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Researchers in health sciences will find much of great use and interest in the Health Sci. Q.

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ORIGINAL ARTICLE

The effects of monocyte/high-density lipoprotein ratio on hospital stay in patients with mild acute pancreatitis

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Abstract

In this study, we aimed to evaluate the effect of monocyte/high-density lipoprotein (MHR), which is associated with systemic inflammation: on prolonged hospitalization in patients with mild acute pancreatitis. Patients hospitalized for acute edematous pancreatitis between 01.01.2021 and 31.12.2021 were retrospectively screened. Arrival Ranson scores of the patients were calculated. Those with a Ranson score <3 were considered as mild acute pancreatitis and were included in the study. Patients with mild acute pancreatitis were divided into 2 groups with a hospital stay of <8 days and ≥8 days. Monocyte/HDL, biochemical and metabolic parameters were compared between the groups. The study was conducted with a total of 39 patients, 23 male (59%) and 16 female (41%). While 28 (71.8%) of the patients were discharged within <8 days, 11 (28.2%) were hospitalized for ≥8 days. Group ≥8 days was considered as prolonged hospitalization. It was determined that the monocyte/HDL ratio was significantly higher in the group with prolonged hospitalization between the groups. In univariate analyzes, it was determined that the presence of Diabetes Mellitus and MHR increased the risk of prolonged hospitalization by 5.25 times and 1.085 times, respectively. In the multivariate analysis of these two parameters, MHR was found to be an independent risk factor for prolonged hospitalization. It was concluded that monocyte/HDL can be used as a simple and reliable parameter to predict the duration of hospitalization in patients with mild acute pancreatitis.

Keywords: Acute pancreatitis, monocyte/high-density lipoprotein ratio, prolonged hospital stay

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Introduction

Acute pancreatitis progresses with cellular damage and inflammation of the pancreas; It is a condition that can lead to local and systemic complications. It can be in a self-limiting mild edematous form; It can show a wide clinical course from severe form with multi-organ involvement that can lead to local and systemic complications [1]. Predicting the severity of acute pancreatitis and the prognosis of the disease contributes to the reduction of disease-related morbidity and mortality. Many scoring systems such as Ranson, APACHE II, Balthazar, Glasgow are used to determine the severity of acute pancreatitis. Ranson scoring is one of the important scoring methods that has been used for many years and gives information about the mortality rate [2].

Monocytes are cells that have an important role in cytokine synthesis. High-density lipoprotein (HDL) has an anti-inflammatory and antioxidant effect and has the effect of protecting the endothelium. The monocyte/HDL ratio has been widely used in recent years and has been shown as a new marker of inflammation(3).

Average length of stay in hospital in acute pancreatitis; It was determined as 4 days in mild severe forms and 9 days in severe pancreatitis [4]. Hospitalizations of 8 days or more are considered as prolonged hospitalization. In previous studies, the effects of diuretic, Angiotensin converting enzyme inhibitor (ACE) / Angiotensin receptor blocker (ARB) use, congestive heart failure, creatinine elevation, and fluid replacement given in the emergency department on the duration of hospitalization in patients with acute pancreatitis were investigated [5,6335 were included in the analysis. Baseline characteristics, determined by vital signs and laboratory parameters, were similar between the short and long hospitalization groups. However, the long hospitalization group received more intravenous crystalloid in the ED, and this group used more diuretics and more angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker (ACEI/ARB]. There is no study evaluating the effect of monocyte/HDL, which is shown as a new inflammation marker in the literature, on the duration of hospitalization in acute pancreatitis. The aim of this study is to evaluate the effect of monocyte/HDL on prolonged hospitalization in acute pancreatitis.

Materials and Methods

Patients hospitalized with acute edematous pancreatitis between 01.01.2021-31.12.2021 in Afyonkarahisar Health Sciences University Faculty of Medicine Hospital Internal Diseases Clinic were retrospectively scanned from the hospital electronic file system. Hospitalization Ranson score of these patients; age >70 years, white blood cell (WBC) >18000 mm^3, glucose >220 mg/dL, lactate dehydrogenase (LDH) >400 U/L, aspartate aminotransferase (AST) >250 U/L parameters. Patients with a Ranson score below 3 were considered as mild pancreatitis and were included in the study. The patients included in the study were divided into two groups with a hospital stay of <8 days and ≥8 days. Monocyte/HDL and other parameters were compared between these two groups.

Statistical Analysis

SPSS 26.0 package program was used for statistical analysis. Categorical variables were presented as percentages and frequencies. Continuous variables were expressed as mean±standard deviation. Conformity of continuous variables to normal distribution was checked with the Kolmogorov Smirnov test. Chi-square test was used to compare categorical variables between groups. Continuous variables were compared with Mann Whitney U test or independent sample t test. Logistic regression analysis was used to identify risk factors for prolonged hospitalization. Parameters with significant differences between groups and parameters with $p<0.2$ in comparison between groups were included in the logistic regression. Parameters found to be risk factors for prolonged hospitalization in univariate logistic regression analysis were included in the multivariate analysis. All the p values presented were bidirectional and the values with $p<0.05$ were expressed as statistically significant.

This study was carried out according to the decision of Afyonkarahisar Health Sciences University Clinical Research Ethics Committee

dated 04.02.2022 and numbered 2022/85.

Results

The study was conducted with a total of 39 patients, 23 male (59%) and 16 female (41%). The mean age of the study group was 53.1±20.2 years. While 28 (71.8%) of the patients were discharged within <8 days, 11 (28.2%) were hospitalized for ≥8 days. When the groups were compared in terms of demographic characteristics, comorbidities and the drugs they used, it was found that diabetes was significantly more common in patients with prolonged hospitalization. The general characteristics of the patients, their comorbidities and the comparison of the drugs they use are presented in Table 1.

When the groups were compared in terms of laboratory parameters, it was found that leukocytosis was more prominent in the group with prolonged hospitalization and the monocyte/HDL cholesterol ratio was found to be significantly higher. Comparisons of the patients in terms of laboratory parameters are presented in Table 2.

In the univariate analyzes, it was found that the presence of DM and MHR increased the risk of prolonged hospitalization by 5.25 times and 1.085 times, respectively. In the multivariate analysis of these two parameters, MHR was found to be an independent risk factor for prolonged hospitalization. Table 3 shows the regression analysis to identify risk factors for prolonged hospitalization.

Discussion

Acute pancreatitis; it is one of the major reasons for hospitalization. With the various scoring systems used, the disease is classified according to its severity (mild, moderate, severe) and information about the prognosis can be obtained. In a community-based study in England, the average hospital stay for mild pancreatitis was found to be 4 days [4]. In some mild pancreatitis, this length of stay is much longer (≥8 days). The factors causing prolonged hospitalization in patients with mild pancreatitis have been tried to be revealed by previous studies. In this study, we aimed to investigate the effect of monocyte/HDL, which is used as a new generation inflammation

Table 1. Comparison of the patients' characteristics, comorbidities and the drugs they use.

Feature	Total (n= 39)	<8 days (n= 28)	≥8 days (n= 11)	*p*
Age (mean±SD)	53,1±20,2	50,1±20,6	60,7±17,7	0,143
Male gender (%-n)	59-23	57,1-16	63,6-7	1*
Ranson (mean±SD)	1±1,05	0,86±1,04	1,36±1,03	0,137
Diabetes mellitus (%-n)	35,9-14	25-7	63,6-7	**0,033***
Hypertension (%-n)	38,5-15	39,3-11	36,4-4	1*
Coronary artery disease (%-n)	10,3-4	7,1-2	18,2-2	0,562*
Heart failure (%-n)	7,7-3	3,6-1	18,2-2	0,187*
Chronic renal failure (%-n)	5,1-2	0	18,2-2	0,074*
ACE inhibitor (%-n)	20,5-8	14,3-4	36,4-4	0,188*
ARB (%-n)	7,7-3	10,7-3	0	0,545*
Diuretic (%-n)	23,1-9	17,9-5	36,4-4	0,238*
Calcium channel blocker (%-n)	20,5-8	21,4-6	18,2-2	1*
Metformin	17,9-7	14,3-4	27,3-3	0,379*
DPP-4 inhibitor (%-n)	10,3-4	10,7-3	9,1-1	1*
Insulin (%-n)	17,9-7	10,7-3	36,4-4	0,083*
Acetyl salicylic acid (%-n)	12,8-5	7,1-2	27,3-3	0,125

*Fisher's exact test

marker, on prolonged hospitalization in patients with mild pancreatitis.

Harkirat et al. In an article in which they evaluated the factors affecting prolonged hospitalization in patients with mild pancreatitis; prolonged hospitalization was observed in 20% of the patient group. Again, in this study, the effect of age, gender, and comorbidities of the patients on prolonged hospitalization could not be demonstrated. The most important risk factor for prolonged hospitalization has been shown to be persistence of pancreatitis-related symptoms and oral intolerance [6a subset of mild acute pancreatitis (AP]. In 11 (28%) of 39 patients in our study, hospitalization was prolonged and, similar to this study, the comorbidities of the patients were found to be similar between both

Table 2. Comparison of the patients in terms of laboratory parameters.

Parameter	Total (n= 39)	<8 days (n= 28)	≥8 days (n= 11)	*p*
Leukocytes (x109/uL)	11520±4260	11170±4013	12241±4929	**0,031**
Hemoglobin (gr/dL)	14,08±1,94	14,31±1,72	13,6±2,36	0,432
Platelets (x109/uL)	225,83±69,6	222,1±57,1	233,4±93,8	0,747
Amylase (U/L)	629,3±639,5	660,3±687,8	567,3±568,8	0,612
Lipase (U/L)	1455,8±2126,6	1610,7±2520,4	1146±1040,4	0,433
BUN (mg/dL)	18,27±26,3	18,86±32,1	17,1±7,6	0,567
AST (U/L)	79,9±222,3	105,6±271,2	28,6±16,2	0,842
Lactate dehydrogenase (U/L)	347,5±245,8	377,7±286,6	287,1±112,2	0,701
Calcium (mg/dL)	8,84±0,46	8,84±0,5	8,85±0,3	0,346
Glucose (mg/dL)	133,2±56,1	120,5±45,3	158,3±69,8	0,221
CRP (mg/L)	10,6±19,77	12,7±23,8	8,41±5,8	0,483
Absolute monocytes (x109/uL)	832,5±34,6	702,5±26,6	1092,5±355,2	**<0,001**
HDL cholesterol (mg/dL)	35,52±13,7	36,1±12,3	34,56±16,9	0,958
Monocyte/HDL ratio	26,73±15,2	21,28±10,9	37,63±17,1	**0,001**

Table 3. The results of the regression analysis performed to determine the risk factors for prolonged hospitalization.

	Univariate analysis		Multivariate analysis	
Parameter	RR (%95 GA)	*p*	RR (%95 GA)	*p*
Age	1,028 (0,990-1,067)	0,146		
Ranson	1,588 (0,809-3,119)	0,179		
DM	5,250 (1,175-23,457)	**0,03**	3,896 (0,639-23,766)	0,141
Heart failure	6,000 (0,485-74,289)	0,163		
KRF	50,2 (0-502,592)	0,999		
ACE inh.	3,429 (0,677-17,353)	0,136		
Insulin	4,762 (0,856-26,476)	0,075		
ASA	4,875 (0,689-34,499)	0,113		
Monocyte/HDL	1,085 (1,019-1,157)	**0,011**	1,082 (1,012-1,158)	**0,021**

DM: diyabetes mellitus, KRF: chronic renal failure ACE inh.: anjiyotensin converting enzym inhibitörs, ASA:acethylsalicylic acid

patient groups. Although it differed between diabetes patient groups, it was not found to be an independent risk factor in multivariate analysis.

In a study by Koçkan et al. investigating the determinants of prolonged hospitalization in patients with mild to moderate pancreatitis who applied to the emergency department, the use of diuretics was found to be higher in the group hospitalized long. Liver function tests and electrolytes were similar in both groups [5335 were included in the analysis. Baseline characteristics, determined by vital signs and laboratory parameters, were similar between the short and long hospitalization groups. However, the long hospitalization group received more intravenous crystalloid in the ED, and this group used more diuretics and more angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker (ACEI/ARB]. Unlike in our study, no effect of diuretic use on hospital stay was observed. Similar to this study, liver function tests and electrolytes were similar between the two groups.

In recent years, many articles aiming to show the relationship between hematological inflammation parameters and the severity of acute pancreatitis have been published [7,8]. Kaya et al. in a study conducted by 418 acute pancreatitis patients admitted to the emergency department were evaluated. In this study, the Ranson score and the platelet lymphocyte ratio (PLR) ratio at the time of admission to the emergency department were compared and it was shown that PLR is an independent factor in predicting the severity of the disease [7]. Han et al. in a study conducted by; A positive correlation was found between the neutrophil lymphocyte ratio (NLR), another inflammation parameter, and Ranson criteria [9and theirs utility for predicting severity of AP was evaluated by receiver operator characteristic (ROC]. In a study by Önmez et al., NLR was shown to be an independent risk factor in showing the severity of acute pancreatitis [8].

