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An Overview of Biological Warfare and SARS-CoV-2 as a Potential Biological Agent

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Review

Case Report

Original Clinical Research

Editorial

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This is the third issue this year and includes a number of papers from the region including review papers, case report, and original research papers.

Mansour et al., reviewed the conflict between humans did not stop throughout the ages, and humans have used everything in nature to serve this conflict since the first ages of history, during the First World War the world witnessed the actual use of chemical weapons, and a nuclear weapons during World War II By the United States of America against Japan, which greatly developed a biological warfare program before and during World War II, and a lot of information regarding this program was withheld by an agreement between Japan and the USA after Japan's defeat in the war. Finally, the countries of the world succeeded in signing a Biological Warfare Convention (BWC) in 1972, and the Ninth Review Conference will be held for this convention during 2021 to discuss its articles and try to develop its mechanisms to prevent the development and use of biological weapons in the conflict between nations.

Helvaci et al., looked at Pulmonary hypertension and chronic obstructive pulmonary disease in sickle cell diseases. All patients with sickle cell diseases (SCD) were included. The study included 434 patients (212 females) with similar mean ages in males and females (30.8 versus 30.3 years, p>0.05, respectively). The authors concluded that SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened red blood cells (RBC) into tissues. Although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, stroke, and COPD-like atherosclerotic events were higher in males, PHT and DVT and/or varices and/or telangiectasias were similar in both genders. Similarly, although the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalences of PHT in both genders also support its nonatherosclerotic nature. In another definition, COPD may have an atherosclerotic whereas PHT a hardened RBC-induced chronic thromboembolic background in the SCD.

Bukhari, et al., did a cross-sectional study to assess the prevalence of depression and anxiety among patients with breast cancer and risk factors associated with it. This cross-sectional study enrolled 74 patients diagnosed with breast cancer. From the 74 patients with breast cancer, 36% of the women were found to have depression and 24% were found to have anxiety and the prevalence of having both depression and anxiety was 23.0%. This study showed that the prevalence of depression and anxiety was similar to previously conducted studies; it also showed no associations between the risk factors studied and anxiety or depression in patients with breast cancer.

Alkubaisi et al., did a retrospective chart review (baseline audit) was conducted on 245 health records of children attended well-baby clinic for three. The aim is to ensure that well-baby services provide clinical care according to children's age as per well-baby service protocol within primary health care centers, to find gaps if any and, generate action plan for further improvement. Performance for criterion on relevant clinical history taking (feeding and bowel history) has slightly increased from the baseline for each of the following age groups: from 71% to 82% at 4 months, 77% to 80% at 18 months and, 76% to 81% at 30 months, however, a declination shown at 2 months 88% to 80%. Assessment of developmental milestones at 2, 18 and 30 months of age increases by 5% (76% to 81%), 13% (70% to 83%) and 19% (50% to 69%) respectively and, at 4 months performance remain the same 69%. The authors concluded that impactful audits with actionable recommendation make real difference in practice and compliance. In conclusion, action plan implemented further to the baseline audit are effective in increasing the compliance in most of the areas.

Helvaci, et al., looked at positive and negative acute phase reactants in sickle cell diseases. The studies looked at consecutive patients with the SCD and controls were studied. The study included 193 patients (98 females) and 132 controls (67 females). Although the body weight and body mass index (BMI) were retarded in the SCD (58.9 versus 71.1 kg and 21.5 versus 26.8 kg/m2, respectively, p<0.000 for both), the body heights were similar in both groups (164.8 versus 162.8 cm, p>0.05). Parallel to the retarded body weight and BMI, fasting plasma glucose (FPG) (93.4 versus 102.4 mg/dL, p=0.025), low density lipoproteins (LDL) (70.4 versus 98.1 mg/dL, p<0.000), high density lipoproteins (HDL) (24.2 versus 35.8 mg/dL, p<0.000), and systolic (117.6 versus 127.9 mmHg, p=0.001) and diastolic blood pressures (BP) (77.3 versus 86.0 mmHg, p<0.000) were all retarded in the SCD. The authors concluded that body weight, BMI, FPG, LDL, HDL, systolic and diastolic BP, and Hct may be some negative whereas TB, LDH, WBC and PLT counts, and MCV may be some positive APR in the body.

Alrobiaee et al., did a cross-sectional survey was conducted among women seeking Antenatal care (ANC) at PHCCs in Unaizah city, during 2021. The aim of this study is to assess women's expectations and satisfaction with the quality of ANC provided at primary health care centers (PHCCs) in Unaizah city, Qassim region, Saudi Arabia. A total of 204 women participated in the survey; 54.5% were 30 years or less in age and 50.5% had university or higher degree. The majority of women were satisfied regarding overall information received (n=189, 92.7%), care received from physicians (n=201, 98.5%) and general quality of the health care provided (n=189, 92.7%). The authors concluded that the overall satisfaction with the quality of ANC was high. However, few aspects of services need improvement including waiting time and the instructions about danger signs and seeking emergency care. Regular satisfaction surveys should be carried out to identify problem areas and to improve the quality of services.

Karrar, et al., reviewed cystic fibrosis. The authors stressed that Cystic Fibrosis consider one of the most common autosomal recessive diseases that are associated with a decrease in the length of age in a Caucasian population. also, it's considered as one of the most common life-shortening diseases in the white population in the United States. Cystic fibrosis affects around 30,000 people in the United States and more than 80,000 people worldwide. The incidence rate of this disease is 1 out of 3,500 births per year in the whites' population in the United States. While the incidence rate of the person becoming a carrier is 1:25 in the Caucasian population, and also the incidence of the disease is 1:2,500. The main cause for this disease is the mutation in Fibrosis Transmembrane Conductance Regulator (CFTR) gene. This disease considers a life-threatening genetic disease that causes a buildup of thick, viscous mucus secretions in organ systems. Cystic Fibrosis consider a multiple system disease, but in most cases, the disease gets worsen and mortality increase because of respiratory manifestation such as bronchiectasis. Also, Pancreatic damage in children followed by severe wasting, malabsorption, and mortality is one of the recorded observations in children. This article aims to provide a brief introduction, the clinical picture of the disease, Etiology, Pathophysiology, Epidemiology, Nutrition, Prevention, and good practice management advice.

Abdulla Saleh, et al., did a retrospective descriptive study, in which we reviewed the medical records of all patients with vitiligo attending two private clinics in Aden during the period January 2019 to December 2020. The objective of the study was to evaluate the different clinical features of vitiligo diseases and to assess the comorbidity disorders in Aden. The majority (49.7%) patients were aged ≤ 20 years old and the positive family history of vitiligo was found in 28.6%. Vulgaris is the predominant vitiligo type (57.8%) followed by acrofacial type (13.0%).

Extremities involvements were higher in females and males (17.4%) and (9.9%), respectively. Face with extremities involvement and trunk with extremities involvement in female patients seem to be similar with (9.9). The patient concluded that Vitiligo disease more common in females and the most common form was vitiligo vulgaris. Third of patients had positive family history of vitiligo and the most site involvements were extremities.

Dr Ebtisam, reports a case of early-onset CTCL, localized and unilateral. The patient is a 39-year-old man who attended with itchy single red skin lesion on his left leg that was unresponsive to topical steroids for the past two-weeks. Apart from that, he had no other complaint. He was fit and well. Examination showed a unilateral localized red slightly-scaly, non-blanchable skin plaque on his lower left leg. Other skin parts were not affected. Physical examination was otherwise unremarkable without any detectable lymphadenopathies. The histology report concluded that the immunohistochemical profile is consistent with T-cell proliferation and the picture suggests cutaneous T-cell lymphoma.

Prevalence of depression and anxiety among patients with breast cancer: a cross-sectional study

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Abstract

Background: Breast cancer patients have a significant rate of depression, according to prior studies. During some phases of patient management, particularly early after surgery, these patients are at risk for depression.

Objectives: to assess the prevalence of depression and anxiety among patients with breast cancer and risk factors associated with it.

Methods: This cross-sectional study enrolled 74 patients diagnosed with breast cancer in the general surgery clinic at King Abdulaziz University Hospital in Jeddah, Saudi Arabia. Two questionnaires were used, Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7), filled in by patients who attended the clinic or electronically by sending the questionnaires to the patients. Significant depression was defined as PHQ-9 score ≥ 10 and significant anxiety was defined as GAD-7 score ≥ 10. Sociodemographic and medical data were also collected. This research was approved by the unit of biomedical ethics at King Abdulaziz University Faculty of Medicine.

Results: From the 74 patients with breast cancer, 36% of the women were found to have depression and 24% were found to have anxiety and the prevalence of having both depression and anxiety was 23.0%. Mean PHQ-9 score was (8.9, SD: 5.8). The mean GAD-7 score was (6.7, SD: 5.2). Significant depression and significant anxiety were found to be more in Saudi nationals, those who did not go for surgical therapy, patients with metastatic disease at the time of filling in the questionnaire and married women. These results were not statistically significant.

Conclusion: This study showed that the prevalence of depression and anxiety was similar to previously conducted studies; it also showed no associations between the risk factors studied and anxiety or depression in patients with breast cancer.

Keywords: Breast Cancer, depression, anxiety, Saudi Arabia, PHQ-9, GAD-7

Introduction

Breast cancer is the most frequent type of cancer in women all over the world. Breast cancer rates are greater among women in more developed countries, and rates are rising in almost every country (1). In Saudi Arabia, it accounts for 16.9% of all adult cancer patients (2), with a 13.08 percent fatality rate (3). The cost of treatment was found to be 50 billion Saudi Riyals ($13 billion USD) per year during the year 2018 (4). Breast cancer is treated using a multimodal approach that includes surgery, radiation, hormone therapy, immunotherapy, and chemotherapy, depending on the patient's symptoms, stage, and overall health (5).

Depression is a mood illness that causes a person to feel gloomy and disinterested all of the time (6,7). According to previous studies, depression affects 38.2 percent to 68.6 percent of all breast cancer patients (8,9,10). Depression was more prevalent in patients with breast cancer throughout various times of patient management, notably early after surgical therapy, according to studies conducted in South Korea, Egypt, and Croatia (8,11,12). It has also been found to be more likely after radical mastectomy compared with breast conserving surgery (13). Other studies have found risk factors for depression in patients with breast cancer were age between 40 and 60 years, being divorced or widowed, lower education level, diagnosis of other diseases, radical mastectomy, presence of lymphedema, rural residence, unorthodox Christianity, bad/very bad symptoms burden, medium or low self-esteem, and poor body image (9,10).

When anxiety becomes severe and chronic, it is known as Generalized Anxiety Disorder (GAD) (14). Previous research has found that the prevalence of GAD in individuals with breast cancer ranges from 25% to 73.3 percent (8,9,15,16). Anxiety levels were observed to be higher before surgery (17) and in radical mastectomy compared to breast conserving surgery (18). Anxiety was found to be worse before chemo/radiotherapy (15,17,18). Being divorced or widowed, having a lower educational level, living in a rural area, practising unorthodox Christianity, and having a lot of unpleasant/very terrible symptoms were all risk factors for GAD (9).

The Patient Health Questionnaire-9 (PHQ-9) questionnaire was established in 1999 (19) and Generalized Anxiety Disorder-7 (GAD-7) questionnaire in 2006 (20). PHQ-9 was validated in 2001 and it was shown that for a score of 10 or more the questionnaire had a sensitivity of 88% and specificity of 88% and a likelihood ratio of 7.1 that is suggestive of major depression (21). GAD-7 was published with its validation, and a score of 10 or higher was proposed as a cutoff for likely GAD, with a sensitivity of 89 percent, specificity of 82 percent, positive predictive value of 29, negative predictive value of 99, and a likelihood ratio of 5.1 (20).

This study aimed to assess the prevalence of depression and anxiety among patients with breast cancer, and the risk factors associated with it.

Methodology

Study design: a cross-sectional study was carried out. Study setting: the general surgery clinic at King Abdulaziz University Hospital in Jeddah, Saudi Arabia.

Study population: patients who attended the study setting and were diagnosed based on histopathology reports with invasive ductal carcinoma, invasive lobular carcinoma, invasive carcinoma of undetermined type, ductal carcinoma in situ, lobular carcinoma in situ, and phyllodes tumour were included in this study.

Data collection: standardised questionnaires (PHQ-9) (19,20) and (GAD-7) (20) were sent to be filled electronically by the participants on their own, over the phone, or via paper questionnaires in the clinic. Significant depression was defined as PHQ-9 score ≥ 10 (19,20) and significant anxiety was defined as GAD-7 score ≥ 10 (20). In conjunction with the questionnaires, sociodemographic and medical data were collected which included: age, sex, marital status, number of children and nationality, date of diagnosis, presence or absence of metastasis at the time of diagnosis, if the patient had undergone surgical treatment, type of the surgery (mastectomy vs. lumpectomy), and preoperative hemoglobin (g/dl).

Data analysis: Statistical analysis was performed using the SPSS V.20 software package (SPSS, Chicago, Illinois, USA). For descriptive analysis, continuous variables were presented as mean and standard deviation. Categorical variables were summarized using counts and percentages. Missing variables are computed with respect to available/total data. For comparative analysis, a chi-squared test was used to compare dichotomous data. Independent samples t-test was used to compare continuous data with normal distributions, and Mann–Whitney U test for continuous data without normal distributions. Statistical significance was defined as a p-value ≤0.05.

Ethical approval: the Unit of Biomedical Ethics Research Committee at King Abdulaziz University, Faculty of Medicine approved the use of indicated data along with the requirement of written informed consent (Reference No 199-21).

Results

From the people who have been reached out to fill the questionnaires, a total of 104 responses were returned, of which 25 were found to be duplicates, 3 non cancerous breast lesions, and 2 non-breast related conditions. In addition to this, five entries were found to have the wrong medical record number so no data from the medical record system was collected about them. The final sample included 74 participants with a mean response rate of 71.2%.

The mean age was 50 (standard deviation [SD]: 11.9) and the average number of children was 3.1 (SD: 2.4). All study participants were female: 48 (64.9%) were married, 9 (12.2%) single, 9 (12.2%) widowed, and 8 (10.8%)

divorced. Saudi nationals comprised 35 (47.3%) of the participants and the rest were of multiple different nationalities. A total of 8 (10.8%) were found to have distant metastasis, 55 (83.8%) had surgery of whom 17 (23%) underwent lumpectomy, whereas 37 (50%) underwent mastectomy. The mean PHQ-9 score was 8.9 (SD: 5.8). The mean GAD-7 score was 6.7 (SD: 5.2). The prevalence of depression (PHQ-9 score ≥ 10) and anxiety (GAD-7 score ≥ 10) was 27 (36.5%) and 18 (24.3%), respectively (Table 1).

Responses from the PHQ-9 questionnaire are displayed (Figure 1) (Table 2), and responses from the GAD-7 questionnaire are displayed (Figure 2) (Table 3).

Our study showed that the positive predictive value of the GAD-7 as a predictor for depression using PHQ-9 as a standard was 94% and the negative predictive value to be 82%. Using PHQ-9 as a predictor for anxiety with GAD-7 as standard reveals a positive predictive value of 63% and a negative predictive value of 98% (Table 4); whereas the prevalence rate of having both depression and anxiety was 17 (23.0%).

Our analysis did not show any significant correlation between either depression or anxiety and the risk factors studied for patients with breast cancer (Tables 5 and 6). Saudis who exhibited depression 10 (82.90%) were fewer than non-Saudis 17 (69.20%); the same pattern was seen in Saudis who exhibited anxiety 6 (71.40%) compared with non-Saudis 12 (56.40%).

From the women who had metastasis, 3 (62.50%) were found to have significant depression and 2 (75%) were found to have significant anxiety, while among those who were free from metastasis 22 (62.10%) displayed significant depression and 15 (74%) displayed significant anxiety.

Of participants who did not undergo surgical therapy those who were found to have marked depression were 3 (75%) and those who were found to have marked anxiety were 2 (83.30%). Of the participants who received surgical management 10 (41.20%) from the lumpectomy group were shown to be depressed and 7 (58.80%) were shown to have anxiety, while 12 (67.60%) from the mastectomy group were shown to have depression and 8 (78.40%) were shown to have anxiety.

Among married women with breast cancer, 15 (68.80%) had significant depression and 10 (79.20%) had significant anxiety, which is higher than the 3 (66.70%) single women who had depression and the 2 (77.80%) who had anxiety; 6 (33.30%) widowed had depression while 4 (55.60%) had anxiety, and as for divorced ladies 3 (62.50%) had depression when 2 (75%) had anxiety.

Table 1: Baseline characteristics for the 74 participants

Variables		*N (mean)*	*Percentage (SD)*
Age (in years)		(50)	(11.9)
Saudi nationality		35	47.3
Marital status	Married	48	64.9
	Single	9	12.2
	Widowed	9	12.2
	Divorced	8	10.8
Female		74	100
Number of children		(3.1)	(2.4)
Age at Diagnosis (in years)[a]		(48)	(12.1)
Presence of Metastasis[b]		8	10.8
Patient did not have surgery[c]		12	16.2
Patient did have surgery, type[c]	Lumpectomy[d]	17	23
	Mastectomy[d]	37	50
Hemoglobin (g/L)[e]		(12)	(1.4)
PHQ-9 score		(8.9)	(5.8)
GAD-7 score		(6.73)	(5.2)
PHQ-9 score ≥ 10		27	36.5
GAD-7 score ≥ 10		18	24.3
Missing variables present: a (N= 7), b (N = 8), c (N = 7), d (N = 8), e (N = 8)			

Figure 1: Proportions of participants' responses to PHQ-9

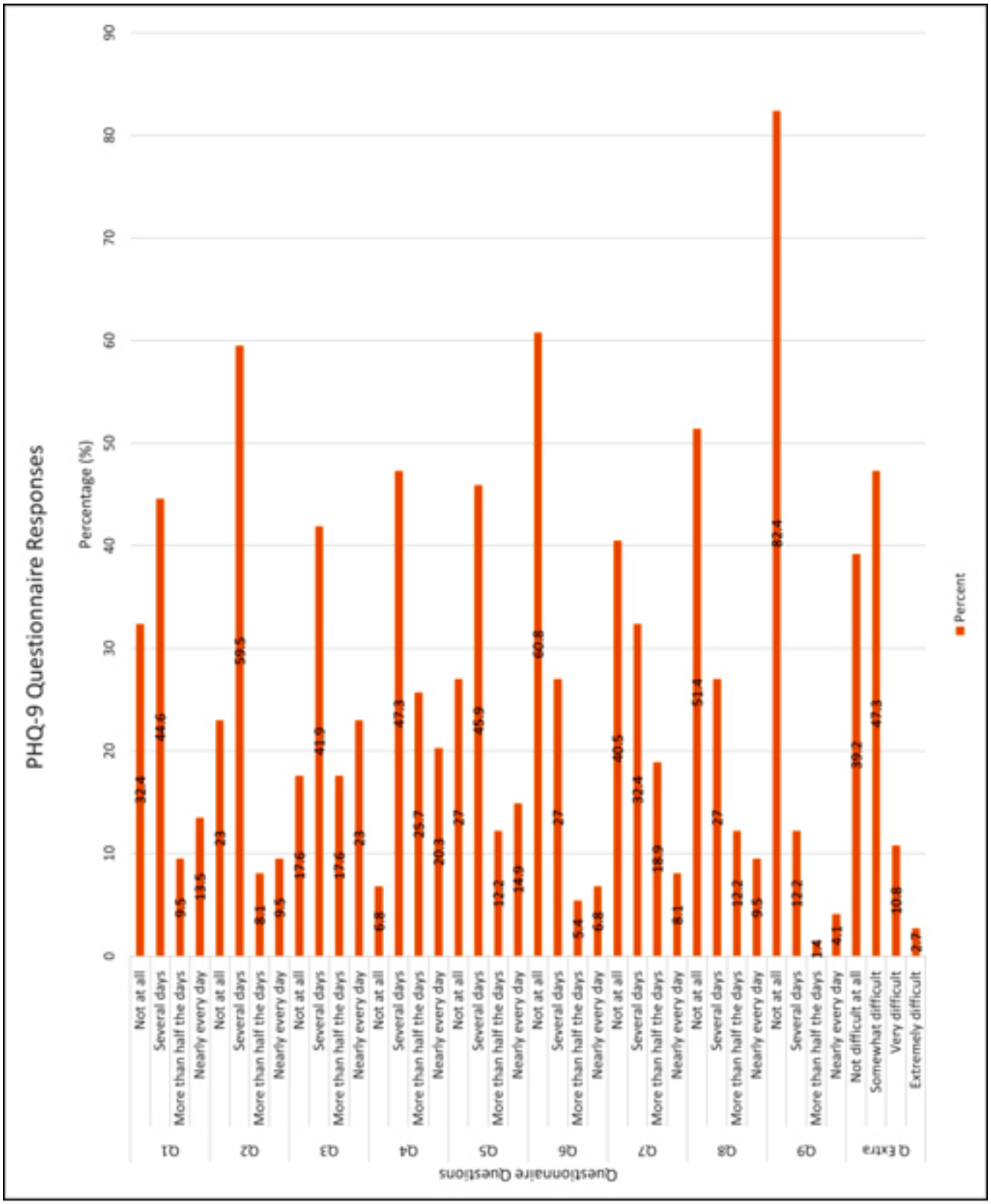

Table 2: PHQ-9 Questionnaire

Q1-Little interest or pleasure in doing things
Q2-Feeling down, depressed, or hopeless
Q3-Trouble falling or staying asleep, or sleeping too much
Q4-Feeling tired or having little energy
Q5-Poor appetite or overeating
Q6-Feeling bad about yourself or that you are a failure or have let yourself or your family down
Q7-Trouble concentrating on things, such as reading the newspaper or watching television
Q8-Moving or speaking so slowly that other people could have noticed. Or the opposite, being so fidgety or restless that you have been moving around a lot more than usual
Q9-Thoughts that you would be better off dead, or of hurting yourself
Q Extra-If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Table 3: GAD-7 Questionnaire

Q1-Feeling nervous, anxious, or on edge
Q2-Not being able to stop or control worrying
Q3-Worrying too much about different things
Q4-Trouble relaxing
Q5-Being so restless that it is hard to sit still
Q6-Becoming easily annoyed or irritable
Q7-Feeling afraid as if something awful might happen
Q Extra-If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Figure 2: Proportions of participants' responses to GAD-7

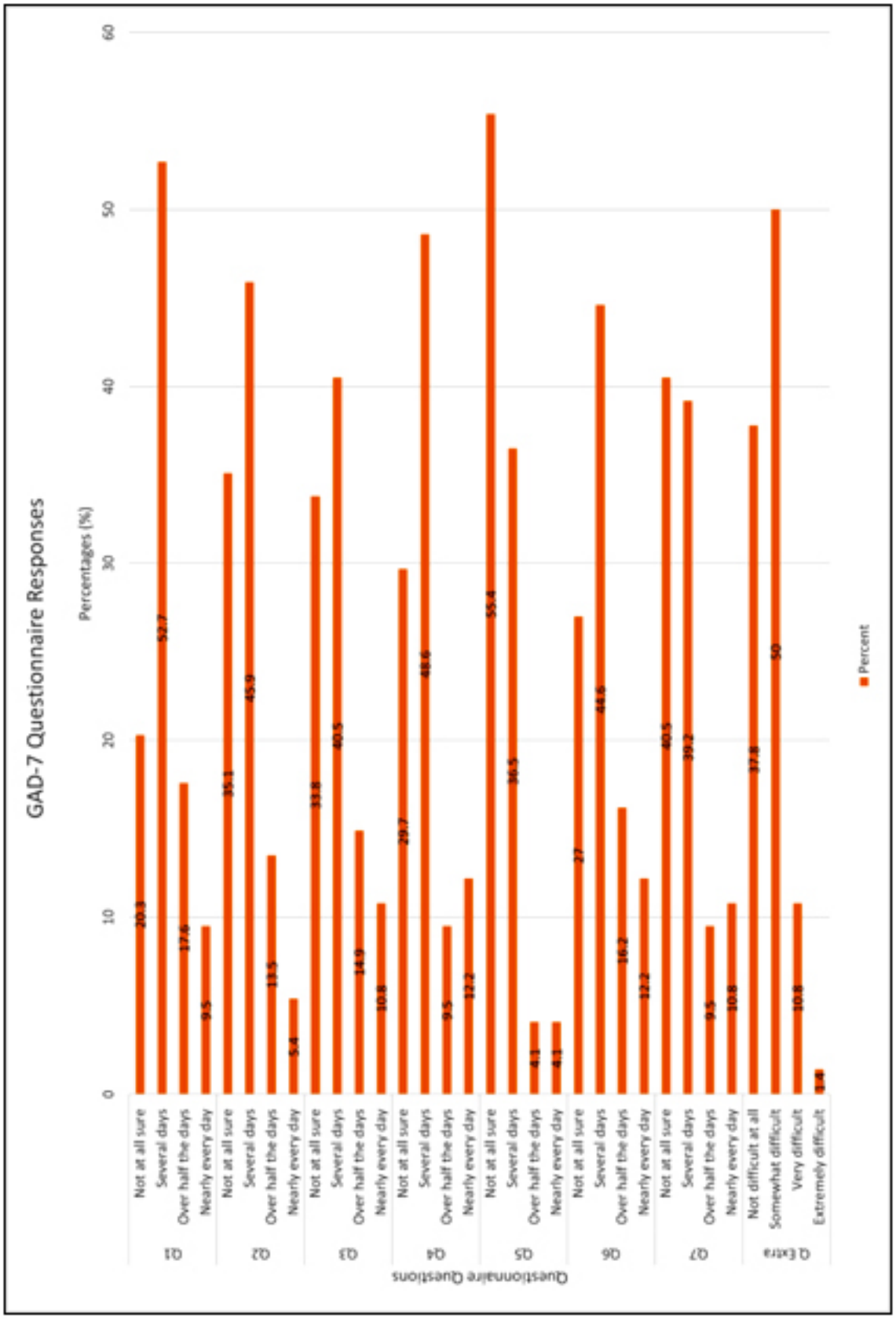

Table 4: Concordance between PHQ and GAD scoring system

		PHQ-9 Score ≥ 10		
		Yes	No	Total
GAD-7 Score ≥ 10	Yes	17	1	18
	No	10	46	56
	Total	27	47	74

Table 5: Risk Factors (categorical) associated with high PHQ or GAD score

	PHQ ≥ 10	P-value	GAD ≥ 10	P-value
Nationality				
Saudi	82.90%	0.19	71.40%	0.23
Non-Saudi	69.20%		56.40%	
Surgery Status				
None	75%	0.11	83.30%	0.23
Lumpectomy	41.20%		58.80%	
Mastectomy	67.60%		78.40%	
Metastasis				
Yes	62.50%	0.98	75%	0.95
No	62.10%		74%	
Marital Status				
Married	68.80%	0.25	79.20%	0.51
Single	66.70%		77.80%	
Widowed	33.30%		55.60%	
Divorced	62.50%		75%	

Table 6: Risk Factors (Continuous) associated with high PHQ or GAD score

Variable	*PHQ-9 ≥ 10*		*GAD-7 ≥ 10*	
	Mean difference	*P-value*	*Mean difference*	*P-value*
Age	0.80	0.44	0.79	0.81
Number of children	0.29	0.87	0.7	0.29
Age at diagnosis	0.57	0.41	1.9	0.58
Hemoglobin	0.88	0.70	0.1	0.89

Discussion

This study aimed to assess the prevalence of depression and anxiety among patients with breast cancer. In a patient who scores <10 in the PHQ-9 it is unlikely that he/she has concomitant anxiety; thus, GAD-7 may not be necessarily filled in by him/her. On the other hand, in a patient who scores >10 on GAD-7 it is likely that he/she has concomitant depression; thus, PHQ-9 is necessary to be filled in.

Our study found the prevalence of depression to be 36.5%, which is similar to the result of Tsaras et al (38%) and it was lower than the results of other studies such as Alagizy et al (68.7%) and Boing et al (49.2%) (8,9,10). For GAD, the prevalence in our study was 24.3%, which is lower than the reports in other studies such as Tsaras et al (32%), Villar et al (48.6%), and Alagizy et al (73.3%) (8,9,15). We theorize that the results of our study were lower than that of other papers due to the variable timing of the questionnaire in relation to the time from diagnosis and stage of management and therefore that might influence their answers.

It's possible that among oncology patients, treatment focuses mostly on the medical issues, while psychological suffering receives less attention. Lueboonthavatchai discovered that psychosocial challenges such as poor family relationships and functioning, maladaptive problems, and conflict resolution can contribute to sadness and anxiety in breast cancer patients (22). According to Helgeson et al., even after the physical ailment has been treated, psychological suffering may persist and accompany the patient for a long time after therapy, negatively affecting the patient's quality of life (23). Understanding these common psychiatric disorders and associated psychosocial factors in patients with breast cancer can help in planning their treatment. Determining the exact prevalence of depression and anxiety in these patients can also help policymakers to design better preventive plans for depression and anxiety.

It is our belief that the therapeutic journey of patients with cancer can be filled with feelings of anxiety and uncertainty, especially those undergoing their first cycle of chemotherapy compared with other treatment methods such as surgery or radiotherapy. As it has the longest duration and socially recognized side effects such as hair loss, Jimenez-Fonseca et al found that younger, poorly educated patients and those undergoing their first chemotherapy session recorded higher levels of anxiety compared with older, well-educated patients and those who had multiple episodes of chemotherapy (24). Another noteworthy point made by Lee et al is that patients who suffer anxiety before starting chemotherapy sessions may have a higher risk of chemotherapy-induced peripheral neuropathy, which provides insight into how managing anxiety before treatment can affect a patient's overall well-being (25). We feel that a better knowledge of these components and their roles will aid in the reduction of stress in patients through therapy, and that this could be a future research topic.

Managing anxiety and depression in patients with breast cancer is particularly important as an increased risk of attempted/successful suicide has been found among patients with anxiety disorders (26) and depression (27) in general. Carreira et al has even shown in a systemic review of different adverse mental health issues among patients with breast cancer that breast cancer survivors have a 37%–60% higher risk of attempted suicide than women in the comparison groups (28). Particular attention needs to be paid in this population for any self-harm or suicidal ideation.

Limitations

There were some limitations to our study. The sample size of 74 participants is considered small, thus the results cannot be generalized to the whole population of patients with breast cancer. Another limitation was the large number of questions answered by the participants that may have been tiresome to some participants and therefore could have affected the accuracy of their answers. Moreover, the data was collected in a cross-sectional manner with some patients filling in the questionnaire immediately after the diagnosis while others filled it in during or after completion of treatment.

Conclusion

In our study, 36 percent of breast cancer patients were found to be depressed, while 24 percent were found to be anxious. There were no links found between the risk factors investigated and anxiety or depression in breast cancer patients. A prospective study analysing the stage of highest risk for GAD and depression among patients with breast cancer undergoing therapy is suggested as a future research option.

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Women's Expectations and Satisfaction with the Quality of Antenatal Care at the Primary Health Care Centers in Unaizah City

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Abstract

Background: Antenatal care (ANC) is an aspect of preventive medicine that aims to promote maternal and fetal health. The quality of ANC has a great impact on the pregnancy experience and outcome.

Aim: The aim of this study is to assess women's expectations and satisfaction with the quality of ANC provided at primary health care centers (PHCCs) in Unaizah city, Qassim region, Saudi Arabia.

Methods: A cross-sectional survey was conducted among women seeking ANC at PHCCs in Unaizah city, during 2021. Two-stage cluster sampling method was used for selection of participants from 5 randomly selected PHCCs. Data were collected by self-administered questionnaire and SPSS software was used for analyzing data.

