean preoperative AOFAS score was 37.7 ± 7.1 (poor). This score improved to 80.7 ± 13.7 (good to excellent), two years after surgery. However, this indicates a significant change in the functional outcome after the operation (p-value < 0.05). The complexity of the multi-planar foot deformity requires early intervention, good surgical planning, and the choice of the appropriate soft tissue and or bone procedures. Excellent postoperative functional outcome was found among patients aged 18 - 23 years 18 (50%) p-value: 0.021. The majority of patients 36 (90%) were fully satisfied with the operation, 2 (5%) partially satisfied and 2 (5%) were unsatisfied.

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The functional outcome of this operation is comparable to other procedures like triple Arthrodesis, double osteotomies, and gradual corrections by external fixators.

Keywords: Neglected; relapsed clubfoot; outcome; acute surgical correction.

1. INTRODUCTION

Neglected clubfoot is defined as untreated equi- no-cavo-adducto-varus in older children or adults. Relapsed clubfoot is the residual deformity that remains after single or multiple surgical interventions. Severely neglected clubfoot rarely exists today in developed countries, except in some emigrants from low- and middle-income countries. Acute surgical management with corrective mid-foot osteotomy and elongation of the Achilles tendon has an excellent functional outcome. The ankle joint is made up of 3 bones (tibia-fibula-talus) that allow up and down movements. The subtalar sat below the ankle joint and allowed side-to-side motions. Numerous ligaments (made of tough-movable tissues) surround the true ankle and subtalar joints—binding the bones of the legs to each other and those of the foot [1]. Recently, severe clubfoot that is untreated is uncommon in developed nations, except for a few immigrants from LMICs. However, up to 50% of children worldwide with clubfeet do not receive treatment in LMIC nations due to inadequate access to modern medical care [2]. The study of Kulkarni et al. [3] evaluated the outcome of the proposed surgical procedure in the correction of complex clubfoot deformities. On radiological assessment, postoperatively optimal radiological values were achieved. From virgin to neglected clubfoot, situations are variable and strategies are different when surgery is necessary. If conservative treatment is no longer effective, surgery should be considered. Mini-invasive surgery is a complementary procedure to nonoperative treatment [4]. After regular 18-month follow-ups, superficial infection and pin-track infection were noted in less than five patients. Shingade et al. [5] evaluated the outcome of the management of neglected clubfoot. Follow-up ranged from 36 - 62 months (mean 44.07 ± 8.22 months). Of 77 feet, results were excellent in 41 (53.25%) feet, good in 28 (36.36%), fair in six (7.8%), and poor in two (2.6%) feet. The outcome of excellent and good results was statistically significantly higher in neglected feet as compared with relapsed feet (p ¼ 0.007). However, the surgical procedure had statistically good outcomes in relapsed feet along with neglected feet as well. In the study of Prasad et al. [6], they assessed the triple arthrodesis and posterior Tendoachilis lengthening for rigid neglected clubfoot deformities in adult patients, and its effects on clinical and radiological results. The AOFAS score in preoperative assessment rose from 36 (range: 26 to 52) to 90 (range: 86 to 94) in the postoperative follow-up period ($p < 0.0001$). Excellent outcome was found in 12 out of 16 feet, the rest 4 were good. Significant clinical improvement was obtained between preoperative and postoperative surgical periods significant improvements were observed in radiographic parameters. Radiographic angels' assessments were optimal to normal physiological limits [7]. On the other hand, adults are less flexible than children thus correction of Talipes Equinovarus may require more extensive repair. Therefore, in this study, we ought to find out the functional outcome of Talipes Equinovarus in adults.

2. METHODOLOGY

2.1 Study Design

Cross-sectional, hospital-based study.

2.2 Study Area

The study was conducted at Bashaer University Hospital and Future Hospital in Khartoum, Sudan. All surgeries were done by the same foot and ankle surgery team in both hospitals.

2.3 Study Duration

The study was conducted in the period from January 2020 to December 2020.

2.4 Study Population

Adult patients from both genders with neglected or relapsed clubfoot who un-underwent acute surgical correction were included in this study. Patients with poor soft tissue conditions or other foot deformities were excluded.

2.5 Sample Size and Sampling Technique

Total coverage of all patients who had neglected TEV and were treated with acute surgical correction and met the inclusion criteria.

2.6 Data Collection and Analysis

Data were collected using a structured questionnaire including patient's demographic data, history, examination findings, and investigations this questionnaire is filled by the researcher. Collected questionnaires were revised for completeness and accuracy and clearance. Data were entered using the Statistical Package for Social Sciences (SPSS) version 26.0 for data analysis.

Descriptive terministic in terms of frequency tables with percentages and graphs. Chi-square test to assess associations, (a p-value of 0.05 or less is considered significant).

2.7 The Surgical Technique and Post-Operative Plan

Careful clinical and radiological assessment of patients is finished before surgery. Spinal anaesthesia was the choice in this series. Open elongation of the Achilles tendon is done through the medial para-median approach in the supine (Fig. 1). The posterior capsule of the ankle joint is released by the same wound.