Monocyte/HDL is one of the new inflammation parameters frequently used in recent years [3]. In many previous studies, it can be a marker of inflammation and oxidative stress; it has been shown to be closely related to the presence and prognosis of some cardiovascular diseases [10,11]. In our study, in the patient group with prolonged hospitalization; monocyte/HDL was found to be statistically higher than the other group. In the regression analysis, it was seen that monocyte/HDL is an independent risk factor over the length of hospital stay in acute pancreatitis. This can be explained by the fact that monocytes play an active role in inflammation, an increase in the number of monocytes is expected, and HDL is an antioxidant type of cholesterol. Peng et al. in a study in which they measured HDL and apolipoprotein A-1 levels in patients with severe acute pancreatitis, they found that HDL level showed an inverse correlation with the severity of pancreatitis. In the same study, HDL was also shown to be low in patients with organ damage in acute pancreatitis [12]. In our study, HDL levels were similar between groups. This situation can be explained by mild pancreatitis in both groups.

The retrospective planning of our study, the small number of patients, and the evaluation of pancreatitis severity only by Ranson score are among the limitations of our study.

Conclusion

In conclusion, in mild acute pancreatitis, Monocyte/HDL may be helpful in predicting the length of stay in the hospital. There is a need for comprehensive prospective studies with more patient participation on this subject.

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Conflict of Interest

No potential conflict of interest was reported by the authors.

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ORIGINAL ARTICLE

The usability of telephone-based telemedicine in primary healthcare: A quantitative evaluation and a hypothesized framework of determinants from the physicians' perspective in Oman

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Abstract

Telemedicine has been appreciated as a smart solution to bridge the gaps in the delivery and coverage of healthcare worldwide. With the great impetus to integrate this service into primary healthcare facilities, evaluating its usability should be an ongoing process. This study aimed to quantitatively evaluate the usability of telemedicine from the primary healthcare physicians' perspective in Oman. The evaluation was conducted using a cross-sectional study design. A self-administered online questionnaire was developed and validated as a scale to evaluate the usability of telemedicine as a safe and useful communication channel and outpatient record. Following a pilot study, the questionnaire was distributed to a sample of primary healthcare physicians who ran telemedicine clinics in Oman during 2020-2022. The questionnaire was completed by 143 primary healthcare physicians from different governorates. The total mean scale and subscale scores were computed. In addition, the frequency distribution of responses to each question was presented. The results showed that the total mean scale score of the usability of telemedicine in our clinics was 3.43/5.00. The subscale scores of the usability of telemedicine as a safe and useful service, the usability of telemedicine as a communication channel, and the usability of telemedicine as an outpatient record were 3.42/5.00, 3.23/5.00, and 3.99/5.00, respectively. In conclusion, the current telemedicine service in Oman's primary healthcare facilities has some usability features, but there is still much room for improvement. With logical reasoning, a framework of potential determinants was inferred and proposed to improve the usability of telemedicine services in the future and comply with the principles of biomedical ethics.

Keywords: Oman, physicians, primary healthcare, scale, telemedicine usability, usability determinants

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Introduction

The hopeful promise of the growing field of information and communication technology (ICT) has been recently appreciated as a smart solution to bridge the gaps in healthcare delivery and coverage. Accordingly, the WHO has greatly advocated and supported telemedicine for the last three decades and frequently iterated this innovation in its resolutions and recommendations [1-5].

In many countries, the implementation of restrictive measures that reduced people's social and physical contact and limited their transportation within and between cities to overcome the spread of Coronavirus Disease 19 (COVID-19) was the provoking event that led to the wide adoption of telemedicine as a structured healthcare service [6-8]. The situation in the Sultanate of Oman was not different [9-12]. Despite the growing impetus to widely integrate telemedicine in primary healthcare (PHC) facilities, this service – in its various forms – may not be used by all healthcare providers. Although it may not be an example of state-of-the-art telemedicine [13], telephone-based consultations may be the most appropriate form in many places where advanced forms of telemedicine are not feasible [3,4,14] or physicians and patients (especially females) have reservations about using audiovisual calls [15,16]. In May 2020, shortly after implementing restrictive measures to contain the spread of COVID-19 in Oman, Hasani et al. conducted a qualitative study to explore the perception of twenty-two PHC physicians on implementing telephone-based consultation in Muscat, the capital governorate of Oman [12]. The researchers found that although PHC physicians appreciated some of the telemedicine benefits, most showed concerns about the infrastructure, the technical and financial support, the patient-physician interaction, and the privacy and confidentiality of communication. Though not stated by the researchers, those perceptions imply that the usefulness of a health service does not guarantee its use. In other words, the usefulness is necessary but not sufficient to define the usability of a service [17].

The usability of service, though it has many definitions [17-20], is mainly determined by the extent to which specified users can completely and accurately achieve their goals or tasks (*i.e.*, effectiveness) in a reasonable time (*i.e.*, efficiency) without any discomfort (*i.e.*, satisfaction) in a specified context of use [21]. The overarching principle for any definition of usability, however, is the user-centered design approach in which the end-users are put at the center of the design process, and their needs, preferences, expectations, and constraints are taken into consideration [17,22]. In other words, this service is expected to be usable if it helps physicians contact and manage their patients effectively, efficiently, and satisfactorily. However, the usability of a service or a product cannot be directly measured or computed [17-21]. Still, it might be inferred from the responses to validated sets of questions designed to quantify its different aspects or features [17].

With all the above in mind, we find an opportunity to quantitatively evaluate the usability of our current telemedicine service in PHC facilities from the physicians' perspective at a national level using a newly developed and validated scale. In addition to providing a quantitative measure of telemedicine usability that can be compared at different times and places, the responses to the constituting questions uncover the proportion of physicians who have concerns about the current telemedicine service or encounter difficulties while running telemedicine clinics. Such an evaluation should raise decision-makers' awareness of the existing gaps in service provision and address the potential features to improve in the future.

Materials and Methods

A research proposal was prepared according to Oman's Ministry of Health Research Proposal Guideline, after which an ethical approval (MoH/CSR/21/24835) was issued by the Health Studies and Research Approval Committee at the Ministry of Health on August 12, 2021.

Study Setting

The Sultanate of Oman is a high-income Arab country [23]. It spans an area of approximately 309,500 square kilometers of varying topography

and comprises eleven governorates [24]. By the end of 2021, the total population of Oman was around 4.5 million (62% Omani, 38% Non-Omani), and about 80% of them were living in urban areas [25]. The main healthcare provider in Oman is the Ministry of Health. According to the Oman Ministry of Health, the total number of medical doctors working in Oman was 9058, and the number of medical doctors to 10,000 population was around 20 in 2020 [26]. Out of the total number of medical doctors, 5960 were working in MOH-led facilities, and out of those, 2178 were PHC physicians distributed over 238 PHC facilities led by MOH in 2020 (*i.e.*, MOH-led PHC facilities: 190 health centers, 18 polyclinics, and 30 local hospitals) [26].

Study Design

This cross-sectional study included PHC physicians from different governorates in the Sultanate of Oman to quantitatively evaluate the usability of telemedicine in PHC facilities.

Eligibility Criteria

Participants were considered eligible if they met the inclusion criteria without having any of the exclusion criteria. The inclusion criteria define the broad characteristics that are essential for the selection of participants. On the other hand, the exclusion criteria are the presenting features of the participants who meet the inclusion criteria but might not be accessible or bias the final results [27,28]. Based on these definitions, our inclusion and exclusion criteria were as follow:

Inclusion criteria: PHC physicians running telemedicine clinics in Oman during 2020 – 2022 (*i.e.,* from January 2020 to December 2021).

Exclusion criteria: PHC physicians running telemedicine clinics in Oman during 2020 – 2022 but used audio-visual consultation or working in non-MOH-led PHC facilities.

At the time of the study, nine governorates out of eleven in Oman had implemented telemedicine clinics in MOH-led PHC facilities, and out of 2178 physicians working in those facilities, only 186 (82% were female) were running telemedicine clinics (telephone-based consultation) during 2020 - 2022. Therefore, only 186 PHC physicians were eligible for participation in our study.

Developing a Questionnaire

From our literature review, we identified many questionnaires/scales developed to evaluate the usability of telemedicine [29-37]. However, we found several items in those questionnaires/scales inapplicable or inadequate to evaluate telephone-based consultation. Nevertheless, those questionnaires/scales were acknowledged as invaluable references to build our theoretical concept of usability and spur our questionnaire's development process.

Our questionnaire was developed following some best-practice recommendations for developing a validated scale [38]. Details are provided in a separate paper [39].

Sampling and Sample Size

The sample size calculation was estimated at around 140 participants to suffice the conservative sample size computed by Cochran's formula for proportion estimation from a finite population [40]. The calculated sample size also met the acceptable sample size to validate our questionnaire by exploratory factor analysis (EFA) and covered 75% of the eligible population. However, because of the expected low response rate to self-administered online questionnaires, all 186 PHC physicians who ran telemedicine clinics during 2020 – 2022 were considered for contact and invitation.

Questionnaire Administration

For several reasons, including the difficulty of sending and receiving on-paper questionnaires, the large number of healthcare facilities, and the large area of different governorates, the evaluation was planned to be conducted through a self-administered online questionnaire. Following a pilot study, the questionnaire was administered over two months (from September 2021 to November 2021) to all approached eligible participants. All approached physicians received an official communication and an agreed-on telephone call from the researcher to explain the purpose of the study and take verbal consent to e-mail the physician an information sheet and a link to an online self-administered questionnaire form.

Statistical Analyses

Statistical analyses were conducted with SPSS (Version 23). The distribution of descriptive characteristics of participants is presented as numbers and percentages. The questionnaire's validity and reliability are detailed elsewhere [39]. But in brief, EFA was conducted using FACTOR software (Version 12.01.02) to support the validity of the questionnaire as a summated scale and to identify the questions that can be combined under a common facet (*i.e.,* aspect). The unweighted least squares extraction method was selected because of its suitability for ordinal data with oblique promin rotation to provide more realistic solutions [41,42]. The results of EFA indicated three common facets or factors with very good internal consistency reliability (> 0.8). The first factor was saliently loaded by nine items (*i.e.,* questions) representing the usability of telemedicine as a *Safe and Useful* service. The second factor was saliently loaded by eleven items representing the usability of telemedicine as a *Communication Channel.* The third factor was saliently loaded by four items representing the usability of telemedicine as an *Outpatient Record*. The three facets/factors construct a summated scale named the *SUCCOR* scale (an acronym formed by the initial letters of the constituting facets).

A facet score was computed by summing each participant's responses to that facet's questions, then converted into a (1 – 5) scale by dividing over the number of that facet's questions (*i.e.,* mean subscale score). Similarly, the overall scale was computed by summing the responses to all questions, then converted into a (1 – 5) scale by dividing over the number of all questions to get the mean total scale score [43]. For a more intuitive scale, the mean subscale and total scale scores were converted into a (0 – 100) scale by a transformation formula [44]. Furthermore, the frequency distribution of responses to each question was presented as percentages to find the features that influence the total score or subscale scores. The mean scores were further compared based on gender, qualification, level of PHC facility, place of PHC facility, and the frequency of running telemedicine clinic.

Results

During the period 2020-2022, the telemedicine service was implemented in all governorates except Al-Wusta and South Sharqiya. Out of 186 PHC physicians who ran telemedicine clinics, 162 physicians were approached, and 143 physicians completed the questionnaire, reaching a response rate of 76.9% and a completion rate of 88.3% (Figure 1.a and 1.b).

The basic characteristics of respondents (Table 1) show that 62.2% of participants were in Muscat governorate, and about half (55.2%) were general practitioners. In addition, the majority of all respondents were female physicians (82.5%), worked in health centers (83.2%), ran telemedicine clinics three or more times a month (74.2%), and their last telemedicine clinic was within three months of the study period (92.3%).

The mean scores of telemedicine usability and its subscales are shown in Table 2. The overall mean score was 3.43/5.0 (equivalent to 60.7/100), denoting the weighted mean score of the three constructing subscales. The mean subscale score of the usability of telemedicine as a safe and useful service was 3.42/5.00, and the distribution of responses to the nine constituting items is shown in Table 2.a. The mean subscale score of the usability of telemedicine as a communication channel was 3.23/5.00, and the distribution of responses to the eleven constituting items is shown in Table 2.b. The mean subscale score of the usability of telemedicine as an outpatient record was 3.99/5.00, and the distribution of responses to the four constituting items is shown in Table 2.c.