Results: A total of 204 women participated in the survey; 54.5% were 30 years or less in age and 50.5% had university or higher degree. The majority of women were satisfied regarding overall information received (n=189, 92.7%), care received from physicians (n=201, 98.5%) and general quality of the health care provided (n=189, 92.7%). However, 22.5% of the participants were dissatisfied with waiting time at the clinic and 32.3% either did not receive any instructions or thought that the instructions were insufficient regarding danger signs and seeking emergency care during pregnancy. Out of a total 15 score for adequacy of information, the mean score for 31-50 years women was 12.37±3.24 while it was 10.63±4.02 for 18-30 years age group (p=0.001). The pregnancy number (p=0.015) and the number of children (p=0.001) were also statistically significantly associated with perceived adequacy of information received during ANC visit.

Conclusions: The overall satisfaction with the quality of ANC was high. However, a few aspects of services need improvement including waiting time and the instructions about danger signs and seeking emergency care. Regular satisfaction surveys should be carried out to identify problem areas and to improve the quality of services.

Key words: antenatal care, expectations, satisfaction, primary health care centers, Unaizah, Saudi Arabia

Introduction

Globally, 295,000 maternal deaths were reported in 2017. Although the number of deaths has declined from 451,000 in the year 2000 yet over 800 women are dying each day from complications of pregnancy and childbirth. For every woman who dies, approximately 20 others suffer from serious health problems and disabilities [1]. Saudi Arabia had a Maternal Mortality Rate (MMR) of 24 in 100,000 live births in 2008. While this rate has decreased to 11.9 per 100,000 in 2018, variation between regions is seen with mortality rates highest in rural and poorer regions. The noticeable decrease in MMR reflects the country's efforts for achieving the target of 75% reduction in MMR by 2030, as outlined by the millennium development goals [2].

Antenatal care (ANC), also known as prenatal care is considered one aspect of preventive medicine which is comprehensive medical care provided to pregnant women by skilled health care professionals. It consists of health education, counseling, testing, treatment as well as promotion of maternal and fetal well-being [3]. It is estimated that ANC alone can reduce maternal mortality by 20% with good quality and regular care [4].

Primary health care provides the entry point into the healthcare delivery system of the country and thus represents an ideal setting for prevention of pregnancy complications by detecting high risk patients and by providing early intervention and referral in case of emergency, leading to better pregnancy outcomes.

Patient satisfaction has traditionally been linked to the quality of provided services and the extent to which specific needs are met. Satisfied patients are likely to come back for the services and recommend services to others [5]. Various studies in different parts of the world demonstrate that maternal satisfaction with ANC is affected by health care provider attitudes, quality of service provided, adequacy of information provided, sociodemographics of participants, type of pregnancy and history of still birth, social and cultural norms as well as patients' previous experience [6].

World Health Organization (WHO) emphasizes patient satisfaction as a secondary prevention of maternal mortality. The purpose of evaluating patient satisfaction is firstly to understand patient experiences and response to health care; and secondly to measure the quality of care received and identify problem areas [7].

Women's satisfaction with antenatal care can be determined by the interaction between their expectations and the characteristics of the health care they receive [8]. Expectations for prenatal care of pregnant women can be divided into four main categories: desire for adequate information, emotional support, general advocacy support, and desire for professional care [9].

In spite of the increasing importance of quality of antenatal care worldwide, detailed information about the quality or effectiveness of ANC practices is less often investigated in many of the populations where they are most needed [10]. In Saudi Arabia, there is a dearth of literature regarding quality of ANC. To bridge this gap, we designed the current study with the objectives to determine the satisfaction level of pregnant women seeking ANC at PHCCs in Unaizah city, to explore their expectation, to assess the perceived quality of antenatal care and to identify association of sociodemographic factors with the level of expectations and satisfaction of pregnant women seeking ANC at PHCCs in Unaizah city.

Materials and Methods

1. Study Design, Setting and Study Population

It was a cross-sectional study, conducted at primary health care centers (PHCCs) in Unaizah City. Unaizah is the second largest city in Qassim province with a population of 163,729 persons. In 2020, a total of 2,390 PHCCs were distributed all over the Kingdom of Saudi Arabia. There are 16 PHCCs in Unaizah City. Basically, the PHCCs focus on preventive and curative primary care services such as health promotion and education, environmental hygiene, maternity and childcare, vaccinations, diagnosis and treatment of common diseases and providing drug supplies as well as protecting the community against contagious and endemic diseases [11].

Saudi pregnant women seeking antenatal care services at PHCCs in Unaizah, were included in this study. Women physically handicapped or having mental health conditions were excluded from the study.

2. Sampling Procedure and Data Collection

Two-stage cluster sampling method was used. In the first stage, 5 PHCCs out of the total 16 were randomly selected by using Microsoft Excel software. In the second stage, 40 women were selected from each center. All women attending antenatal clinics were invited to participate in the study till completion of sample size from that centre. After their exit from the clinic, women were invited to participate in the study by the physicians (general practitioner or family physician) at the end of the consultation. Data was collected by the first author and the physicians at the PHCCs. The physicians were trained for data collection. Data collectors explained the aims of the study and gave the patient the opportunity to ask any questions about the survey or the questionnaire. The illiterate women were interviewed by the data collector. The survey was conducted from December 2020 to June 2021.

3. Study Questionnaire

A semi-structured self-administered questionnaire was used. The questionnaire was adapted from the validated and standardized questionnaire developed by World Health Organization for the assessment of perceived quality of antenatal care services [12]. Scale of expectations and satisfactions were adapted from a validated questionnaire used in the study conducted to determine expectations and satisfaction of women with antenatal care [8]. The questionnaire was modified according to local requirements. It consisted of four parts. The first part collected information about sociodemographic data and obstetrical history such

as age, level of education, occupation, family income, gestational age, and number of children. The second part included questions about perceived quality of ANC such as waiting time, consultation time, and relevant information received. There were five statements for assessing perceived adequacy of information. Each statement had four options including no information received, not enough, as much as wanted and too much information. The third part comprised questions about women's expectations regarding same doctor preference, waiting time, and number of antenatal visits. The options provided for expectation response included less than expected, same as expected and more than expected. The fourth part gathered information about satisfaction level which included statements to be rated on 5-point Likert scale, ranging from strongly disagree to strongly agree. Moreover, there were questions about further visits to the clinic and recommendation of the clinic to others. Finally, suggestions for improvement of services were obtained from the participants. Pilot study was done to test the clarity and understandability of the questionnaire.

4. Statistical Analysis

Data was entered and analyzed using Statistical Package for Social Science (SPSS) program version 23. Descriptive statistics were calculated as frequencies and percentages for categorical variables, and mean and standard deviation for numerical variables. Chi square, t test and ANOVA were used for inferential statistics. The results with p value ≤0.05 were considered statistically significant.

Total information adequacy scores were calculated by assigning 0 to 'no information received' response; 1 to 'not enough'; 2 to 'too much information', and 3 to 'as much as wanted'. There were five statements regarding adequacy of information leading to a total possible score of 15 (5 items *3 score), with a minimum of 0 and a maximum of 15 score. The total information adequacy score was categorized into adequate (0 to 8 score) and inadequate (9 to 15 scores).

A five-point Likert scale was used for assessing the level of satisfaction. One score was assigned to 'strongly disagree' response while five score to 'strongly agree' response. There were seven satisfaction statements leading to total possible score for satisfaction as 35 (7 items *5 score), with a minimum of 7 and a maximum of 35 score. The level of satisfaction was categorized into low (7-21 score), medium (22-27 score) and high (28-35 score).

5. Ethical consideration

Ethical approval of study was taken from Qassim Regional Research Ethics Committee. Permission was obtained from administrative authorities, and before distributing the questionnaire, permission was taken from each PHCC Director. Informed consent was obtained from all study participants, and confidentiality and privacy were maintained at all levels.

Results

1. Survey Response rate

Out of 220 women invited for survey participation, 204 consented to participate in the study, leading to a response rate of 92.7%.

2. Sociodemographic characteristics of the Participants

More than half (54.5%) of the women were 30 years old or less. A total of 103 (50.5%) women had educational level of university or higher. The majority (80%) were housewives, and 55.9% of the participants had family income of 5000-10,000 Saudi Riyals. Regarding obstetric and reproductive health profile, about half (48%) of women had given birth to one to three children while 55 (27%) women were experiencing their first pregnancy (Table 1).

3. Adequacy of Information

Table 2 shows responses of the participants regarding adequacy of information given to the women on different aspects of their health during pregnancy. Regarding information given about medication needed or avoided during pregnancy, the majority of women (82.4%) responded that they received information as much as they wanted. However, more than one-third (36.3%) of the women either did not receive information about breast feeding or they believed it was not enough. With regards to family planning and contraception, 42.2% of women either did not receive any information or they thought it was not enough.

Table 1: Socio-demographic characteristics of study participants (n=204)

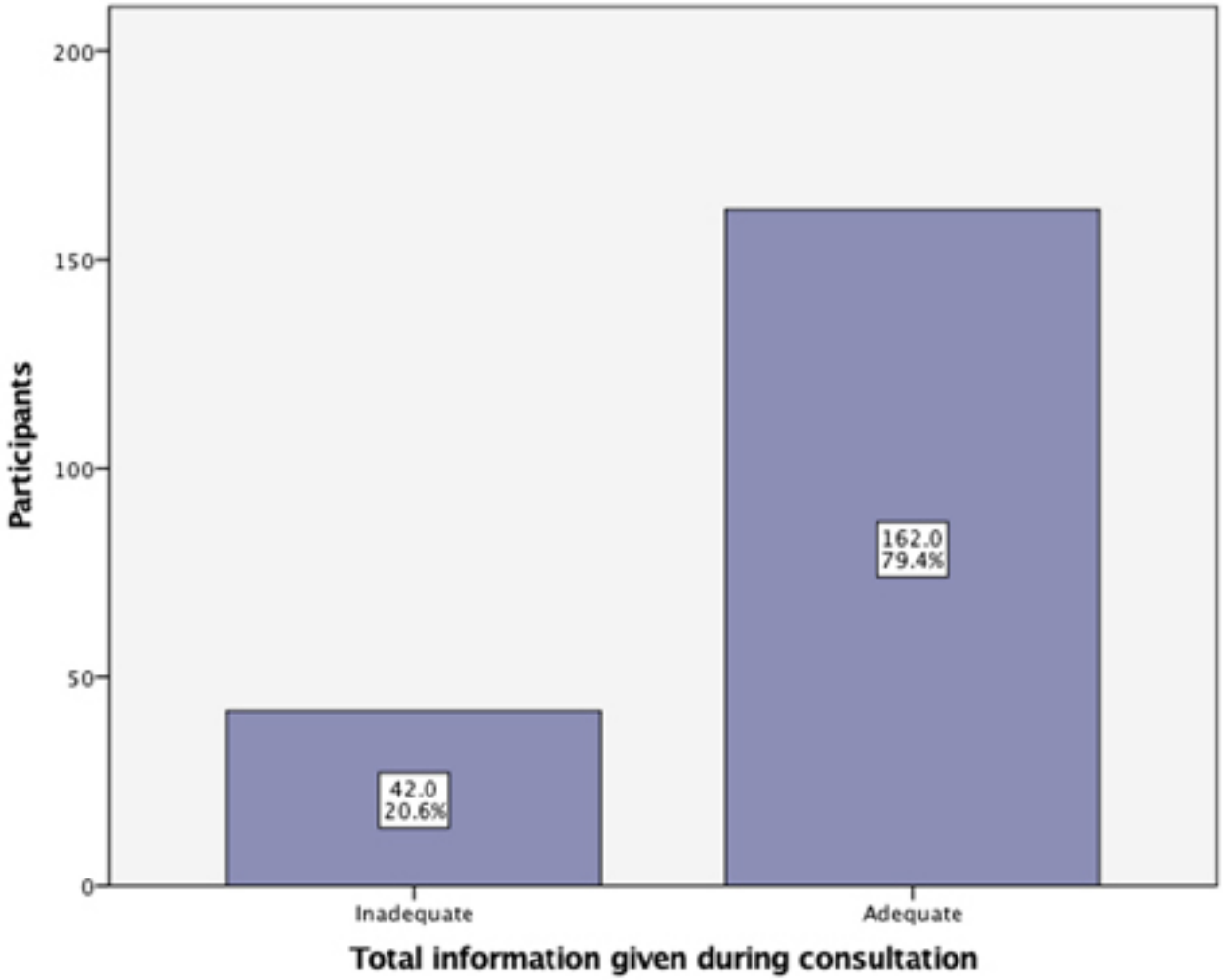
Socio-demographic characteristic	Number	Percentage
Age (Years)		
18-25	56	27.5
26-30	55	27
31-35	51	25
>35	42	20.5
Educational level		
Literate/read & write	6	2.9
Primary	12	5.9
Secondary	10	4.9
Tertiary	73	35.8
University and above	103	50.5
Occupation		
Housewife	163	79.9
Working	41	20.1
Family income		
<5000 Saudi Riyal	42	20.6
5000-10000 Saudi Riyal	114	55.9
11000-20000 Saudi Riyal	45	22
>20000 Saudi Riyal	3	1.5
Gestational period		
1st trimester (0-13weeks)	76	37.3
2nd trimester (14-26weeks)	69	33.8
3rd trimester (27-40weeks)	59	28.9
Number of pregnancies		
1	55	27
2-4	98	48
5-8	51	25
Number of children		
0	61	29.9
1-3	103	50.5
4-7	40	19.6
Number of Prenatal visits		
1	56	27.5
2-4	116	56.9
5-9	32	15.6

Table 2: Adequacy of information received during Antenatal visit (n=204)

Information	Not enough/ No information received n (%)	As much as wanted n (%)	Too much n (%)
Information about health care	14 (6.8)	161 (79)	29 (14.2)
Information about medicines	17 (8.3)	168 (82.4)	19 (9.3)
Information about delivery	40 (19.7)	145 (71)	19 (9.3)
Information about breast feeding	74 (36.3)	103 (50.5)	27 (13.2)
Information about family planning	86 (42.2)	100 (49)	18 (8.8)

Figure 1 illustrates the adequacy of overall information given to participants during consultation with their physicians. Among the total 204 participants, 42 (20.6%) received inadequate overall information.

Figure 1: Participants' responses regarding adequacy¶ of overall information provided during antenatal care visit (n=204)



¶Adequacy of information categories based on a total score of 15:
Inadequate: score 0-8 Adequate: score 9-15

The participants were also asked if they received any instructions about danger signs during pregnancy, and when to seek emergency care. Around one-third (32.3%) of the women either did not receive any instructions or thought that the instructions were insufficient for them.

4. Women's expectations about quality of Antenatal care available at PHCC

Most women (80.4%) considered consultation time the same as they expected. Around two thirds (64.7%) of women expected the same physician attending them in every visit. A total of 141 (69.1%) women expected management from their physician on facing minor health problems. Only 20 (9.8%) women expected an immediate referral on facing minor health issues (Table 3).

Table 3: Women's expectations about quality of Antenatal care available at PHCC

Expectations among women visiting ANC.	Number	Percentage
Visits number (n=203)		
more than expected	14	6.9
less than expected	39	19.1
same as expected	150	73.5
Waiting time (n=204)		
more than expected	45	22.1
less than expected	38	18.6
same as expected	121	59.3
Time spent with doctor: (n=204)		
more than expected	27	13.2
less than expected	13	6.4
same as expected	164	80.4
Same doctor every visit: (n=204)		
No	20	9.8
Yes	132	64.7
No preference	52	25.5
Health problem: (n=204)		
Management	141	69.1
Referral immediately	20	9.8
Referral when needed	43	21.1

5. Women's Satisfaction with antenatal care services

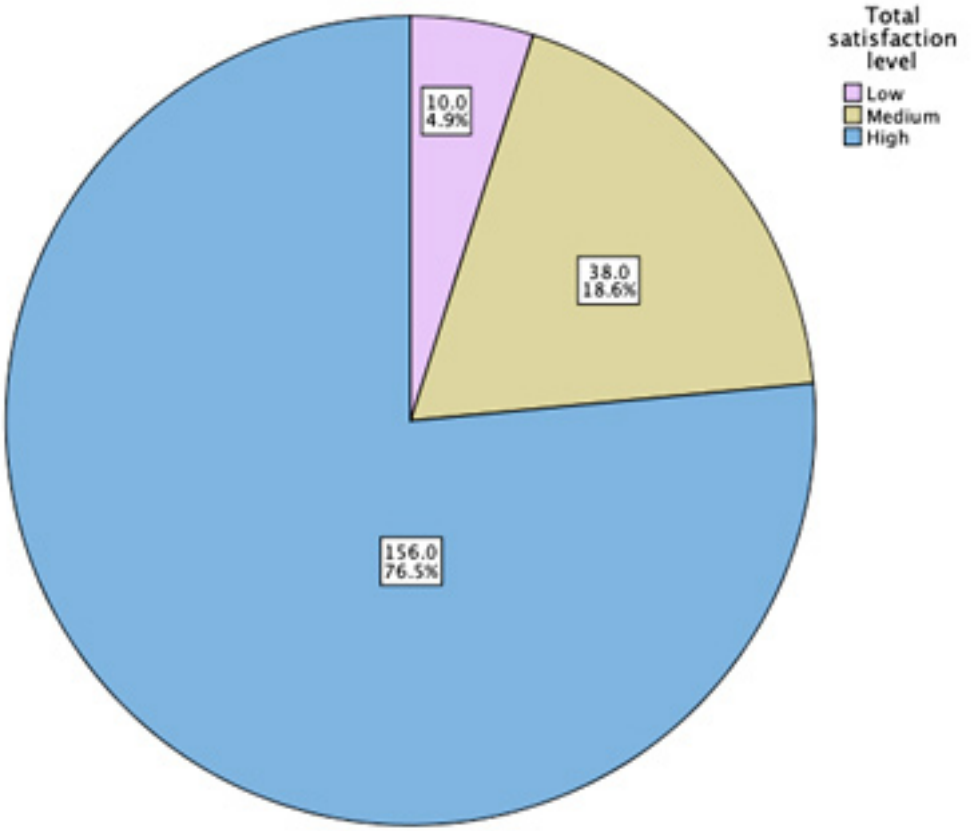
The majority of women were satisfied regarding overall information received (n=189, 92.7%), care received from physicians (n=201, 98.5%) and general quality of the health care provided (n=189, 92.7%). In contrast, around one quarter (22.5%) of the participants were neutral or dissatisfied about the waiting time at the clinic and about one-fifth were neutral or dissatisfied with the total time spent from entering the clinic to leaving it (Table 4).

Table 4: Women's Satisfaction with antenatal care services at Primary Health Care Centers (n=204)

Statement	Strongly Agree/Agree No. (%)	Neutral No. (%)	Strongly disagree/ disagree No. (%)
I am satisfied with overall information received during my visit	189 (92.7)	6 (2.9)	9 (4.4)
I am satisfied with the way physician treats the patient	201 (98.5)	2 (1)	1 (0.5)
I am satisfied with the quality of care received from physician	189 (92.6)	6 (2.9)	9 (4.4)
I am satisfied with the waiting time	158 (77.5)	28 (13.7)	18 (8.8)
I am satisfied with the total time spent in clinic	165 (80.9)	19 (9.3)	20 (9.8)
I am satisfied with the number of visits I made until now	177 (86.8)	19 (9.3)	8 (3.9)
In general I am satisfied with the quality of care I received so far.	186 (91.1)	13 (6.4)	5 (2.5)

The mean total satisfaction score was 29.6±4.5, with a minimum score of 12 and a maximum of 35. The mean scores were categorized into low (7-21), medium (22-27) and high (28-35) level of satisfaction. A total of 156 (76.5%) participants expressed a high level of satisfaction with the antenatal care services provided at the primary health care center (Figure 2).

Figure 2: Level of satisfaction among women visiting antenatal care clinic (n=204)



On stratifying level of satisfaction according to age groups, 82.8% of the women in 31-50 years age group were highly satisfied with the antenatal care services as compared to 71.2% of the women in 18-30 years age group.

On enquiring whether the participant would come back to the clinic for ANC follow up, 143 (70.1%) women responded in affirmation, however, 61 (29.9%) either refused to come back or were not sure about it. When asked regarding recommendation of the clinic to others, 77.8% of women stated that they would recommend the clinic to a friend or relative while 22.2% either refused to recommend or were not sure about it.

The association of sociodemographic factors with mean satisfaction scores was analyzed. None of the demographic factors had a statistically significant association with the satisfaction scores, however, various categories of demographic factors had differences in the mean scores. The mean scores for satisfaction with antenatal care progressively increased with decreasing household incomes with the highest mean score (30.36±5) for women with household income of 5,000 SR or less, and the lowest mean score (26.67±1.5) for those having household income of 20,000 SR or more. Women in third trimester had slightly higher mean satisfaction scores (30.41±0.45) as compared to the women in first (29.86±5.38) and second trimester (28.87±4.39).

The association of sociodemographic factors with total mean score of perceived adequacy of information was explored. Out of the total 15, the mean score for women of 31-50 years age group was 12.37±3.24 while the 18-30 years age group had a mean score of 10.63±4.02; this difference was statistically significant at p=0.001. The pregnancy number (p=0.015) and the number of children (p=0.001) were also statistically significantly associated with perceived adequacy of information received during antenatal care visit.

6. Suggestions by study participants

Twenty-five (12.3%) participants provided suggestions for improvement of antenatal care. The suggestions included availability of ultrasound, improvement in management of ANC clinics such as better organization to minimize waiting time, special clinic and doctor for ANC follow up and overall improved care and equipment. Moreover, provision of more health education about delivery and postpartum period and distribution of health education brochures, were also suggested by the study participants.

Discussion

The current study was conducted to assess pregnant women's expectations about antenatal care and to measure their overall level of satisfaction with the quality of care provided at PHCCs in Unaizah city. Furthermore, we investigated the association of demographic factors with the level of expectations and satisfaction. In our study, the response rate was 92.7% which is considered an excellent survey response [13].

Waiting time is reported to influence the level of satisfaction of clients, as it is imaged as an important predictor of satisfaction. Long waiting time is found to be associated with dissatisfaction with care in many studies [3, 14, 15, 17-20]; the more the time of waiting the less the level of satisfaction. There are no set standards for waiting time, however, studies have reported that the duration of waiting time before antenatal care for some of the women was perceived as long [18, 21]. In our study, approximately one quarter (22.5%) of the participants were dissatisfied about the waiting time at the clinic and about one-fifth were dissatisfied with the total time spent from entering the clinic to leaving it. The long waiting times might be explained by shortage of medical staff as compared to the number of clients attending the PHCCs. Moreover, lack of appointment system at PHCCs may also lead to long waiting times. A systematic review of maternal satisfaction studies done in developing countries, including Saudi Arabia, concluded that promptness of care is considered a major determinant of maternal satisfaction [22]. Another study conducted in Oman also had similar findings [23].
One of the main goals of ANC is the provision of adequate information that is essential for maintaining and improving pregnancy outcomes [15]. In our study, the majority of women responded that they received relevant information as much as they wanted. However, a substantial proportion of women did not receive information, or they believed it was not enough especially about breast feeding, family planning and contraception. Moreover, crucial instructions about signs of danger and when to seek emergency care in pregnancy, were also reported insufficient by a noticeable proportion of the study participants. The findings concur with another study in Saudi Arabia which found that 22% of pregnant women were unsatisfied with the antenatal care counseling [24]. A study conducted in Egypt also reported low satisfaction with health education components [9]. This finding underscores the importance of continuous training programs to health care providers to improve their knowledge and communication skills.

In our study, higher mean scores for adequacy of information were obtained by older and multiparous women. This may be explained by the fact that increasing age and multiparity may lead to better awareness regarding pregnancy issues because of previous experiences, resulting in being satisfied with the information received from the healthcare provider.

In the current study, more than two thirds of women expected to be seen by the same physician on every visit. This suggests that the patient felt more comfortable with the doctor they followed with, which is a good predictor for patient-doctor relationship. In another study [22], preference for female providers emerged as a significant determinant of satisfaction which can be attributed to the cultural values. In a study conducted in 4 countries: Saudi Arabia, Thailand, Cuba and Argentina; only Saudi women expressed a clear preference for being seen by female doctors in antenatal care [25]. This can be explained by the religious and cultural values of Saudi Arabia. In our study, we did not explore female preference as generally in most PHCCs in Saudi Arabia and specifically in our study setting Unaizah, female physicians are responsible for antenatal care follow up.

Few participants in our study expected an immediate referral on facing minor health issues. As per referral protocol, there are specific indications for referral to secondary care, and it is not advisable to refer the patient to a higher-level health facility for minor health issues. This finding in our study, underscores the importance of addressing the misconception among some women that PHCC is just a referral facility.

The overall level of satisfaction among women visiting antenatal care clinic was high. This finding is in accordance with other studies [3, 6, 23, 26] which also showed high satisfaction level with antenatal care services. In contrast, the overall maternal ANC service satisfaction was found to be sub-optimal in a study conducted in Ethiopia [17].

Returning to the same health care facility and recommending it to others are important indicators of satisfaction with the care provided at the facility. In our study, a substantial proportion of participants did not intend to come back or recommend the clinic to a friend or relative. Further research is recommended to explore the reasons of refusal to come back to the same clinic and for not recommending the clinic to others.

Various studies have found association of antenatal care satisfaction to demographic factors such as age, education, and occupation. In a study conducted in Saudi Arabia [3], it was found that older, less educated women, and housewives were more satisfied with client- provider interaction and with the quality of antenatal care. Other studies [14-16] also found that low educated women had high satisfaction level. This may be attributed to low education leading to lack of awareness about care they could expect at the antenatal clinic. In contrast to the studies mentioned above, our study did not find a statistically

significant association of any of the demographic factors with the antenatal care satisfaction; however, we noticed that various categories of demographic factors had differences in the mean scores. The mean scores for satisfaction with antenatal care progressively increased with decreasing household incomes. Furthermore, women in third trimester had slightly higher mean satisfaction scores as compared to women in first and second trimester. The reasons for these differences need to be explored in future research.

This study has certain limitations. As our study was conducted within the PHCCs, there might be overestimation of the level of satisfaction. However, efforts were made to minimize this bias by ensuring the participants that the questionnaires were processed anonymously. Furthermore, our study surveyed the patients attending selected PHCCs in only one city which may limit generalization to other cities. However, other cities of the country are expected to have a similar demographic profile of general population, and similar standard of health care services in PHCCs, making it possible to generalize our findings to other areas.

Conclusions

The present study found that the overall satisfaction with the quality of antenatal care was high. The majority of women were satisfied with the overall information received, care received from physicians and general quality of health care provided. However, some aspects of services showed dissatisfaction including waiting time and the total time spent in the clinic. Around one third of the participants either refused or were not sure whether they will visit the same PHCC again, and approximately one quarter responded that either they would not recommend the clinic to a friend or relative or were not sure about it. Improvement in the management of ANC clinics and provision of equipment such as ultrasound, and enhancement of health education were the suggestions by the participants. Based on the findings of our study, we recommend that administrative measures should be taken to improve the management of ANC clinics especially regarding waiting time. Improvement in health education regarding breast feeding and contraception is also required. The health care providers need to be trained to provide clear instructions regarding danger signs during pregnancy and when to seek emergency care. Moreover, regular patient satisfaction surveys should be carried out to identify problem areas and to improve the quality of services.

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Pulmonary hypertension and chronic obstructive pulmonary disease in sickle cell diseases

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Abstract

Background: Pulmonary hypertension (PHT) is a common consequence of chronic obstructive pulmonary disease (COPD).

Methods: All patients with sickle cell diseases (SCD) were included.

Results: The study included 434 patients (212 females) with similar mean ages in males and females (30.8 versus 30.3 years, p>0.05, respectively). Smoking (23.8% versus 6.1%, p<0.001), alcohol (4.9% versus 0.4%, p<0.001), disseminated teeth losses (<20 teeth present) (5.4% versus 1.4%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), coronary heart disease (CHD) (18.0% versus 13.2%, p<0.05), chronic renal disease (CRD) (9.9% versus 6.1%, p<0.05), stroke (12.1% versus 7.5%, p<0.05), and COPD (25.2% versus 7.0%, p<0.001) were higher but not PHT (12.6% versus 11.7, p>0.05) and deep venous thrombosis (DVT) and/or varices and/or telangiectasias (9.0% versus 6.6%, p>0.05) in males.

Conclusion: SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened red blood cells (RBC) into tissues. Although smoking, alcohol, disseminated teeth losses, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, stroke, and COPD-like atherosclerotic events were higher in males, PHT and DVT and/or varices and/or telangiectasias were similar in both genders. Similarly, although the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalence of PHT in both genders also supports its nonatherosclerotic nature. In another definition, COPD may have an atherosclerotic whereas PHT a hardened RBC-induced chronic thromboembolic background in the SCD.

Key words: Sickle cell diseases, pulmonary hypertension, chronic obstructive pulmonary disease, endothelial damage, atherosclerosis, metabolic syndrome, aging

Introduction

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human beings (1). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, which eventually reduces blood supply to the terminal organs, and increases systolic and decreases diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, excess weight, animal-rich diet, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, aging, and death (2, 3). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medical literature, extensively (4-6). On the other hand, sickle cell diseases (SCD) are a chronic inflammatory process on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failure and a shortened survival in both genders (7, 8). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem since sickling is rare in peripheric blood samples of the patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during the whole lifespan, but exaggerated with inflammation, infection, and various stresses of the body. The hard RBC induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia all over the body (9). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (10, 11), since the capillary system is the main distributor of the hard cells into the tissues. The hard RBC induced chronic endothelial damage builds up an advanced atherosclerosis in early decades of life. Vascular narrowing and occlusions induced tissue ischemia and infarctions are the final consequences of the SCD, so the mean life expectancy is decreased by 25 to 30 years in such patients (8). We tried to understand the underlying mechanisms of pulmonary hypertension (PHT) and COPD in the SCD.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University between March 2007 and June 2016. All patients with the SCD were included. The SCD were diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography (HPLC). Medical histories including smoking, alcohol, painful crises per year, transfused units of RBC in their lives, leg ulcers, stroke, surgical operations, deep venous thrombosis (DVT), epilepsy, and priapism were learnt. Patients with a history of one pack-year were accepted as smokers, and one drink-year were accepted as drinkers. A complete physical examination was performed by the Same Internist, and patients with disseminated teeth loss (<20 teeth present) were detected. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including serum iron, iron binding capacity, ferritin, creatinine, liver function tests, markers of hepatitis viruses A, B, and C, a posterior-anterior chest x-ray film, an electrocardiogram, a Doppler echocardiogram both to evaluate cardiac walls and valves and to measure systolic BP of pulmonary artery, an abdominal ultrasonography, a venous Doppler ultrasonography of the lower limbs, a computed tomography (CT) of brain, and a magnetic resonance imaging (MRI) of hips were performed. Other bones for avascular necrosis were scanned according to the patients' complaints. So avascular necrosis of bones was diagnosed via MRI (12). Associated thalassemia minors were detected with serum iron, iron binding capacity, ferritin, and hemoglobin electrophoresis performed via HPLC since the SCD with associated thalassemia minor show a milder clinical indication than the sickle cell anemia (SCA) alone (13). Systolic BP of the pulmonary artery of ≥40 mmHg are accepted as PHT (14). The criterion for diagnosis of COPD is post-bronchodilator forced expiratory volume in one second/ forced vital capacity of <70% (15). Acute chest syndrome is diagnosed clinically with the presence of new infiltrates on chest x-ray film, fever, cough, sputum production, dyspnea, or hypoxia (16). An x-ray film of abdomen in upright position was taken just in patients with abdominal distention or discomfort, vomiting, obstipation, or lack of bowel movement, and ileus was diagnosed with gaseous distention of isolated segments of bowel, vomiting, obstipation, cramps, and with the absence of peristaltic activity. CRD is diagnosed with a persistent serum creatinine level of ≥1.3 mg/dL in males and ≥1.2 mg/dL in females. Cirrhosis is diagnosed with physical examination findings, laboratory parameters, and ultrasonographic evaluation. Digital clubbing is diagnosed with the ratio of distal phalangeal diameter to interphalangeal diameter which is >1.0, and with the presence of Schamroth's sign (17, 18). An exercise electrocardiogram is performed in cases with an abnormal electrocardiogram and/or angina pectoris. Coronary angiography is taken for the

exercise electrocardiogram positive cases. So CHD was diagnosed either angiographically or with the Doppler echocardiographic findings as the movement disorders in the cardiac walls. Rheumatic heart disease is diagnosed with the echocardiographic findings, too. Stroke is diagnosed by the CT of brain. Sickle cell retinopathy is diagnosed with ophthalmologic examination in patients with visual complaints. Eventually, mean age, associated thalassemia minors, smoking, alcohol, painful crises per year, transfused units of RBC in their lives, disseminated teeth loss, COPD, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, stroke, PHT, autosplenectomy, DVT and/or varices and/or telangiectasias, rheumatic heart disease, avascular necrosis of bones, sickle cell retinopathy, epilepsy, acute chest syndrome, mortality, and mean age of mortality were detected in both genders. Mann-Whitney U test, Independent-Samples t test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 434 patients with the SCD (222 males and 212 females). Mean ages of the patients were similar in males and females (30.8 versus 30.3 years, p>0.05, respectively). Prevalence of associated thalassemia minors were similar in both genders, too (72.5% versus 67.9%, p>0.05, respectively). Smoking (23.8% versus 6.1%) and alcohol (4.9% versus 0.4%) were higher in males, significantly (p<0.001 for both) (Table 1). Similarly, transfused units of RBC in their lives (48.1 versus 28.5, p=0.000), disseminated teeth loss (5.4% versus 1.4%, p<0.001), ileus (7.2% versus 1.4%, p<0.001), cirrhosis (8.1% versus 1.8%, p<0.001), leg ulcers (19.8% versus 7.0%, p<0.001), digital clubbing (14.8% versus 6.6%, p<0.001), CHD (18.0% versus 13.2%, p<0.05), CRD (9.9% versus 6.1%, p<0.05), stroke (12.1% versus 7.5%, p<0.05), and COPD (25.2% versus 7.0%, p<0.001) were all higher in males, significantly. On the other hand, prevalence of PHT (12.6% versus 11.7, p>0.05) and DVT and/or varices and/or telangiectasias were similar in both genders (9.0% versus 6.6%, p>0.05), significantly (Table 2).