The lateral approach is done to expose the midfoot from the lateral side. The incision is in the line from the lateral malleolus to the 4th toe. Closing wedge osteotomy is done and based dorsally and laterally to correct the equinus and varus components of the deformity. The osteotomy takes place across the navicular, medial cuneiform, and cuboid bones with the excision of the articular

surfaces of these bones. The proximal line of the osteotomy goes through the navicular bone (taking the distal articular surface) and the cuboid. The distal line of the osteotomy passes across the three cuneiforms (involving the proximal articular surface) bones and the cuboid (Fig. 2).

Correction is checked after each step and the final correction is fixed in place by bone staples.

Immobilization in Plawas star cast was applied for three months followed by ankle foot orthosis for twelve months (Fig. 3).

Several physiotherapy sessions were scheduled for all patients.

Fig. 1. Show pre-operative clinical photo and X-ray

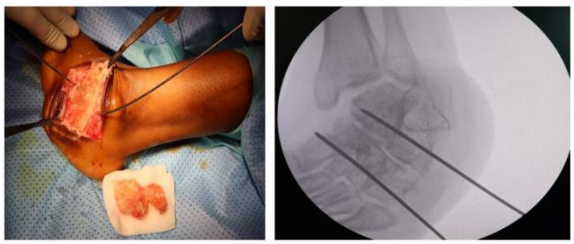

Fig. 2. Shows an intraoperative clinical photo and X-ray

Fig. 3. Shows the final correction

3. RESULTS

Forty patients were included in this study. In the age group (18 - 23) years there were 17 patients (42.5%), while 13 patients (32.5%) were between (24 - 34) years and 10 (25%) aged 35 - 45 years. The mean age was 19.9 ± 4.7 years. Most of the participants were males 25 (62.5%) and females 15 (37.5%) with a male-to-female ratio of 1.7:1. The mean duration of follow-up was 28.3 months. In the majority of the patients 26 (65%), no co-morbidities were reported. The reported morbidities were neuromuscular disorders 7 (17.5%), diabetes mellitus 4 (10%), and hypertension 3 (7.5).

The correction was bilateral in 16 candidates (40%), the right side was affected in 16 patients (40%) and the left side was included in 8 patients (20%).

Postoperative complications were: ankle pain 3 (7.5%), wound dehiscence 2 (5%), recurrence 2 (5%), and nerve injury 1 (2.5%) (Table 1).

The majority of the patients 36 (90%) were fully satisfied with the operation, 2 (5%) partially satisfied and 2 (5%) were not satisfied. In all patients preoperative AOFAS score [8] was poor. After surgery, excellent scores were reported by 24 (60%), good 7 (17.5%), fair 6 (15%), and poor 3 (7.5%) (Table 2).

The mean value of the preoperative AOFAS score was 37.7 ± 7.1 (within the poor level) and increased after surgery to 80.7 ± 13.7 (within good to excellent level) which indicates a significant change in the functional outcome after the operation (p-value < 0.05).

Table 1. The frequency of postoperative complications

Postoperative complications	Yes		No		Total	
	N	%	N	%	N	%
Ankle pain	3	7.5	37	92.5	40	100%
Wound infection	2	5	38	95	40	100%
Recurrence	2	5	38	95	40	100%
Nerve injury	1	25	39	97.5	40	100%

Table 2. Preoperative and postoperative functional outcome (AOFAS score)

Preoperative AOFAS score	N	%
<60 poor	40	100.0
TOTAL	40	100.0
POST operative AOFAS score	N	%
Poor 60>	3	7.5
Fair 69 - 60	6	15.0
Good 79 - 70	7	17.5
Excellent 92 - 80	24	60.0
Total	40	100.0

Table 3. The correlation between the post-operative AOFAS scale and the age, gender, and satisfaction

		Postoperative Fair AOFAS score								p-value
		<60 Poor		60-69		70-79 Good		80-92 Excellent		
		N	%	N	%	N	%	N	%	
Age	12-23	0	00	3	50	2	28.6	12	50.0	
	24-34	2	66.7	2	33.3	1	14.3	8	33.3	0.021
	35-45	1	33.3	1	16.7	4	57.1	4	16.7	
Gender	Male	1	33.3	3	50	5	71.4	16	66.7	
	Female	2	66.7	3	50	2	28.6	8	33.3	0.015
Patient's satisfaction	Fully satisfied	0	00	5	83.3	7	100	24	100	
	Partially satisfied	2	66.7	0	00.0	0	00.0	0	0	0.001
	Not satisfied	1	33.3	1	16.7	0	00.0	0	0	

The p-value <0.05 is considered significant

There was a significant statistical association between functional outcomes and younger age group < 23 12 (50%), for the patients aged (24 - 34) years 8 (33.3%), and least significant for the patients aged more than 35 years was 4 (16.7%) (p-value = 0.021).