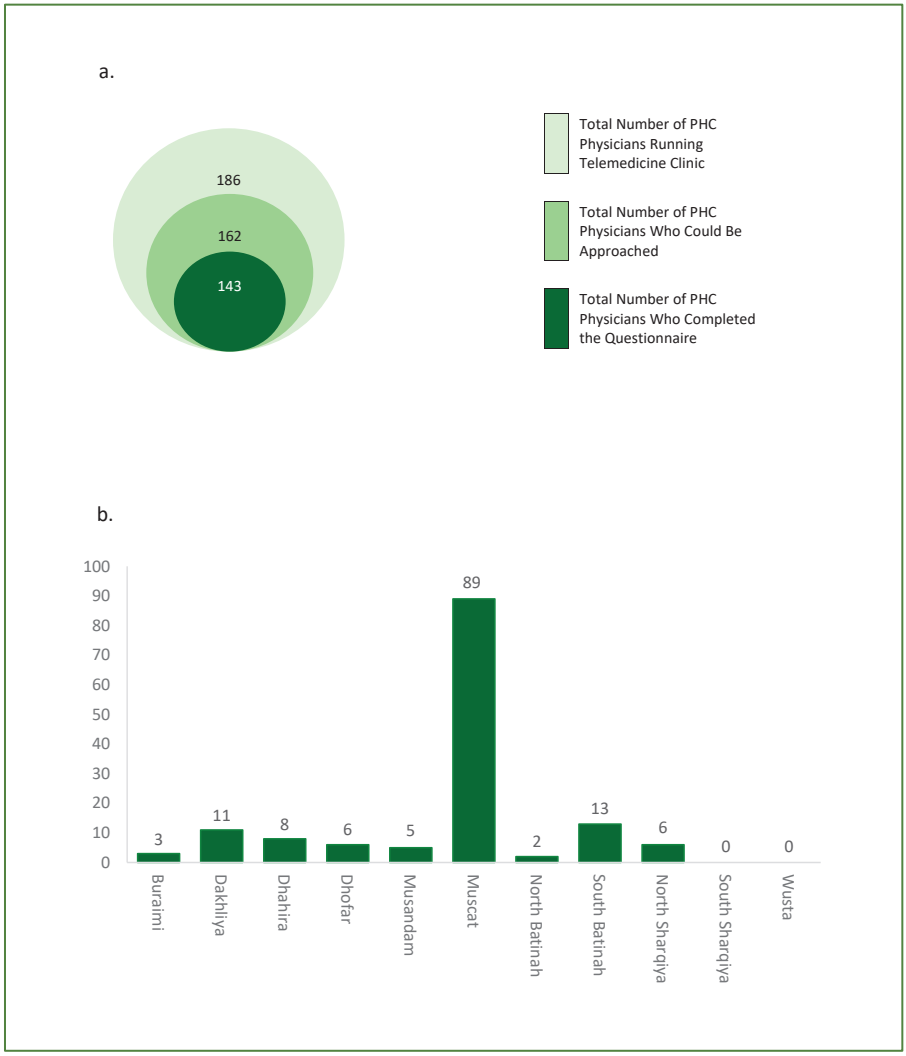


Figure 1. The total number of participants and their distribution by governorate. a. Out of all 186 eligible primary healthcare (PHC) physicians running telemedicine clinics, 162 could be approached, and out of those, only 143 physicians participated and completed the questionnaire. b. The distribution of participating PHC physicians by governorate.

Table 1. The basic characteristics of respondents. N= 143 (100%).

Category		Number (%)
Gender	Male. Female.	25 (17.5%) 118 (82.5%)
Governorate of Work	Muscat Governorate. Other Governorates.	89 (62.2%) 54 (37.8%)
Qualification	Specialist. General Practitioner.	64 (44.8%) 79 (55.2%)
Level of Primary Healthcare Facility	Health Center. Polyclinic and Local hospital.	119 (83.2%) 24 (16.8%)
Frequency of Running Telemedicine Clinic	Once a month. Twice a month. ≥ 3 times a month.	15 (10.5%) 22 (15.4%) 106 (74.1%)
Last Time of Running Telemedicine Clinic	Within this month. 1 – 3 months ago. > 3 months ago.	109 (76.2%) 23 (16.1%) 11 (7.7%)

Table 2. The mean scores of telemedicine usability scale and the distribution of responses to the constituting items. N= 143 (100%).

Usability Feature	(1 – 5) Scale		(0 – 100) Scale	
	Mean	SD	**Mean**	SD
Usability as a Safe and Useful Service	**3.42**	0.61	**60.5**	15.3
Usability as a Communication Channel	**3.23**	0.54	**55.7**	13.4
Usability as an Outpatient Record	**3.99**	0.81	**74.8**	20.2
Usability as a SUCCOR	**3.43**	**0.50**	**60.7**	**12.4**

a.	**Usability of Telemedicine as a Safe and Useful Service**			
The current telemedicine service is provided to the right patients (availability of criteria to categorize patients requiring virtual and non-virtual clinic).				
Not at all agree 1 (0.7%)	Slightly agree 12 (8.4%)	Somewhat agree 44 (30.8%)	Strongly agree 62 (43.4%)	Totally agree 24 (16.8%)
The current telemedicine service ensures privacy of patient information (availability of specified room).				
Not at all agree 11 (7.7%)	Slightly agree 24 (16.8%)	Somewhat agree 43 (30.1%)	Strongly agree 46 (32.2%)	Totally agree 19 (13.3%)
The current telemedicine service ensures patients' compliance.				
Not at all agree 5 (3.5%)	Slightly agree 28 (19.6%)	Somewhat agree 63 (44.1%)	Strongly agree 42 (29.4%)	Totally agree 5 (3.5%)
The current telemedicine service is legally protected (availability of standard operating procedure).				
Not at all agree 13 (9.1%)	Slightly agree 45 (31.5%)	Somewhat agree 52 (36.4%)	Strongly agree 29 (20.3%)	Totally agree 4 (2.8%)
The usefulness of the current telemedicine service in ensuring continuity of care.				
Not at all useful 1 (0.7%)	Slightly useful 16 (11.2%)	Somewhat useful 53 (37.1%)	Very useful 56 (39.2%)	Extremely useful 17 (11.9%)
The usefulness of the current telemedicine service in improving patients' condition.				
Not at all useful 3 (2.1%)	Slightly useful 16 (11.2%)	Somewhat useful 63 (44.1%)	Very useful 56 (39.2%)	Extremely useful 5 (3.5%)
The usefulness of the current telemedicine service in providing support for self-management.				
Not at all useful 2 (1.4%)	Slightly useful 15 (10.5%)	Somewhat useful 47 (32.9%)	Very useful 71 (49.7%)	Extremely useful 8 (5.6%)
The usefulness of the current telemedicine service in reducing the crowding in health facilities				
Not at all useful 2 (1.4%)	Slightly useful 10 (7.0%)	Somewhat useful 30 (21.0%)	Very useful 59 (41.3%)	Extremely useful 42 (29.4%)
The usefulness of the current telemedicine service in reducing the unnecessary consultation costs.				
Not at all useful 4 (2.8%)	Slightly useful 13 (9.1%)	Somewhat useful 27 (18.9%)	Very useful 63 (44.1%)	Extremely useful 36 (25.2%)
b.	**Usability of Telemedicine as a Communication Channel**			
The frequency of having difficulties in obtaining a device to contact patients (availability of landline or a phone) when running the telemedicine clinic.				
Always 3 (2.1%)	Usually 15 (10.5%)	Sometimes 60 (42.0%)	Rarely 40 (28.0%)	Never 25 (17.5%)
The frequency of having difficulties in reaching patients (i.e., the phone number was wrong or out of reach) when running the telemedicine clinic.				
Always 1 (0.7%)	Usually 21 (14.7%)	Sometimes 106 (74.1%)	Rarely 15 (10.5%)	Never 0 (0.0%)

Table 2. (continued) The mean scores of telemedicine usability scale and the distribution of responses to the constituting items. N= 143 (100%).

The frequency of having difficulties in talking to patients through the phone (quality of network) when running the telemedicine clinic.				
Always 1 (0.7%)	Usually 7 (4.9%)	Sometimes 59 (41.3%)	Rarely 64 (44.8%)	Never 12 (8.4%)
The frequency of having difficulties in hearing patients through the phone (quality of network) when running the telemedicine clinic.				
Always 0 (0.0%)	Usually 5 (3.5%)	Sometimes 48 (33.6%)	Rarely 65 (45.5%)	Never 25 (17.5%)
The frequency of spending a long time to contact patients when running the telemedicine clinic.				
Always 3 (2.1%)	Usually 31 (21.7%)	Sometimes 53 (37.1%)	Rarely 49 (34.3%)	Never 7 (4.9%)
The rate of satisfaction with contacting patients (obtaining a device, reaching, talking, hearing) using the current telemedicine service.				
Not at all satisfied 3 (2.1%)	Slightly satisfied 26 (18.2%)	Somewhat satisfied 61 (42.7%)	Very satisfied 52 (36.4%)	Extremely satisfied 1 (0.7%)
The frequency of having difficulties in taking proper history from patients through the phone when running the telemedicine clinic.				
Always 2 (1.4%)	Usually 16 (11.2%)	Sometimes 72 (50.3%)	Rarely 50 (35.0%)	Never 3 (2.1%)
The frequency of having difficulties in getting patients' measurements (e.g., blood pressure measurement, blood sugar profile) through the phone when running the telemedicine clinic.				
Always 22 (15.4%)	Usually 46 (32.2%)	Sometimes 42 (29.4%)	Rarely 32 (22.4%)	Never 1 (0.7%)
The frequency of having difficulties in managing patients through the phone when running the telemedicine clinic.				
Always 1 (0.7%)	Usually 11 (7.7%)	Sometimes 70 (49.0%)	Rarely 52 (36.4%)	Never 9 (6.3%)
The frequency of spending a long time to communicate with patients through the phone when running the telemedicine clinic.				
Always 2 (1.4%)	Usually 29 (20.3%)	Sometimes 66 (46.2%)	Rarely 42 (29.4%)	Never 4 (2.8%)
The rate of satisfaction with communication (taking proper history, getting patients' measurements and managing) using the current telemedicine services.				
Not at all satisfied 2 (1.4%)	Slightly satisfied 31 (21.7%)	Somewhat satisfied 72 (50.3%)	Very satisfied 35 (24.5%)	Extremely satisfied 3 (2.1%)
c.	**Usability of Telemedicine as an Outpatient Record**			
The frequency of having difficulties in opening telemedicine visits.				
Always 5 (3.5%)	Usually 5 (3.5%)	Sometimes 20 (14.0%)	Rarely 47 (32.9%)	Never 66 (46.2%)
The frequency of having difficulties in typing, editing and saving notes of telemedicine visits.				
Always 3 (2.1%)	Usually 2 (1.4%)	Sometimes 16 (11.2%)	Rarely 36 (25.2%)	Never 86 (60.1%)
The frequency of spending a long time to document the telemedicine visit notes.				
Always 5 (3.5%)	Usually 15 (10.5%)	Sometimes 36 (25.2%)	Rarely 47 (32.9%)	Never 40 (28.0%)
The rate of satisfaction with documentation (opening visits, typing, editing, saving notes) using telemedicine visits.				
Not at all satisfied 3 (2.1%)	Slightly satisfied 10 (7.0%)	Somewhat satisfied 37 (25.9%)	Very satisfied 69 (48.3%)	Extremely satisfied 24 (16.8%)

Discussion

Evaluating the usability of telemedicine is a multi-aspect inquiry that considers the effectiveness and efficiency of the service and the satisfaction of end-users. Physicians, the most frequent end-users and main service providers should be involved throughout the development cycle of any health service, and their perspective and experience should be taken into account to ensure the appropriateness and applicability of that service. This study was conducted using a scale developed and validated to quantitatively evaluate the usability of telephone-based consultations from the PHC physicians' perspective. Although the computed scores for the total usability scale and its subscales are not discouraging, the frequency distribution of responses to some questions calls for handling some challenges and strengthening some elements.

The Infrastructural and Technological Challenges

Knowing that a great percentage (45% - 90%) of respondents reported having difficulties in contact and communication with patients at least sometimes (*i.e.*, including sometimes, usually, and always) during telemedicine visits in addition to spending a long-time during telemedicine visits, raises the concern about the effectiveness and efficiency of the current telephone-based consultation as a communication channel between physicians and patients. Obviously, "one size does not fit all," and telephone-based consultation is not the right option for all conditions or patients. However, these findings also address the need for continuously improving our infrastructure and imply the demand for developing innovative technological solutions.

Telemedicine technology evolved many years before the beginning of the 21st century [45]. Several technological modalities, such as audio-visual visits, secure messaging, and remote patient monitoring, exist worldwide to overcome the limitations of telephone-based consultation [46]. Adding the visual component (*i.e.*, sight) to the audio component (*i.e.*, hearing) in virtual clinics makes the audio-visual visits more comparable to in-person visits than the telephone-based consultation. Where audio-visual technology is not preferred or non-available, telephone-based consultation may improve for some patients who can "store and forward" some measurement (e.g., weight, blood pressure, blood glucose level, or peak flow rate) or some pictures of body parts (e.g., skin lesion, swelling or visible abnormalities) to their physicians via a secure platform before or during telephone consultation to get clinical advice if an in-person visit is not required. With more advanced modalities, physicians can remotely monitor the patient's chronic conditions or vitals using wearable devices that can transmit data to healthcare providers' platforms using a wireless network [46].