Table 1: Characteristic features of the study cases

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Prevalence	51.1% (222)	Ns†	48.8% (212)
Mean age (year)	30.8 ± 10.0 (5-58)	Ns	30.3 ± 9.9 (8-59)
Associated thalassemia minors	72.5% (161)	Ns	67.9% (144)
Smoking	***23.8% (53)***	***<0.001***	***6.1% (13)***
Alcoholism	***4.9% (11)***	***<0.001***	***0.4% (1)***

*Sickle cell diseases †Nonsignificant (p>0.05)

Table 2: Associated pathologies of the study cases

Variables	Male patients with SCD*	*p*-value	Female patients with SCD
Painful crises per year	5.0 ±7.1 (0-36)	Ns†	4.9 ±8.6 (0-52)
Transfused units of RBC‡	*48.1 ± 61.8 (0-434)*	*0.000*	*28.5 ± 35.8 (0-206)*
Disseminated teeth losses (<20 teeth present)	*5.4% (12)*	*<0.001*	*1.4% (3)*
COPD§	*25.2% (56)*	*<0.001*	*7.0% (15)*
Ileus	*7.2% (16)*	*<0.001*	*1.4% (3)*
Cirrhosis	*8.1% (18)*	*<0.001*	*1.8% (4)*
Leg ulcers	*19.8% (44)*	*<0.001*	*7.0% (15)*
Digital clubbing	*14.8% (33)*	*<0.001*	*6.6% (14)*
CHD¶	*18.0% (40)*	*<0.05*	*13.2% (28)*
*CRD***	*9.9% (22)*	*<0.05*	*6.1% (13)*
Stroke	*12.1% (27)*	*<0.05*	*7.5% (16)*
PHT***	12.6% (28)	Ns	11.7% (25)
Autosplenectomy	50.4% (112)	Ns	53.3% (113)
DVT**** and/or varices and/or telangiectasias	9.0% (20)	Ns	6.6% (14)
Rheumatic heart disease	6.7% (15)	Ns	5.6% (12)
Avascular necrosis of bones	24.3% (54)	Ns	25.4% (54)
Sickle cell retinopathy	0.9% (2)	Ns	0.9% (2)
Epilepsy	2.7% (6)	Ns	2.3% (5)
Acute chest syndrome	2.7% (6)	Ns	3.7% (8)
Mortality	7.6% (17)	Ns	6.6% (14)
Mean age of mortality (year)	30.2 ±8.4 (19-50)	Ns	33.3 ±9.2 (19-47)

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Red blood cells §Chronic obstructive pulmonary disease ¶Coronary heart disease **Chronic renal disease ***Pulmonary hypertension ****Deep venous thrombosis

Discussion

PHT is a condition of increased BP within the arteries of the lungs. Shortness of breath, fatigue, chest pain, palpitation, swelling of legs and ankles, and cyanosis are common symptoms of the PHT. Actually, it is not a diagnosis itself, instead solely a hemodynamic state characterized by resting mean pulmonary artery pressure of ≥25 mmHg. An increase in pulmonary artery systolic pressure, estimated noninvasively by the echocardiography, helps to identify patients with the PHT (19). The cause is often unknown. The underlying mechanism typically involves inflammation and subsequent remodelling of the arteries. It probably affects 1% of the world population, and its prevalence may reach 10% above the age of 65 years (20). Onset is typically seen between 20 and 60 years of age (21). The most common causes are left heart diseases and chronic inflammatory lung pathologies, particularly the COPD in the society (21, 22). The cause of PHT in COPD is generally assumed to be hypoxic pulmonary vasoconstriction leading to permanent medial hypertrophy (23). But the pulmonary vascular remodeling in COPD may have a much more complex mechanism than just being the medial hypertrophy secondary to the long-lasting hypoxic vasoconstriction alone (23). In fact, all layers of the vessel wall appear to be involved with prominent intimal changes (23). The specific pathological picture could be explained by the combined effects of hypoxia, prolonged stretching of hyperinflated lungs-induced mechanical stress and inflammatory reaction, and the toxic effects of cigarette smoke (23). According to World Health Organization, there are five groups of PHT including pulmonary arterial hypertension, PHT secondary to left heart diseases, PHT secondary to lung diseases, chronic thromboembolic PHT, and PHT with multifactorial mechanisms (21). On the other hand, PHT is also a common consequence of the SCD (24). The authors detected its prevalence between 20% and 40% in the SCD in the literature (25). Whereas we detected the ratio as 12.2% in the present study. Although the highly atherosclerotic background of the COPD (26), PHT may actually have a different underlying mechanism in the SCD since 52.8% of the PHT and 78.8% of the COPD cases were males in the present study (p<0.001). Additionally, although the higher prevalences of smoking, alcohol, disseminated teeth loss, ileus, cirrhosis, leg ulcers, digital clubbing, CRD, and stroke-like other atherosclerotic events in male gender, the prevalence of PHT was not higher in males with the SCD, significantly (12.6% versus 11.7%, p>0.05). Similarly, although the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalences of PHT in both genders also support its

nonatherosclerotic nature. As a risk factor for pulmonary thromboembolic events, prevalences of DVT and/or varices and/or telangiectasias were similar in males and females (9.0% versus 6.6%, p>0.05, respectively) parallel to the prevalence of PHT. Similarly, the left heart diseases are the other common causes of PHT in society (27), and although the higher prevalence of CHD in males in the present study (18.0% versus 13.2%, p<0.05), PHT was not higher in them again. In another definition, the hardened RBC-induced chronic thromboembolism may be the predominant underlying mechanism of PHT in the SCD (28, 29).

COPD is the third leading cause of death with various triggering causes in the world (30). Male gender, aging, smoking, and excess weight may be the major underlying etiologies. As also observed in the present study, regular alcohol consumption may also be important in the pulmonary and systemic inflammatory process. For instance, COPD was one of the most common diagnoses in patients with alcohol dependence (31). Furthermore, 30-day readmission rates were higher in the COPD patients with alcoholism (32). Probably an accelerated atherosclerotic process is the main structural background of functional changes, characteristics of the COPD. The inflammatory process of vascular endothelium is enhanced by release of various chemicals by inflammatory cells, and it terminates with an advanced atherosclerosis, fibrosis, and pulmonary losses. COPD may actually be the pulmonary consequence of the systemic atherosclerotic process. Since beside the accelerated atherosclerotic process of the pulmonary vasculature, there are several reports about coexistence of associated endothelial inflammation all over the body (33, 34). For example, there may be close relationships between COPD, CHD, PAD, and stroke (35). Furthermore, two-thirds of mortality cases were caused by cardiovascular diseases and lung cancers in the COPD, and the CHD was the most common cause in a multi-center study of 5.887 smokers (36). When the hospitalizations were researched, the most common causes were the cardiovascular diseases again (36). In another study, 27% of mortality cases were due to the cardiovascular diseases in the moderate and severe COPD cases (37). As also observed in the present study, COPD may just be the pulmonary consequence of the systemic atherosclerotic process induced by the hardened RBC in the SCD (26).

Digital clubbing is characterized by the increased normal angle of 165° between nailbed and fold, increased convexity of the nail fold, and thickening of the whole distal finger (38). Although the exact cause and significance is unknown, the chronic tissue hypoxia is highly suspected (39). In the previous study, only 40% of clubbing cases turned out to have significant underlying diseases while 60% remained well over the subsequent years (18). But according to our experiences, digital clubbing is frequently associated with smoking and pulmonary, cardiac, renal, or hepatic diseases, all of which are characterized with chronic tissue hypoxia (5). As an explanation for that hypothesis, lungs, heart, kidneys, and liver are closely related organs that affect their function in a short period of time. On the other hand, digital clubbing is also common in patients with the SCD, and its prevalence was 10.8% in the present study. It probably shows chronic tissue hypoxia caused by disseminated endothelial damage, inflammation, edema, and fibrosis at the capillary level in the SCD. Beside the effects of SCD, smoking, alcohol, cirrhosis, CRD, CHD, and COPD, the higher prevalence of digital clubbing in males (14.8% versus 6.6%, p<0.001) may also show some additional role of male gender on systemic atherosclerosis.

Leg ulcers are seen in 10% to 20% of the SCD (40), and the ratio was 13.5% in the present study. Its prevalence increases with age, male gender, and SCA (41). Similarly, its ratio was higher in males (19.8% versus 7.0%, p<0.001), and mean age of the patients with leg ulcers was higher than the others (35.3 versus 29.8 years, p<0.000) in the present study. The leg ulcers have an intractable nature, and around 97% of healed ulcers relapse in a period of one year (40). As evidence of their atherosclerotic nature, the leg ulcers occur in distal areas with less collateral blood flow in the body (40). The abnormally hardened RBC induced chronic endothelial damage, inflammation, edema, and fibrosis at the capillary level may be the major underlying cause in the SCD (41). Prolonged exposure to the hardened bodies due to the pooling of blood in the lower extremities may also explain the leg but not arm ulcers in the SCD. The hardened RBC induced venous insufficiencies may also accelerate the process by pooling of causative hardened bodies in the legs, and vice versa. Pooling of blood may also have some effects on development of venous ulcers, diabetic ulcers, Buerger's disease, digital clubbing, and onychomycosis in the lower extremities. Furthermore, probably pooling of blood is the cause of delayed wound and fracture healings in the lower extremities. Smoking and alcohol may also have some additional atherosclerotic effects on the ulcers in males. Hydroxyurea is the first drug that was approved by Food and Drug Administration in the SCD (42). It is an orally-administered, cheap, safe, and effective drug that blocks cell division by suppressing formation of deoxyribonucleotides which are the building blocks of DNA (11). Its main action may be the suppression of hyperproliferative white blood cells (WBC) and platelets (PLT) in the SCD (43). Although presence of a continuous damage of hardened RBC on vascular endothelium, severity of the destructive process is probably exaggerated by the patients' own immune systems. Similarly, lower WBC counts were associated with lower crises rates, and if a tissue infarct occurs, lower WBC counts may decrease severity of pain and tissue damage (44). According to our experiences, prolonged resolution of ulcers with hydroxyurea may also suggest that the ulcers may be secondary to increased WBC and PLT counts induced exaggerated endothelial inflammation and edema at the capillaries.

Cirrhosis was the 10th leading cause of death for men and the 12th for women in the United States in 2001 (6). Although the improvements of health services worldwide, the increased morbidity and mortality of cirrhosis may be explained by prolonged survival of the human being and increased prevalence of excess weight all over the world.

For example, nonalcoholic fatty liver disease (NAFLD) affects up to one third of the world population, and it has become the most common cause of chronic liver disease even at childhood at the moment (45). NAFLD is a marker of pathological fat deposition combined with a low-grade chronic inflammation, which results with hypercoagulability, endothelial dysfunction, and an accelerated atherosclerosis (45). Beside terminating with cirrhosis, NAFLD is associated with higher overall mortality rates as well as increased prevalence of cardiovascular diseases (46). Authors reported independent associations between NAFLD and impaired flow-mediated vasodilation and increased mean carotid artery intima-media thickness (CIMT) (47). NAFLD may be considered as the hepatic consequences of the metabolic syndrome and SCD (9, 48). Probably smoking also plays a role in the endothelial inflammatory process of the liver, since the systemic inflammatory effects of smoking on endothelial cells is well-known with Buerger's disease and COPD (49). Increased oxidative stresses, inactivation of antiproteases, and release of proinflammatory mediators may terminate with a systemic atherosclerosis in smokers. The atherosclerotic effects of alcohol are much more prominent in hepatic endothelium probably due to the highest concentrations of its metabolites in the liver. Chronic infectious and inflammatory processes may also terminate with an accelerated atherosclerosis all over the body (50). For example, chronic hepatitis C virus (HCV) infection raised CIMT, and normalization of hepatic function with HCV clearance may be secondary to reversal of favourable lipids observed with the chronic infection (50, 51). As a result, beside COPD, ileus, leg ulcers, digital clubbing, CHD, CRD, and stroke, cirrhosis may also be found among the atherosclerotic consequences of the metabolic syndrome and SCD.

The increased frequency and complications of CRD may be explained by aging of the human being and increased prevalence of excess weight all over the world (52, 53). Aging, physical inactivity, excess weight, smoking, alcohol, and inflammatory or infectious processes may be the major causes of the renal endothelial inflammation. The inflammatory process is enhanced by release of various chemicals by lymphocytes to repair the damaged renal tissues, especially endothelial cells of the renal arteriols. Due to the continuous irritation of the endothelial cells in the above pathologies, prominent changes develop in the architecture of the renal tissues with advanced atherosclerosis and tissue hypoxia and infarcts. Excess weight induced hyperglycemia, dyslipidemia, elevated BP, and insulin resistance may cause tissue inflammation and immune cell activation (54). For example, age ($p= 0.04$), high-sensitivity C-reactive protein ($p= 0.01$), mean arterial BP ($p= 0.003$), and DM ($p= 0.02$) had significant correlations with the CIMT (53). Increased renal tubular sodium reabsorption, impaired pressure natriuresis, volume expansion due to the activations of sympathetic nervous system and renin-angiotensin system, and physical compression of kidneys by visceral fat tissue may be some mechanisms of the increased BP with excess weight (55). Excess weight also causes renal vasodilation and glomerular hyperfiltration which initially serve as compensatory mechanisms to maintain sodium balance due to the increased tubular reabsorption (55). However, along with the increased BP, these changes cause a hemodynamic burden on the kidneys in the long term that causes chronic endothelial damage (56). With prolonged weight excess, there are increased urinary protein excretion, loss of nephron function, and exacerbated HT. With the development of dyslipidemia and DM in cases with excess weight, CRD progresses much more easily (55). On the other hand, the systemic inflammatory effects of smoking on endothelial cells may also be important in the CRD (57). The inflammatory and atherosclerotic effects of smoking are much more prominent in the respiratory endothelium due to the highest concentrations of its metabolites there. Although some authors reported that alcohol was not related with the CRD (57), various metabolites of alcohol circulate even in the blood vessels of the kidneys and give harm to the renal vascular endothelium. Chronic inflammatory or infectious processes may also terminate with the accelerated atherosclerosis on the renal endothelium (50). Although CRD is mainly an advanced atherosclerotic process of the renal vasculature, there are close relationships between CRD and other consequences of the metabolic syndrome including CHD, COPD, PAD, cirrhosis, and stroke (58). For example, the most common cause of death was the cardiovascular diseases in the CRD again (59). In another definition, CRD may just be one of the several atherosclerotic consequences of the metabolic syndrome and SCD, too (60).

Stroke is an important cause of death, and an acute thromboembolic event on the atherosclerotic background is the most common cause. Male gender, aging, smoking, alcohol, increased serum glucose and lipids, elevated arterial BP, and excess weight may be the major triggering causes. Stroke is also a common complication of the SCD (61, 62). Similar to the leg ulcers, stroke is particularly higher in the SCA (63). Additionally, a higher WBC count is associated with a greater incidence of stroke (43). Sickling induced endothelial damage, activations of WBC, PLT, and coagulation system, and hemolysis may terminate with chronic endothelial inflammation, edema, and fibrosis (64). Probably, stroke is a complex and terminal event in the SCD, and it may not have a macrovascular origin, instead disseminated capillary inflammation induced endothelial edema may be much more important. Infection and other stresses may precipitate stroke, since increased metabolic rate during such episodes may accelerate sickling. A significant reduction of stroke with hydroxyurea may also suggest that a significant proportion of strokes develop secondary to the increased WBC and PLT counts induced exaggerated capillary inflammation and edema (65).

The venous endothelium is also involved in the SCD (66). For example, varices are abnormally dilated veins with tortuous courses, and they usually occur in the lower extremities. Normally, leg muscles pump veins to return blood against the gravity, and the veins have pairs of leaflets of valves to prevent blood from flowing backwards. When

the leaflets are damaged, varices and/or telangiectasias develop. DVT may also cause varicose veins. Varicose veins are the most common in superficial veins of the legs, which are subject to higher pressure when standing up, thus patient's physical examination should be performed in upright position. Although the relatively younger mean ages of the patients in the present study (30.8 and 30.3 years in males and females, respectively) and significantly lower body mass index of the SCD patients in the literature (10), DVT and/or varices and/or telangiectasias of the lower limbs were higher in the study cases (9.0% versus 6.6% in males and females, p>0.05, respectively), indicating an additional venous involvement in the SCD. Similarly, priapism is the painful erection of penis that cannot return to its flaccid state within four hours in the absence of any stimulation (67). It is an emergency since damage to the blood vessels may terminate with a long-lasting fibrosis of the corpus cavernosa, a consecutive erectile dysfunction, and eventually a shortened, indurated, and non-erectile penis (67). It is seen with hematological and neurological disorders including SCD, spinal cord lesions (hanging victims), and glucose-6-phosphate dehydrogenase deficiency (68, 69). Ischemic (veno-occlusive), stuttering (recurrent ischemic), and nonischemic priapisms (arterial) are the three types of priapism (70). Ninety-five percent of clinically presented priapisms are the ischemic (veno-occlusive) disorders in which blood cannot return adequately from the penis as in the SCD, and they are very painful (67, 70). The other 5% are nonischemic (arterial) type usually caused by a blunt perineal trauma in which there is a short circuit of the vascular system (67). Treatment of arterial type is not as urgent as the veno-occlusive type due to the absence of risk of ischemia (67). RBC support is the treatment of choice in acute phase in the SCD (71). Whereas in chronic phase, hydroxyurea should be the treatment of choice. According to experiences, hydroxyurea is an effective drug for prevention of attacks and consequences of priapism if iniatiated in early years of life, but it may be difficult due to the excessive fibrosis around the capillary walls if initiated later in life.

As a conclusion, SCD are severe inflammatory processes on vascular endothelium, particularly at the capillary level since the capillary system is the main distributor of hardened RBC into the tissues. Although smoking, alcohol, disseminated teeth loss, ileus, cirrhosis, leg ulcers, digital clubbing, CHD, CRD, stroke, and COPD-like atherosclerotic events were higher in males, PHT and DVT and/or varices and/or telangiectasias were similar in both genders. Similarly, although the male gender alone is a risk factor for the systemic atherosclerosis, the similar prevalences of PHT in both genders also support its nonatherosclerotic nature. In another definition, COPD may have an atherosclerotic whereas PHT a hardened RBC-induced chronic thromboembolic background in the SCD.

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Positive and negative acute phase reactants in sickle cell diseases

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Abstract

Background: We tried to understand some positive and negative acute phase reactants (APR) in sickle cell diseases (SCD).

Methods: Consecutive patients with the SCD and controls were studied.

Results: The study included 193 patients (98 females) and 132 controls (67 females). Although the body weight and body mass index (BMI) were retarded in the SCD (58.9 versus 71.1 kg and 21.5 versus 26.8 kg/m2, respectively, p<0.000 for both), the body heights were similar in both groups (164.8 versus 162.8 cm, p>0.05). Parallel to the retarded body weight and BMI, fasting plasma glucose (FPG) (93.4 versus 102.4 mg/dL, p=0.025), low density lipoproteins (LDL) (70.4 versus 98.1 mg/dL, p<0.000), high density lipoproteins (HDL) (24.2 versus 35.8 mg/dL, p<0.000), and systolic (117.6 versus 127.9 mmHg, p=0.001) and diastolic blood pressures (BP) (77.3 versus 86.0 mmHg, p<0.000) were all retarded in the SCD. On the other hand, total bilirubin (TB) and lactate dehydrogenase (LDH) were both increased (4.0 versus 0.7 mg/dL and 638.9 versus 268.4 U/L, respectively, p<0.000 for both) in the SCD. Similarly, white blood cell (WBC) and platelet (PLT) counts (16.338 versus 7.407 /μL and 421.424 versus 268.612 /μL, respectively) and mean corpuscular volume (MCV) (90.3 versus 78.3 fL) were all increased whereas the hematocrit (Hct) level was decreased (23.2 versus 36.6%) in the SCD (p<0.000 for all).

Conclusion: Body weight, BMI, FPG, LDL, HDL, systolic and diastolic BP, and Hct may be some negative whereas TB, LDH, WBC and PLT counts, and MCV may be some positive APR in the body.

Keywords: Sickle cell diseases, positive acute phase reactants, negative acute phase reactants, chronic endotelial damage, atherosclerosis, body weight, body mass index

Introduction

Chronic endothelial damage may be the major underlying cause of aging and death by causing end-organ insufficiencies in human beings (1-3). Much higher blood pressures (BP) of the afferent vasculature may be the major accelerating factor by causing recurrent injuries on vascular endothelial cells. Probably, whole afferent vasculature including capillaries are mainly involved in the process. Therefore the term of venosclerosis is not as famous as atherosclerosis in the medical literature. Due to the chronic endothelial damage, inflammation, edema, and fibrosis, vascular walls thicken, their lumens narrow, and they lose their elastic nature, \which eventually reduces blood supply to the terminal organs, and increases systolic and decreases diastolic BP further. Some of the well-known accelerating factors of the inflammatory process are physical inactivity, sedentary lifestyle, excess weight, animal-rich diet, smoking, alcohol, chronic inflammations, prolonged infections, and cancers for the development of terminal consequences including obesity, hypertension (HT), diabetes mellitus (DM), cirrhosis, peripheric artery disease (PAD), chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), chronic renal disease (CRD), mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, aging, and death (4-7). Although early withdrawal of the accelerating factors can delay terminal consequences, after development of HT, DM, cirrhosis, COPD, CRD, CHD, PAD, mesenteric ischemia, osteoporosis, stroke, dementia, other end-organ insufficiencies, and aging, endothelial changes cannot be reversed completely due to their fibrotic nature. The accelerating factors and terminal consequences are researched under the titles of metabolic syndrome, aging syndrome, or accelerated endothelial damage syndrome in the medical literature, extensively (8-10). On the other hand, sickle cell diseases (SCD) are chronic inflammatory processes on vascular endothelium terminating with accelerated atherosclerosis induced end-organ failures and a shortened survival in both genders (11, 12). Hemoglobin S causes loss of elastic and biconcave disc shaped structures of red blood cells (RBC). Probably loss of elasticity instead of shape is the major problem since sickling is rare in peripheric blood samples of the patients with associated thalassemia minors, and human survival is not affected in hereditary spherocytosis or elliptocytosis. Loss of elasticity is present during the whole lifespan, but exaggerated with inflammation, infection, and various stresses of the body. The hard RBC induced chronic endothelial damage, inflammation, and fibrosis terminate with disseminated tissue hypoxia in whole body (13, 14). As a difference from other causes of chronic endothelial damage, the SCD may keep vascular endothelium particularly at the capillary level (15), since the capillary system is the main distributor of the hard cells into the tissues. The hard RBC induced chronic endothelial damage builds up an advanced atherosclerosis in early decades of life. Vascular narrowing and occlusions induced tissue ischemia and infarctions are the final consequences of the SCD, so the mean life expectancy is decreased by 25 to 30 years in such patients (16). We tried to understand some positive and negative acute phase reactants (APR) in the SCD patients in the present study.

Material and Methods

The study was performed in the Medical Faculty of the Mustafa Kemal University on consecutive patients with the SCD and age and sex-matched control cases between March 2007 and June 2016. The SCD are diagnosed with the hemoglobin electrophoresis performed via high performance liquid chromatography. Medical histories of the SCD patients were learnt. A complete physical examination was performed by the Same Internist. Body mass index (BMI) of each case was calculated by the measurements of the Same Internist instead of verbal expressions. Weight in kilograms is divided by height in meters squared (9). Systolic and diastolic BP were checked after a 5-minute rest in seated position by using the mercury sphygmomanometer (ERKA, Germany), and no smoking was permitted during the previous 2-hours. Cases with acute painful crisis or any other inflammatory event were treated at first, and the laboratory tests and clinical measurements were performed on the silent phase. Check up procedures including routine hematological parameters, fasting plasma glucose (FPG), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG), total bilirubin (TB), and lactate dehydrogenase (LDH) were performed. Eventually, the mean body weight, height, BMI, FPG, LDL, HDL, TG, TB, LDH, systolic and diastolic BP, white blood cell (WBC) and platelet (PLT) counts, mean corpuscular volume (MCV), and hematocrit (Hct) level were detected in each group, and compared in between. Mann-Whitney U Test, Independent-Samples t Test, and comparison of proportions were used as the methods of statistical analyses.

Results

The study included 193 patients with the SCD (98 females and 95 males) and 132 control cases (67 females and 65 males). Although the mean body weight and BMI were retarded in the SCD patients, significantly (58.9 versus 71.1 kg and 21.5 versus 26.8 kg/m2, respectively, $p<0.000$ for both), the mean body heights were similar in both groups (164.8 versus 162.8 cm, $p>0.05$). Parallel to the retarded mean body weight and BMI, FPG (93.4 versus 102.4 mg/dL, $p=0.025$), LDL (70.4 versus 98.1 mg/dL, $p<0.000$), HDL (24.2 versus 35.8 mg/dL, $p<0.000$), and systolic (117.6 versus 127.9 mmHg, $p=0.001$) and diastolic BP (77.3 versus 86.0 mmHg, $p<0.000$) were all retarded in the SCD patients, significantly. On the other hand, mean TB and LDH values were both increased (4.0 versus 0.7 mg/dL and 638.9 versus 268.4 U/L, respectively, $p<0.000$ for both) in the SCD patients, significantly (Table 1). Similarly, the mean WBC and PLT counts (16.338 versus 7.407 /µL and 421.424 versus 268.612 /µL, respectively) and MCV (90.3 versus 78.3 fL) were all increased whereas the mean Hct level was decreased (23.2 versus 36.6%) in the SCD patients, significantly ($p<0.000$ for all) (Table 2).

Table 1: Characteristic features of the study cases

Variables	Patients with SCD*	*p*-value	Control cases
Number	193		132
Mean age (year)	31.6 ± 9.7 (10-59)	Ns†	31.6 ± 12.4 (9-60)
Female ratio	50.7% (98)	Ns	50.7% (67)
Weight (kg)	*58.9 ± 12.2 (31-100)*	*0.000*	*71.1 ± 17.3 (31-120)*
Height (cm)	164.8 ± 9.7 (145-194)	Ns	162.8 ± 9.0 (134-185)
BMI‡ (kg/m²)	*21.5 ± 3.7 (14.5-35.8)*	*0.000*	*26.8 ± 6.5 (15.2-49.3)*
FPG§ (mg/dL)	*93.4 ± 13.2 (56-119)*	*0.025*	*102.4 ± 42.2 (71-447)*
TB‖ (mg/dL)	*4.0 ± 3.0 (0.6-23.4)*	*0.000*	*0.7 ± 0.6 (0.1-3.8)*
LDL¶ (mg/dL)	*70.4 ± 28.2 (20-164)*	*0.000*	*98.1 ± 40.8 (21-208)*
*HDL** (mg/dL)*	*24.2 ± 8.7 (9-60)*	*0.000*	*35.8 ± 13.3 (5-72)*
TG*** (mg/dL)	118.8 ± 54.6 (31-348)	Ns	123.1 ± 74.5 (24-382)
*LDH**** (U/L)*	*638.9 ± 462.5 (108-2.842)*	*0.000*	*268.4 ± 180.7 (101-1.318)*
*Systolic BP***** (mmHg)*	*117.6 ± 18.5 (80-170)*	*0.001*	*127.9 ± 21.1 (90-200)*
Diastolic BP (mmHg)	*77.3 ± 12.0 (50-120)*	*0.000*	*86.0 ± 12.9 (60-120)*

*Sickle cell diseases †Nonsignificant (p>0.05) ‡Body mass index §Fasting plasma glucose ‖Total bilirubin ¶Low density lipoproteins **High density lipoproteins ***Triglycerides ****Lactate dehydrogenase *****Blood pressures

Table 2: Routine hematological parameters of the study cases

Variables	Patients with SCD*	*p*-value	Control cases
WBC† count (/µL)	*16.338 ± 7.417 (1.580-48.500)*	*0.000*	*7.407 ± 3.620 (1.760-37.550)*
Hct‡ level (%)	*23.2 ± 5.2 (8-39)*	*0.000*	*36.6 ± 8.6 (12-54)*
MCV§ (fL)	*90.3 ± 11.8 (55-124)*	*0.000*	*78.3 ± 12.7 (45-128)*
PLT‖ count (/µL)	*421.424 ± 204.693 (52.000-1.029.000)*	*0.000*	*268.612 ± 125.529 (12.000-929.000)*

*Sickle cell diseases †White blood cell ‡Hematocrit §Mean corpuscular volume ‖Platelet

Discussion

SCD affects all vascular systems of the body (17, 18). Aplastic crises, sequestration crises, hemolytic crises, acute chest syndrome, avascular necrosis of the femoral and humeral heads, priapism and infarction of the penis, osteomyelitis, acute papillary necrosis of the kidneys, CRD, occlusions of retinal arteries and blindness, pulmonary HT, bone marrow necrosis induced dactilitis in children, chronic punched-out ulcers around ankles, hemiplegia, and cranial nerve palsies are only some of the several presentation types of the SCD. Eventually, the median ages of death were 42 years in males and 48 years in females in the literature (16). Delayed diagnosis, delayed initiation of hydroxyurea therapy, and inadequate RBC supports during emergencies may decrease the expected survival time in the SCD patients further (19). Actually, RBC supports must be given immediately during all medical or surgical events in which there is evidence of clinical deterioration in the SCD (20). RBC supports decrease sickle cell concentration in the circulation and suppress bone marrow about the production of such abnormal RBC. So it decreases sickling induced endothelial damage and inflammation all over the body. Due to the great variety of clinical presentation types, it is not surprising to see that the body weight and BMI were significantly retarded in the SCD in the present study. As an opposite finding to some other reports (21, 22), the body heights were similar in the SCD and control cases, here. Parallel to the significantly retarded body weight and BMI, FPG, LDL, HDL, and systolic and diastolic BP were also suppressed in the SCD in the present study, which can be explained by definition of the metabolic syndrome (23, 24).