As shown in Table 3 there was a significant statistical association between post-operative functional outcome and males gender 16 (66.7%) compared to 6 females. There was a significant statistical association between satisfaction and excellent outcome of surgery. Patients who scored excellent in postoperative functional outcomes were fully satisfied 24 (100%) (p-value = 0.001).

4. DISCUSSION

The complexity of the multi-planar foot deformity requires early intervention, good surgical planning, and the choice of the appropriate soft tissue and or bone procedures. The surgical management aimed to achieve plant-grade, stable, and pain-free feet and restore the alignment of bones and the movement of joints. In our series, all patients were adults coming with relapsed or neglected deformities because of the local beliefs in traditional bone setters. This makes the surgical treatment more challenging because of the soft tissue contractures and the changes in the bones and joints as a result of the long-standing deformity. Sever-al soft tissues and bone procedures were documented for the treatment of severe club foot deformity with a variety of clinical, functional, and radiological out- comes. The described bony procedures are numerous in the literature. Evan's procedure, medial column lengthening, double midfoot osteotomies [9], and many other types of osteotomies were tried with some degrees of success. Gra- dual correction by Ilizarov frame is a suitable option for severe deformities with poor soft tissue status but needs an experienced surgeon and compliant patient. Acute surgical correction was the choice in this study as its one session intervention and more convenient to our patient's budget rather than gradual correction with circular frames. For all patients, we performed Achilles tendon lengthening, the release of the posterior capsule, and multi-planar closing wedge osteotomy in the midfoot. Those who have pressure ulcers or poor soft tissue conditions were not chosen for this procedure. According to these study's findings, excellent functional results, as determined by AOFAS, were reported one year after sur- gery in 24 patients who had excelled in all functional activities regards to Prasad S, et al. [6] evaluated the effects of triple arthrodesis and posterior Tendoachilis lengthening for stiff neglected clubfoot in adult patients and its effect on clinical and radiological outcomes had excellent outcome in Alignment of foot and support mainly. Similarly, Chandak and Khatri evaluated the outcome of a sin- gle-stage procedure for neglected congenital Talipes Equinovarus. They studied a total of 13 patients, all of whom had a unilateral deformity [10]. In a rural tertiary care setting, Jacob et al. determined the functional outcome and patient satisfaction after a triple arthrodesis procedure on patients with neglected Talipes Equinovarus. According to AOFAS AHS, 94% of the 22 cases reported satisfactory functioning. The AHS score improved statistically significantly with TRA, indicating a better functional outcome and 95% of patients were satisfied with the outcome [11]. J. Correll and A. Forth performed

gradual correction for 43 cases of neglected or relapsed foot [12]. They defined good outcomes as the ability of the patient to walk normal distances and the absence of gross defer satisfactory outcome is defined as mild residual deformity without skin break- down. The bad outcome is labelled as a recurrence of the deformity after the removal of the frame. Good results were achieved in 20 patients and satisfactory results in 11 patients. Recurrence of the deformity was encountered in 3 cases. The residual deformity is found in 11 candidates. Khan and Chinoy [13,14] found that these feet are often rigid and severely deformed and surgical correction is the predominant treatment option taken to attain a plant-grade foot, and the extent of correction required predisposes to wound-healing problems. The outcome and satisfaction rates in the above series are comparable to our study with more relapses and less satisfaction seen in the gradual correction study.

5. CONCLUSION

Acute correction of neglected Talipes Equinovarus in adult patients by corrective midfoot osteotomy and elongation of the Achilles tendon has a good functional outcome. High satisfaction levels and lower complication rates were reported with the above procedure. Therefore we recommend it as the procedure of choice in neglected TEV in adults as it is an easy, relatively safe, and intervention procedure. The functional outcome of this operation is comparable to other procedures like triple Arthrodesis, double osteotomies, and gradual corrections by external fixators.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We declare that we have:

- Written ethical clearance and approval for conducting this research were obtained from Sudan Medical Specialization Board Ethical Committee and by (EDC).
- Written permission was obtained from the administrative authority of Ba-shaer Hospital, Future Hospital.
- Confidentiality was considered intentional, data was used anonymously by using code Numbers instead of names to participants' identities and keep secure, and information Was used for research purposes only.

AUTHORS' CONTRIBUTIONS

This work was carried out in collaboration among all authors. Author SN did conceptualization, performed methodology, and resources, helped in project administration, and wrote the original draft. Author HMH did conceptualization, data curation, performed methodology and assisted in writing the original draft of the manuscript. Author AMMK did conceptualization, assist in data collection, wrote the original draft. Author DS did data curation, and formal analysis helped in software development and assisted in writing the original draft. Author HMAA did data curation, and resources, did data validation, and reviewed and edited

the manuscript. Author MF resources, helped in data visualization, did data validation and assisted in analysis and editing of the paper. All authors have read and agreed to the published version of the manuscript.

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COMPETING INTERESTS

The authors have declared that no competing interests exist.

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