However, it is important to note that the availability of more advanced telemedicine modalities does not guarantee its usability. In Turkey, about 60% of sampled family physicians indicated technical prerequisites as obstacles to using telemedicine in different scenarios [47]. Technical difficulties were also considered a common barrier by about 62% of responding medical specialists using various telemedicine forms, including audio-only phone calls, video calls, text chats, or e-mails in Malaysia [48]. In Quebec and Massachusetts, where both audio and audio-visual visits are implemented, Breton et al. documented similar difficulties, such as those found in our study, including reaching, hearing, understanding the patients, making proper diagnoses, and providing high-quality care [49]. Additionally, Heyer et al. cited divergent thoughts about the clinical effectiveness of audio-visual visits in the United States [50]. These common findings indicate the need to explore other barriers to implementing telemedicine.

The Financial and Organizational Challenges

Our study revealed that less than 10% of PHC physicians ran telemedicine clinics during 2020-2022. In addition, the study showed that telemedicine clinics varied in terms of their implementation in governorates. For example, more than 60% of respondents were from Muscat governorate, while Al-Wusta and South Sharqiyah were not approached as telemedicine

was not implemented. These figures may not necessarily mean a low service demand but rather a lack of resources. Being the capital of Oman and the most populated governorate [25], Muscat has the greatest number of specialized healthcare facilities and healthcare workers [26]. However, this fact should not deprive other governorates of development where the percentage of Omani doctors is small and the number of specialists per 10000 population is very low compared to Muscat [26]. Qualifying healthcare providers with the necessary skills to run telemedicine clinics is another fundamental requirement to ensure the proper delivery of healthcare via telemedicine if this service is planned to sustain [4,22,51]. At a minimum, such qualification or training has to target healthcare providers from all governorates to ensure equitable distribution and implementation of telemedicine clinics. Some experts, however, recommend earlier integration of telemedicine training into medical students' curricula [51-54].

In addition, the availability of adequate and sustainable financial support is a common challenge in many developing countries [55,56]. It was ranked the first among many barriers to implementing telemedicine in Saudi Arabia [57]. Many telemedicine projects have not succeeded or have not been sustained in some countries because of the high expenditure of its implementation, which includes the initial costs of purchasing and installing telemedicine equipment/devices as well as the ongoing costs that are required to maintain the equipment/devices and to pay for internet and electricity bills in addition to the salary of technical support staff [56].

The Regulatory or Legal Challenges

Many authors, including Shore et al. have addressed the privacy of patient data in telemedicine [58]. With less than 50% of respondents reporting that they agree that the current telemedicine services ensure the privacy of patient information (*i.e.*, strongly agreed and totally agreed), it makes patient privacy vulnerable. Moreover, Abd Ghani and Jaber highlighted patient privacy as a barrier to implementing telemedicine in Iraq [59]. At the same time, Alkraiji et al. raised ethical concerns surrounding the privacy and confidentiality of medical information in some Arabian Gulf countries [60]. Additionally, the lack of legal protection to deliver care through telemedicine, as perceived by more than 70% of respondents (*i.e.*, including respondents who not at all agreed, slightly agreed, and somewhat agreed), may negatively influence the physicians' acceptance of telemedicine as a safe service. The lack of a clear legal framework also concerned a considerable percentage of questioned doctors in Saudi Arabia [61] and Türkiye [47]. Therefore, developing a regulatory framework or standards is essential to support physicians in their care delivery and to maintain patients' trust in the provided service.

Such regulatory or legal frameworks may not be uniform across countries. However, they can be built using the same elements [62]. A review of telemedicine regulatory frameworks developed by neighboring countries such as the United Arab Emirates [63] or the Kingdom of Saudi Arabia [64] should encourage the development of regulatory frameworks in culturally-similar countries. The regulatory framework should govern the licensure for service provision in healthcare facilities and the scope of permitted telemedicine services. In addition, it should describe the requirements for healthcare providers and their responsibilities. It should also govern the health information exchange and indicate the approved devices, equipment, technologies, or software applications. Furthermore, the insurance coverage of any telemedicine service or payment procedure should be clear and specified. More importantly, the regulation should address the patient's rights and consent as well as the privacy and confidentiality of information. Monitoring and evaluation should also be integral to telemedicine regulation by ensuring healthcare facilities and providers' compliance with the regulation. Reassuringly, the regulation of telemedicine services was not ignored in Oman. However, it was an internal policy on the use of telemedicine in PHC facilities located in the capital governorate only [65].

The Cultural and Environmental Challenges

More respondents felt that the current telemedicine services were useful in reducing crowding and unnecessary consultation costs (about 70%) than those reporting its usefulness in ensuring continuity of care, improving patients' conditions, and supporting self-management (43% to 55%). This warrants further examination of the current services in improving patients' clinical status to help establish mechanisms for improvement. Besides, we should not ignore the fact that telemedicine is a two-way communication process, and the complete readiness of healthcare facilities is insufficient to determine the usability of this service. In other words, the patients should also be ready in terms of the available basic infrastructure, devices, equipment, technologies, or software applications in addition to affordable and efficient network connectivity. Moreover, as patients' clinical status, needs, education levels, and preferences differ, we should avoid the pitfall of appointing virtual visits to patients who may find it challenging to use this new service [66] and consequently miss their appointments, relax their control, and slip into complications. Apart from that, educating the patients or caregivers about telemedicine services should be offered to more than just those who inquire about them. Rather, it should be presented to the public as alternative healthcare services with known benefits. This should make people appreciate the progress in advancing the provision, improving accessibility, and increasing the utilization of healthcare services.

Nevertheless, the geographical diversity in Oman has shaped the culture and lifestyle of its people. The Bedouin desert-bound and nomadic lifestyle in some areas of Oman, like those in Al-Wusta and South Sharqiya governorates [67,68], may not favor telemedicine to seek healthcare. Yet, with the government's directions to support the development of all citizens and empower them, many Bedouins started accepting some features of the urban lifestyle without abandoning their nature-loving standards or traditions-rich culture [68].

Encouragingly, the current coverage of the fourth generation (4G) of the wireless network in Oman that exceeds 90% of the population, and the launch of the fifth generation (5G) of wireless network that started in 2019 [69,70] in addition to the firm will to create sustainable smart cities with advanced technological infrastructure [71,72], furnish the environment for more advanced forms of telemedicine technologies in PHC facilities [73,74]. This exceptional development in ICT is an outcome of the Digital Oman Strategy, which has among its objectives the elimination of digital literacy and empowering all members of the society to communicate and interact electronically [75]. In fact, we have started witnessing the cultural acceptance of this transformation in healthcare delivery and the demand to sustain it [10,11]. In 2021, a survey to assess the accessibility and use of information technology and telecommunication showed that the percentage of those who owned smartphones and internet access was almost equal (around 94%) among respondents from different governorates in Oman [76]. Undoubtedly, this should make us more prepared and accountable to meet the expectation of our people and future generations.

IT-FORCE Framework: A Scheme to Improve the Usability of Telemedicine and Advance Healthcare

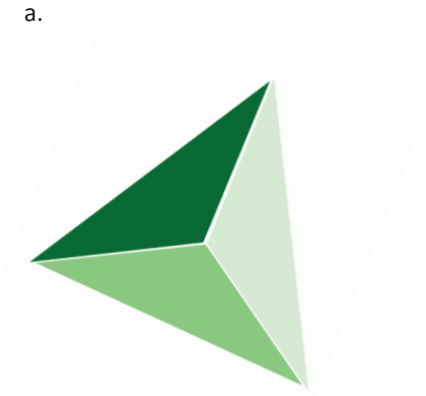
Based on our findings and context, the inferred challenges in our study (*i.e.*, Infrastructural & Technological, Financial & Organisational, Regulatory, Cultural & Environmental) can be organized in a hypothesized framework of determinants (IT-FORCE) that best explains our results, directs the improvement of our telemedicine service, and predicts its sustainable usability (Figure 2). Though our proposition is not unprecedented and comparable frameworks exist [77,78], our framework's peculiar feature lies in constructing a regular triangular pyramid (Figure 2.a) to visualize the concept of interdependence of telemedicine usability on the four inferred categories of determinants (Figure 2.b).

Thus, as four equilateral triangles of the same length are all – without exception – necessary to form a regular triangular pyramid, the four categories of usability determinants all –

without exception – require interventions to improve the telemedicine usability features. In other words, setting up the infrastructure of healthcare facilities for the more advanced form of telemedicine does not guarantee the usability of telemedicine unless sufficient fund is allocated to maintain and sustain the service, qualified physicians are equitably distributed, a regulatory framework is approved and followed, the patient's environment is ready in terms of infrastructure, and the patients are fit, willing and equipped with the essential tools for the scheduled telemedicine visit.

Undeniably, one of the lessons learned during the COVID-19 pandemic was leveraging telemedicine services and sustaining them in the

a.



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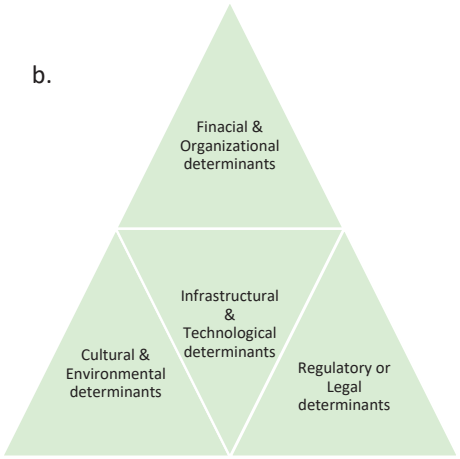

c.

IT-FORCE	Interventions
Infrastructural & Technological	▪ Set up healthcare facilities to accommodate telemedicine clinic. ▪ Equip healthcare facilities with the appropriate and approved devices and software applications to run telemedicine clinic. ▪ Ensure high quality network and technical support.
Financial & Organizational	▪ Allocate sufficient budget to implement, maintain and sustain telemedicine clinic. ▪ Qualify physicians with the necessary skills to run telemedicine clinic. ▪ Increase the number of telemedicine clinics in all governorates.
Regulatory/Legal	▪ Develop a regulatory framework for telemedicine services.
Cultural & Environmental	▪ Empower people with digital knowledge and skills. ▪ Increase the people knowledge and awareness of the available telemedicine services and their benefits. ▪ Create technology-encouraging environment and improve network connectivity at national and subnational levels.

Figure 2. A hypothesized framework of determinants and interventions to improve telemedicine. a. A regular triangular pyramid, which requires all four triangular faces to join, is proposed to explain the dependence of telemedicine usability on all of the four categories of hypothesized determinants. b. The four categories of hypothesized determinants are displayed on the four triangular faces of a regular triangular pyramid. c. The four categories of the hypothesized determinants form the IT-FORCE acronym, which represents the framework of usability determinants. Each category can be governed by a set of interventions to improve the usability of telemedicine.

post-pandemic era [9,79-82]. Hence, developing a telehealth strategy is unnegotiable, and waiting for another pandemic or crisis to decide and react is unwise. Without exaggeration, telemedicine is highly anticipated to be a public demand and a common requirement for the future digitally-literate generations. Optimistically, with the rapid pace of ICT development and the future strategic direction to utilize technology in healthcare delivery, the diffusion of this "new normal" is not unexpected within the coming years in Oman and other countries.

Collectively, the interventions that are proposed to govern and control the inferred determinants (Figure 2.c) should improve the usability features of telemedicine service, which in turn will not only improve the accessibility and coverage of healthcare services but also build an inclusive, equitable and resilient healthcare system that is in alignment with future directions of Oman and the world (Figure 3) where healthy lives, well-being, and sustainable development are enjoyed by all [83-85].