Higher BP indicates that heart and blood vessels are being overworked. In most people with HT, increased peripheral vascular resistance (PVR) accounts for HT while cardiac output remains normal (25). The increased PVR is mainly attributable to structural narrowings of small arteries and arterioles, although a reduction in the number of capillaries may also contribute (26). HT is rarely accompanied by symptoms in the short-term. Symptoms attributed to HT in that period may actually be related with associated anxiety rather than HT itself. However, HT may be the major risk factor for CHD, CRD, cirrhosis, COPD, stroke, dementia, and PAD-like end-organ insufficiencies in long-term. For example, a reduction of the BP by 5 mmHg can decrease the risk of stroke by 34% and CHD by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular diseases (27). On the other hand, the physicians can not detect any absolute cause in the majority of patients with HT. Physical inactivity, sedentary lifestyle, animal-rich diet, excess weight, smoking, alcohol, chronic inflammations, prolonged infections, and cancers may be found among the possible risk factors of HT by means of the accelerated atherosclerotic process.

Probably excess weight may be the most common cause of vasculitis, worldwide, and the leading cause of major health problems in the century. It leads to both structural and functional abnormalities in many organ systems of the body (28). Adipose tissue produces leptin, tumor necrosis factor-alpha, plasminogen activator inhibitor-1, and adiponectin-like cytokines, all of those behave as APR in the plasma (29). Excess weight induced chronic low-grade vascular endothelial inflammation may play a significant role in the pathophysiology of disseminated atherosclerosis all over the body (1, 2). On the other hand, excess weight may cause an increased blood volume as well as an increased cardiac output thought to be the result of an increased oxygen need of the excessive fat tissue. The prolonged increase in the blood volume may lead to myocardial hypertrophy, terminating with a decreased cardiac compliance. Combination of these cardiovascular risk factors will eventually terminate with an increased left ventricular stroke work and higher risks of arrhythmias, cardiac failure, and sudden death. Similar to the present study, FPG and total cholesterol (TC) increased parallel to the increased BMI (30). Additionally, the prevalence of CHD and stroke increased parallel to the increased BMI in another study (31), and risk of death from all causes including cancers increased throughout the range of moderate to severe weight excess in all age groups (32). The relationship between excess weight, increased BP, and higher plasma TG was described in the literature, extensively (33). Similarly, prevalence of smoking (42.2 versus 28.4%, $p<0.01$), excess weight (83.6 versus 70.6%, $p<0.01$), DM (16.3 versus 10.3%, $p<0.05$), and HT (23.2 versus 11.2%, $p<0.001$) were all higher in the hypertriglyceridemia group in another study (34). Interestingly, the greatest number of deteriorations in the metabolic parameters was observed just above the plasma TG value of 60 mg/dL (35). In our opinion, although excess weight does not affect each individual with the same severity, durations of overweight, obesity, severe obesity, and morbid obesity should be added to the calendar age with various scores during calculation of physiological age. Although the obvious consequences of excess weight on health, nearly three-quarters of cases above the age of 30 years have excess weight (36). The prevalence of excess weight increases by decades, particularly after the third decade, up to the eighth decade of life (36). So 30th and 70th years of age may be the breaking points of life for body weight, and aging may be the major determining factor of excess weight. Relatively decreased physical and mental stresses after the age of 30 years, and debility and comorbid disorders induced restrictions after the age of 70 years may be the major causes for the changes of BMI at these ages. Interestingly, the mean age increased up to the plasma TG value of 200 mg/dL and BMI increased just up to the plasma TG value of 150 mg/dL in the above study (35). So smoking remained as the major underlying factor for the hypertriglyceridemia above the plasma TG value of 200 mg/dL. Beside that, the mean BMI values were 24.6, 27.1, 29.4, 29.9, and 30.0 kg/m2 in the five study groups, respectively (35). In other words, only cases with the plasma TG values lower than 60 mg/dL had a normal BMI (35). On the other hand, the mean age and TG value of the first group were 35.6 years and 51.0 mg/dL, respectively (35). They were 43.6 years and 78.3 mg/dL in the second, 47.7 years and 122.2 mg/dL in the third, and 51.2 years and 174.1 mg/dL in the

fourth groups, respectively (35). In another definition, TG values increased about 7.8 mg/dL for each year of aging up to 200 mg/dL in the plasma (35). So aging alone may be another risk factor for chronic low-grade inflammation on vascular endothelium all over the body.

Although their normal limits could not been determined clearly yet, high plasma TG values may be significant indicators of the metabolic syndrome (7). Due to the significant association between high plasma TG values and CHD, Adult Treatment Panel (ATP) III adopts lower cutpoints for TG abnormalities than did ATP II (8, 9). Although ATP II determined the normal upper limit of TG as 200 mg/dL in 1994, World Health Organisation in 1999 (10) and ATP III in 2001 reduced the normal upper limit as 150 mg/dL (9). Although these cutpoints are usually used to define borders of the metabolic syndrome, there are suspicions about whether or not much lower limits provide additional benefits for human health remains unclear (37). Similar to the recent study (38), prevalence of smoking was the highest in the highest TG having group in the above study (35) which may also indicate the inflammatory role of smoking on vascular endothelium since TG may behave as APR in the plasma. BMI, FPG, HT, DM, COPD, and CRD increased parallel to the increased plasma TG values from the first up to the fifth groups in the above study, continuously (35). Just as an opinion, significantly increased mean age by the increased plasma TG values may be secondary to aging induced decreased physical and mental stresses, which eventually terminates with excess weight and its consequences. Interestingly, although the mean age increased from the lowest TG having group up to TG value of 200 mg/dL, then it decreased (35). The similar trend was also seen with the mean LDL values (35). These trends may be due to the fact that although the borderline high TG values (150-199 mg/dL) are seen together with physical inactivity and overweight, the high TG (200-499 mg/dL) and very high TG values (500 mg/dL or higher) may be secondary to genetic factors, smoking, and terminal consequences of the metabolic syndrome including obesity, DM, HT, COPD, cirrhosis, CRD, PAD, CHD, and stroke (9). But although the underlying causes of the high and very high plasma TG values may be a little bit different, probably risks of the terminal endpoints of the metabolic syndrome do not change in them. For example, prevalence of HT, DM, and COPD were the highest in the highest TG having group in the above study (35). Eventually, although some authors reported that lipid assessment can be simplified by measurement of TC alone (39), most of the other studies indicated a causal relationship between higher TG values and irreversible end-points of the metabolic syndrome (40).

Cholesterol, TG, and phospholipids are the major lipids of the body. Cholesterol is an essential structural component of animal cell membrane, bile acids, adrenal and gonadal steroid hormones, and vitamin D. TG are fatty acid esters of glycerol, and they are the major lipids transported in the blood. The bulk of fat tissue deposited all over the body is in the form of TG. Phospholipids are TG that are covalently bound to a phosphate group. Phospholipids regulate membrane permeability, remove cholesterol from the body, provide signal transmission across the membranes, act as detergents, and help in solubilization of cholesterol. Cholesterol, TG, and phospholipids do not circulate freely in the plasma instead they are bound to proteins, and transported as lipoproteins. There are five major classes of lipoproteins including chylomicrons, very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), LDL, and HDL in the plasma. Chylomicrons carry exogenous TG from intestine to liver via the thoracic duct. VLDL are produced in the liver, and carry endogenous TG from the liver to the peripheral organs. In the capillaries of adipose and muscle tissues, 90% of TG is removed by a specific group of lipases. So VLDL are converted into IDL by removal of TG. Then IDL are degraded into LDL by removal of more TG. So VLDL are the main sources of LDL in the plasma. LDL deliver cholesterol from the liver to other parts of the body. Although the liver removes the majority of LDL from the circulation, a small amount is uptaken by scavenger receptors on macrophages which may migrate into arterial walls and become the foam cells of atherosclerotic plaques. HDL remove fats and cholesterol from cells, including within arterial wall atheroma, and carry the cholesterol back to the liver and steroidogenic organs including adrenals, ovaries, and testes for excretion, reutilization, and disposal. All of the carrier lipoproteins in the plasma are under dynamic control, and are readily affected by diet, illness, drug, body weight, and BMI. Thus lipid analysis should be performed during a steady state. But the metabolic syndrome alone is a low-grade inflammatory process on vascular endothelial cells all over the body. Thus the metabolic syndrome alone may be a cause of the abnormal lipoproteins levels in the plasma. On the other hand, although HDL are commonly called 'the good cholesterol' due to their roles in removing excess cholesterol from the blood, and protecting the arterial walls against atherosclerosis (41), recent studies did not show similar results, and low plasma HDL levels should alert the physicians about additional pathologies in the body (42, 43). Normally, HDL may show various anti-atherogenic properties including reverse cholesterol transport and anti-oxidative and anti-inflammatory properties (43). However, HDL may become 'dysfunctional' in pathological conditions which means that relative compositions of lipids and proteins, as well as the enzymatic activities of HDL are altered (42). For example, properties of HDL may be compromised in DM due to the oxidative modification and glycation as well as the transformation of HDL proteomes into proinflammatory proteins. Similarly, the highly effective agents of increasing HDL levels such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors did not reduce all cause mortality, CHD mortality, myocardial infarction, or stroke (44). While higher HDL levels are correlated with cardiovascular health, medications used to increase HDL did not improve the health (44). In other words, while high HDL levels may correlate with better cardiovascular health, specifically increasing one's HDL values may not increase cardiovascular health (44). So they may just be some APR instead of being the main actors of the process. Beside that, HDL particles that bear apolipoprotein C3 are associated with increased risk of

CHD (45). Additionally, BMI, FPG, DM, and CHD were the lowest between the HDL values of 40 and 46 mg/dL, and the prevalence DM was only 3.1% between these values against 22.2% of outside of these limits in the other study (46). In another definition, the moderate HDL values may also be the results instead of the causes of the better health parameters.

As a conclusion, body weight, BMI, FPG, LDL, HDL, systolic and diastolic BP, and Hct may be some negative whereas TB, LDH, WBC and PLT counts, and MCV may be some positive APR in the body.

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An Overview of Biological Warfare and SARS-CoV-2 as a Potential Biological Agent

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Abstract

The conflict between humans did not stop throughout the ages, and humans have used everything in nature to serve this conflict since the first ages of history, during the First World War when the world witnessed the actual use of chemical weapons, and nuclear weapons during World War II By the United States of America against Japan, which greatly developed a biological warfare program before and during World War II, and a lot of information regarding this program was withheld by an agreement between Japan and the USA after Japan's defeat in the war. Finally, the countries of the world succeeded in signing a Biological Warfare Convention (BWC) in 1972, and the Ninth Review Conference will be held for this convention during 2021 to discuss its articles and try to develop its mechanisms to prevent the development and use of biological weapons in the conflict between nations.

According to the British novelist George Orwell, "Life is a race between education and catastrophe". As the great development in the field of genetic technologies and the production of vaccines collided with the emergence of new pathogens, the latest of which is the emerging SARS-CoV-2 virus that caused the COVID-19 pandemic around the world, and once again the major countries have been accused by each other of spreading this virus in the world intentionally or by accident. We must carefully examine these allegations before making decisions, because these allegations may have negative repercussions on the future of humanity.

Key words: biological, warfare, weapons, BWC, genetic engineering, COVID-19 pandemic

Introduction

Biological weapons intentionally use pathogens to cause death or harm to humans, animals or plants. Modern biological weapons (BW) and nuclear weapons belong to the category of weapons of mass destruction [1]. Infectious diseases have been used as weapons during conflicts throughout history, and the availability of a number of criteria makes infectious diseases more powerful and ripe for use in biological warfare or bioterrorism, which include:
1) High morbidity and lethality.
2) Severe infection or high toxicity.
3) Mass production and storage without losing the possibility of causing diseases.
4) The possibility of being widespread and with little resistance to delivery operations.
5) Resistance to environmental factors after spread, causing injury and disease.
6) Be suitable as a biological agent in terms of the potential for developing the genetic engineering and weaponization process [2].

The National Institute for Infectious Diseases and Allergy in America (NIAID) has classified pathogens within a list of pathogens likely to be used the most in biological warfare, and that represent a threat to national security and public health andit divides into three categories (A, B and C). This classification depends on the ease of separation and transmission, mortality rate, public health readiness and degree of public panic and chaos in society.

Richard Preston's novel "The Cobra Event" published in 1997 was fictional, including the bioterrorism scenario with the deployment of genetically modified superviruses. Preston says: "To think that the power of the genetic code is not being bent toward weapons is to ignore the growing body of evidence, the lessons of history, and the reality of human nature. As Thucydides pointed out, hope is an expensive commodity. It makes better sense to be prepared." [3], US President Bill Clinton's reading of this novel raised his concerns about the threat of bioterrorism and bioweapons, so he issued two presidential directives to address the deficiencies in national security related to bioterrorism and biological and chemical warfare [4].

Human coronaviruses were not considered harmful before the year 2002, and they were a common cause of influenza, and unlike animals, coronaviruses did not cause serious diseases to humans, but that has changed completely since 2002, when three new dangerous human coronaviruses appeared: SARS-CoV, MERS-CoV, and SARS-CoV-2 (the cause of COVID-19) [5]. In the mechanism of viral infection there are two proteins involved in viral penetration of cells, Angiotensin-Converting Enzyme II (ACE2) and Trans-membrane protease, serine 2 (TMPRSS2) [6]. Coronaviruses have a special host, and depending on the spike protein that its special shape fits only one host, and the shape of this protein is determined by the S gene, so if the coronavirus jumps to a new host, this leads to change in the S gene, which is not caused by a small group of point mutations. A significant change in the S gene was found in the three coronaviruses, therefore there are two possible reasons for this big change: recombination which is a natural process or genetic engineering [5].

History of Biological Warfare and Biological Weapons program in the World

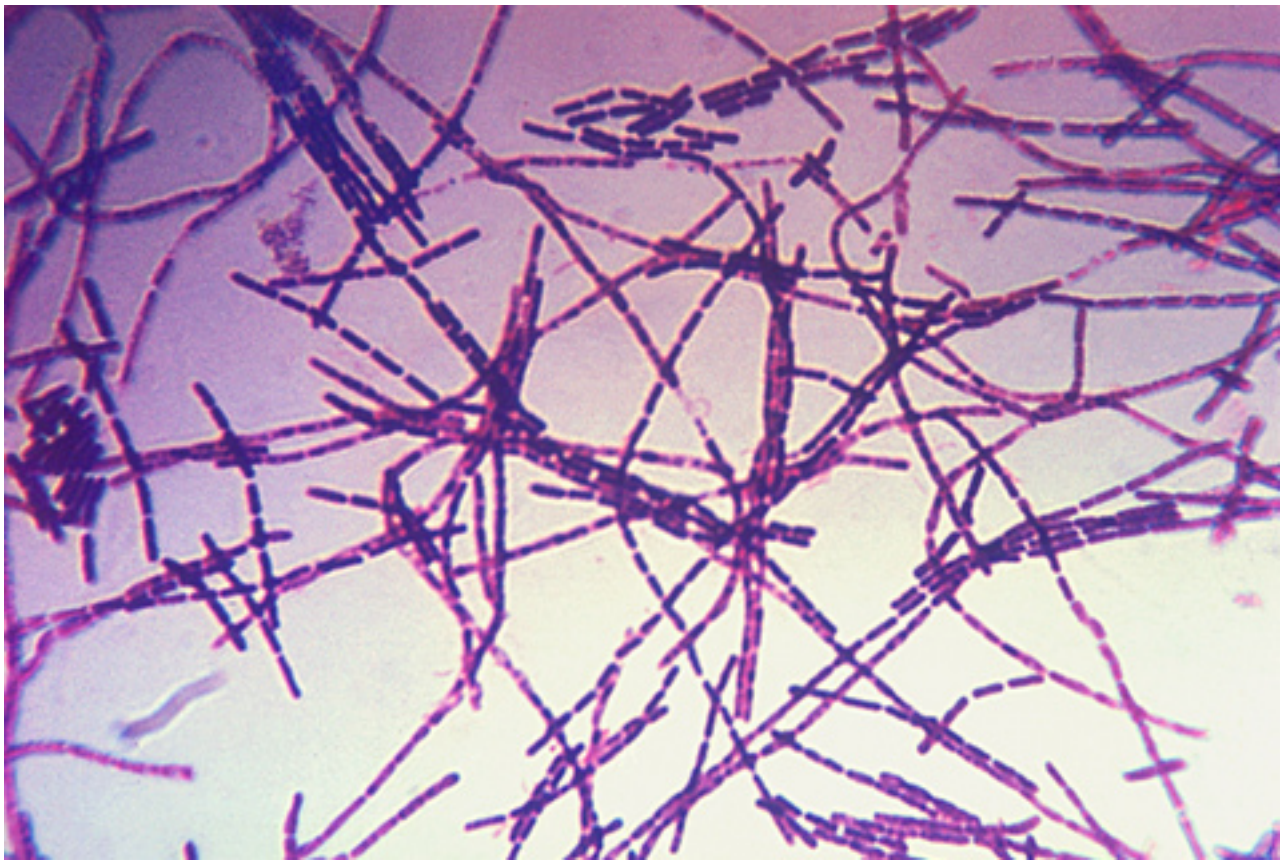
Attempts to use biological weapons began in 148 BC when Hannibal ordered his soldiers to bring pottery vessels that he filled with poisonous snakes and threw them on the back of enemy ships, it was also reported that in ancient civilizations such as the Greeks, Romans and Persians, warriors polluted the drinking water of hostile parties, either with the corpses of dead animals or decomposing human corpses. In 1346 AD the Tartar army retained victims of the plague disease in the city of Kaffa (Feodosia, Ukraine) until the infection passed to uninfected people in this city and they were exterminated, and in 1763 AD the British army provided assistance to Indians in the form of blankets that were used by plague patients [7].

Biological warfare as we understand it today is a modern concept that did not exist until the middle of 19th century as a result of the research of both Pasteur in France and Robert Koch in Germany, which showed that microorganisms cause diseases. Before that it was believed that disease occurs for supernatural reasons. Therefore, it is not surprising that the Romans used the same word *veneficium* to denote poisoning and practicing sorcery[8].

The beginning of modern microbiology came with Casimir-Joseph's success in isolating anthrax in 1863, and Robert Koch's success in obtaining pure culture of *Bacillus Anthraces* (Figure 1). Koch's hypotheses [9] allowed him and other scientists to isolate, produce and store of specific microorganisms, which had a great impact on potential biological warfare. Concerns were noted at the international level in Brussels in 1874 when the International declaration on laws and customs during War included a ban on poisons and poisoned arms [10].

Fundamental evidence indicated the existence of an ambitious biological warfare program in Germany during World War I, and numerous allegations were made that it was characterized by covert operations. During World War I numerous reports circulated that the Germans attempted to ship horses and livestock inoculated with pathogenic germs such as *Bacillus antracis* (the cause of anthrax), and *Pseudomonas pseudomallei* (that causes glanders) to USA and other countries, as well as the use of the same aforementioned pathogen to transmit the infection to Roman sheep that were intended for export to Russia, as well as other allegations of German attempts to spread cholera in Italy and the plague in Saint Petersburg in Russia. The Provisional Subcommittee of the League of Nations, which was formed of multiple nationalities in 1924, confirmed that there is no conclusive evidence of the use of biological weapons during this war, but the document issued by this committee confirmed the use of

Figure (1): Micrograph of Gram-positive anthrax bacilli [11]



chemical weapons by German forces [12]. in comparison with Americans who had barely developed ricin, a toxin extracted from castor beans by 1918, and was not yet ready for use in war [13].

All this prompted global diplomacy to work to limit the proliferation and use of biological and chemical weapons. On June 17, 1925, the Geneva Protocol was signed by 28 countries. This document did not address issues related to verification and compliance with the commitment to it, which made it "toothless" [10].

During World War II, many countries began ambitious research programs of biological warfare. Allegations and counter-allegations loomed over events during and after World War II [12]. Many studies indicate that about 20 countries developed biological weapons programs between the years 1945 and 2015, which differed in their size and sophistication. The largest biological weapons program was in the Soviet Union (about 60,000 scientists, engineers, technicians, and others were employed), while the smallest one was in Rhodesia (currently Zimbabwe), where the number of workers did not exceed about six technicians. It's known that only the USA and the Soviet Union developed operational capabilities to spread biological agents over large areas using sophisticated aircraft and missile launch systems. Many programs were terminated before the final negotiations on Biological Weapons Convention (Canada, France, United Kingdom and USA), In some countries (France and United Kingdom) a competition occurred between biological weapons and nuclear weapons, and nuclear weapons were given priority and allocated resources because they were considered more strategically important [8].

Japan conducted a research program related to biological weapons from 1932 until the end of World War II. The program was under the supervision of Shiro Ishii (1932-1942) and Kitano Misage (1942-1945). Many units of the Japanese army were established related to research and development of biological weapons, the most important of these was "Unit 731", which was stationed in Manchuria near the town of Benevgan, as Shiro Ishii gave permission to build the first major facility in the world related to biological warfare in this town in 1932. The annual operating cost was estimated between 6-12 million yen [10]. The most important pathogens involved in this program were: *B. anthracis, Neisseria meningitides, Vibrio cholera, Shigella spp* and *Yersinia pestis*. In subsequent years Japanese officials considered these experiments "unfortunate" from a human point of view [12].

The United States' biological weapons program began in 1942, and included a research and development facility at Camp Detrick in Maryland (renamed Fort Detrick in 1956, and today known as the United States Army Medical Research Institute for Infectious Diseases [USAMRIID]), and with test sites in Mississippi, Utah, and a production facility in Terra Hot, Indiana. The microorganisms that the program looked at were *B. anthracis* and *Brucellasuis.* Despite the production of about 5,000 bombs laden with anthrax bacilli at Camp Detrick, the production facility lacked engineering safety measures which prevented the production of these biological weapons during the Second World War on a large scale [12]. The United States ended the American bioweapon program in the year 1969 by US President Richard Nixon (the work on poisons did not stop until later), as the US National Security Agency confirmed

the lack of strategic viability of biological weapons, and they came to the conclusion that these weapons did little to the security of the USA, as it complicated Arms Control Negotiations with the Soviet Union [8].

At the same time, the Soviet Union doubled its efforts in the field of offensive and defensive biological research. Numerous reports were mentioned in the sixties and seventies of the twentieth century despite the Soviet Union's official claim that it did not possess any biological or chemical weapons [12], and in 1989 the Soviet scientist Dr. Vladimir Pasechnik (responsible for the former in the Russian biological weapons program Biopreparat) revealed that the Soviet Union maintained a stockpile of 20 tons of smallpox virus that was cultivated in eggs, and was constantly replenished when the previous stock lost its validity, and he also claimed that the Soviet Union built three factories in wartime with an estimated production capacity of 1,800 Tons of Bacillus anthracis. Pasechnik's allegations centered on four points related to the Soviet Union's biological weapons program: (1) the Soviets possessing genetically modified bacteria and viruses, (2) they prepared weapons from them in the form of powders, (3) they loaded them in various munitions, (4) they introduced biological weapons into their combat doctrine and set specific plans for the use of those weapons [4]. It is not clear if the Russians ended all activities of the former Soviet biological weapons program. In 1992, former Russian President Boris Yeltsin admitted that the Soviet Union had operated programs to develop biological weapons in contravention of the obligations of the BWC and promised to end it, and the Russian government officially recognized some of its previous activities in a report to the United Nations in 1992, but it retreated from this recognition by the year 1994 [8].

Biological Weapons Convention

Global efforts to limit the proliferation of biological weapons began after the First World War, and the Geneva Protocol of 1925 (the Protocol for the Prohibition of the Military Use of asphyxiating, poisonous or other gases, and of all analogous liquids, materials or devices and bacteriological methods of warfare), which banned the use of chemical weapons as well as biological weapons. In the 1930s, many attempts were made to prohibit the production and storage of Biological weapons at the World Conference on Disarmament, but the attempts were unsuccessful due to the conference's collapse in 1937 [1].

On April 10, 1972, the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and the destruction of those weapons was signed, also known as the Biological Weapons Convention (BWC) [14], which prohibited the development, production, storage or possession of biological agents and toxins. This agreement was opened for signature in London, Moscow and Washington on April 10, 1972, and it entered into force on March 26, 1975 after 22 governments deposited ratification documents, including the depositary governments, and this agreement is valid for an unlimited period and requires if withdrawing from it, giving advance notice of three months. The number of state parties to this convention reached 183, and the number of signatory states 109. We point out that Israel is still not a party to this convention and has not signed it yet (it participates in the review conferences of this convention as an observer). Under this convention, the states parties undertook to submit annual reports, using agreed forms, on specific activities related to the BWC including: data on research centers and laboratories; information about vaccine production facilities; information on national biodefense research and development programs; publicize past activities in offensive and/or defensive biological research and development programs; and information on the spread of infectious diseases and similar events caused by toxins; disseminating results and encouraging the use of knowledge and communication; and information on legislation, regulations and other measures, and the agreement stipulated that a "review conference" be held five years after its entry into force to review its operations, where the Preparatory Committee for the ninth Review Conference was postponed due to the COVID-19 pandemic as agreed at the Meeting of States Parties, the Preparatory Committee held at the Palais des Nation on 20 December 2021. It resumes its work in April 2022 (United Nations, 2022).

Biological Weapons and Genetic Engineering

Genetic engineering techniques began in the seventies of the last century, and in the eighties it became a global industry generating billions of dollars in profits, which increased exponentially during the last decade of the twentieth century [4]. In 2007; Garfinkel et al. estimated the number of companies that manufacture DNA in all parts of the world that are capable of providing gene and genomic products to about 45 companies (24 of which are in the United States alone and the rest are distributed in the rest of the world) [15]. In 2009 the International Gene Synthesis Consortium (IGSC) was established, which is a commercial industrial organization that aims to promote the beneficial application of technologies synthesizing genes while preserving biosecurity [16], and the Union also works to this end with governmental and international organizations and other interested parties to achieve this goal. IGSC members account for approximately 80% of gene manufacturing capacity around the world (IGSC, 2021).

Genetic engineering did not have a major role in the early stages of biological warfare, as some pathogens found in nature (such as smallpox, plague, anthrax) are dangerous and deadly enough in themselves, and genetic engineering was not necessary for these agents to be used as biological weapons. Some studies indicated that the former Soviet Union had reached, through a biological weapons program, the so-called "Invisible Anthrax", which resulted from the introduction of a new gene into *anthrax bacilli,* which changed its immune characteristics, and made it resistant to existing conventional vaccines, which turned out to be ineffective against this new, genetically modified strain [17].

The development of effective biological weapons relying on genetic engineering requires an extensive research program with adequate resources, which may encounter several obstacles that must be addressed, namely:

- Buying strains of appropriate agents.
- Mass production of agents without loss of pathogenicity.
- Development.
- An effective means of delivery.

The third step in particular is very difficult and rarely accomplished, and we can say that, with the exception of the previous massive biological warfare programs in both the United States of America and the Soviet Union, after years of the active programs, only initial methods have been developed for the delivery of these biological agents. Accordingly, genetic engineering is a relatively late step in developing biological warfare capabilities, which will not be used until the basic first steps are completed. We must not lose sight of the fact that some natural pathogens are not suitable for use as biological agents in the military field, which would happen when the following requirements are met:

- Mass production.
- The speed of the effect.
- Resistance to environmental factors.
- The possibility of treating the disease caused by these agents, or the availability of an appropriate vaccine, which allows the protection of individuals (soldiers) who use such weapons.

Anthrax is the first choice here, since the pathogen (*anthrax bacillus*) meets nearly all of these requirements. Potential victims of an anthrax attack can be treated with antibiotics even several days after infection, as evidenced by the 2001 anthrax attacks in the USA [17].

Tight restrictions are imposed at the present time on access to dangerous pathogens, in particular Smallpox, which was eradicated in 1980 (WHO, 2021) and it is preserved and stored officially only in laboratories with high security measures in each of the United States of America (Center for Disease Control and Prevention "CDC" in Atlanta) and the Russian Federation (the Russian Center for Virology and Biotechnology "Vector" in Koltsovo) [18]. Ken Alibek published in his book "Biohazard" that the former Soviet Union was conducting research related to the introduction of genetic modifications to the smallpox virus in 1992, in addition to that by 1992; the Soviet Union had produced 52 different pathogens or a combination of these agents, including the deadly Marburg virus, Ebola virus and smallpox virus, which had been placed within weapons suitable for use. The agents, including the most infectious and easiest to produce and transmit microbes, were labeled "battle stains", and the "836" anthrax was the best among the battle strains, according to Alibek [19].

The success of the experiment of a research team at Stony Brook University in New York to synthesise the polio virus (not considered a biological weapon) starting from scratch, as they built small sequences of DNA and merged them together to form the complete genome of this virus (which is available on the network), then this synthetic virus was activated by adding a chemical mixture, which made it an active and pathogenic virus [20]. This experiment sheds light on the great development that molecular biology has reached and sheds light on its problems as well. In principle, it is possible to use this technology to synthesise other viruses with a short DNA sequence. This includes at least five viruses that are considered potential biological agents, including: Ebola virus, Marburg virus and Venezuelan equine encephalitis virus. As for Smallpox, the assessment of the current risks related to it, and although it is considered a very effective and ideal biological weapon, the possibility of using it for biological attacks is very low, as countries other than the USA and Russia can't access it, but if it becomes possible to reconstruct the genome of this virus in laboratories (DNA sequence of the virus genome is available on the world wide web), this assessment will change, and the relative safety that we assume today will disappear. We note here that the poliovirus synthesis technology can't be applied in the case of smallpox virus (the virus genome is very large), even if the complete genome sequence of the virus can be reconstructed in the laboratory, converting it into an active and effective virus is very difficult, but there may be other methods for this, including starting with a closely related virus such as monkey pox or rat pox virus, and then changing the bases and DNA sequence to reach the human smallpox virus [17].

The viral genome synthesis technique has become possible thanks to advances in many fields of science, including the use of restriction enzymes to genome synthesis and sequencing techniques, such as the 454 Roche, Illumina, and SOLiD systems. The synthesis of the synthetic genome was performed by a combination of two different strategies: chemical synthesis and PCR amplification [21]. PCR technology is widely used in the field of biology, which uses the enzyme DNA polymerase [22]. Although treating viral genomes with the aim of modifying viral properties has become routine in many laboratories, developing completely new artificial genomes without using templates and genetic circuits as units to assemble genomes is a new topic and remains relatively ambiguous and involves security risks that must be answered before this method becomes popular. The creation of completely new viral genomes is one of the most promising techniques for developing new, more effective and selective antibiotics, as well as for preparing vaccines and antiviral drugs with fewer side effects, as well as in the detection of living microorganisms in hospitals and manufacturing places where strict control of these microorganisms is essential [21].