IT-FORCE Framework and the Principles of Biomedical Ethics

Today, the clinical applications of telemedicine span the whole spectrum of medicine with different degrees of maturity [86,87]. Teleradiology and telepathology are considered the most mature applications in telemedicine. However, in the last few decades, other specialties such as telepsychiatry, teledermatology, telecardiology,

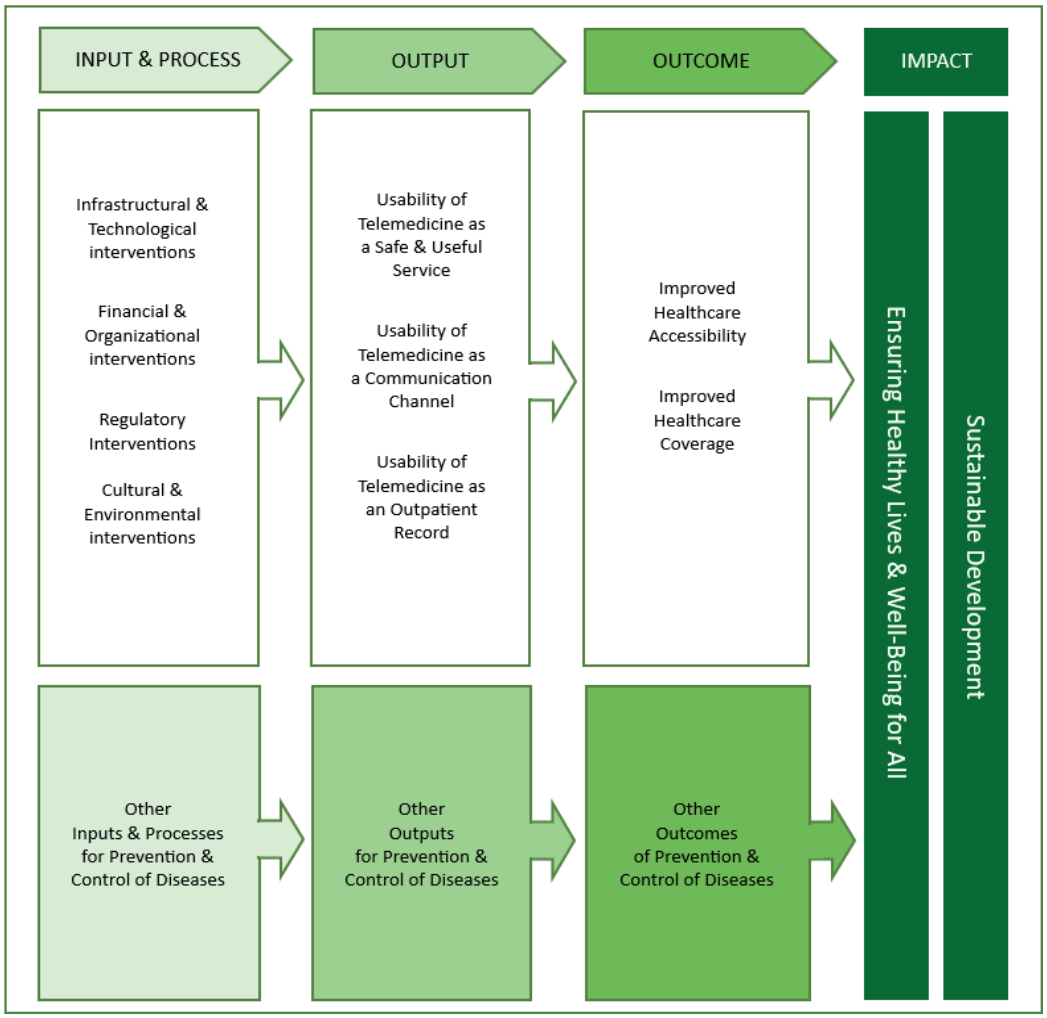

Figure 3. Promoting telemedicine as a means to achieve sustainable development. Ensuring healthy lives and well-being for all and achieving sustainable development depend on preventing and controlling diseases, including improving healthcare accessibility and coverage. This outcome might be achieved by improving its requirements and preconditions, including the usability of telemedicine and the hypothesized determinants.

and teleophthalmology have been recognized as maturing applications, while telesurgery is gently emerging [86,87]. This might be attributed to many factors, such as feasibility, quality, and cost [87]. Above all, however, the provision of telemedicine, like any healthcare service, should be guided by ethics. Beauchamp and Childress proposed four biomedical ethics principles: respect for autonomy, nonmaleficence, beneficence, and justice [88]. In simple words, a healthcare service is considered ethical if it is chosen by the patient (respect of autonomy), not expected to cause harm (nonmaleficence), intended to benefit the patient (beneficence), and provided to all who need it (justice). Our hypothesized IT-FORCE framework supports the fulfillment of these principles. Thus, the readiness of healthcare institutions and patients'

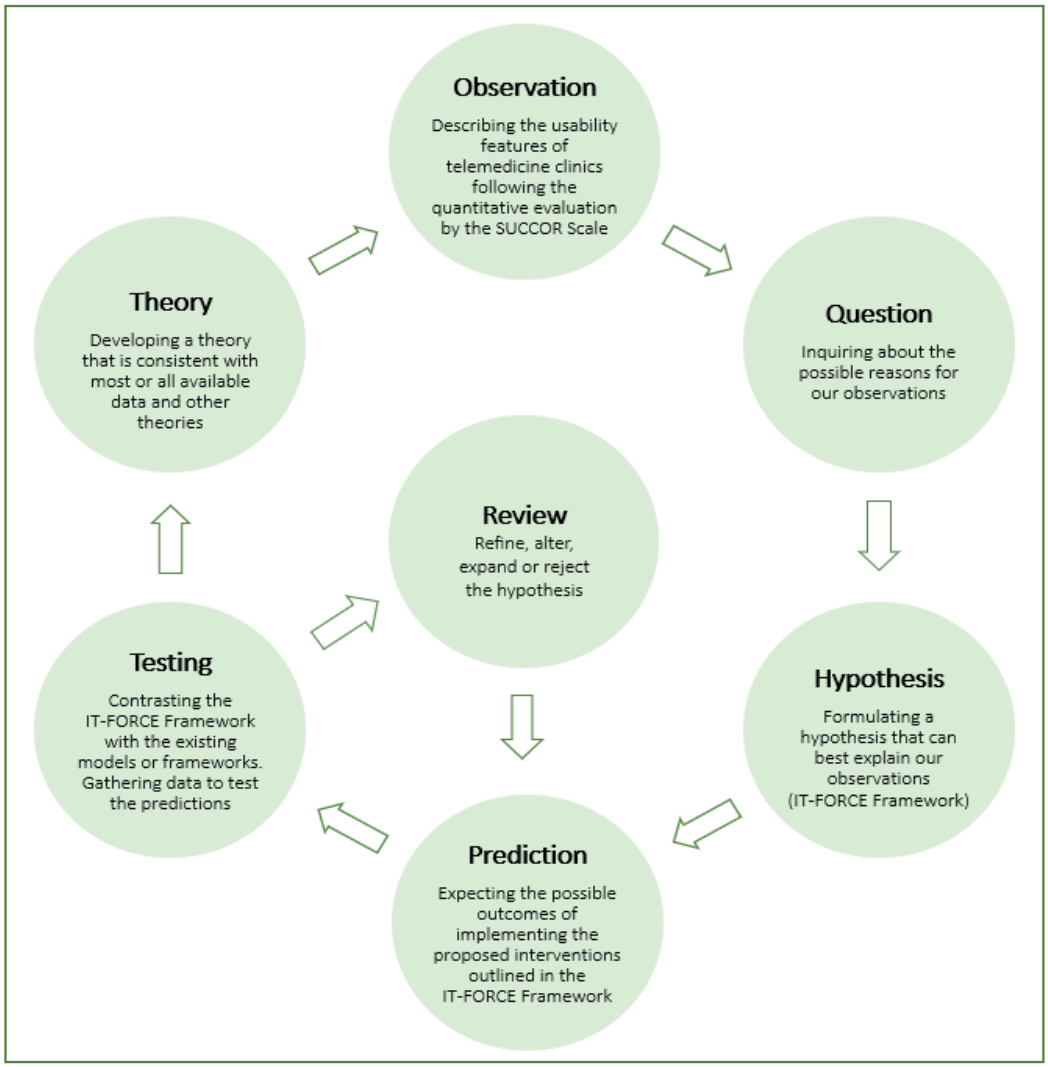

Figure 4. The scientific method in our study. The scientific method is an ongoing process. By answering our research question, we made our observation about the usability of our telemedicine clinics. This step was followed by inquiring about the possible reasons. With logical reasoning, we could formulate a hypothesized framework of determinants that join the infrastructural, technological, financial, organizational, regulatory, cultural, and environmental (IT-FORCE) determinants to explain our observations. Based on the level of imposed governance on the outlined determinants, the hypothesized framework may have a positive or negative influence on the usability of telemedicine. Evaluating the effectiveness of the implemented interventions is a future step to test the proposed predictions. Further studies might be required to refine, alter, expand or reject our hypothesis before drafting a theory. The last step will be the starting point for the subsequent development of a rigorous and reliable theory that precisely explains our observations.

The sketch of this Figure was inspired by Garland, cited by Dai and Boos [89].

homes to accommodate telemedicine conforms with equitable access to healthcare services and hence the principle of justice. By tackling the aforementioned determinants of usability, telemedicine might be considered an optional modality of delivering healthcare services equivalent to in-person visits where safety and satisfactory outcomes are expected, complying with the principles of nonmaleficence and beneficence. Having these standard features characterizing telemedicine services encourages people to prefer and autonomously request this type of healthcare service whenever possible. However, these principles might be integrated only if telemedicine services are mature enough and advanced to meet the same expectations as in-person visits or if the outcomes of both types of visits, when provided to the right patients, are not different.

Strengths and Limitations

In our study, we initiated the cyclic process of a scientific method (Figure 4) [89,90]. Thus, to answer our research question and quantify the usability of telemedicine service in our PHC facilities, we built and developed our instrument (The SUCCOR Scale) following a literature review and conceptual understanding of usable healthcare service. It was discernible that the descriptive numbers and statistics were not the end of our analysis or the core of our discussion but instead the door to enter the field of logical reasoning [91-93]. Interestingly, formulating a hypothesis that best explains the observations is a creative process combining knowledge and imagination [94]. Our explanatory hypothesis integrated the most plausible determinants of telemedicine usability in a conceptual framework (IT-FORCE). Using our framework of determinants, we can conceptually predict the outcomes of leveraging telemedicine or tackling its barriers and consequently plan our next steps. In addition to being in line with the existing models and frameworks, our framework has its unique analogy to mirror our perception of the interdependence of telemedicine usability on all of the hypothesized determinants and to support our argument for the need of multi-sectoral interventions. Following the implementation of the proposed interventions, testing our predictions to refine, alter or expand our hypothesis is recommended for subsequent development of the theory. The latter is not the end of the scientific method but the restart point of the cyclic process.

Similar to any study, however, limitations are innate. First, being evaluated from the perspective of PHC physicians, the usability results cannot be generalized to other healthcare facilities or specialties in which different forms of telemedicine might be used, and various challenges might be encountered. Nevertheless, we argue that the proposed framework of determinants is expected to help decision-makers monitor any form of telemedicine in any setting in the country. Second, measurement bias is not unexpected as the evaluation was based on a questionnaire requiring the respondents to recall their experiences. However, using Likert item questions with a 5-point-unipolar response scale should reduce measurement bias. Third, because of the small sample size, the study had a low power to detect any difference in the scores between different subgroups. Yet, the respondents were more representative of a national sample owing to the number and distribution of eligible participants at the time of the study.

Conclusion

Telemedicine service has some usability features in Oman, according to PHC physicians. However, there is still much room for improving this service by tackling some infrastructural, technological, financial, organizational, regulatory, cultural, and environmental challenges. This should qualify our telemedicine service as a safe and useful communication channel and outpatient record devoted to facilitating access to high-quality healthcare.

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Conflict of Interest

No conflict of interest declared.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

COVID-19 vaccination rate and factors affecting non-vaccination in pregnant women

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Abstract

Examining the Coronavirus disease 2019 (COVID-19) vaccination rates and associated factors for acceptance of vaccination in pregnant women during the pandemic. The present study has a cross-sectional survey-based design that evaluated 448 pregnant women, and data were collected between October 1 and December 31, 2021. A composite questionnaire with an instrument was utilized in the survey to examine vaccine rates, including socio-demographic data, maternal characteristics, vaccination history, and reasons for not vaccinating. The vaccination rate was 48% (n=216). The main concerns and barriers to non-vaccination were: (i) concerns about pregnancy (82.9%), (ii) possible vaccine side effects (76.3%), and (iii) insufficient trust in the reliability of the vaccine (20.3%). A multiple logistic regression analysis revealed that following factors affect COVID-19 vaccination rate: first trimester of pregnancy [Odds ratio (OR): 3.40 (95% *confidence interval* (CI):1.84-6.27), $p<0.001$], age 35 and over [OR: 2.96 (*95% CI*:1.40-6.27), $p=0.004$], active working status [OR: 4.88 (*95% CI*:2.57-9.23), $p<0.001$]. Our study indicated that rates of COVID-19 vaccination are still low in pregnant women. Pregnant females constitute a special vulnerable part of the community. Therefore, targeted communication is needed to raise awareness of vaccine safety in healthcare professionals and pregnant women, and strategies to solve vaccine hesitation. In addition, post-vaccination monitoring is required to collect additional data.

Keywords: COVID-19, vaccination, pregnancy, vaccine hesitancy, perinatal

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Introduction

Maternal-child health is the most important indicator of the quality of health care. The historic challenge facing quality healthcare is the global pandemic. The main way out of the pandemic is social vaccination, starting with the vulnerable population. Out of the populations that are most vulnerable to the virus, pregnant women are considered a highly vulnerable population. Vaccination is introduced as an efficient way to stop severe medical conditions in vulnerable people [1].

While 'Severe Acute Respiratory Syndrome Coronavirus-2' (SARS-CoV-2) vaccination was not available at the beginning of the pandemic, having Coronavirus disease 2019 (COVID-19) during pregnancy leads to serious medical conditions such as premature birth, preeclampsia, cesarean section, and perinatal death [2]. The findings of these studies show that fetal and maternal death is reduced due to vaccination in those who intend to become pregnant or pregnant patients. On the other hand, due to the exclusion in the initial phase 3 clinical trials, little was known about the COVID-19 vaccines' effectiveness and safety [3]. It is stated that any authorized vaccine can be used for people who are breastfeeding or are pregnant without choosing the vaccine type. In addition, cumulative observational data from the vaccination initiation have shown no adverse effects and showed that after maternal vaccination with mRNA vaccines, the maternal immune response is generated, and maternal antibodies are conveyed to the breast milk and placenta, which causes SARS-CoV-2 passive immunity in infants [4].

Furthermore, recent research has established that the mortality rate is higher in pregnant patients compared to non-pregnant patients of the same age (9 versus 2.5 deaths per 1000 COVID-19). And, none of moreover patients were fully vaccinated [5]. The Centers for Disease and Prevention (CDC) and Advisory Committee on Immunization Practice guidelines advise COVID-19 vaccines for pregnant females [6-8]. From January 2021, vaccination practices against SARS-CoV-2 began in Türkiye, and vaccination studies continue worldwide. In Türkiye; inactivated virus vaccines and mRNA vaccines are administered. In mRNA vaccines, the portion of the SARS-CoV-2 genome encoding the spike (S) protein is embedded in lipid nanoparticles together with the mRNA molecule. When given to the person in this way, mRNAs cause S protein production by entering the cells. Antigen-presenting cells detect these produced antigenic structures and present them to the immune system and cause the development of antibodies against S proteins [9]. The way inactivated virus vaccines work is by using beta-propionylactone and inactivating SARS-CoV-2 viruses. After vaccination, it is expected for the body to produce particular antibodies for the SARS-CoV-2 S protein, neutralizing the virus and preventing it from binding to its specific receptor [10,11].

Injection site pain or tenderness, rash, muscle pain, fatigue, fever, chills, headache, and joint pain are the most common side effects of COVID-19 vaccines. These side effects are usually self-limiting and mild [12]. Unfortunately, the probability of being vaccinated is significantly lower in pregnant women than in non-pregnant women of reproductive age [13]. Furthermore, there is little published data on vaccine hesitations or attitudes in pregnant women. Therefore, this study investigates the situation of pregnant women in our province about being vaccinated against COVID-19, their opinions on this issue, and how we should better inform pregnant women about vaccination by learning the reasons for their reservation.

Materials and Methods

This cross-sectional survey-based study was conducted from October 1 to December 31, 2021. The study population consisted of pregnant women followed in family health centers in Afyonkarahisar city center. The logistic regression test's sample size was calculated, which allows for 95% statistical power and 5% alpha error. Unfortunately, no study in Türkiye was conducted in a similar setting, so we assumed the prevalence to be 50% to reach the maximum sample. The sample size of the present study was 462, which was calculated by taking the pattern

effect as 1.2 for the largest sample size (n=385). Four hundred forty-eight patients were enrolled, with a 96.9% success rate.

Afyonkarahisar city center was divided into low, middle and high based on socioeconomic family health centers were randomly selected from each stratum. Criteria for eligibility of participation were: (1) being over 18 years of age, (2) being pregnant, and (3) filling out the informed consent form for participation. Fourteen pregnant women were excluded from the recruitment process; who did not want to participate in the research.

The survey was structured from 13 components, including socio-demographic data, maternal characteristics, vaccination history, and reasons for not getting vaccinated. The questionnaire form was applied to 448 pregnant women by taking pandemic measures. In addition, participants were informed about the COVID-19 vaccine.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Chicago, Illinois, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the data's suitability for normal distribution. Numerical variables with normal distribution were presented as mean±standard deviation and categorical variables as percentages (%). Any variable (*i.e.*, age, education level, working status, trimester, having children, previous COVID-19 diagnosis, and chronic disease history) with a p-value<0.05 in a univariate model was accepted as a candidate for the multiple models along with all variables of possible vaccine hesitance cause. Odds ratios and 95%*CI* for each independent variable were also calculated. Statistical significance was accepted as p<0.05.

Ethical Considerations

The study was approved by the Ethical Committee of the Afyonkarahisar Health Sciences University (Registration Number: 2021/493). Also, research approval was taken from the Scientific Research Commission of the General Directorate of Health Services of the Turkish Ministry of Health (2021-09-30T15-42-08) and the Health Directorate of Afyonkarahisar Province (2021/20).

Results

In the survey of our study, 448 pregnant women with a 96.9% response rate were included. The mean [standard deviation (SD)] age of the participants was 27.5±5.3; 61.6% (n=276) of the pregnant had children, 35.9% (n=161) of the participants were university school degrees, 23.4% (n=105) of the participants diagnosed for COVID-19, 56% (n=251) of the participants were in the third trimester, 27% (n=121) of the participants were employed (Table 1).

Table 1. Characteristics of the study group.

	Characteristics	**n**	
	Age (mean±SD)	27.5±5.3	
	Pregnancy week (mean±SD)	27.2±9.9	
	Characteristics	**n**	**%**
Educational Status	*None*	6	1.4
	Primary school	20	4.5
	Secondary school	127	28.3
	High school	134	29.9
	University	161	35.9
Children	*Yes*	276	61.6
	No	172	38.4
Chronic Disease	*Yes*	25	5.6
	No	423	94.4
Employed	*Yes*	121	27
	No	327	73
Diagnosed for COVID-19	*Yes*	105	23.4
	No	343	76.6
Gestational Age	*1st trimester*	63	14.1
	2nd trimester	134	29.9
	3rd trimester	251	56
Total		448	100

SD: *Standard deviation*

Furthermore, only 16% (n=73) of the pregnant women took a single dose of vaccine, 32% (n=143) were vaccinated with at least two doses considered fully vaccinated, and 52% (n=232) were not vaccinated (Figure 1).

The full-dose vaccination of the study population with Pfizer-BioNTech (n=98) and Sinovac-CoronaVac (n=45) was 68.5% and 31.5%, respectively. In addition, most of the third dose was preferred as Pfizer-BioNTech (n=11, 84.6%). Another interesting finding was that 94% (n=423) of participating pregnant women received or intended to receive a tetanus vaccine.

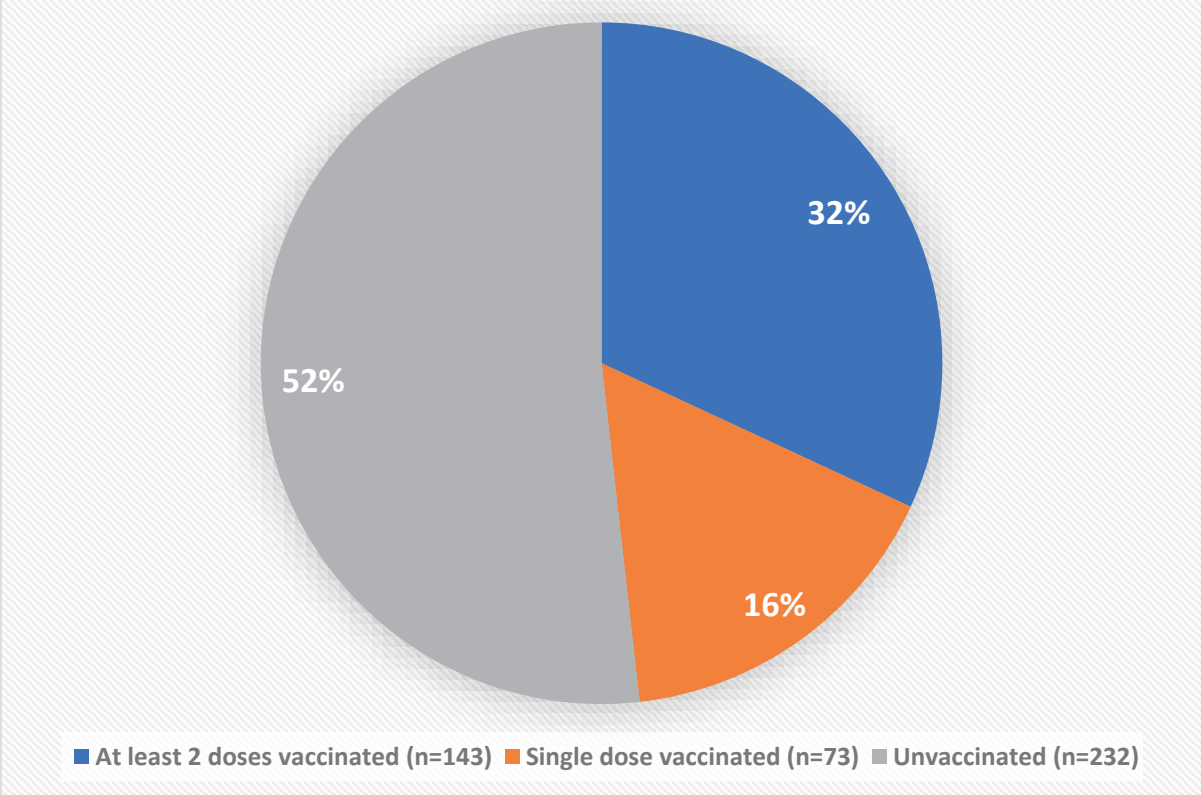

Figure 1. COVID-19 vaccination rate illustration.

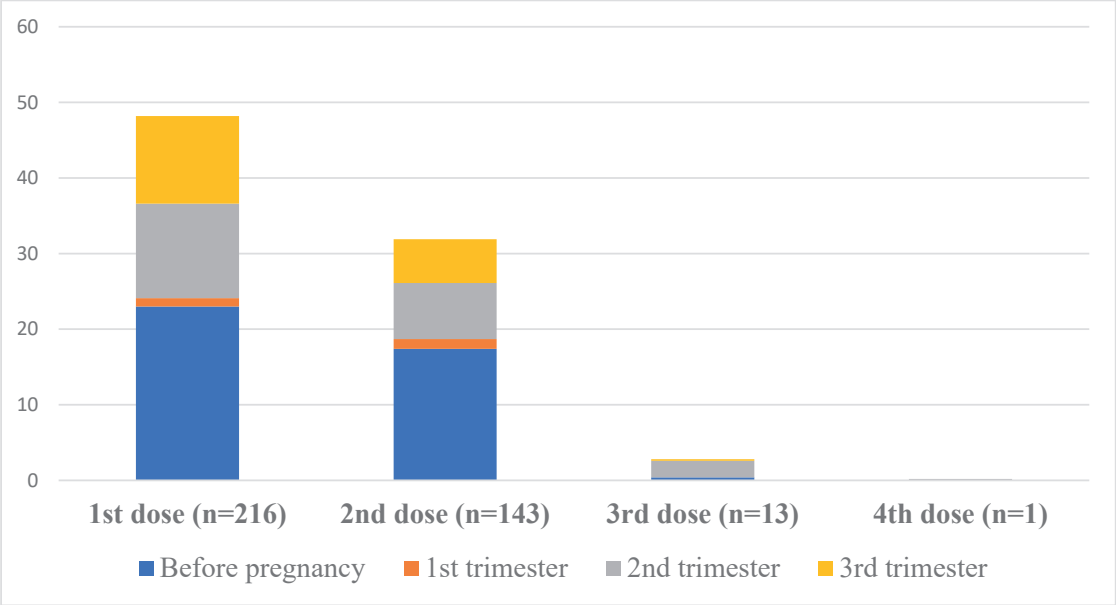

Figure 2. Vaccination times in pregnant women according to trimester.

However, only 1.3% (n=6) of the participants had received the flu vaccine for 2021. A total of 3.6% (n=16) of the pregnant women did not have any vaccination. When we look at the vaccination time of the subjects according to trimester, we see that 17.2% of them were fully vaccinated before pregnancy (Figure 2). Although most of our study population consisted of third-trimester pregnant women (56.0%, n=251), this group was also at least COVID-vaccinated (38.6%, n=97). Table 1 shows a steady fall in the vaccination number while the pregnancy trimester increases.

In response to "What was the reason for not getting vaccinated?" 82.3% of non-vaccinated respondents said they had concerns about pregnancy, especially safety issues about their fetus coming to the fore. Another important comment was the vaccine's reluctance to face possible side effects, with 76.3%. In addition, 20.3% of the respondents say: They do not trust the reliability of the vaccination. At the same time, 12.1% said they did not have sufficient information about the vaccine (Figure 3).

When we look at the affecting factors for the status of vaccination in pregnant women, significant relationships were found with age groups, educational status, trimester and employment status (p<0.001 for all, Table 2). According to the logistic regression analysis in Table 3; vaccination was higher; 4.88 times in working pregnant [*95% CI*= 2.57-9.23], p<0.001), 2.96 times in the ≥35 age group compared to the 18-24 age group (*95% CI* = 1.40-6.27, p=0.004), 3.4 times in the first trimester compared to third trimester (*95% CI* = 1.84-6.27, p<0.001), 1.76 times in the second trimester compared to third trimester (*95% CI* = 1.09-2.83, p=0.019). A positive correlation between education level and vaccination rate was found, while no correlation could be demonstrated in the multiple logistic regression model.