A research group from the University of Bern has published a paper entitled "Rapid Reconstruction of SARS-CoV-2 Using a Synthetic Genomics Platform" in which the authors say they are able to engineer and activate chemical-synthesized clones of the emerging SARS-CoV-2 virus through a yeast-based synthetic genomics platform

template, where they formed parts of the viral genome using viral isolates, cloned viral DNA, clinical samples, or synthetic DNA, and then these parts were reassembled in one-step in yeast template "*Saccharomyces cerevisiae*" using transformation-associated recombination cloning to maintain the genome as a yeast artificial chromosome. Then the researchers in this study used the enzyme T7 RNA Polymerase to activate the virus, and that was only one week after obtaining the DNA fragments [23]. Scientists resort to these technologies with the aim of accelerating access to treatment and development of vaccines, but due to the dual-use nature of this technology (it has high biosecurity risks), care must be taken regarding publishing the results of such research without observing biosecurity/ safety rules [24].

The mutation rate is defined as the probability that the change in the genetic information will be transmitted to the next generation, and in viruses the generation is often defined as a cell infection cycle, which includes (attachment to the cell surface, entry, gene expression, replication, encapsulation and release of infectious particles). Mutations are not limited to replication because they may also result from modification of the genetic material or spontaneous destruction of DNA. The mutation rate should not be confused with the frequency of mutations for a particular viral group. This frequency is a measure of the genetic variation, which depends on the number of processes such as natural selection, random genetic drift, and recombination. High mutation rates lead to greater genetic diversity, but we cannot directly infer the mutation rate from the frequency of the recorded mutations of a viral group [25], and knowing the rate at which virus mutation occurs is important to understanding their evolution and mechanisms of combating them, as the results of a study to estimate the rate of mutation occurrence using a new statistical method conducted by Rafael Sanjua'n and colleagues in 2010 indicated that there is a negative correlation between the rate of mutation and the size of the genome in both DNA and RNA viruses [26], and it can be said that the rate of viral mutations ranges approximately in a range between 10-8 – 10-4 per nucleotide per cell infection, in DNA viruses; this range was 10-8 – 10-6 (s/ n/c), while in RNA viruses it ranged between 10-6 – 10-4 (s/n/c). These differences have many mechanisms, one of them that the vast majority of RNA viruses lack the 3'-exonuclease needed to correct the error, therefore it is more error-prone than DNA viruses, and the exception is Corona viruses, which are Positive-strand RNA viruses that contain the RNA polymerase in which the 3'-nuclease, Unlike all other known RNA viruses, it has developed an error-correcting ability, and it also has the largest genome among RNA viruses (30 - 33 kb) [25].

Is SARS -CoV-2 virus a Biological agent?

First, we must ask the question about the impact of the Corona pandemic on the state of the global economy, which is greatly affected by the economic situation of China (the second largest economic power in the world), and the question is about the beneficiary of a contraction in the Chinese economy, as several economic reports indicated that the rate the overall GDP growth in 2020 was as follows:

- The United States of America ranked first with 22.3 trillion US dollars.
- Then China with 15.7 trillion US dollars (but at a higher rate of growth than the United States of America).
- Japan, third, with 5.4 trillion US dollars [27].

The world's great powers accuse each other of being behind the spread of the new Corona virus, as Americans refer to the participation of Chinese facilities in this process (Wuhan Institute of Virology, Wuhan, the center of the virus's spread at the beginning), and in return China accuses the United States of America of having military laboratories to produce biological agents around the world, and the Israelis blame the Chinese, while the Russians blame the Americans, but there has not yet been any scientific evidence for these allegations, which can be compared to the period after World War II when the conflicting powers resorted to accusing each other of using biological weapons [28].

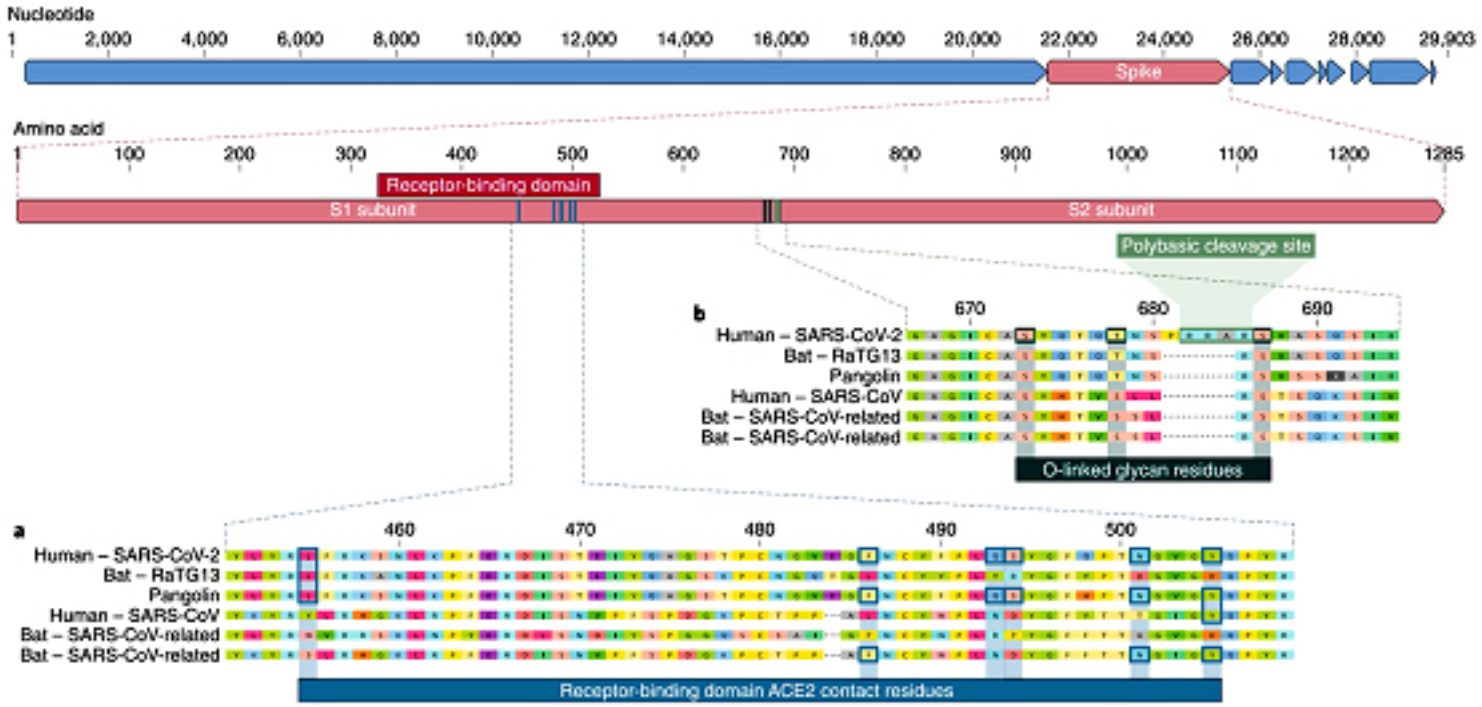
But we must mention that for ten years they have been producing Chimera Coronavirus in Wuhan, China, and therefore the data on the possibility of accidental leakage of SARAS-CoV-2 from the Wuhan Institute of Virology, the Center for the Initial Infection, remains an existing possibility that needs further research and scrutiny [29]. However, it is known that in order to perform genetic modification experiments on the emerging SARS-CoV-2 virus, researchers must use the current Coronavirus RNA as a backbone, but the available studies indicate that there are no known viruses recorded in the scientific literature that can serve as the basis for SARS-CoV-2 formation [30].

Could the emerging SARS-CoV-2 virus have been synthesised in laboratories? The scientific evidence available to us to date indicates that it is unlikely that it was synthesised in laboratories either on purpose or by accident, due to the following facts:

1) The SARS-CoV-2 genome contains several differences from previous coronaviruses along with 12 pairs of bases for introduction, and the virus with the greatest genetic similarity to it is the RaTG13 bat coronavirus, which only shares about 96% of its genome with SARS-CoV-2 (1,200 pairs of different nitrogenous bases) (Figure 2).

2) The presence of specific sites for glycosidic bonds (O-glycosidic bonds) in the SARS-Cov-2 genome, is another evidence that the virus is natural, as sugars form a mucin shield that protects the virus from attack by the immune system, and since cell cultures in laboratories do not contain an immune system, so it is unlikely that this adaptation will occur in a virus growing in the laboratory,

Figure (2): The human corona virus genome and its similarities in bats and Malayan pangolins, and also shows the presence of RBD, glycoprotein binding sites, and the Spike protein [31], [32].



and this undermines the hypothesis that the virus has multiplied from tissue culture.

3) The presence of the receptor binding domain (RBD) is very similar to SARS-CoV-2 in the Malayan Pangolin corona virus, allowing us to conclude that this may have occurred also when the virus transmitted to humans, indicating that the multiple entry founded at the cleavage site have occurred when the virus transmitted from human to human.

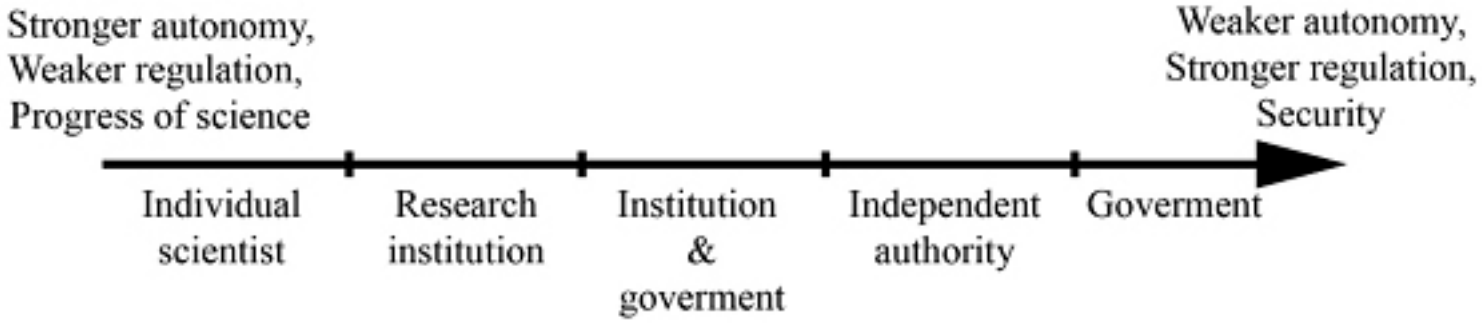
4) The RBD in SARS-CoV-2 differs from that in SARS-CoV-1 and the binding of the emerging SARS-CoV-2 virus to the ACE-2 receptor (ACE II) is not ideal, which means that there are other binding mechanisms (down "RBD" and polybasic cleavage site providing pre-activation via Furin), which resulted from natural selection, so not because of the strength of this naturally occurring process but also because of the presence of weaknesses in SARS-CoV-2 virus, all of this indicates that this virus has not been artificially modified [31], [32].

Conclusion

José Saramago said in his novel Blindness: ((*I don't think we did go blind, I think we are blind, Blind but seeing, Blind people who can see, but do not see.*)) [33], Whoever looks at what we are living today can say that, given the current development and progress in the field of genetic engineering and molecular biology, the twenty-first century will be worthy of the biological century, and there are those who say today that the First World War was chemical, while the Second World War was nuclear, and that the Third World War if it took place; would be biological [4], And we can describe the COVID-19 pandemic that the world is experiencing today due to its ferocity and its pathogenic mechanisms as a typical storm resulting from the use of an effective biological weapon [34]. Until now there is still no scientific evidence that the emerging corona virus has been synthesised or genetically modified in the laboratory, or it was intentionally spread. In the context of biological warfare, and there is no evidence proving that the virus leaked from the Wuhan Institute of Viruses in China accidentally, which are hypotheses that need proof, and that the great countries exchange accusations about the origin and source of the virus, similar to what the world witnessed during the Second World War, and it may have a background related to nationalism and intolerance, which will not be in the interest of mankind and the world. Here we have to recall the speech of doctor William Osler (one of the greatest physicians of modern times) which he addressed in 1902 to the Canadian Medical Association, speaking about "chauvinism in medicine", and according to him, "chauvinism" and "nationalism" are unforgivable sins, but at the same time he expressed his hope that because of the libertarian ideas and friendliness among nations, the worst aspects of medicine, namely "nationalism", might disappear. Long before Osler accepted the ethics of Chinese folk medicine he advocated the principle of "yi nai renshu", meaning "medicine as a way to humanity" which was founded based on the principles of Confucius, and the ancient Chinese name for medicine according to the great Tao (Way), and these ideas fall under the principle that medicine and science are not a means of glorification of a particular ethnicity, or state or nation's particular ethnicity, but rather they aim to serve the well-being of all humanity, and in the era of COVID-19, reviving such moral visions can be a vital matter for the cause of strengthening global oversight of biosafety and biosecurity [24]. and the pursuit during the fight against this virus to search for effective and safe vaccines, and ensuring coordination and cooperation for the manufacture and supply of vaccines in the production stage to meet the needs [35] also highlights the role of the 1972 Convention "Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin

Weapons and on their Destruction" as a collective action mechanism among the countries of the world, which formed the first agreement banning an entire class Weapons, as the conditions of the Cold War and the meeting of the prominent players in the international arena in both NATO and the Warsaw Pact in 1972 pushed this agreement forward and gave it a true global dimension. The international community came together to brand these weapons as "repugnant to the conscience of mankind" [36]. Therefore; the role of this agreement must be strengthened in limiting the production and storage of biological agents, and global cooperation to prevent states from resorting to biological warfare, activate monitoring mechanisms and verify compliance with their obligations, and work to include countries that are still outside it, including Israel, and also the need to impose strict control on Scientific achievements in the field of biotechnology and molecular biology that may be misused. As we refer here to the need to focus equally on Encouraging innovation in the field of biotechnology and its possession, and the importance of legislation and laws related to biosafety and biosecurity as much as possible, and supervision over compliance with mandatory biosafety and safety rules and procedures must be tightened, and researchers in the field of biotechnology must be subjected to training and educational courses on a regular basis and their credibility must be ensured. The publication of research related to biotechnology and the success in the manufacture and development of some pathogens should also be supervised so as not to be misused, in a manner that does not conflict with intellectual freedom and guarantees biological safety and biosecurity. Figure (3) shows five theoretical and practical models for decision-making ranging from an individual researcher to a complete government agency [24].

Figure 3: Five theoretical and practical models for decision-making ranging from an individual researchers to a complete government agency [24].



There may be some problems when the regulatory authorities are distributed on both sides of the left and right axis (Figure 3), where the interest of scholars or individual research institutions (on the left of the axis) is focused on developing technologies at the expense of other values, and they may also lack the skills required to assess the political, economic and ethical aspects resulting from the development of a particular biotechnology. While on the right side of the axis government agencies often lack the expertise necessary to judge rapidly changing biotechnologies, and they may overemphasize safety / social security values and strictly adhere to formal standards, thus hindering flexible case-by-case decisions. While we find, in the case of independent regulatory agencies composed of scientists, ethicists, jurists and government regulators, and due to the multiplicity of their members 'competencies, their ability to conduct a comprehensive review of new scientific research from a scientific, economic, political and legal perspective increases in a balance between safety/social security values and technical development [24].

Following the historical pattern of the interaction between war and disease, the two relatively new phenomena: unprecedented biotechnology and terrorists ready to inflict mass casualties are likely to intersect in the future, which calls for vigilance, caution and global cooperation to prevent this from happening [4].

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Clinical Audit on Well Baby Services at Primary Health Care Corporation, Qatar

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Abstract

Background: Regular well-baby visits during the first three years of childhood are critical to identify health, behavioral and development problems that could have long-lasting effects into adulthood. WHO stresses the importance of child health, and states that ensuring the healthy growth and development of children should be the prime concern.

Aim: To ensure that well-baby services provide clinical care according to children's age as per well-baby service protocol within primary health care centers, to find gaps if any and to generate an action plan for further improvement.

Methodology: A retrospective chart review (baseline audit) was conducted on 245 health records of children who attended well-baby clinic for three months (March 01, 2018 to May 31, 2018). Further to the implementation of the action plan, a re-audit with retrospective chart review of 477 health records for three months (June 01, 2019 to August 31, 2019) was conducted to evaluate the improvements in the practice.

Results: Performance for criterion on relevant clinical history taking (feeding and bowel history) has slightly increased from the baseline for each of the following age groups: from 71% to 82% at 4 months, 77% to 80% at 18 months and, 76% to 81% at 30 months, however, a declination was shown at 2 months 88% to 80%. Assessment of developmental milestones at 2, 18 and 30 months of age increased by 5% (76% to 81%), 13% (70% to 83%) and 19% (50% to 69%) respectively and, at 4 months performance remained the same at 69%.

Examination of congenital hip dislocation/abduction has demonstrated a significant improvement where its performance increased by 79% (8% to 87%) at 2 months, and 82% (2% to 84%) at 4 months of age. On the other hand, at ages 18 & 30 months which were not measured in the baseline audit in the re-audit, it was 68% and 45% respectively. Screening for vision at 2 months of age has increased by 13% (78% to 91%), but, there was a slight drop of 10% in the screening of hearing from 86% to 76% at 2 months.

Screening of autism spectrum disorder using a tool in children 18 and 30 months of age dropped from 86% to 83% and from 86% to 75% respectively. Conversely, request laboratory investigation to rule out anemia has increased by 46% (47% to 93%) at 18 months and 61% (23% to 84%) at 30 months.

Conclusions: Impactful audits with actionable recommendations make real difference in practice and compliance. In conclusion, action plans implemented further to the baseline audit are effective in increasing the compliance in most of the areas.

Key Words: Well-baby services audit, primary health care, Qatar

Introduction

Well baby services especially for ages 0-5 years are critical to address behavioral, developmental, social and other health issues for children. These services also give parents confidence that their children have achieved all the developmental milestones(1).

Considering the significance of healthy children, the State of Qatar in its vision 2030 clearly set out the strategic plan on the early years of childhood and recommended various integrated programmes to promote healthy (optimal) child development in infancy, using a combination of parental and familial based interventions backed up by services of primary health center and social facilities(2). To achieve these National Goals PHCC has established a network of well- baby clinics across its health centers in Qatar with a robust guideline and framework adapted from WHO, MOPH and other practice based models.

WHO have promoted well baby initiatives for ensuring proper growth and development of children through early detection of childhood diseases and disabilities, taking appropriate interventions and simultaneously emphasizing on vaccination and breast-feeding practices(1). Therefore, well baby visits are considered essential and can do so much to identify developmental disabilities, and connect parents to early intervention services to ensure that their little ones are healthy and have the best quality of life possible. Well-baby care is one of the important elements of primary care given to children in their early childhood to support healthy child development(3).

Childhood vaccines have a major role in the reduction of the global infant mortality rate from 64 per 1,000 lives in 1991 to 29 in 2018. Vaccines are found to be the most cost-effective approach for reducing childhood disease burden(1,4). Well-baby clinics help to track the vaccination status of the baby and make sure all the vaccinations are given at the right time.

The early detection of congenital problems such as Autism disorders can be managed to some extent if routine checks from 0-5 years are performed. Many studies have shown that early identification and early interventions are associated with more positive outcomes in communication, social interaction and cognitive development(5).

Setting up well-baby clinics is an important way to monitor a baby's growth and development and check for problems. These types of clinics help to track growth of the child, monitor development, follow up on vaccination, establish health trends and provide preventive treatment.

As part of Quality assurance and clinical effectiveness, a clinical audit was planned and conducted to evaluate the effectiveness of services offered by the well-baby clinic in 27 health centers across Qatar and to make recommendations to address the gap, if any.

Two audits were conducted, a baseline audit and a re-audit to assess the change improvement in practice.

Methods

The baseline audit was conducted on three months practice (March 01, 2018 to May 31, 2018). A retrospective chart review of children who attended the well-baby clinic during these three months was conducted. A representative sample of randomly selected 245 electronic records of children (2-30 months ages) were retrieved for review in the baseline audit.

Based on the baseline audit findings action plans were developed such as an official communication via memos to all clinicians to perform screening for congenital hip dislocation/abduction according to child age as recommended in the guideline, refresher training emphasis on assessment of milestone development according to age of the child, use of clinical information system to develop alert functionality for autism screening and laboratory investigation for iron deficiency anemia screening according to child age, arranging group discussion session for mothers on growth and anticipatory guidance by MCH counselor and to re-allocate the counselling duties to MCH and nurses in the well-baby clinic.

As part of the clinical audit cycle the re-audit was conducted to assess the change improvement based on the baseline audit recommendations. In this re-audit a representative sample of 477 electronic records were retrieved to review the practice for the period from June 01, 2019 to August 31, 2019. An agreed criterion was derived from the applicable PHCC Guidelines and well-baby protocols.

Results

Overall, an optimal level of improvement was noticed in the re-audit when compared to the baseline audit. Declination in the percentage was also exhibited in some cases. Performance for criterion on relevant clinical history taking (feeding and bowel history) slightly increased from the baseline for each of the following age groups: from 71% to 82% at 4 months, 77% to 80% at 18 months and, 76% to 81% at 30 months, however, a declination was shown at 2 months, 88% to 80%. Assessment of developmental milestones at 2, 18 and 30 months of age increased by 5% (76% to 81%), 13% (70% to 83%) and 19% (50% to 69%) respectively and, at 4 months performance remained the same at 69%.

Examination of congenital hip dislocation/abduction has demonstrated a significant improvement whereby its performance increased by 79% (8% to 87%) at 2 months, and 82% (2% to 84%) at 4 months of age. On the other hand, for age 18 & 30 months which was not measured in the baseline audit in the re-audit it was 68% and 45% respectively. Screening for vision at 2 months of age increased by 13% (78% to 91%), but there was a slight drop of 10% in the screening of hearing from 86% to 76% at 2 months.

Screening of autism spectrum disorder using a tool in children 18 and 30 months of age dropped from 86% to 83% and from 86% to 75% respectively. Conversely, request laboratory investigation to rule out anemia has increased by 46% (47% to 93%) at 18 months and 61% (23% to 84%) at 30 months.

Table 1

Criterion	At 2 months		At 4 months	
	Baseline audit (n=51)	Re-audit (n=126)	Baseline audit (n=55)	Re-audit (n=125)
History & Examination				
Relevant clinical history taken (feeding and bowel history)	88%	80% ↓	71%	82% ↑
Developmental milestone assessed	76%	81% ↑	69%	69%
Examine for congenital Hip dislocation/abduction	8%	87% ↑	2%	84% ↑
Screening				
Hearing screening requested	86%	76% ↓	n/a	n/a
Vision screening performed	78%	91% ↑	n/a	n/a

Criterion	At 18 months		At 30 months	
	Baseline audit (n=73)	Re-audit (n=124)	Baseline audit (n=66)	Re-audit (n=102)
History & Examination				
Relevant clinical history taken (feeding and bowel history)	77%	80% ↑	76%	81% ↑
Developmental milestone assessed	70%	83% ↑	50%	69% ↑
General physical examination	92%	92%	76%	79% ↑
Examine for congenital Hip dislocation/abduction	n/a	68% ↑	n/a	45% ↑
Screening				
Autism screening done by using tool*	86%	83% ↓	86%	75% ↓
Management				
Request laboratory investigation to rule out Anemia	47%	93% ↑	23%	84% ↑

Discussion

The primary objective of this clinical audit was to evaluate well-baby care and identify areas where patient care can be improved. Infant malnutrition has been associated with increased severity and frequency of infections, raising energy requirements, while reducing appetite and nutrition absorption(6). This is ultimately increasing the risk of death. Another effect of malnutrition is cognitive development which can affect school performance and has negative effects on long term careers(6). Baseline audit evaluation elucidated clinical history taking (feeding and bowel history) need further improvement. After the baseline audit measures like refresher training to staff emphasising assessment of milestone development according to age of the child was provided as a result performance for criterion on relevant clinical history taking (feeding and bowel history) and has slightly increased from the baseline for each of the following age groups: 11% at 4 months, 3% at 18 months and 5% at 30 months. However, a small declination was exhibited at 2 months by 8%.

Studies shows that late diagnosis of congenital hip dislocation/abduction can lead to dysplasia(7). The consensus is that diagnosis after three months of age is late(7). The baseline shows screening results for congenital hip dislocation/abduction were found to be low (8% and 2%) at 2 months and 4 months respectively. Action plans such as an official communication via memos to all clinicians to perform screening for congenital hip dislocation/abduction according to child age is recommended in the guideline followed by repeated official reminders to the clinicians. As a result, compliance has increased dramatically by 79% to reach 87% at 2 months. Similarly, at 4 months it increased from 82% to reach 84%.

Autism Spectrum Disorder (ASD) is a development disorder that hinders an individual's skills in socialization, creates repetitive behaviors, and impacts expressive or verbal communication with disruptions from moderate to severe. Studies say symptoms of autism are more visible and easier to identify in children two to three years of age. As per the study done in USA by Towle, P., Patrick P, one out of every 68 children has autism(8). Medical experts and psychiatrists across the world developed screening techniques to identify autistic traits in their primitive stage for further treatment(9). Autism screening was one of the important criteria for the baseline audit, the audit findings showed 86% of records showed a screening test for autism and added to that 86% of records had evidence of a hearing test conducted and 78% of records had evidence of vision screening. For further improvement an action plan has been developed with the help of a clinical information system to give an alert function to request Autism screening and related screenings according to the child's age. However, in the re-audit the percentage of compliance was not up to expectation; on contrary, a small declination was exhibited. The baseline audit recommendation to develop an alert on autism screening assessment with help of the Clinical Information System is not fully implemented, which is expected to be the foremost reason for the declination in the re-audit. A further action plan to speed up installing the alert system and officially mandating the use of the ASD tool by physicians will be implemented and effectiveness of this will be measures in the next audit cycle.

Iron deficiency among children is one main factor that leads to retardation of normal growth. Insufficient intake of iron, and excessive intake of cow's milk leading to gastrointestinal loss, and rapid growth are some of the reasons. The only way to prevent iron deficiency related complications is investigation and elimination of the cause leading to iron deficiency, replacement of deficiency, improvement of nutrition and education of the patient and family(10). A baseline audit conducted shows ordering laboratory investigations to rule out iron deficiency anemia for 18 months and 30 months are 46% and 61% respectively. To improve the monitoring of iron deficiency with help of the Clinical Information System developed an alert functionality to request for Laboratory investigations for Iron Deficiency Anemia screening according to the child's age, has been developed and implemented as an action plan. In the re-audit the monitoring of iron deficiency has been improved at 18 months and 30 months to 93% and 84% respectively.

Conclusion

Impactful audits with actionable recommendations make a real difference in practice and compliance. In conclusion, action plans implemented further to the baseline audit are effective in increasing the compliance in most of the areas. Re-training for the staff and reinforcement of appropriate documentation was implemented. As a result performance for criterion on relevant clinical history taking (feeding and bowel history) has slightly increased from the baseline for each of the following age groups: 11% at 4 months, 3% at 18 months and 5% at 30 months. Official reminders pertaining to screening for congenital hip dislocation/ abduction according to child age compliance has been increased dramatically from 79% to reach 87% at 2 months. Similarly, screening at 4 months increased by 82% to reach 84%. Creating an alert with the help of the CIS improved timely laboratory investigations for Iron Deficiency Anemia. Although, an action plan has been developed with help of Clinical Information System (CIS) to give an alert function to request for Autism screening, this action plan could not be implemented fully before the re-audit as a result the percentage of compliance reduced to 83% in 18 months and 75% in 30 months. A further action plan will be developed in order to speed up the full implementation of the alert function in the CIS. Also, a further action plan will be developed to improve those criteria which exhibited low performance in the re-audit and will be measured in the next audit cycle. This cycle will continue until an optimal level of compliance is reached.

Implication:
The continuous cycle of clinical auditing is a framework that can identify the needed improvement areas in well-baby services, and help in establishing the SMART action plans to sustain the improvements.

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Letter to the Editor

I woud like to inform your readers about our coming event, **MENA Stem Cells Forum,** supported and participated by the Dubai Health Authority (DHA). It is the first event of its kind in the Middle East and North Africa to focus on this sector and scheduled on 18 - 19 March 2022 in Dubai.

The forum is also CME-accredited where attendees will obtain CME credit hours by attending the conference.

Key trends and topics, such as stem cell banking, scientific research, applications, public awareness, and regulations will be discussed. There are hands-on workshops providing the participants latest expertise and knowledge on the advancements and updates of stem cells research and therapy.

Key sessions and topics include:

- Perinatal stem cell application in clinic
- CAR-T Cells – Successes and obstacles
- Cord blood hematopoietic stem cell expansion - Impact on transplant outcomes
- How can Mesenchymal Stem Cell (MSC) make Hematopoietic Stem Cell Transplant (HSCT) more successful?
- Regenerative applications for degenerative spinal pathologies
- The role of stem cell in infertility

The event will be the region's biggest platform where local, regional, and international experts, key opinion leaders, researchers, physicians and other expert from academia and industry will share their experiences and knowledge on the latest advancements, crucial topics and the challenges in the stem cells research and therapy.

Advisory Board includes:

- Alaa El Haddad, Head of the Pediatric Oncology Department, & Bone Marrow Transplant Unit, Children Cancer, Hospital Egypt -CCHE 57357, Egypt
- Hatim Al Abbas, Acting Director, Dubai Cord Blood & Research Centre, UAE
- Nagwa El-Badri, Professor and Founding Chair, Biomedical Sciences Program, Director, Center of Excellence for Stem Cells and Regenerative Medicine, Zewail City of Science and Technology, Egypt
- Yasser Elborai, Consultant of Pediatric Hematology/Oncology and Hematopoietic Stem Cell Transplant (HSCT), Prince Sultan Military Medical City, Riyadh, Saudi Arabia, National Cancer Institute, Cairo University, Egypt

Should you need further details of the event, please feel free to contact me at arni@gmevents.ae.

Best regards
Arni David
Marketing Manager, Great Minds Event Management

Fake Covid vaccine found in Iran – and beyond?

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We are bringing this matter to our readers and regional doctors attention as sadly there is always someone prepared to prey on others misfortune.

The original article is on the WHO website and they provide detail on how to identify fake vaccines and those vials that have been tampered with. It was Astra Zeneca fake vaccine discovered in the original report.

https://www.who.int/news/item/04-11-2021-medical-product-alert-n-7-2021-falsified-covid-19-vaccine-astrazeneca

It is not clear if fake vaccine is still circulating or has been fully removed from circulation but all patients, doctors, health systems and governments should remain vigilant.

We stress that all vaccine should be acquired from a reliable and long trusted source.

There are implications on various levels, i.e. a systemic flaw where not all vaccines in the system can be trusted and from the population health viewpoint where not all people will necessarily have the immunity they assumed they had.

We also need to be aware that whatever was injected was also not necessarily harmless.

Ideally the Iranian government should pay for re-vaccination as it is the national system that was flawed and ordinary Iranian people can ill afford the cost of vaccination. We have also found that immunity decreases after vaccination and after infection with COVID-19, and with new variants arising in the community, free (re)vaccination of all citizens will cover any shortfalls caused by fake vaccines and will be a positive population health approach on many levels.

It has also been suggested that there may be further corruption within the system whereby casting doubt on A-Z, which is a reputable vaccine, allows some other vaccine vendors to push their own brand and after this reported subterfug,e can providers of competing vaccines/sources all be trusted?

It is a systemic failure that a fake vaccine could be introduced in the first place and proper precautions need to be taken to prevent fake vaccines entering the system in all countries.

POSTSCRIPT: WAR

Once again we have innocent people being slaughtered by the armies of, let us be frank, evil and insane men. The dangerously mentally ill rule most of the planet. How on earth does this happen? How on earth does it still happen in 2022?