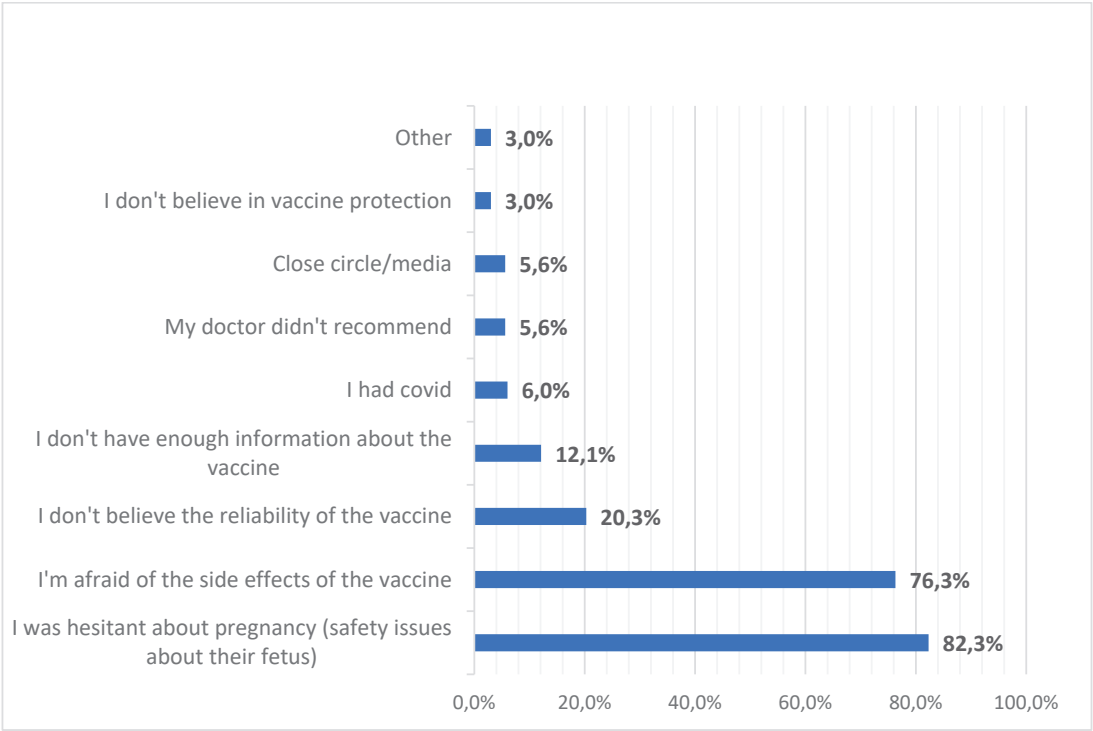

Figure 3. Factors for not getting vaccinated in the study population (n=232).

Table 2. Factors affecting vaccination status in the study group.

	Variables	n	Have you had the COVID 19 vaccine?			
			Yes (%)	No (%)	χ2	*p*-value*
Age	*18-24*	141	33.3	66.7	21.781	0.000
	25-34	258	52.7	47.3		
	≥35	49	67.3	32.7		
Children	*Yes*	276	51.8	48.2	3.726	0.054
	No	172	42.4	57.6		
Education Level	*None/Prim/Sec School*	153	35.3	64.7	28.839	0.000
	High School	134	43.3	56.7		
	University	161	64.6	35.4		
Trimester	*1st Trimester*	63	65.1	34.9	21.743	0.000
	2nd Trimester	134	58.2	41.8		
	3rd Trimester	251	38.6	61.4		
Working Status	*Yes*	121	76.9	23.1	54.48	0.000
	No	327	37.6	62.4		
COVID-19 History	*Yes*	105	45.7	54.3	0.343	0.558
	No	343	49	51		
Chronic Disease History	*Yes*	25	52	48	0.152	0.697
	No	423	48	52		

*: Analyses chi-squared

Discussion

This survey-based, cross-sectional study reports that 52% of pregnant women did not vaccinate against COVID-19. Moreover, 16% of the participants were vaccinated with a single dose and 32% with a full dose. Our regression models shed light on the positive factors influencing vaccine uptakes, such as first-trimester pregnancy, age over 35, and active employment. In particular, we found that active working pregnant women were more likely to take the COVID-19 vaccination. Therefore, it is quite surprising that 94.4% of participants received or planned to receive the tetanus vaccination. However, the flu shot rate for that year was very low. Finally, we found definite vaccine refusal at only 3.6% (n=16).

Compared to the general population or non-pregnant women, it is known that pregnant women have a higher risk of developing severe illness, intensive care hospitalization and the necessity for mechanical ventilation due to COVID-19 [14]. Moreover, various studies on pregnant women populations have shown that SARS-CoV-2 infection during pregnancy increases complications, including preterm delivery, preeclampsia, and several other clinical complications [15,16]. Vaccination of pregnant

Table 3. Factors affecting vaccination status according to Univariate and multiple logistic regression analysis results.

Variables		Univariate Logistic				Multiple Logistic			
		OR	*95% CI*		*p*-value	OR	*95% CI*		*p*-value
			Lower bound	*Upper bound*			*Lower bound*	*Upper bound*	
Working Status: Yes		5.5	3.41	8.88	0.000	4.88	2.57	9.23	0.000
Trimester	*2nd*	2.21	1.44	3.38	0.000	1.76	1.09	2.83	0.019
	1st	2.95	1.66	5.26	0.000	3.4	1.84	6.27	0.000*
Age	*25-34*	2.23	1.45	3.41	0.000	1.53	0.95	2.47	0.077
	≥35	4.12	2.06	8.24	0.000	2.96	1.4	6.27	0.004*
Education	*High School*	1.39	0.86	2.25	0.167	1.28	0.77	2.12	0.326
	University	3.34	2.1	5.31	0.000	1.02	0.54	1.92	0.941*

OR: Odds ratio, ***CI:*** Confidence interval

*Those who are not employed, are in the third trimester, are between the ages of 18-24, and are none/primary/secondary school graduates are taken as reference.

people against COVID-19 is therefore very important and effective health policies should be developed to increase vaccination rates. Identifying these people's concerns about the vaccine, informing them effectively about this issue, and raising awareness about the possible complications of the disease will be effective in encouraging vaccination.

In Türkiye, COVID-19 vaccines are free and easily accessible healthcare services. Further, the public health units inform and remind people who have not been vaccinated. Despite this, we found that the overall rate of non-vaccination among pregnant women is 52%. These findings were lower than recent studies showing acceptance or willingness for SARS-CoV-2 vaccination of pregnant women (respectively 49.1% and 52%) [17,18]. This discrepancy could be attributed to our research methodology assessing confirmed vaccination status. The difference between demand and execution may have brought us to this interpretation.

The three main factors behind vaccine reluctance in pregnant women were: (i) concern about pregnancy, particularly potential harm to the fetus, (ii) doubts about possible side effects of the vaccine, and (iii) disbelief in the vaccine's reliability. In a similar study conducted in Türkiye, insufficient confidence in the vaccine was found to be the most common cause of not getting the vaccine for COVID-19 [19]. In another study, the most important reason pregnant women refused the COVID-19 vaccine, even though it was proven safe, was that they feared hurting their developing babies because of side effects [20]. The biggest issue regarding the vaccination in the refusal group was hesitation due to its possible harmful effect on the fetus. Although CDC and health authorities in Türkiye declared that COVID-19 infection has devastating consequences in pregnant women, participants were unanimous in the view that potential long-term effects on the baby rise from the antivaccine qualitative data and arguments [21,22]. The mentioned hesitation may have been fueled somewhat by insufficient safety considerations in pregnant women in the initial phase 3 vaccine trials [3]. However, at the time of the study, there were no doubts or worrying signals regarding the vaccine's safety in peripartum women [23-25]. In addition, cumulative observational data provide an important foundation, such as the V-Safe registry [26].

Among participants, the highest COVID-19 vaccination rate was almost five-times among employed pregnant women. This is probably caused by working people seeing themselves as riskier. Working life causes inevitable social contact. In addition, the proximity of vaccination centers to work areas may have prompted pregnant women to vaccinate impulsively. This finding also accords with our earlier observations, which showed a high vaccination rate among working pregnant women [27,28].

If we compare gestation times, first-trimester women have the highest vaccination after the second and third trimesters. This result is consistent with Goncu Ayhan et al. [6]. Moreover, the 35-age group pregnant women were about 2.96 times more likely to have COVID-19 vaccination compared to pregnant women in the 18-24 age group. This result agrees with previous studies [20,29,30]. There are several possible explanations for these results. First, mature pregnant females could be aware of the severe COVID-19 complications and more focused on the protective effects of the vaccines. This finding may reflect that pregnant women of younger maternal ages have less experience with pregnancy-related losses and complications. In addition, comorbidities such as diabetes, and hypertension can emerge with age, lowering pregnant mothers' immunity and increasing COVID-19 morbidity and mortality rate. Consequently, this may cause anxiety in older pregnant and may encourage them to get the COVID-19 vaccine.

A positive correlation was found between education level and vaccination rate, while this relation disappeared in the multiple logistic regression model. Pregnant females with higher education levels might have partial information about COVID-19 vaccines, leading to a negative attitude. Studies on this subject in Türkiye, Italy, and Qatar found similar results [31-33]. Therefore, we should strengthen the transparency of vaccine trials and increase health literacy.

Regarding influenza vaccination, we found that the flu shot rate was very low for that year. This hesitation may arise from miscarriage observations reported in vaccinated pregnant persons during the H1N1 pandemic in 2009 [25]. However, in contrast to the COVID-19 and flu vaccination rates, 94.4% of the participants received or intended to receive the tetanus vaccine. Tetanus vaccine is usually administered to pregnant women in our country and vaccine applications are followed and recorded by family physicians. Therefore, the willingness for tetanus vaccines was significantly higher among study participants compared to influenza and COVID-19 vaccines.

Contrary to expectations, the rate of tetanus vaccination in our study did not differ between individuals with and without COVID-19 vaccination. This observation could support the hypothesis that most pregnant women are not against the vaccine but have reluctant toward the COVID-19 vaccine [34]. This result supports our view that pregnant women are worried for the possible vaccine side effects and should be informed about it.

Study Limitations

Due to some limitations, this study's findings should be interpreted cautiously. The first limitation is that the study's questionnaire was not tested for validity and reliability. Second, we examined the reasons and rates of vaccination but did not follow the unvaccinated group, who may change their beliefs in the future. Thus, all possible problems in real situations may not have been addressed in this study, which indicates the need for further studies in this field.

Conclusion

It is very important to vaccinate the pregnant population, which is at high risk of developing a severe condition against COVID-19, to protect it from the complications of this disease. However, pregnant women are unsure about getting vaccinated for fear of possible side effects, concern that it will harm the baby, and lack of knowledge about the vaccine. Informing them about possible complications of the disease and vaccine side effects will be effective in increasing vaccination rates in these people.

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Conflict of Interest

Authors report no conflict of interest.

Data Availability Statement

The dataset collected and analyzed for the current study is available from the corresponding author and can be obtained upon reasonable request.

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ORIGINAL ARTICLE

Errors in nursing practices: What are the attitudes of nurses toward medical errors?

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Abstract

This study aims to determine the attitudes of nurses towards medical errors and related factors. The study was designed as a descriptive and cross-sectional study. A total of 119 nurses completed a questionnaire on personal information and Medical Errors Attitude Scale. It was determined that nurses' attitudes towards medical errors were positive. It was found that nurses' awareness of medical errors and reporting errors was high. The medical error perception of nurses with less years of work experience in the unit was found to be more negative. Many medical errors are actually caused by preventable conditions. At this point, the best way to prevent medical errors is to create an institutional culture based on patient safety. Within the scope of quality control studies in health institutions, the development of patient safety culture and development of nurses' attitudes towards medical errors should be supported.

Keywords: Nursing, medical error, attitudes, patient safety, hospital errors, quality assurance

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Introduction

Patient safety is a basic principle in the provision of healthcare services. Medical errors are among the most important factors that threaten patient safety in health institutions [1]. The National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) defines a "medication error" as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer [2].-

One in every five adults in the USA who claim that they personally experienced a medical error at some point in their livesare among the millions of patients who suffer from various medical errors and adverse events in the healthcare field each year. In addition, 72.000 of the patients who were exposed to healthcare-related infections during their stay in the hospital died [3] and 12 million outpatients experience diagnostic errors [4]. It has been stated that adverse events handled within the scope of medical errors are observed, especially in one-third of hospital admissions, and one out of five people who receive qualified nursing care experience adverse events [5].

Today, medical errors tend to increase dramatically. At the same time, it continues to exist as the main problem of the health system [6]. Medical errors can include medications, surgery, diagnostics, equipment, or laboratory reports. At the same time, factors such as nurse-to-patient ratio, nurse training and hospital procedures have been identified as important and hidden risk factors for patient safety [7,8]. In a study, it was determined that 91 percent of errors were related to drug administration and 9% were related to medical procedures [9]. The most common type of medication error was determined as giving the wrong dose to the patient at a rate of 32%. Other types of medication errors include wrong medication (12%), wrong patient (20%), missed dose (10%), wrong route (6%), intravenous pump errors (5%), and near misses (6%).