Family medicine deals with the physical, mental and psychological health of all people and as Publisher of World Family Medicine Journal I feel obliged to speak up about the endless slaughter, the endless brutalisation, and the endless dispossession. Today it is Ukraine, yesterday it was Myanmar and who knows who it will be tomorrow.

It must stop now and we have to find a way to make it stop forever as it is the biggest family medicine issue on the planet and always has been.

Cystic Fibrosis: A Review Article

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Abstract

Cystic Fibrosis is considered one of the most common autosomal recessive diseases that is associated with a decrease in the length of age in a Caucasian population. Also, it is considered as one of the most common life-shortening diseases in the white population in the United States. Cystic fibrosis affects around 30,000 people in the United States and more than 80,000 people worldwide. The incidence rate of this disease is 1 out of 3,500 births per year in the white population in the United States, while the incidence rate of the person becoming a carrier is 1:25 in the Caucasian population, the incidence of the disease is 1:2,500. The main cause for this disease is the mutation in Fibrosis Transmembrane Conductance Regulator (CFTR) gene. This disease is considered a life-threatening genetic disease that causes a buildup of thick, viscous mucus secretions in organ systems. Cystic Fibrosis is considered a multiple system disease, but in most cases, the disease gets worse and mortality increases because of respiratory manifestations such as bronchiectasis. Also, pancreatic damage in children is followed by severe wasting, malabsorption, and mortality is one of the recorded observations in children. This article aims to provide a brief introduction and the clinical picture of the disease, Etiology, Pathophysiology, Epidemiology, Nutrition, Prevention, and good practice management advice.

Keywords: Cystic Fibrosis, Bronchiectasis, Review Article, Airway Clearance Therapy, Fibrosis Transmembrane Conductance Regulator gene.

Introduction

Cystic Fibrosis is considered one of the most common life-limiting autosomal recessive genetic diseases which are spread mostly in Europe, North America, and Australia. Cystic Fibrosis has been associated with a decrease in the length of age in the Caucasian population (1, 2). Also, it is considered as one of the most common life-shortening diseases in the white population in the United States (3). Cystic Fibrosis is mainly diagnosed early during infancy (4). The most common technique used to diagnose Cystic Fibrosis is Sweat Testing Technique (5). The Sweat Testing Technique works by analysis of electrolyte concentration in the content of sweat. Mainly this technique measures Chloride and sodium concentration after 48 hours of birth because sweat start rises over the first 24 hours of the infant's life. If the chloride level is very high this indicates the presence of Cystic Fibrosis (6, 7). Patients with Cystic Fibrosis may present acutely to their local hospital with a variety of complaints but the prominent respiratory component, bronchiectasis, is responsible for most of the morbidity and, eventually, the mortality. The main cause for this disease is the mutation in Fibrosis Transmembrane Conductance Regulator (CFTR) gene. This gene has a major role in encoding epithelial ion channel which is responsible for transporting the chloride and bicarbonate ions, therefore mutation in this gene will lead to impaired mucus hydration and clearance (8). This disease considers a life-threatening genetic disease that affects epithelial cells and causes a buildup of thick, viscous mucus secretions in various organ systems, most commonly the gastrointestinal, pulmonary, and genitourinary systems (9). Cystic Fibrosis consider a multiple system disease, but in most cases, the disease worsens and mortality increases because of the respiratory manifestations such as bronchiectasis. (8, 10). This article aims to provide a brief introduction and the clinical picture of the disease, Etiology, Pathophysiology, Epidemiology, Nutrition, Prevention, and good practice management advice.

Epidemiology

Cystic fibrosis affects around 30,000 people in the United States and more than 80,000 people worldwide. The incidence rate of this disease is 1 out of 3,500 births per year in the white population in the United States (3). While the incidence rate of the person becoming a carrier is 1:25 in the Caucasian population, the incidence of the disease is 1:2,500 (1).

Pathophysiology

Pathophysiology of Cystic Disease starts with the mutation in Fibrosis Transmembrane Conductance Regulator (CFTR) gene (11). Mainly this gene controls the encoding epithelial ion channel which is responsible for transport and movement of the chloride and bicarbonate ions across the epithelial cell membrane (11-13). When the mutation occurs in one or multiple copies of this gene, the ion transport across the epithelial cell membrane will be affected and defective (13, 14). Consequently, a thick mucus membrane will build up throughout the body cavities, leading to respiratory insufficiency with other fetal systemic obstructions and abnormalities (15, 16). Also, the combination of altered ions transportation, accumulation of mucus, and decreased mucociliary clearance will permit organism colonization especially bacteria (17). The most common Bacteria which colonize include Pseudomonas, Haemophilus influenza, and staphylococcus aureus. Less common bacteria which colonize include Burkholderia, Stenotrophomonas, Achromobacter, Pandorea, and Ralstonia (17-25). Mainly these organisms will affect the respiratory tract and will cause severe repetitive inflammation. Consequently, Repetitive inflammation and chronic infection by these organisms will lead to respiratory destruction (26, 27).

Diagnosis

Most cases of cystic fibrosis are diagnosed during early infancy (4).

1. Sweat Testing Technique

The loss of Fibrosis Transmembrane Conductance Regulator (CFTR) gene function in Cystic Fibrosis patients will lead to elevating the levels of sodium and chloride in the sweat gland secretions because of poor reabsorption of these electrolytes in the ducts of glands. The sweat test technique is the analysis of electrolyte concentration in the content of sweat because chloride is more dependent on CFTR function and sodium flux can be mediated by CFTR independent pathway. But, sweat chloride is the main ion analyzed. Some institutions measure sodium to evaluate quality control. Also, the large discrepancy between sodium and chloride may give the alarm that there is a measurement error. Unaffected individuals have a sweat chloride less than 40 mmol/L. Values between 40 to 59 mmol/L are considered indeterminate and need further evaluation. This measurement should be obtained after 48 hours because sweat electrolytes rise over the first 24 hours of the infant's life. Sweat chloride levels rise over days after birth. The normal maximum limit of the level of chloride sweat in infants aged less than 3 months is 30 mmol/L. Finally, the patient is diagnosed with Cystic Fibrosis if the sweat chloride level is higher than 60 mmol/L (6, 7).

2. Newborn screening

Cystic Fibrosis newborn screening (NBS) started in Colorado (1982) then continued in Wisconsin (1985) (28). In (2003), The Centers for Disease Control and Prevention convened a workshop devoted to reviewing the outcomes of Cystic Fibrosis newborn screening and the potential benefits and risks. The final results of this workshop were that Cystic Fibrosis newborn screening is justified and the potential benefits outweigh the risks. Nowadays, several states in the United States have started performing this screening of newborn neonates, and in the future, all states in the United States will have this screening test (7).

Gene Expression

Cystic fibrosis is the result of a mutant gene located on chromosome 7 (29, 30). Cystic fibrosis is caused by mutations in the transmembrane conductance regulator (CFTR) gene (31, 32). Cystic Fibrosis transmembrane conductance regulator (CFTR) is located in the membranes of most of the cell lines and is responsible for chloride ion conduction. In addition, CFTR influences the expression of several other gene products (33). More than 2,000 different CFTR mutations have been reported (12), but there are six common classes of mutation and the most common one is class 2 mutation which is a protein processing abnormality and it includes F508del which accounts for 70% of all mutations (34).

Nutrition

Cystic fibrosis is the most common association with energy deficiency in children and adults. Chronic malnutrition will lead to failure to thrive, wasting, and stunting of linear growth. Nutrition and survival are strongly related to cystic fibrosis. Cystic Fibrosis can be considered as an energy imbalance. The most common specific nutrient deficiencies in Cystic Fibrosis are the deficiency in fat-soluble vitamins such as vitamin A, Vitamin D, Vitamin E, and Vitamin K. Recent studies highlight the problems with bone density and prevalence of fat-soluble vitamins deficiency. Management of problems related to nutrition can be complex (35-38).

Management

1 Bronchodilator

Cochrane Review 2005 guidelines recommended the use of both short-acting and long-acting b2-adrenergic receptor agonists because they provide better outcomes, such as decreased exacerbations or increase the quality of life (QOL) (39).

2 Mucolytic Agents

Nowadays, there are two drugs given through aerosol that have been used to treat abnormal pulmonary secretions in Cystic Fibrosis patients such as N-acetylcysteine and dornase alfa. Both drugs have the same mechanism of action which is to act by disrupting the disulfide bonds in mucus (NAC) or enzymatically breaking down DNA (dornase alfa) in airway secretions (40).

3 Anti-Infectives

3.1 Azithromycin can be used in individuals with persistent Pseudomonas aeruginosa in airway cultures. Cochrane Review 2005 guidelines highlight the efficacy for improving lung function and reducing exacerbations (41).

3.2 Inhaled Aztreonam attacks Pseudomonas aeruginosa which is the most common pathogen that affects the respiratory tract inpatient with Cystic Fibrosis. It is used to improve FEV1 by (6.3 – 10.3) percentage. The dose of inhaled aztreonam ranges from 75 mg up to 225 mg, administered three times daily for 28 days (42, 43).

4 Steroids

Steroids can be given to patients with bronchial hyperreactivity which is a common feature of cystic fibrosis. Patients with intermittent or persistent wheezing have little or no response to inhaled ipratropium bromide, disodium cromoglycate, or inhaled steroids. Some patients respond to bronchodilators alone, but if not, then oral steroids are effective. The suggestion is that prednisolone given on alternate days may help lung function in mildly affected patients (44, 45).

5 CFTR modulators

Utilization of CFTR modulator therapies such as Ivacaftor by a dose of 50-75 mg given twice daily, have been shown to be safe in children 2-5 years of age with CFTR gating mutations. After using Ivacaftor the sweat chloride concentration decreased by a mean of 47 mmol/L and weight, height, and body mass index improved during treatment. After 24 weeks of treatment, the FEV1 increased by (5.5) percentage points and body weight increased by 3.3 kg (46, 47).

6 Lung Transplant

Lung disease is considered a primary cause of death in cystic fibrosis disease; in around 80% of patients (1, 10). Around 14% of all lung transplants are for patients with Cystic Fibrosis. A lung transplant may be under consideration if the Forced Expiratory Volume (FEVI) falls below 30% and the function becomes limited. Some important points should be mentioned before preparation and assessment of patients for transplantation, such as (Optimal Nutrition, Body Mass Index [BMI] less than 17, bone density, control of extrapulmonary manifestations such as Diabetes and liver, and the psychological status because it may affect the adherence to therapy). Additionally, Post-transplant management is very complex and needs good communication between the patient and the transplant center. Also, patient adherence to their immunosuppressant medications is one of the major complications of lung transplantation (10, 48-50).

7 Novel Therapy

Gene Therapy for selective gene mutation has become one of the options that can treat patients who suffer from Cystic Fibrosis, Furthermore, this type of treatment is designed to treat lung disease only (29). Also, new small-molecule agents that aim to facilitate defective CFTR function of processing have now been developed. Ivacaftor is a new agent that has recently been investigated in patients carrying the G551D mutation (6% of all CF patients) (51).

Monitoring

Monitoring of bacterial pathogens should be done regularly (monthly) through throat swabs or specimens of sputum to detect the right antibiotic treatment. A routine following with a health care unit every 1.5 to 3 months is recommended to detect any prognosis and check the medication compliance. Additionally the monitoring includes weight, height, and lung function (including chest radiograph every 6 months). An abdominal ultrasound

development of the condition, such as enlargement in the spleen and gallstone. Finally, it is important to educate and counsel the patient and their family on how to manage the disease (52-54).

Multisystem Co-morbidities

1 Endocrine, and bone mineral.
Cystic fibrosis has a strong relation with reduced bone mineral density (BMD) and an increased incidence rate of fracture (55). The most common endocrine disorder in Cystic Fibrosis patients is Cystic Fibrosis related diabetes (CFRD) (56).

2 Gastrointestinal Health/Nutrition
It is a very important component of Cystic Fibrosis patients' care to achieve an optimal nutritional status and reduce gastrointestinal morbidity. There are specific nutritional parameters that can help in continuing to improve growth in the Cystic Fibrosis population. Also, early diagnosis in pancreatic insufficient patients may lead to increase in adult height and magnitude of growth in a person in a long-term follow-up (57).

3 Thrombosis
Thrombosis is considered a major complication in patients with Cystic Fibrosis. This thrombosis may be for a short duration (weeks) or long duration (years) (58).

4 Mental Health
Depression and anxiety are consider some of the most common important targets of Cystic Fibrosis because research demonstrates that there is a high increased prevalence of Cystic Fibrosis compared to the general population and this can adversely affect other health outcomes (59).

Prevention

1 Mucolytic Agents
Chronic endobronchial sepsis and profuse airway have strong relation with Cystic Fibrosis, So, mucolytic agents are considered one of the good option treatments for Cystic Fibrosis patients. Mucolytic treatment helps in reducing the acute exacerbations. The evidence related to the usage of these drugs is still limited and needs further investigation (60).

2 N-Acetylcysteine
In 1999, a Systematic review article highlighted the use of inhaled N-acetylcysteine as treatment of Cystic Fibrosis, but the finding shows there is no benefit on lung function in short-term and long-term trials. Also, no evidence shows the efficacy in reducing the severity of respiratory exacerbations or the number of episodes in patients who have Cystic Fibrosis (61).

3 Hypertonic saline
Usage of Inhaled hypertonic saline has been shown to increase mucociliary clearance and produce improvements in lung function in people with Cystic Fibrosis in short-term trials (62).

Special Cases

1 Pregnancy
In Cystic Fibrosis, the percentage of premature birth is common, especially in reduced lung function, low body mass index, Cystic Fibrosis-related diabetes, chronic microbial colonization, and transplanted lungs. In this case, the optimization of treatment is recommended during pregnancy planning (63-65).

2 Children
Cystic fibrosis used to be considered a fatal disease of childhood. With improved treatments and better ways to manage the disease, many people with cystic fibrosis now live well into adulthood. Adults with cystic fibrosis experience health problems affecting the respiratory, digestive, and reproductive systems. Also, there are related GIT disturbances in infants with CF dysfunction (66, 67).

Conclusion

As we mentioned before Cystic Fibrosis is considered one of the most common autosomal recessive diseases that is associated with a decrease in the length of age in the Caucasian population and also, it is considered one of the most common life-shortening diseases in the white population in the United States. But, nowadays, the improving state of Cystic Fibrosis has became predominant and the outlook is bright thanks to novel small molecule pharmacological treatments.

DEFINITIONS, ACRONYMS, ABBREVIATIONS
CFTR: Fibrosis Transmembrane Conductance Regulator

Authors' Contributions
'H. Karrar' supervised the team and direct the research. 'M. Nouh' wrote the nutrition, epidemiology, complication, and Conclusion paragraph. 'A. Alanzi' Wrote the Special Cases paragraphs. 'S. Alharbi' and 'R. Alhendi' will revise the article. 'F. Almutairi Wrote the diagnosis paragraph. 'H. Alhammad' Wrote the Monitoring paragraph. 'A. Sadeeg' Wrote the Special Cases paragraph. 'M. Alsheikh' Wrote the Introduction paragraph. 'W. Alshaikh' Wrote the Gene Expression paragraph. 'M. Alyahya' Wrote the Pathophysiology paragraph. 'W. Makki' Wrote the Treatment paragraph. 'H. Alhazmi' Wrote the Prevention paragraph. 'A. Almutairi Wrote the Gene Expression paragraph. The authors had full access to the data and take full responsibility for the integrity of the data. All the authors gave their approval for the submission of the final manuscript.

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Early-onset CTCL, localized and unilateral – case review

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Vignette

A 39-year-old man attended with an itchy single rounded red non-scaly skin lesion, with slightly raised edge, on his left leg that was unresponsive to topical steroids for the past two-weeks (figure-1). Apart from that, he had no other complaint. He was fit and well. Examination showed a unilateral localised red slightly-scaly, non-blanchable skin plaque on his lower left leg. Other skin parts were not affected. Physical examination was otherwise unremarkable without any detectable lymhadenopathies.

Based on the clinical examination I could not align this skin lesion to any other dermatological disease. However; I agreed with the patient to take a punch biopsy from the skin lesion that he had presented with, in order to find out the actual pathology.

The histology reading showed perivascular and peri-adnexal lymphocytic infiltration in the dermis. Some lymphoid cells were larger and neomorphic. There was no exocytosis.

Histopathlogy with immune histochemical profile showed CD-3 positive and CD-20 negative. The report concluded by the histopatholgist that the immunohistochemical profile is consistent with T-cell proliferation and the picture suggests cutaneous T-cell lymphoma. This diagnosis should not be missed. When the condition at its earlier stage, usually it shows erythematous patches with fine scales, however, when it starts to infiltrate, it can involve blood, lymph nodes and many viscera ultimately. It is abnormal lymphocytes proliferation and mostly males predominan with an incidence of 1 per 100,000 per year.

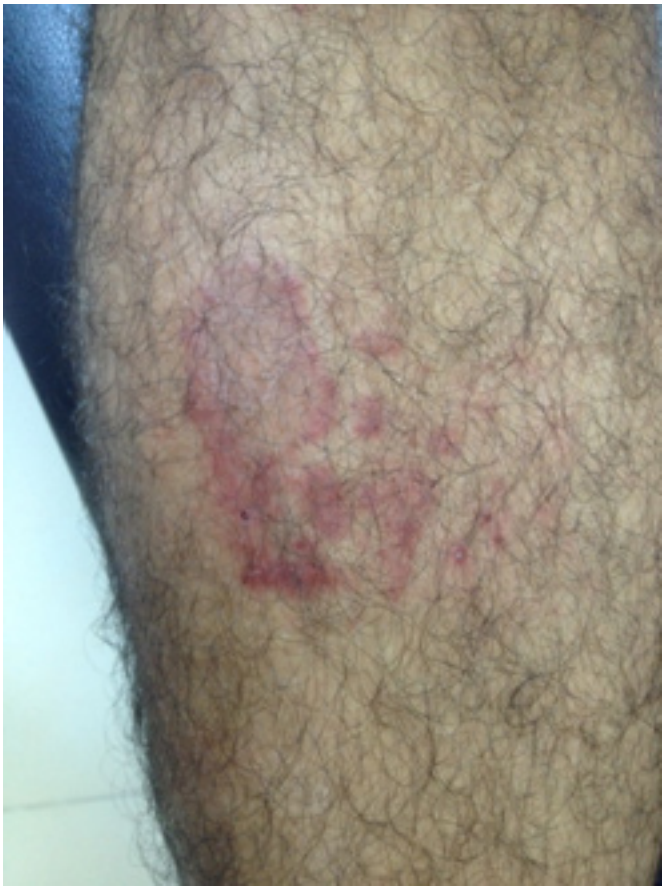

Figure 1: Left lower leg

Discussion

Diagnosis is difficult early in the course of this disease because it mimics quite a lot of benign skin disorders, namely discoid eczema, psoriasis, lichen planus, tinea corporis, pustular psoriasis, dermatitis, pityriasis lichenoides, pemphigus foliaceus, pseudolymphoma, parapsoriasis and contact dermatitis. Thus, multiple biopsies are essential, in order, to not miss it.

Biopsy was taken and histology reading revealed that this is cutaneous T-cell lymphoma (CTCL). CTCL is a collection of skin lymphomas that comprise some skin conditions. This may possibly be like, for example, mycosis fungoids (MF) (the commonest), CD30+ anaplastic large cell lymphoma (ALCL) (which represent a cluster of groups of large cell lymphomas), lymphomatoid papulosis (which is considered as a low-grade variant of cutaneous T cell lymphoma) (CTCL), and natural killer lymphoma (NK). MF is however the commonest. The incidence of MF is nearly 0.36 per 100.000 persons-years, with a median age of 55-60.
The condition can sometimes also be seen on the other parts of the body. It is often associated with increased age. Conversely, it may occur in children and adolescents.

This presented case poses a significant diagnostic challenge to experienced clinicians and dermatopathologists, as in some cases, it can be missed for many years. This is because, MF is well known as a cutaneous T-cell lymphoma with a lengthened long-term clinical path that can progress into diverse phases with an increasing aggression at terminal stages. It can take an indolent phase for ages. Furthermore, the clinical scenario and the histology of MF in the earliest stages is very hard to distinguish from other well-known and commonest inflammatory skin ailments which were mentioned in the differentials. For that reason, the judgment of these premature stages of the lymphoma is merely probable when clinical, histopathological, and molecular attributes are incorporated into the analysis to complement each other, particularly when none of the individual disease features are explicit.

A study by Skov AG, Gniadecki R, 2015, concluded that the possibility of a biopsy resultant in a diagnosis of MF was 25%, regardless of the quantity of the biopsy taken in the sequence (1,2). Additionally, cutaneous T-cell lymphomas (CTCLs) comprise 65% of all lymphomas, of which 50% are patients with MF (3).

At whatever time lesions similar to inflammatory skin disease, such as, psoriasis or nummular eczema continue nonresponsive to topical steroids for several weeks to months, in that instance, MF should be assumed. Therefore, clinicians must be vigilant with high index of suspicion and multiple biopsies should be performed and subjected to histopathological examination to recognize early stage of a potentially lethal disease.

Patient consent for writing up was obtained.

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Study of the clinical features of vitiligo among Yemeni patients in Aden

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Abstract

Objective: The objective of the study was to evaluate the different clinical features of vitiligo diseases and to assess the comorbidity disorders in Aden.

Patients and method: This was a retrospective descriptive study, in which we reviewed the medical records of all patients with vitiligo attending two private clinics in Aden during the period January 2019 to December 2020.

Results: The study patients were (33.5%) males and (66.5%) females (male : female 1: 2).

The mean age of the study patients was 23.6 ± 12.9 years and the age ranged between 2 and 65 years. Nearly half (49.7%) of patients were aged ≤ 20 years old and a positive family history of vitiligo was found in 28.6%.

Vulgaris is the predominant vitiligo type (57.8%) followed by acrofacial type (13.0%).

Extremities involvement were higher in females than males (17.4%) and (9.9%), respectively. Face with extremities involvement and trunk with extremities involvement in female patients seemed to be similar with (9.9).

Significant differences were found between vitiligo involvement types and the sex of patients, ($p < 0.05$).

In the age group ≤ 20 years old we found (28%) vulgaris type of vitiligo followed by acrofacial (7.4%). Vitiligo onset on extremities represented the highest site involvement (27.3%).

Twelve (7.4%) of the patients had associated diseases distributed as follows: diabetes mellitus (4.3%) followed by thyroid diseases (1.9%) and atopic disorders (1.2%). The associated diseases occurred among the age group ≤ 20 years old and the age group 21 – 40 years old; ($p = 0.043$).

Conclusion: Vitiligo disease is more common in females and the most common form was vitiligo vulgaris. A third of patients had a positive family history of vitiligo and the most sites involved were extremities.

Key words: clinical futures, vitiligo, Yemeni patients, Aden

Introduction

Vitiligo is a common acquired, probably heritable, progressive depigmenting skin disorder characterized by destruction of melanocytes within the epidermis, the mucous membranes, the eyes, and occasionally in some hair bulbs [1]. The skin depigmentation is in varying patterns, varying from small macules with scalloping borders to near-total depigmentation of body [2,3].

The disorder affects nearly 1%–2% of the world population irrespective of race and ethnicity [2,3,4,5].

The exact etiology of vitiligo is poorly understood and is often considered as a multifactorial disease with a complex pathogenesis encompassing several postulations implicating autoimmune, cytotoxic, biochemical, oxidant–antioxidant, viral, and neural mechanisms for destruction of the melanocyte function in the genetically predisposed. The presence of autoimmune diseases like autoimmune thyroiditis, Grave's disease, Addison's disease, diabetes mellitus, alopecia areata, and pernicious anemia in patients and their first-degree relatives favors its autoimmune etiology [6].

Most commonly, the disease begins during childhood or young adulthood with onset of 10 to 30 years but can occur at any age [4,5].

Lacovelli et al [7] reported in their study that the usual age of onset is before 20 years of age in nearly half of the cases. It affects both genders equally at any age but most studies report a peak incidence between 18 and 21 years (mean 24 years) [8,9].

Vitiligo patches can appear anywhere on the skin, but common sites are usually around the orifices, the genitals, or sun-exposed areas such as the face and hands. In addition to white patches on the skin, people with vitiligo may have poliosis of the scalp hair, eyelashes, eyebrows, and beard [10].

The aim of the study was to evaluate the different clinical features of vitiligo diseases and to assess the comorbidity disorders in Aden.

Patients and Methods

This was a retrospective descriptive study, in which we reviewed the medical records of all patients with vitiligo attending two private clinics in Aden during the period January 2019 to December 2020.

The patients' charts were retrieved and information about sex, age, site involvement, type of vitiligo and associated diseases were obtained.

SPSS program, version 17, was used to analyze the data. The continuous data are presented as means and categorical variables are presented as frequencies and percentages. The t-test was used to determine whether the difference between means is significant and we used also Pearson Chi-Square Test. A p-value <0.05 was considered statistically significant.

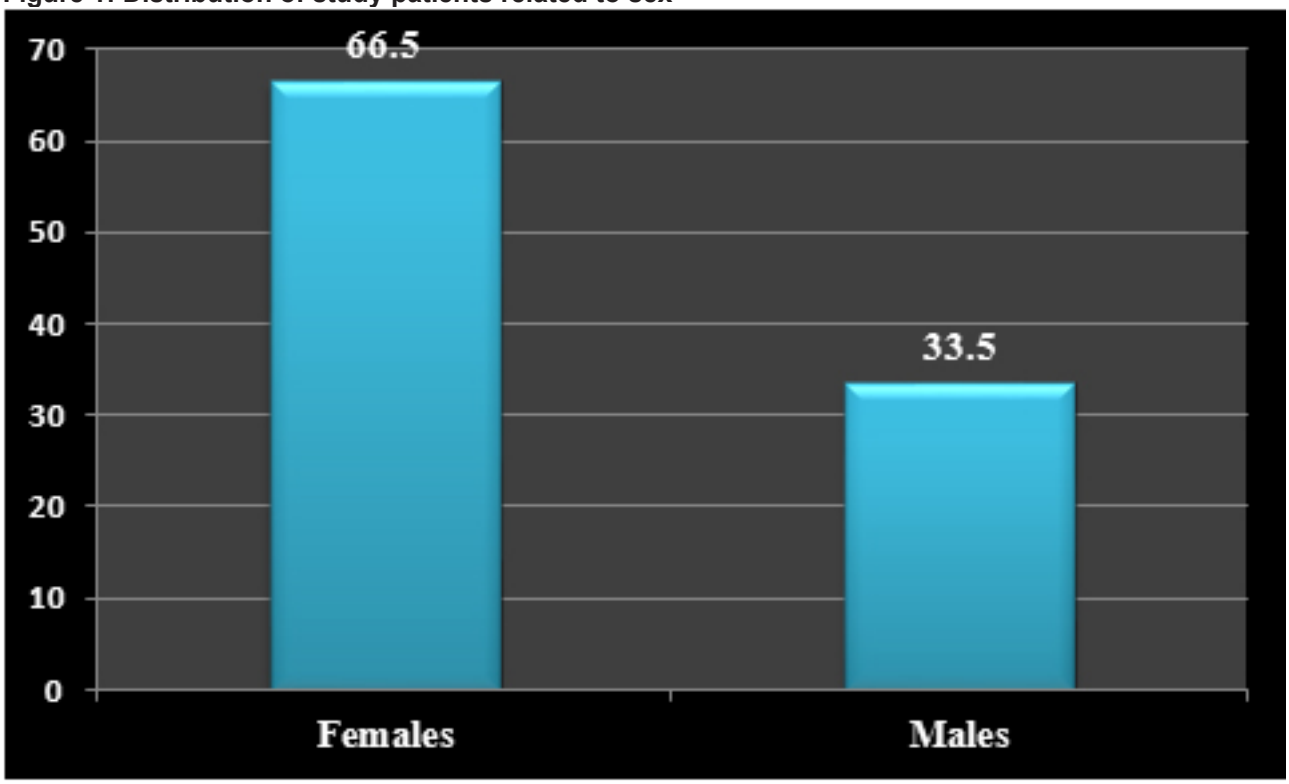
Results

This retrospective study comprised 161 patients with vitiligo attending two private dermatology clinics in Aden during the study period. There were 54 (33.5%) males and 107 (66.5%) females (male : female 1: 2); as shown in Table 1 and Figure 1.

Table 1: Vitiligo patients related to demographic variable (n=161)

Variables	Mean & range	No	%
Sex:			
Males		54	33.5
Females		107	66.5
Age (years):			
Mean age of all patients ± SD*	23.6 ± 12.9		
Range of age of all patients	2 - 65		
Females' mean age	22.7 ± 11.9		
Males' mean age	25.4 ± 14.8		
Females' age range	4 – 52		
Males' age range	2 – 65		
P-value between groups	> 0.05		
Age groups (years):			
≤ 20		80	49.7
21 – 40		65	40.4
> 40		16	9.9
Family history:			
Positive		46	28.6
None		115	71.4

Figure 1: Distribution of study patients related to sex



SD* = Standard deviation

The mean age of the study patients was 23.6 ± 12.9 years and the age ranged between 2 and 65 years. The mean age of females was 22.7 ± 11.9 years, and the age ranged between 4 – 52 years, while the mean age of males was 25.4 ± 14.8 years and the age range was 2 to 65 years. The difference between age means of gender showed no statistical significance (p > 0.05). The patients were divided into three age groups and the age groups were ≤ 20 years, 21 – 40 years and > 40 years.

The majority of patients 80 (49.7%) were aged ≤20 years, followed by the age group 21 – 40 years with 65 (40.4%) and the age group > 40 years with 16 (9.9%).

Forty six (28.6%) of the cases had a positive family history of vitiligo. All mentioned variables are summarized in Table 1.

Table 2 revealed the vitiligo types and site involvement related to sex among the study patients. Vulgaris is the predominant vitiligo type 93 (57.8%) followed by acrofacial type 21 (13.0%), focal type 19 (11.8%), segmental type 16 (9.9%), mucosal type 8 (5.0%) and universalis 4 (2.5%), as shown in Table 2 and Figure 2. In females vulgaris is the predominant type with 59 (36.7%) followed by acrofacial 16 (9.9%) then segmental types with 13 (8.1%) while in males vulgaris types are more with 34 (21.1%) followed by focal types with 8 (5.0%), Table 2. No significant differences were found between vitiligo types and the sex of patients, ($p > 0.05$). Table 2 shows distribution of vitiligo type and site involvement related to sex. Extremities involvement were higher in females and males, 28 (17.4%) and 16 (9.9%), respectively. Face with extremities involvement and trunk with extremities involvement in female patients seem to be similar with 16 (9.9) for each one. In male patients face and extremities involvement were the second with 9 (5.6%). Significant differences were found between vitiligo involvement types and the sex of patients, ($p < 0.05$).

Table 2: Distribution of vitiligo type and site involvement related to sex (n=161)

Variables	Sex						p-value
	Female (n=107)		Male (n=54)				
	No	(%)	No	(%)	No	(%)	
Type of vitiligo:							
Vulgaris	59	(36.7)	34	(21.1)	93	(57.8)	
Acrofacial	16	(9.9)	5	(3.1)	21	(13.0)	P > 0.05
Focal	11	(6.8)	8	(5.0)	19	(11.8)	
Segmental	13	(8.1)	3	(1.9)	16	(9.9)	
Mucosal	5	(3.1)	3	(1.9)	8	(5.0)	
Universalis	3	(1.9)	1	(0.6)	4	(2.5)	
Site involvement:							
Extremities	28	(17.4)	16	(9.9)	44	(27.3)	
Face and extremities	16	(9.9)	9	(5.6)	25	(15.5)	
Trunk and extremities	16	(9.9)	4	(2.5)	20	(12.4)	
Face, trunk and extremities	14	(8.7)	3	(1.9)	17	(10.6)	
Face	12	(7.4)	4	(2.5)	16	(9.9)	P =
Genitalia	1	(0.6)	5	(3.1)	6	(3.7)	0.049
All body	4	(2.5)	1	(0.6)	5	(3.1)	
Lips	4	(2.5)	1	(0.6)	5	(3.1)	
Periorbital	4	(2.5)	1	(0.6)	5	(3.1)	
Back	3	(1.9)	1	(0.6)	4	(2.5)	
Face and trunk	0	(0.0)	4	(2.5)	4	(2.5)	
Abdomen	2	(1.2)	1	(0.6)	3	(1.9)	
Face, extremities and genitalia	1	(0.6)	2	(1.2)	3	(1.9)	
Trunk	1	(0.6)	2	(1.2)	3	(1.9)	
Scalp	1	(0.6)	0	(0.0)	1	(0.6)	

Figure 2: Percentage of vitiligo types

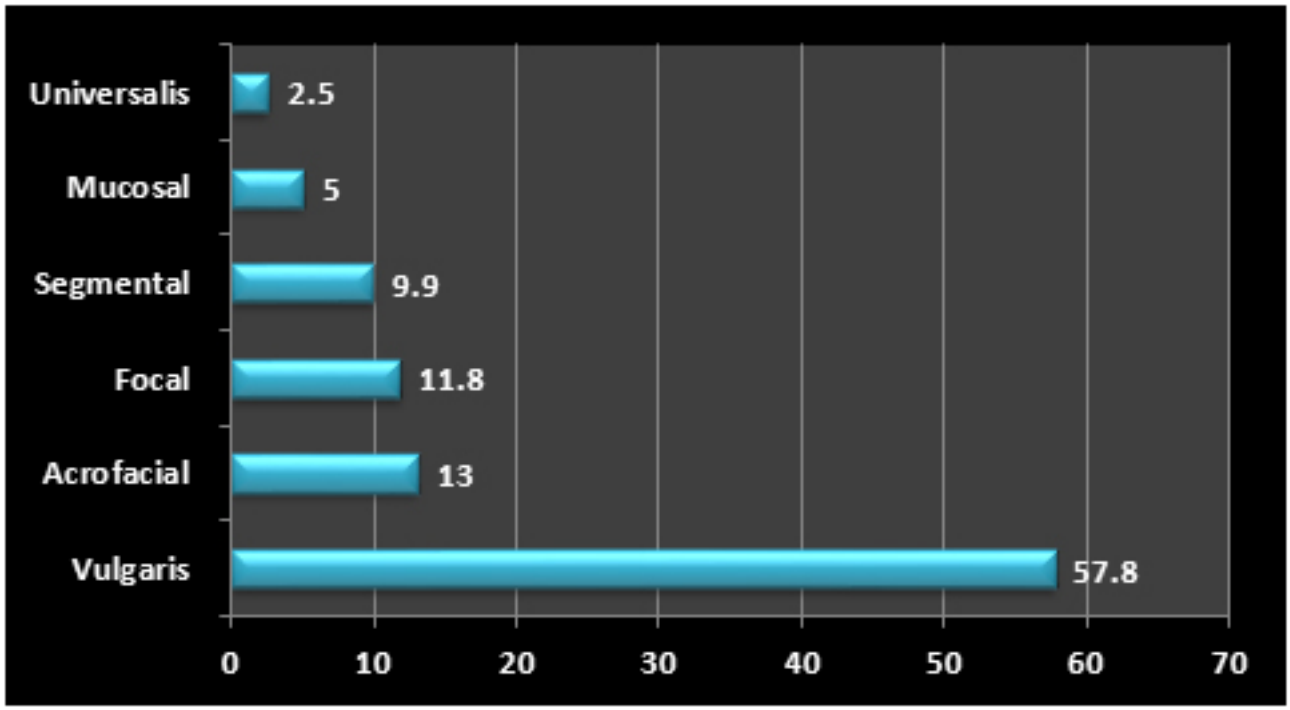


Table 3 shows the distribution of vitiligo type and site involvement related to age groups. Vulgaris type of vitiligo in the age group ≤ 20 years old, in the age group 21 – 40 years old and > 40 years old was higher than the other types of vitiligo in the different age groups.

In the age group ≤ 20 years old we found (28%) vulgaris type of vitiligo followed by acrofacial type 12 (7.4%), focal 13 (8.1%) and segmental involvement with 9 (5.5%). In the age group 21-40 years old we found acrofacial involvement followed the vulgaris involvement with 8 (5.0%).

No o significant differences were found between vitiligo types and the age groups ($p > 0.05$).

Site involvement of vitiligo in extremities, face and extremities, trunk and extremities, face trunk & extremities and face seem to be higher than that in the age group > 40 years old as shown also in Figure 3. No significant differences were found between vitiligo involvement and the age groups ($p > 0.05$).

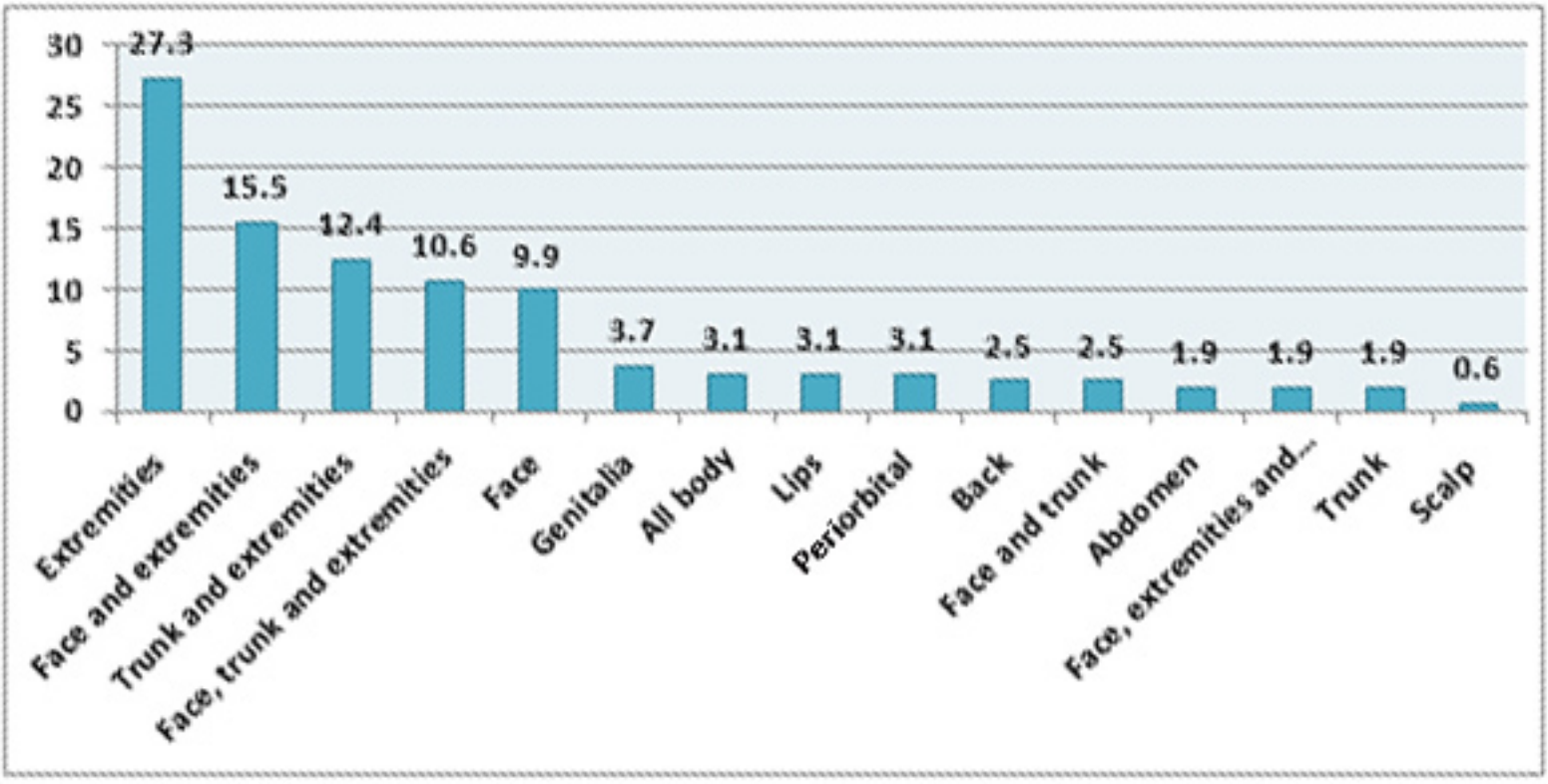
Vitiligo onset on extremities represented the highest site involvement 44 (27.3%) followed by face and extremities with 25 (15.5%), trunk and extremities 20 (12.4%), face, trunk and extremities with 17 (10.6%) and onset on face with 16 (9.9%). The less affected site is genitalia 6 (3.7%) followed by all body, lips and periorbital each one with 5 (3.1%) and the lowest onset was on scalp 1 (0.6%).

Table 3: Distribution of vitiligo type and site involvement related to age groups (n=161)

Variables	Age (years)				p-value
	≤ 20 (n=80) No (%)	21-40 (n=65) No (%)	> 40 (n=16) No (%)	No (%)	
Type of vitiligo:					
Vulgaris	45 (28.0)	37 (23.0)	11 (6.8)	93 (57.8)	
Acrofacial	12 (7.4)	8 (5.0)	1 (0.6)	21 (13.0)	P > 0.05
Focal	13 (8.1)	5 (3.1)	1 (0.6)	19 (11.8)	
Segmental	9 (5.5)	6 (3.8)	1 (0.6)	16 (9.9)	
Mucosal	1 (0.6)	6 (3.8)	1 (0.6)	8 (5.0)	
Universalis	0 (0.0)	3 (1.9)	1 (0.6)	4 (2.5)	
Site involvement:					
Extremities	17 (10.6)	18 (11.2)	9 (5.6)	44 (27.3)	
Face and extremities	14 (8.7)	10 (6.2)	1 (0.6)	25 (15.5)	
Trunk and extremities	12 (7.5)	7 (4.3)	1 (0.6)	20 (12.4)	
Face, trunk, extremities	9 (5.6)	7 (4.3)	1 (0.6)	17 (10.6)	
Face	8 (5.0)	6 (3.7)	2 (1.2)	16 (9.9)	P > 0.05
Genitalia	1 (0.6)	5 (3.1)	0 (0.0)	6 (3.7)	
All body	0 (0.0)	4 (2.5)	1 (0.6)	5 (3.1)	
Lips	0 (0.0)	4 (2.5)	1 (0.6)	5 (3.1)	
Periorbital	5 (3.1)	0 (0.0)	0 (0.0)	5 (3.1)	
Back	4 (2.5)	0 (0.0)	0 (0.0)	4 (2.5)	
Face and trunk	3 (1.9)	1 (0.6)	0 (0.0)	4 (2.5)	
Abdomen	2 (1.2)	1 (0.6)	0 (0.0)	3 (1.9)	
FEG**	3 (1.9)	0 (0.0)	0 (0.0)	3 (1.9)	
Trunk	1 (0.6)	2 (1.2)	0 (0.0)	3 (1.9)	
Scalp	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	

FEG** = face, extremities and genitalia

Figure 3: Percentage of site involvement of vitiligo among study patients



Twelve (7.4%) of the patients had associated diseases distributed as follows: diabetes mellitus 7 (4.3%) followed by thyroid diseases 3 (1.9%) and atopic disorders 2 (1.2%). We observed that the associated diseases occurred among the patients of age group ≤ 20 years old and the age group 21 – 40 years old without any associated disease in the age group > 40 years old; as shown in Table 4.

Significant differences were found between associated diseases and the age groups of patients (p = 0.043).

We distributed the positive and non-positive of family history related to age groups and we found 29 (18.0%) of positive family history were among patients ≤ 20 years old followed by the age group 21 – 40 years old with 14 (8.7%) and the age group > 40 years old with 3 (1.9%).

No significant differences were found between family history and the age groups of patients (p > 0.05).

Table 4: Distribution of associated diseases related to age groups (n=161)

Associated diseases	Age (years)						Total		p-value
	≤ 20 (n=80)		21-40 (n=65)		> 40 (n=16)				
	No	(%)	No	(%)	No	(%)	No	(%)	
Atopic disorders	2	(1.2)	0	(0.0)	0	(0.0)	2	(1.2)	
Diabetes mellitus	1	(0.6)	6	(3.7)	0	(0.0)	7	(4.3)	P < 0.05
Thyroid diseases	0	(0.0)	3	(1.9)	0	(0.0)	3	(1.9)	
None	77	(47.9)	56	(34.8)	16	(9.9)	149	(92.6)	
Family history:									
Positive	29	(18.0)	14	(8.7)	3	(1.9)	46	(28.6)	P > 0.05
None	51	(31.7)	51	(31.7)	13	(8)	115	(71.4)	

Discussion

Vitiligo, a depigmenting skin disorder, is characterized by the selective loss of melanocytes, which in turn leads to pigment dilution in the affected areas of the skin. The characteristic lesion is a totally amelanotic, non-scaly, chalky-white macule with distinct margins. Considerable recent progress has been made in our understanding of the pathogenesis of vitiligo, and it is now clearly classified as autoimmune disease, associated with genetic and en¬vironmental factors together with metabolic, oxidative stress and cell detachment abnormalities [11,12]. Vitiligo should not be dismissed as a cosmetic or insignificant disease, as its effects can be psychologically devastating, often with a considerable burden on daily life [13].

Vitiligo is the most common depigmenting skin disorder, with an estimated prevalence of 0.5–2% of the population in both adults and children worldwide [2,3,14].

Our study comprised 161 patients with vitiligo. They were (33.5%) males and (66.5%) females (male : female 1: 2).

Vitiligo affects both genders almost with equal frequency in most reports or with a predilection for women being affected two times more often than men as an exception [2,3,15].

In the present study we found the mean age of the study patients was 23.6 ± 12.9 years and the age ranged between 2 and 65 years.

Fatani et al [16] reported in their study in Makkah region, Saudi Arabia, that of the 135 patients, (67.4%) were females and (32.6%) were males. The mean age of patients was 24.5 years.

We found in our present study that (28.6%) of the cases had positive family history of vitiligo. Osman et al [17] found in their study in Sudan that 35 % of patients with vitiligo had positive family history.

Alissa et al [18] from Saudi Arabia, mentioned that (42.8%) of the patients had a positive family history of vitiligo, and 0.6% were not sure of the presence of vitiligo in their families. Al-fahaad [19] reported that of the 101 study cases, 5.9% had a family history of vitiligo, while the remaining 94.1% did not give such history.

Familial cases of vitiligo are common, indicating a hereditary factor, between 6-38% of vitiligo patients have family history of the disease [20].

In the current study vulgaris is the predominant vitiligo type (57.8%) followed by acrofacial type (13.0%), focal type (11.8%), segmental type (9.9%), mucosal type (5.0%) and universalis (2.5%).

Similar to our finding was reported by Alissa et al [18] from Saudi Arabia that the most common type of vitiligo was vitiligo vulgaris (42.2%), followed by acrofacial vitiligo (24.0%), focal vitiligo (11.8), acral vitiligo (8.3%), and universal vitiligo (6.2%).

Our finding agreed with the studies done in India [21], South Tunisia [22], and Turkey [1], whereas acrofacial vitiligo was noted to be the most common form in studies performed in India [23] and Libya [24].

In our study vitiligo vulgaris in females was predominant with (36.7%) followed by acrofacial (9.9%) then segmental types with (8.1%). In males, vulgaris types were (21.1%) followed by focal types with (5.0%).

Vitiligo vulgaris was more likely to be seen in females and mucosal vitiligo was more likely to be seen in males [25].

In our study there were no significant differences found between vitiligo types and the sex of patients, ($p > 0.05$).

Poudyal et al [25] reported in their study from Nepal there was no difference between the distribution pattern of vitiligo types among male and female patients. Other studies mentioned that there were no significant differences in distribution of vitiligo types among the genders [26,27].

In the current study extremities involvement were higher in females than males 28 (17.4%) and 16 (9.9%), respectively. Face with extremities involvement and trunk with extremities involvement in female patients seem to be similar with 16 (9.9) for each one. In male patients face and extremities involvement were the second most common with 9 (5.6%). Significant differences were found between vitiligo involvement types and the sex of patients, ($p < 0.05$).

Tsadik et al [28] reported in their study from Ethiopia that the most commonly affected site were limbs (44.5%) followed by the head and neck (24%), trunk (14.8%), chest (12%), genital (2.8%), and mucosal areas (1.9%). They added that sites of vitiligo were not significantly associated with age ($p > 0.05$) and sex ($p > 0.05$) of the cases.

In our study we found 12 (7.4%) of the patients had associated diseases distributed as follows: diabetes mellitus 7 (4.3%) followed by thyroid diseases 3 (1.9%) and atopic disorders 2 (1.2%).

We observed in our study that the associated diseases occurred among the patients of age group ≤ 20 years old and the age group 21 – 40 years old without any associated disease in the age group > 40 years old. Significant differences were found between associated diseases and the age groups of patients ($p = 0.043$).

Spritz et al [29] reported that patients with vitiligo have been found to have a higher incidence of autoimmune diseases such as thyroiditis, Type 1 diabetes, lupus, Addison disease, pernicious anemia, and alopecia areata. Thyroid dysfunction was found in one large study to precede the onset of vitiligo [30].

We found in our study that out of 28.6% of cases with positive family history of vitiligo (18.0%) were among patients ≤ 20 years old, followed by the age group 21 – 40 years old with (8.7%) and the age group > 40 years old with 3 (1.9%). No significant differences were found between family history and the age groups of patients ($p > 0.05$).

Similar to our finding reported by a study conducted in China by Zhang et al [31] that children and adolescents aged (0-19 years old) with vitiligo had a higher positive rate of a family history of vitiligo (11.4%) than did adults aged (20-59 years old) with (5.4%) and patients of advanced age (≥ 60 years old) with (3.8%).

Conclusion

Vitiligo disease is more common in females and the most common form was vitiligo vulgaris. This form was more common in female patients and affected more patients' age ≤ 20 years old. A third of patients had positive family history of vitiligo and the most site involvements were extremities and they were higher in females and males. Further studies are needed to evaluate the epidemiology related to governorates, demographic characteristics and treatment of the disease.

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Surgical treatment and Survival of Gallbladder Cancer Patients: A Systematic Review

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Abstract

Objective: To assess the outcome and overall survival of surgery for gallbladder cancer.

Methods: A systematic literature search was performed in PubMed. The review question was structured in PICO format. Then, the search was conducted according to a certain research strategy and certain limitations. The titles and abstracts of all retrieved citations were assessed by two medical consultants, who decided which articles to read in full text. The selected full text articles were independently screened by the researcher and the two colleagues. In a consensus meeting, it was determined which articles fulfilled the pre-defined inclusion criteria and eligibility.

Results: A total of four citations were identified as fulfilling the predetermined eligibility criteria (two prospective cohort studies and two retrospective studies), while 630 studies which did not fulfill the inclusion criteria were excluded.

Conclusions: Optimal treatment of gallbladder cancer is still evolving. Radical surgery in combination with standardized lymph node dissection constitutes the cornerstone of the surgical treatment. Patients' overall survival depends upon their tumor stage, levels of CA199, and tumor location in gallbladder.

Key Words: Gallbladder cancer, Surgery, Survival, Systematic Review.

Introduction

Gallbladder cancer (GBC) is a rare cancer, where most patients are diagnosed at advanced stages, with an aggressive nature and subsequent high mortality. Its worldwide incidence is less than 2/100,000 (1). It has broad geographical and ethnic distributions, with low incidence in Saudi Arabia (2), and higher incidence among Mexican and Indian Americans, and Eastern Europeans. Well-established risk factors include age, obesity, cholelithiasis, female gender, positive family history, and anomalous junction of the pancreato-biliary duct (3).

Surgery for patients in early stages (i.e., pT1 and pT2) is the only chance for cure, while in advanced stages, radical surgery may be impossible, due to metastases into the liver hilum, other organs or lymph nodes (4). However, recurrence and mortality rates remain high in patients with advanced cancer stages after radical resections and the extensive surgery is associated with high morbidity (5).

Early stages of GBC are often diagnosed incidentally in conjunction with cholecystectomy due to gallstone disease, and an additional radical surgery is mostly needed (6). However, the extent of needed radical surgeries remains a matter of debate, according to several questions, regarding the extent of liver resection, lymph nodes dissection, and the need for bile duct resection and sometimes other organs (7).

The present systematic review aimed to assess the outcome and overall survival of surgery for gallbladder cancer.

Methods

In accordance with the PRISMA checklist, a systematic literature search was performed in PubMed by the researcher. The following review question was structured in PICO format (Table 1):

"In adult patients diagnosed with gallbladder cancer (P), liver resection, lymph node resection, common bile duct resection, or extensive surgery of adjacent structures (I), compared with cholecystectomy alone (C), what is their disease-free survival (O)?".

Then, a literature search was conducted according to the following research strategy:
("gallbladder neoplasms"[MeSH Terms] OR gallbladder cancers[Text Word]) AND "surg [Ti]*

The following search limitations were considered:
- Study design: Cohort, randomized controlled, or retrospective studies. All case reports, case series, and reviews were not included.
- Language: English
- Limits: Abstract, Full text, and Publication years 2020-Present.

The titles and abstracts of all retrieved citations were assessed by two medical consultants (OM and HA), who decided which articles to read in full text. The selected full text articles were independently screened by the researcher and the two colleagues. In a consensus meeting, it was determined which articles fulfilled the pre-defined inclusion criteria and eligibility (Table 1).

The included studies and their design and patient characteristics are presented in Table 2. The articles were critically appraised using the Systematic review - Critical Appraisal Skills (CASP) program. In most studies differences in the overall survival were compared. A graphic presentation of the selection process is presented in Diagram (1):

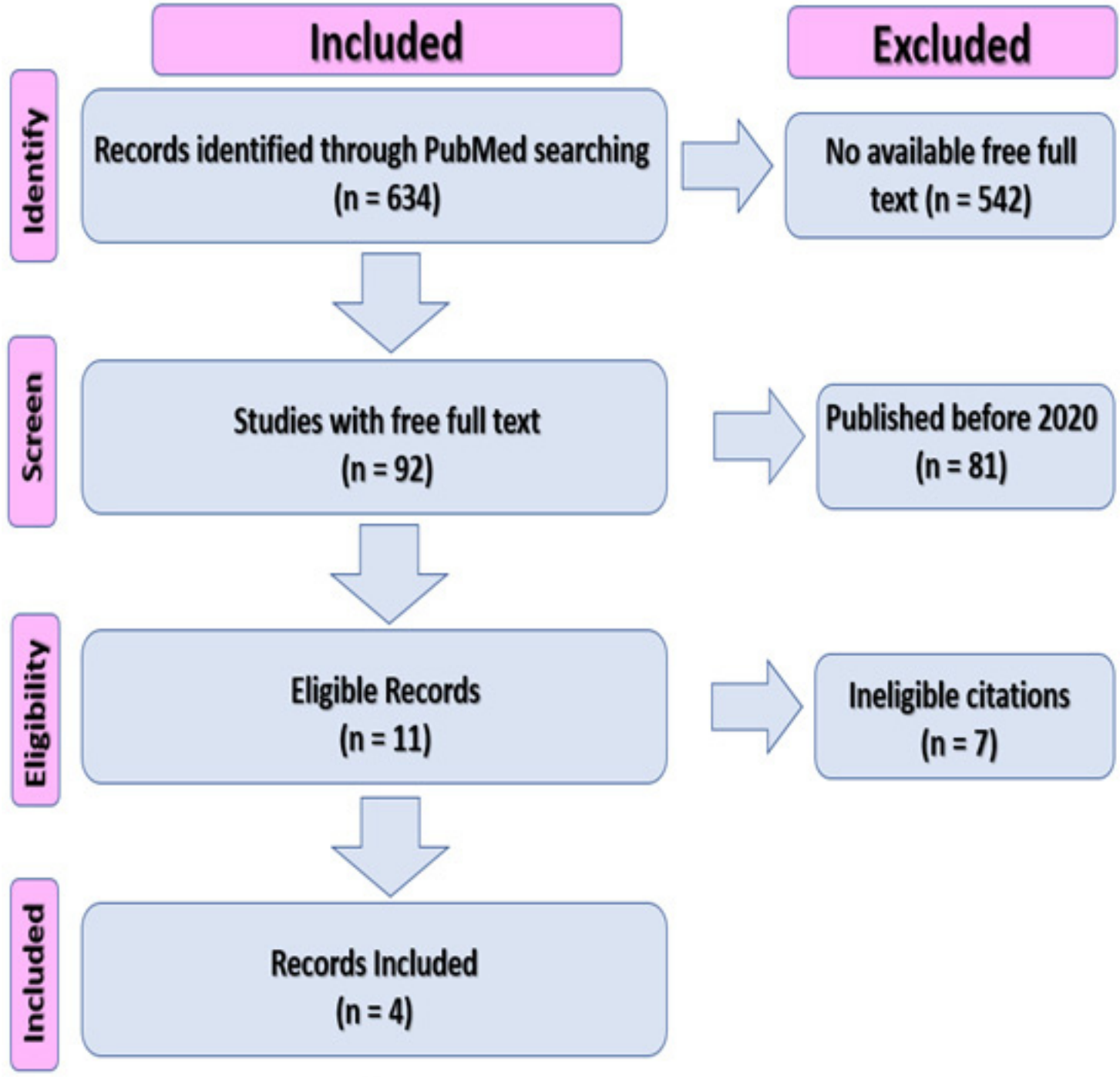
Table 1: The PICO list for the inclusion criteria and eligibility

Population (P)	• Adults • Preoperative diagnosis of gallbladder cancer. • Subgroup evaluation by T-stage or TNM-stage
Intervention (I)	• Liver resection, liver segments 4b & 5 or radical resection • Lymph node resection (standard or extended) • Resection of the common bile duct • Extensive surgery of adjacent structures or/and organs
Comparison (C)	• Cholecystectomy alone
Outcome (O)	• Disease-free survival

Table 2: Description of the studies included in the systematic review

Reference	Study design	Intervention	Outcome
Liu et al. [8]	Prospective Cohort	- 35 patients received hyperthermic intraperitoneal perfusion chemotherapy combined with radical surgery and Capecitabine. The study group induded43 patients received radical surgery and capecitabine	The 1-year survival rates of the study and control groups were 91.4% vs. 76.7% The 2-year survival rates were 26.3% vs. 17.5%, respectively (P<0.05)
Chang et al. [9]	Prospective Cohort	715 GBC cases were divided into three groups who received simple resection (full-thickness cholecystectomy for removal of primary tumor site, n=126), radical resection (gallbladder bed removal combined with partial hepatectomy, n=349), and palliative surgery (treatment at advanced stages, n=240).	Radical resection had best overall survival at clinical stage II, while simple resection had best overall survival at tumor clinical stage IV
Leigh et al. [10]	Retrospective	17 patients received cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy may offer a survival benefit in selected hepatocellular carcinoma patients with peritoneal carcinomatosis
Yuza et al. [11]	Retrospective	47 patients with T1b GBC, 29 (62%) underwent simple cholecystectomy and 18 (38%) underwent radical resection with regional lymph node dissection	Most T1b GBCs had local disease. In T1b GBC patients, the decision of radical resection is justified. Additional radical resection is not required following simple cholecystectomy provided that the penetration depth is restricted toward the muscular layer and that surgical margins are uninvolved.

Diagram 1


Included
Excluded
Identify
Records identified through PubMed searching (n = 634)
No available free full text (n = 542)
Screen
Studies with free full text (n = 92)
Published before 2020 (n = 81)
Eligibility
Eligible Records (n = 11)
Ineligible citations (n = 7)
Included
Records Included (n = 4)

Results

A total of four citations were identified as fulfilling the predetermined eligibility criteria. We excluded 630 studies because they did not completely fulfill the inclusion criteria, having no available free full text (n=542), or being published before 2020 (n=81). The remaining 11 full-text articles were assessed for eligibility of which 7 were excluded. Therefore, we included four studies in the final synthesis (8); Chang et al. (9); Leigh et al. (10); and Yuza et al. (11), with a total number of 857 included patients.

The systematic review comprised two prospective cohort studies Liu et al (8) and Chang et al. (9) in addition to two retrospective studies Leigh et al. (10); and Yuza et al. (11). No randomized controlled trials were found. Outcome variable was mainly overall survival, but no studies described the quality of life of included patients. Prospective cohort studies were sub-grouped according to intervention and comparisons were performed for each intervention.

Management of GBC patients

The study of Liu et al. (8) explored the effect of hyperthermic intraperitoneal perfusion chemotherapy combined with radical surgery and capecitabine on gallbladder cancer. Surgical plans were based on patients' preoperative imaging, important organ functions, liver reserve functions, and resectability of the liver. Resection of the liver was according to the National Comprehensive Cancer Network guidelines (12), with routine liver S4b plus S5 resection at stage T2 and T3; right hepatectomy or enlarged right hepatectomy was performed for patients with liver bed involvement >2 cm, located in the neck of the gallbladder, invading the gallbladder triangle, or involving liver duodenal ligament lymph node metastasis; and according to the results of lymph node biopsy in groups 13a and 16 during the operation, hepatoduodenal ligament lymph node dissection or enlarged lymph node dissection was selected. Cystic duct biopsy was routinely performed during the operation, and the positive patients needed to be combined with extrahepatic bile duct resection, ranging from the upper back of the pancreatic head to the first hepatic hilum, and a Roux-en-Y bile duct jejunum anastomosis (10).

Chang et al. (9) studied the impact of surgical strategies on the survival of gallbladder cancer patients. According to the strategies of received surgical treatment, their patients were divided into: simple resection (i.e., partial or total resection of primary tumor site, n=126); radical resection (i.e., total resection of primary tumor site with other organs, n=349); and palliative surgery (n=240), which was performed in patients with distant metastases cancer, wide tumor invasion, and conditions wherein the patient cannot bear aggressive surgery or they refuse. Patients with tumor location not in gallbladder neck, earlier clinical staging (I/II), T1/T2 stage, normal level of tumor markers, and gallstone were more likely to undergo simple resection. Patients with young age, N1/N2 stage, and poorly differentiated tumor were more likely to receive radical resection. Patients with M1 stage, CA199 ≥ 27 U/ml, CA242 ≥ 20 IU/ml, and unreceived adjuvant therapy were more likely to receive palliative surgery.

The study of Leigh et al. (10) explored whether cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is indicated in hepatobiliary malignancies. Cytoreductive surgery/Hyperthermic intraperitoneal chemotherapy was performed in a standard fashion (13), with diagnostic laparoscopy in all cases to assess the feasibility of cytoreduction prior to hyperthermic intraperitoneal chemotherapy. However, the procedure was aborted at the discretion of the operating surgeon if the tumor burden was deemed too bulky to attempt cytoreduction. The peritoneal cancer index was calculated prior to operative debulking (14), and the completeness of cytoreduction score was recorded at the conclusion of the procedure. All patients who underwent hyperthermic intraperitoneal chemotherapy received 40 mg of mitomycin C at 42 °C for 90 minutes. Creation of anastomoses was performed after the completion of hyperthermic intraperitoneal chemotherapy. Major perioperative complications were graded according to the Clavien-Dindo classification system (III–V), as occurring within 30 days of cytoreductive surgery/hyperthermic intraperitoneal chemotherapy (15).

Yuza et al. (11) retrospectively investigated the long-term outcomes of surgical resection for GBC patients of whom 29 patients (62%) underwent simple cholecystectomy and 18 patients (38%) underwent radical resection with regional lymph node dissection.

Outcome and Survival

The study of Liu et al. (8) reported that GBC patients who underwent hyperthermic intraperitoneal perfusion chemotherapy had longer hospitalization time for patients needed to extend the extubation time of the abdominal drainage tube. Moreover, due to the complexity of gallbladder cancer surgery, the general operation time is long, so intraoperative hypothermia is prone to occur. Cisplatin applied to patients who received hyperthermic intraperitoneal perfusion chemotherapy did not cause significant liver and kidney damage, and only one patient with myelosuppression could be corrected after symptomatic treatment. The most common complication of hyperthermic intraperitoneal perfusion chemotherapy was gastrointestinal reactions, manifested as the discomfort of the abdomen and delayed defecation. However, there were no serious surgical-related complications, e.g., hepatic wound bleeding, bile leakage, and anastomotic leakage. Therefore, cytoreductive surgery/hyperthermic intraperitoneal chemotherapy is associated with improved cancer survival but an increased risk of infection, which was the most important cause of perioperative morbidity and death. The overall infection rate was 30% in the control group and 34% in the hyperthermic intraperitoneal perfusion chemotherapy group.

Moreover, Liu et al. (8) reported that the median survival of the surgery combined with the gemcitabine treatment group was 15.3 months. The median survival time of patients treated with hyperthermic intraperitoneal perfusion chemotherapy was 19.2 months, suggesting that hyperthermic intraperitoneal perfusion chemotherapy may significantly prolong the median survival time of patients. The one-year survival rates of the study groups were 91.43% vs. 76.71%, and the two-year survival rates were 26.29% vs. 17.53%, respectively. The median survival of the surgery combined with the gemcitabine treatment group was 15.3 months. The median survival time of patients treated with hyperthermic intraperitoneal perfusion chemotherapy was 19.2 months, suggesting that hyperthermic intraperitoneal perfusion chemotherapy may significantly prolong the median survival time of patients. The one-year survival rates of the study groups were 91.43% vs. 76.71%, and the two-year survival rates were 26.29% vs. 17.53%, respectively.

The study of Chang et al. (9) reported a high mortality rate within about 12 months after surgery as one of the primary limitations for the utilization of radical surgery at stage II. At advanced stages, compared with simple resection or palliative surgery, the effect of radical surgery on overall survival was significantly decreased. There was no significant difference in 5-year survival at stage III between radical resection and simple resection groups, but palliative surgery groups had the lowest overall survival. Thus, aggressive resection is still an effective therapy at stage III, even if it is only available in some individuals . The difference of overall survival at stage IV between radical resection and palliative surgery groups was not significant. Also, the simple resection groups had good performance for overall survival at stage IV. The median overall survival time of the 715 patients was 24 months. From stage I to IV cases, the survival rates were 85.71%, 64.63%, 36.08%, and 10.42%, respectively. Compared with the palliative surgery groups, patients with simple resection or radical resection had significant longer overall survival time ($p<0.0001$). Patients with simple resection had the best overall survival outcome, with a 47.62% of survival rate and 51 months of median overall survival time. The overall survival outcome of patients with radical resection was moderate, with a 39.83% survival rate and 34 months of median overall survival time. The palliative surgery patient group had the worst overall survival outcome, with an 8.75% of survival rate and 10 months of median overall survival time. The difference of overall survival between simple resection and radical resection in stage I patients was not significant ($p=0.934$). However, patients with radical resection had a better overall survival than patients with simple resection at stage II ($p = 0.042$). Compared with simple resection and radical resection groups, patients with palliative surgery had the worst overall survival at cancer stage III ($p=0.028$). At cancer stage IV, patients with simple resection had the best overall survival ($p = 0.0129$).

Moreover, Chang et al. (9) found that GBC patients from the countryside, those with tumor location of gallbladder body or neck, with increased TNM stages, with poorly differentiated of the tumor, with CA199 ≥ 27 U/mL, with CA242 ≥ 20 IU/mL, and with surgical treatment of radical resection or palliative surgery were related to a worse prognosis.

The study of Leigh et al. (10) reported that the median overall survival for their patients was 23 months with one-year and three-year survival rates of 73% and 41%, respectively, with a longer survival in the hepatocellular carcinoma cohort compared to the other cohorts. Of the pancreaticobiliary malignancies, the longest median survival was seen in patients with cholangiocarcinoma (19 months), though this was still considerably shorter than in hepatocellular carcinoma. The median progression-free survival for the entire cohort was 8 months, with no significant differences between the cohorts. All patients experienced tumor recurrence by 3 years postoperatively. The shortest median progression-free survival was in patients with GBC (2 months), and the longest was in patients with pancreatic cancer (15 months). Age at surgery (HR 1.13, $p = 0.027$) and peritoneal cancer index (HR 1.24, $p = 0.011$) were independent predictors of overall survival, while there were no independent predictors of progression-free survival.

Yuza et al. (11) reported that open surgical approach was more prevalent among patients who underwent open radical resection than among patients who underwent simple cholecystectomy (open in 21 patients; laparoscopic in 8 patients, $P=0.017$). The cumulative 10- and 20-year overall survival rates were 65% and 25%, respectively. The 10-year overall survival rate following simple cholecystectomy was akin to that following radical resection (66% and 64%, respectively, $P=0.618$). The outcome following simple cholecystectomy (10-year disease-specific survival rate of 100%) was equivalent to that following radical resection (that of 86%, $P=0.151$). While old age (> 70 years, hazard ratio: 5.285, $P = 0.003$) and gender (female, hazard ratio: 0.272, $P=0.007$) had a strong effect on patients' overall survival; surgical procedure (simple cholecystectomy vs. radical resection) and surgical approach (open vs. laparoscopic) did not did not affect inclusive survival in patients with T1b GBC.

Discussion

GBC is an uncommon cancer type with a high mortality rate and poor long-term survival outcomes (16). Surgical treatment is the most effective intervention for the cure of GBC patients (17); however, curative resection is feasible in a minority population of GBC patients (18). According to the Guidelines of the National Comprehensive Cancer Network, a radical resection is recommended for T1b and more advanced GBC (12).

Currently, there are no accepted, robust treatment guidelines for T1b GBC. The National Comprehensive Cancer Network guidelines endorsed radical resection along with portal lymph node dissection for T1b GBC (12), whereas the Japanese guidelines recommend simple cholecystectomy, provided that the depth of invasion is histologically restricted to the muscular layer (19).

The present systematic review has focused on surgical approaches for management of GBC. The lack of knowledge in this field highlights the importance of a structured care to centralize experience and to standardize both the surgical procedure and the documentation to gain more knowledge in the future. It is important to perform radical liver resection with tumor free margins, but the extent of liver resection for earlier stages has been insufficiently evaluated (6; 20).

The fact that lymph node metastases deteriorate survival after gallbladder cancer surgery is unquestionable. An adequate lymph node resection seems important not only for staging, but also for survival. Niu et al. (21) reported that, in patients with advanced lymph node infiltration (N2), no benefit was seen despite extended lymph node resection. Interestingly cases with skip lymph node metastases (N2 lymph node tumors despite no N1 tumors) have been described (22) and might explain conflicting data for N2-positive patients, as some report outcome comparable to N1- patients (23).

Eilard et al. (24) stated that the effect of direct radical surgery versus staged operations in a controlled setting where pathology reports are rap idly analyzed and the needed re-resections are scheduled within a very short time span, has not been studied. The current practice is based on the general oncologic principle to aim at direct radical resection. The low survival rate of patients with residual cancer at the time of re-resection supports this principle, though the time passed from the first to the second operation might influence the rate of residual disease.

Liver resection is related to a high mortality rate, while young age would play a protective role for patients with radical resection in the perioperative period. Patients with advanced tumor stages, high levels of tumor markers (CA199, CA242), metastatic cancer (M1), and unreceived adjuvant therapy, were more associated with palliative surgery.

For the metastatic cancer and surgery inoperable patient, palliative surgery would be the treatment for relieving the patient's pain and promoting the patients' quality of life (9).

Hyperthermic intraperitoneal perfusion chemotherapy has achieved unique effects in the treatment of peritoneal cancer. Moreover, cytoreductive surgery combined with hyperthermic intraperitoneal perfusion chemotherapy was applied for the treatment of advanced gallbladder cancer (25-26). Liu et al. (8) included patients with stage III GBC treated with operation and capecitabine or hyperthermic intraperitoneal perfusion chemotherapy combined operation and capecitabine were enrolled to identify the effect of hyperthermic intraperitoneal perfusion chemotherapy on stage III GBC.

Due to the complexity of GBC surgery, the general operation time is long, so intraoperative hypothermia is prone to occur. Compared with the control group, hyperthermic intraperitoneal perfusion chemotherapy has corrected the hypothermia caused by long-term surgery to a certain extent and promoted body temperature recovery. Cisplatin applied to hyperthermic intraperitoneal perfusion chemotherapy did not cause significant liver and kidney damage. After hyperthermic intraperitoneal perfusion chemotherapy treatment, there were no serious surgical-related complications such as hepatic wound bleeding, bile leakage, and anastomotic leakage. Also, there was no difference in the incidence of postoperative complications between the two groups (8).

Cytoreductive surgery/hyperthermic intraperitoneal perfusion chemotherapy is associated with improved cancer survival but an increased risk of infection in patients predominantly for colorectal cancer and pseudomyxoma peritonei. The overall infection rate is 43%, and the most common site of infection is surgical site infection accounting for 27% (27).

Hundal and Shaffer (28) stated that the 5-year survival rates were 8% for stage IIIa and 7% for stage IIIb. Mao et al. (29) showed that the median survival time of patients with advanced GBC was less than one year. The study of advanced cholangiocarcinoma with the value of adjuvant chemotherapy after surgery revealed that the median overall survival of stage III cholangiocarcinoma was about 20 months (30).

Therefore, radical surgery combined with postoperative capecitabine chemotherapy is one of the standard treatments for stage III GBC. Consequently, combined with hyperthermic intraperitoneal perfusion chemotherapy can effectively prolong survival time without increasing surgery-related complications.

Study limitations

This systematic review could not include any randomized controlled trials. In the included retrospective studies, there is always a risk for selection bias, mainly favoring the more extensive treatments, performed on the fittest patients in each subgroup or in the most experienced centers. Moreover, since all studies included in the present systematic review were either retrospective or prospective cohort studies there was an obvious risk for selection bias, more pronounced in more advanced stages. Especially for major interventions, there was a risk for confounding by indication with more extensive surgery in cases with large tumor burden.

Conclusion

Hyperthermic intraperitoneal perfusion chemotherapy combined with radical surgery and capecitabine on stage III gallbladder cancer could increase survival benefits without increasing surgery-related complications.

At tumor stage II GBC, radical resection is the most effective surgical therapy. However, the effect of radical resection at advanced stages could be restricted. Advanced tumor stages, high levels of CA199, and tumor location in

gallbladder body or neck would indicate a poor prognosis. Compared with aggressive resection, palliative surgery groups would have a significantly worse prognosis. The overall survival for GBC mainly depends on the stages of detected tumor; however, aggressive surgery could be the reasonable surgical therapy for patients with GBC, especially, and radical resection could be a most effective surgical strategy for patients with tumor at stage II to obtain a long-term survival. The role of radical resection in advanced stages is restricted, but, in early stages, the utilization of radical surgery should be further developed.

Hepatopancreaticobiliary malignancies with pancreatic adenocarcinoma have poor survival with current palliative systemic therapies. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy may offer a survival benefit for hepatocellular carcinoma with pancreatic adenocarcinoma. However, there does not appear to be any benefit for pancreaticobiliary malignancies.

Most T1b GBCs spread only locally. As pre-operative diagnosis, including tumor penetration of T1b GBC, is difficult, the decision of radical resection is justified. Radical resection may not be essential after simple cholecystectomy provided that the depth of invasion is restricted to the muscular layer and that surgical margins are uninvolved.

Therefore, optimal treatment of GBC is still evolving. Radical surgery in combination with standardized lymph node dissection constitute the cornerstone of the surgical treatment. Overall survival of patients with GBC depends upon tumor stage, levels of CA199, and tumor location in gallbladder. GBC should be rap idly managed.

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Shared Decision-Making and its Impact on Medication Adherence among Hypertensive Patients in Northern Saudi Arabia

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Abstract

Aim: To determine hypertensive patients' and primary healthcare physicians' attitudes toward shared decision-making, and to assess medication adherence among hypertensive patients.

Methods: Following an analytical cross-sectional design, the study included 66 primary healthcare physicians and 209 hypertensive patients attending chronic disease clinics in primary healthcare centers and hospitals in Al-Jouf Region, Saudi Arabia during the period from October 2020 to April 2021.

Results: Out of 209 patients, 145 (69.4%) were males, with mean age 58.0±12.1 years. Out of 66 physicians, 48 (72.7%) were residents or general practitioners and 18 (27.3%) were specialists or consultants. The mean score of medication adherence was 28.8±5.0, indicating good adherence. The mean shared decision-making (SDM) score was 25.3±8.8 for patients indicating medium level of perceived SDM, and for physicians 34.7±7.5, indicating good level of perceived SDM among physicians and a significantly less SDM among hypertensive patients. There was no significant correlation between SDM and adherence scores of sampled patients. SDM was significantly affected by age and educational level of patients (p=0.037 and p=0.012, respectively), and correlated significantly with patients' frequency of daily medication intake (p=0.009). Physicians' SDM is significantly lower among specialists and consultants (P=0.036).

Conclusions: Grade of medication adherence among hypertensive patients in Al-Jouf is good. However, the extent of their SDM is significantly less than that of physicians. Physicians' SDM is significantly lower among specialists and consultants, while SDM is significantly affected by age and educational level of hypertensive patients, in addition to the frequency of daily medication intake. Therefore, SDM should be increasingly encouraged among patients for all their healthcare choices.

Key words: Shared decision-making (SDM), Medication adherence, Hypertension, Saudi Arabia.

Introduction

Shared decision-making (SDM) is defined as the process developed to promote attitude toward therapeutic choices and achieving good adherence/compliance to the treatment plan (1). Patients' choice and satisfaction level can be assessed in multiple methods. Currently, there is an observed growing interest in SDM, where it represents a transfer from paternalism (depending on the physician in all sessions) to a more collaborative pattern of health care (more equal physician-patient relationship) (2). SDM builds on three principles, i.e., having information interchange between the patient and theirhis physician, choosing diagnostic and therapeutic choices, and achieving an agreement (3-7).

It has been found that the main reason for patients' dissatisfaction is being not sufficiently informed about their health problems and treatment options. A survey done in eight European countries revealed that the majority of the patients wanted to have more information about their health situation to assist them in their participation in the decision-making process, even with the diversity of their assumptions regarding their involvement in the process. However, participant patients preferred the paternalism pattern more in Spain and Poland than in Switzerland and Germany. Moreover, younger patients were more likely to prefer patient-based communications and decision-making than older patientones. However, SDM remains a big challenge facing physicians, with little evidence on its influence, even with the huge efforts done to encourage its use. (8).

The Saudi Commission for Health Specialties in its curriculum for Family Medicine training program encourages SDM in several positions, including communication skills and calls for the adoption of this doctrine in models of health care. However, since there is no national study regarding the utilization of SDM and its impact on medication compliance, we conducted this study aiming to determine hypertensive patients' and primary healthcare physicians' attitudes toward shared decision-making, and to assess medication adherence among hypertensive patients.

Materials and Methods

The present study followed an analytical cross-sectional design. The study populations comprised healthcare physicians working within Al-Jouf Health Directorate and hypertensive patients attending 16 chronic disease clinics at primary healthcare centers and hospitals in Al-Jouf Region, Saudi Arabia. The study was conducted during the period from October 2020 until April 2021.

The sample size was calculated according to Dahiru et al. (9); assuming that 50% of patients prefer SDM, 95% confidence level, and 7% margin of error, the estimated minimum sample size was 196 patients. Based on a one-to-four ratio of physicians-to-patients yielded a sample size of 66 for treating physicians. A simple random sampling technique was followed to fulfill the necessary sample size.

Inclusion Criterion:
The study included healthcare physicians working at primary health care centers or secondary care hospitals in Al-Jouf Region for at least one year. The study also included patients with the diagnosis of hypertension since at least one year and receiving their pharmacotherapy from the Chronic Diseases Clinics in primary health care centers or secondary hospitals in the Al-Jouf Region.

Data collection tool and procedure:
The study protocol was approved by the local Ethical Review Committee of Qurayat Region (Reg No: H-13-S-071). We started data collection after obtaining the ethical clearance and the approval from the Directorate of Health Affairs in Al-Jouf. The study was completely self-funded by the researchers, and there was no conflict of interests.

The data collection tools included the following questionnaires:
1. The 9-item Shared Decision-Making Questionnaire (SDM-Q-9, physician and patient versions) (10): This questionnaire consists of 9 statements, which are rated on a 6-point scale from "completely disagree" (0) to "completely agree" (5). Summing up all items leads to a raw total score between 0 and 45. The SDM-Q-9 is a reliable, brief and well accepted instrument. Facing the increasing interest in patient involvement in clinical decision making, the instrument may be used as a quality indicator in quality assurance programs and health services research. All items showed an acceptance above 80%, and corrected item-total correlations between 0.685 and 0.826. Internal consistency yielded a Cronbach's α of 0.938.
2. The Arabic version of General Medication Adherence Scale (11): The Arabic version achieved all required statistical parameters and was validated in Saudi patients with chronic diseases. It is an 11-item self-reporting adherence measure. Each item has 4 outcomes and awards an adherence score. The total score that could be achieved is 33. Sum of all items yields a final score that is interpreted in various levels of adherence; high (30–33), good (27–29), partial (17–26), low (11–16), and poor (<10). It has 78.16% sensitivity, 76.85% specificity and the accuracy of the tool is 77.66% (12).

Before distributing the questionnaires sheets at the study settings, participants fulfilling the inclusion criteria were greeted by the research team and were clearly informed about the objectives of the study. Then, they were assured that, in case they accept to participate in the study, their responses would be completely anonymous, their participation is optional, they can discontinue their participation whenever they want, and they can refuse to respond to any question without resulting in a breach of their right or loss of any benefit provided through the health facility. Moreover, the research team ensured that collected data would be treated confidentially and will not be used for any other purposes other than achieving the objectives of this research.

Data Analysis:
Collected data were entered and analyzed using the Statistical Package for Social Sciences (IBM, SPSS version 25). Descriptive statistics were presented as frequencies and percentages for qualitative data, or as means and standard deviations for quantitative variables. The appropriate tests of significance were applied (i.e., independent samples t-test, Pearson's correlation, and Regression analysis). P-values less than 0.05 were considered as statistically significant.

Results

Table (1) shows that, out of 209 hypertensive patients, 145 (69.4%) were males. Patients' mean age was 58.0±12.1 years. Most patients (87.6%) were Saudi. The mean duration since diagnosis of hypertension was 8.4±6.4 years. Most patients (89%) were married, 44% were school educated, while 28.7% were university educated. About one-quarter of patients (25.8%) were employed, and 20.1% were not employed, while 22% were smokers. About three-quarters of patients (74.6%) had associated comorbidities, other than hypertension. The mean duration since diagnosis of hypertension was 8.4±6.4 years. More than half of patients (57.9%) take on daily anti-hypertension medication, 37.3% take two medications, while 4.8% take three medications or more. The dose of anti-hypertension daily medications is once among 68.9% of patients, while 30.1% take their medications twice, and only 1% take their medications three times or more.

Figure (1) shows that most patients (56%) had high medication adherence, 11.5% had good medication adherence, 29.7% had partial medication adherence, while 2.9% had low medication adherence.

Table (2) shows that the overall mean score of medication adherence was 28.8±5.0, with 15.4±3.1 attributed their behavior as related to non-adherence, 7.7±1.7 attributed it to additional disease and pill burden, and 5.6±0.9 attributed to cost related non-adherence.

Table (3) shows that 72.7% of physicians were residents or general practitioners, while 27.3% were specialists or consultants. The specialty of most physicians was Family Medicine (77.3%), 13.6% were general practitioners, while other specialties constituted 9.1%. Place of work of 43.9% was Al-Jouf City, while 31.8% of physicians worked in Sakaka City, and 24.2% worked in Dawmat Al-Jandal City.

Table (4) shows that patients' shared decision-making mean score was significantly lower than that of primary care physicians (25.3±8.8 vs. 34.7±7.5, respectively, $p<0.001$).

Table (5) shows that physicians' shared decision-making mean scores were significantly higher among residents/general practitioners than specialist/consultants (35.9±5.1 vs. 31.6±11.3, respectively, $p=0.036$). However, their shared decision-making scores did not differ significantly according to their specialty or place of work.
Table (6) shows a significant correlation between shared decision-making scores and frequency of daily medication intake ($p=0.009$), while the correlation with medication adherence scores, number of received medications, and time since diagnosis of hypertension were not statistically significant.

Table (7) shows that patients' shared decision-making is significantly affected by their age ($p=0.037$) and their educational status ($p=0.012$).

Table 1: Personal characteristics of participant hypertensive patients (n=209)

Personal characteristics	No.	%
Gender		
• Male	145	69.4
• Female	64	30.6
Age (Mean±SD)	58.0±12.1 years	
Nationality		
• Saudi	183	87.6
• Non-Saudi	26	12.4
Marital status		
• Single	2	1.0
• Married	186	89.0
• Divorced/widow	21	10.0
Educational status		
• Illiterate	57	27.3
• School level	92	44.0
• University graduate	60	28.7
Employment status		
• Unemployed/housewife	42	20.1
• Employed	54	25.8
• Retired	76	36.4
• Others	37	17.7
Current smoking status		
• Non-smoker	163	78.0
• Smoker	46	22.0
Associated comorbidity	156	74.6
Duration since diagnosis of hypertension (Mean±SD)	8.4±6.4 years	
No. of daily received anti-hypertension medications		
• 1	121	57.9
• 2	78	37.3
• 3+	10	4.8
Daily dose of anti-hypertension medications		
• Once	144	68.9
• Twice	63	30.1
• Three times or more	2	1.0

Figure 1: Patients' grades of medication adherence

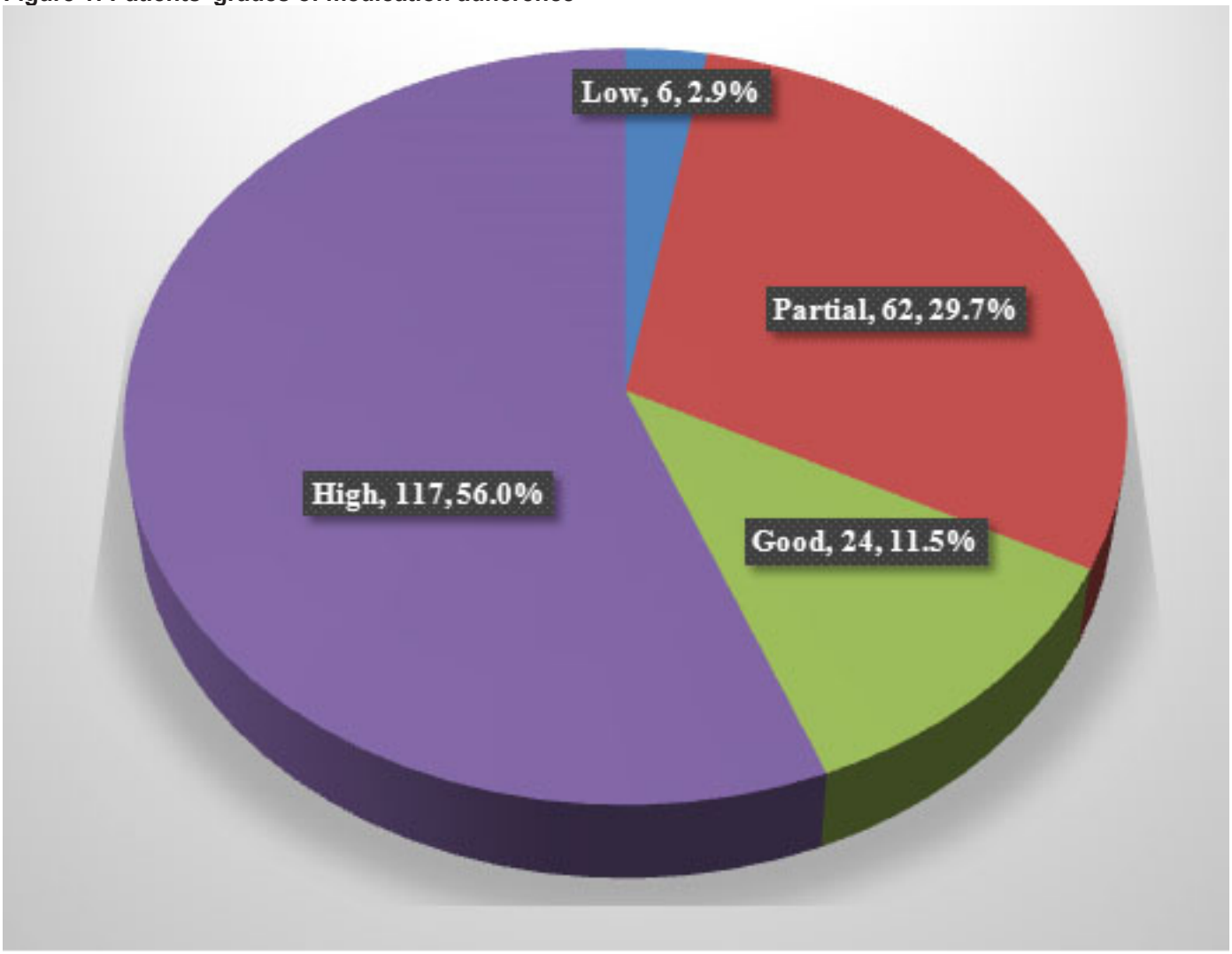

Table 2: Patients' mean scores for medication adherence (n=209)

Medication Adherence Items	Mean	SD
Patient's behavior related non-adherence	15.4	3.1
Additional disease and pill burden	7.7	1.7
Cost related non-adherence	5.6	0.9
Overall medication adherence	28.8	5.0

Table 3: Characteristics of participant physicians (n=66)

Characteristics	No.	%
Position		
• Resident/General practitioner	48	72.7
• Specialist/Consultant	18	27.3
Specialty		
• Family Medicine	51	77.3
• General practice	9	13.6
• Others	6	9.1
Place of work		
• Al-Jouf City	29	43.9
• Sakaka City	21	31.8
• Dawmat Al-Jandal City	16	24.2
Shared decision-making score (Mean±SD)	34.7±7.5	

Table 4: Comparison between hypertensive patients' and primary care physicians' shared decision-making mean scores

Participants	No.	Mean	SD
Patients' shared decision-making score	209	25.3	8.8
Physicians' shared decision-making score	66	34.7	7.5
t-value	7.82		
P-value	<0.001†		

† Statistically significant

Table 5: Physicians' shared decision-making mean scores according to their characteristics

Characteristics	No.	Mean	SD	P-value
Position				
• Resident/General practitioner	48	35.9	5.1	
• Specialist/Consultant	18	31.6	11.3	0.036†
Specialty				
• Family Medicine	51	35.0	7.5	
• General practice	9	35.3	7.2	
• Others	6	31.7	8.2	0.091
Place of work				
• Al-Jouf City	29	33.6	9.2	
• Sakaka City	21	36.0	5.1	
• Dawmat Al-Jandal City	16	35.3	6.7	0.507

† Statistically significant

Table 6: Correlations between shared-decision making and adherence scores of sampled patients (n=209)

Variables	r	p-value
Overall medication adherence score	0.089	0.202
Number of received medications	0.062	0.374
Frequency of daily medication intake	0.181	0.009†
Time since diagnosis of hypertension	-0.027	0.696

† Statistically significant

Table 7: Regression analysis for patients' shared decision making and their characteristics

Patients' Characteristics	Unstandardized Coefficients		Standardized Coefficients	T	P
	B	SE	Beta	Value	Value
Age	-0.126	0.060	-0.174	-2.101	0.037†
Marital status	-0.901	1.070	-0.063	-0.842	0.401
Educational status	2.152	0.851	0.184	2.527	0.012†
Employment	-0.252	0.626	-0.029	-0.403	0.687
Smoking	1.755	1.460	0.083	1.202	0.231
Duration since diagnosis	0.170	0.106	0.123	1.607	0.110
General medication adherence scale	1.041	0.623	0.115	1.671	0.096
Constant	27.585	4.236	---	6.512	0.000

† Statistically significant

Discussion

This study aimed to determine hypertensive patients' and primary healthcare physicians' attitudes toward shared decision-making, and to assess medication adherence among hypertensive patients.

Findings of the present study revealed that hypertensive patients' SDM mean score was significantly lower than that of their physicians (25.3±8.8 vs. 34.7±7.5, respectively, p<0.001). This indicates that our patients tend to prefer the paternalistic SDM, although their physicians have higher preference toward SDM. Moreover, physicians' SDM was significantly less among specialists and consultants.

Coulter et al. (3) stated that, in patient centered medical practice, one of the most important and vital components is the effective and dynamic communication between health professionals and their patients. Therefore, SDM has been developed to minimize the doubt in the medical community about the most suitable way of treatment for some cases. Globally, this was joined by the growing trend on patient-centered care, leading to the belief that patient's preferences, not physician's preferences, should determine disease management.

Johnson et al. (13) added that SDM and creating a management and treatment alliance for more harmony raise the engagement of the patients in healthcare decisions and permit a communication and open exchange between the physician and the patient. Regardless of the evolutionary varieties, the pattern characterized for reaching harmony in consultations is the same as the one that has been characterized for SDM.

Schoenthaler et al. (14) noted that healthcare professionals and patients should have equal partnership, and share their information, knowledge and experiences with each other so that comprehension and realization can be achieved, and a decision about management and treatment of the disease can be made.

It has been noted that, compared with cancer, the literature on SDM in hypertension is more inadequate. This may be due to the fact that hypertension treatment is active and regularly contains a series of decisions made over months or years (i.e., a long time), whereas some cancer-related decisions are disconnected and made within weeks or months (i.e., a short time) (15-16).

Olomu et al. (17) assessed the effect of SDM intervention on controlling blood pressure among 243 patients selected from two federally qualified health centers in Michigan, USA. They found that controlling blood pressure was greater at six months for patients in the intervention group compared with the control group.

The current study showed a significant correlation between SDM and frequency of daily medication intake, but there was non-significant correlation between patients' overall adherence scores and SDM scores. Moreover, results of the present study revealed significant impact of patients' older age and higher educational status on SDM. These findings reflect less SDM among younger and less educated hypertensive patients.

Similar results were reported by Mead et al. (15), who noted that SDM comprises two techniques to provide information (medical and personal) between the physician and the patient regarding all the available choices. Therefore, older and well-educated patients are expected to show higher SDM. Generally, less SDM was reported by these groups of patients during consultations.

The current study had some limitations, including the subjective nature of the study, and the limited geographical setting, covering only three cities in one region. In addition, the followed cross-sectional study design is only good for hypothesis generation, rather than hypothesis testing. All these points limit the generalizability of our results to the whole Saudi community.

Conclusions

Grade of medication adherence among hypertensive patients in Al-Jouf is good. However, the extent of their shared decision-making is significantly less than that of their primary healthcare physicians. Physicians' SDM is significantly lower among specialists and consultants, while SDM is significantly affected by age and educational level of hypertensive patients, in addition to the frequency of daily medication intake. Therefore, SDM should be increasingly encouraged among patients for all their healthcare choices.

Further nationwide studies, in regions other than Al-Jouf, on the assessment of the impact of SDM on medications adherence and associated factors need to be conducted. Also, the Saudi Ministry of Health should organize public awareness campaigns on SDM.

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