Although, there is still no clear data on medical errors in Turkey, it is estimated to be at a level to be considered [10]. Results of 10.000 files examined in the High Health Council between 1999 and 2004 stated that health personnel were more or less at fault. When looking at 219 cases between 2002 and 2008, 21% of medical malpractice allegedly originated from nurses [11]. The Security Reporting System (SRS) that has been active since 2016 in Turkey is an important platform where health professionals report errors encountered in medical processes, common medical errors, and measures to improve them in health facilities. [12]. It is seen in this system that nurses are in the first place with 31.19% in surgical procedure errors and 33.38% in medication errors [11]. Surgical units are places where undesirable events occur frequently. Apart from the surgical technique applied, most of the errors may be related to the situations a rising from the system, such as preventable delays in the treatment, insufficient patient monitoring and supervision, and the role of incompetent and incompetent nurses in patient care, which are among the components of nursing care. Although drug administration is a process that requires a multidisciplinary approach, medication errors are the most common type of medical error for nurses due to the frequent practices performed by nurses and the fact that many stages of the process are within the duties, authorities and responsibilities of nurses [13].

Today, nurseshave many duties, such as watching complex physiological statuses, researching sophisticated life-saving devices, organizing nursing services to be delivered, and providing health care programs worth millions of dollars. With so many duties, nurses are at risk of making medical errors in patient care. Nurses are an indispensable part of the health system and are called the heartbeat of health services [14]. Nurses, like all employees working in the health system, must have information about patient safety, medical errors, and notification systems to fulfill their responsibilities.

Attitude studies are carried out in order to take precautions in order to prevent negative situations that may occur in the future by learning the attitudes of individuals in a certain period. For this reason, determining the attitudes of health professionals that form the basis

of their knowledge, emotions and behaviors towards medical errors [15] is a guiding factor in determining strategies to prevent medical errors.

For this purpose, it is thought that determining the attitudes of nurses toward medical errors since they see patients 24/7 and perform one-to-one patient care will guide the adoption of appropriate policies for safe care and make necessary administrative arrangements. In addition, this study is expected to raise and increase awareness of medical errors.

Materials and Methods

This was a descriptive cross-sectional study. Data were collected between "April 10- July 30 2017, at Yıldırım Beyazıt University Yenimahalle Training and Research Hospital in Ankara, Turkey. The university had 180 nurses working in a hospital in question. The sample consisted of 119 nurses (67%) who agreed to participate in the study that were not on duty or on leave.

Data were collected by the researcher from a face-to-face interview using The Sociodemographic Questionnaire and Medical Errors Attitude Scale. The nurses were informed on the purpose of the research and content of the forms. After written consent to participate was received, forms were distributed to participants to be completed with a face-to-face interview. Data collection was completed in 15 to 20 minutes.

Assessment Tools

The Sociodemographic Questionnaire; consists of 15 questions, prepared by the researchers after researching the literature, questioning the introductory characteristics of nurses (gender, marital status, educational status, *etc.*), their professional characteristics (work experience, unit, *etc.*) and some statements related to medical error (meaning of medical error, witness status, *etc.*).

Medical Errors Attitude Scale**;** was developed by Güleç and İntepeler to determine the attitudes of physicians and nurses in medical errors [16]. It is the only scale that is used to reveal the attitudes of physicians and nurses towards medical errors in our country, and which deals with the cognitive, emotional and behavioral elements of attitude towards medical errors. The scale consists of 16 five-point Likert type questions and three sub-dimension: perception of medical error, approach to medical error and causes of medical error. Two items in the scale (10^{th} and 13^{th} items) are scored in reverse. The sub-dimension score is summed and divided by the number of sub-dimension items. The score obtained is evaluated between 1-5 where the cut-off point of the scale was determined as 3. If an average of less than 3 points is obtained from the scale, medical error attitudes are considered negative, and a score of 3 and above is evaluated as positive medical error attitudes. Having a negative attitude means that employees' awareness of the importance of medical errors and error reporting is low; positive attitude shows that employees are highly aware of the importance of medical errors and error reporting. *Cronbach's* alpha reliability coefficient was found as 0.75 [16]. In this study, *Cronbach'* alpha reliability coefficient of scale 0.715.

Statistical Analysis

Data were evaluated using SPSS for Windows 25.0 software package program. Descriptive statistics (number, percentage, mean, standard deviation, min and max) were used while evaluating the data. Compliance with normal distribution was examined with the Q-Q Plot drawing. For the comparison of normally distributed quantitative data, independent *t* test was used for the difference between two independent groups, and one-way analysis of variance was used for comparing more than two groups. Regression analysis was used to test whether the independent variable had a statistically significant effect on the dependent variable. Four different models were created in which the participants' demographic characteristics were independent variables and scales and sub-dimensions were dependent variables. It was observed that the models created were not statistically significant and regression analysis could not be interpreted. Total score averages and the mean scores of the sub-dimensions were calculated. The results were evaluated in 95% confidence interval and $p < 0.05$ significance value.

Ethical Considerations**:** Ethics committee permission (Reference Number: 2017/07 and date 13.03.2017) for the research, the institution

permit and the permission of the owner of the scaleused were received. Also, researchers explained the purpose, methods used and benefits of the study to the nurses and asked whether they were willing to participate in the study. Participants' written consent was obtained.

Results

The average age of nurses participating in the study was 38.83±5.21years. The findings also included the following: 93.3% of the nurses were women; 79.8% were married; 47.1% completed undergraduate education; 37.8% had 21 years or more work experience; and 47.1% worked in special units (emergency, intensive care, operating room).

The total score average of the nurses on the Medical Errors Attitude Scale was found to be 3.28±0.31. The average scores they received from the sub-dimension were as follows: Medical error perception, 1.15±0.36; medical error approach,1.94±0.21; and medical error causes, 1.85±0.34 (Table 1).

The participants were asked to answer the question "What do you understand by the term medical error?". A total of 115 participants answered this question and stated more than one answer. The expressions most frequently written by the participants are as follows: "misapplication" (n=49), "errors experienced during drug administration" (n=24), "healthcare worker error" (n=24), "patient harm" (n=15), "lack of knowledge and inexperience" (n=6), "insufficient follow-up" (n=5), "Unnecessary action" (n=5), "unintentional error" (n=3), "side effect" (n=1), "I don't know" (n=1).

In another question, participants were asked to give an example of "medical error". A total of 113 nurses answered this question. The three most frequently given answers to this question were as follows: "misapplication" (medication administration errors/blood transfusion errors/ wrong treatment/order application errors); "wrong side for surgery"; and "wrong surgery to the wrong patient."

Table 2 shows the comparison of demographic characteristics of nurses and mean scores obtained from Medical Errors Attitude Scale and its sub-dimensions. There was no statistically significant difference between the nurses' age, gender, educational status, unit of employment, years of work experience, and mean score and sub-dimension ($p > 0.05$). A statistical significance was found between the medical error perception ($p=0.036$) and medical error causes ($p=0.047$) sub-dimension when the nurses' years of work experience in the unit and scale mean scores were compared.

Table 3 shows the total score averages of items related to Medical Errors Attitude Scale sub-dimensions. While the highest average of the first three points is the average of the items "medical errors and reasons must be discussed openly", "commited medical errors and their causes should be discussed among executives" and "high number of care taking patients increases the medical error number respectively, the lowest point average belongs to the item "individual who makes the medical error is innocent".

Discussion

To reduce medical errors, it is important to know the health professionals' perceptions of medical errors, causes of medical errors they encounter, and their approach when they encounter medical errors. Healthcare workers are concerned about being shamed by their colleagues and records of

Table 1. The nurses' average scores medical errors attitude scale and sub-dimension (n=119).

Sub-dimension	Mean±SD	Min	Max
Medical Error Perception	1.15±0.36	1.00	2.00
Approach to Medical Errors	1.94±0.21	1.00	2.00
Medical Error Reasons	1.85±0.34	1.00	2.00
Total	**3.28±0.31**	**2.38**	**3.89**

errors filed on their records [17]. Such anxieties guide their perception and attitude toward medical errors. There are studies examining the attitudes of physicians and nurses, who constitute an important part of the healthcare team, towards medical errors. In a study carried out in our country in which the same scale was used [18], it was indicated that physicians and nurses' mean medical error attitude averages were identical, and their awareness levels towards medical errors were positive. In the other two studies, physicians' total medical error attitude scores were interpreted as positive, with the mean of 3.69 [19] and 3.46 [20], similar to our study. In this study, only nurses' attitudes towards medical errors were investigated and it was found that nurses were quite aware of the importance of medical errors and error reporting. Similar results were found in studies using the same scale [18,21,22]. In this study, no significant difference was found between the mean scores of Medical Errors Attitude Scale and sociodemographic variables.

Table 2. Comparison of the socio-demographic characteristics of nurses with the medical errors attitude scale and sub-dimension (n=119).

Characteristics	Medical Error Perception X±SD	Approach to Medical Errors X±SD	Medical Error Reasons X±SD	Total X±SD
Gender				
Female	1.16±0.37	1.95±0.20	1.87±0.33	3.29±0.30
Male	1.12±0.35	1.87±0.35	1.75±0.46	3.14±0.40
Statistical significance	t=0.275 p=0.784	t=0.994 p=0.322	t=0.988 p=0.325	t=1.318 p=0.190
Marital status				
Married	1.17±0.38	1.96±0.17	1.86±0.34	3.28±0.30
Single	1.08±0.28	1.87±0.33	1.87±0.33	3.28±0.35
Statistical significance	t=1.139 p=0.257	t=1.311 p=0.201	t=-0.151 p=0.880	t=-0.080 p=0.936
Education qualification				
Health vocational high school	1.33±0.50	1.88±0.33	1.66±0.50	3.19±0.42
Associate degree license	1.13±0.34	1.94±0.22	1.86±0.34	3.23±0.30
Bachelor's degree	1.14±0.35	1.94±0.00	1.89±031	3.31±0.32
MSc/Phd	1.17±0.39	2.00±0.00	1.88±0.33	3.31±0.34
Statistical significance	F=0.770 p=0.513	F=0.528 p=0.664	F=1.148 p=0.333	F=0.838 p=0.476
Unit				
Internal units	1.14±035	1.98±0.14	1.92±0.27	3.28±0.27
Surgical units	1.23±0.43	2.00±0.00	1.76±0.43	3.33±0.26
Specialty units (ICU/Emergency / operating room)	1.16±0.37	1.91±0.28	1.83±0.37	3.27±0.35
Statistical significance	F=0.311 p=0.733	F=1.718 p=0.184	F=1.917 p=0.272	F=0.201 p=0.819
Nursing work experience				
1-10 years	1.18±0.39	1.95±0.21	1.95±0.21	3.31±0.31
11-20 years	1.13±0.34	1.94±0.23	1.86±0.34	3.26±0.29
21 years and over	1.17±0.38	1.95±0.20	1.82±0.38	3.28±0.34
Statistical significance	F=0.212 p=0.809	F=0.050 p=0.951	F=1.104 p=0.335	F=0.188 p=0.829
Working time in unit				
1-5 years	1.11±0.32	1.94±0.22	1.90±0.29	3.29±0.30
6 years and over	1.29±0.46	1.96±0.19	1.74±0.44	3.25±0.35
Statistical significance	t=-1.845 **p=0.036**	t=-0.359 p=0.721	t=1.766 **p=0.047**	t=0.581 p=0.562

In this study, nurses were asked to define medical errors and provide examples. Nurses mostly defined medical error as "wrong application" or "making mistakes." In addition, nurses emphasized indirectly harming patients and make a mistake in practice while defining medical errors. Participating nurses in this study prioritized the following examples of medical errors: "medicine application errors", "blood transfusion errors", "wrong treatment", and "errors in order application." In a study by Solak Kabataş et al., nurses listed types of medical errors most frequently encountered in the hospital as "hospital infection", "cutting/ piercing device injuries", and "bed sores" [23]. In another study, the distribution of the types of medical errors of nurses was determined as "wrong drug administration" (56.1%), "drug administration in a wrong way", and "wrong dose of drug administration" [24]. Still in another study, nurses working in the pediatrics clinic stated the conditions with drug errors as "wrong preparation of the drug", "administering the drug in the wrong way", and "administering the drug in the wrong dose" [25]. In fact, medication errors are only one of the areas covered by medical errors. Grober and Bohnen explain the concept of medical error as any negligence or action that contributes or may contribute to undesirable results during planning or implementation [26]. In addition, they emphasizes why the medical error occurs (negligence, planning error, *etc.*) and includes all the processes that cause/may lead to the error whether or not the medical error harms the person [26]. One of the types of medical errors is medication errors. Errors such as drug administration in the wrong dose/form and drug interactions are evaluated within this scope, and the causes of drug errors can be listed as unclear drug administration instructions, drug administration errors, miscalculation of drug doses, wrong drug administration, and drug follow-up errors [27]. The next part of the discussion is within the context of the Medical Errors Attitude Scale sub-dimension.

One of the important factors in preventing medical errors is to be aware of these errors and perceive what constitutes a medical error. In solving a problem, it is important to first identify the problem, accept its existence, and find solutions [28]. In this research, the medical error perception sub-dimension score was found to be low, and

Table 3. Total point averages related items on medical errors attitude scale sub-dimensions (n=119).

Medical Errors Attitude Scale	Mean	SD
Medical Error Perception		
1. The person who has made the medical error is innocent.	2.10	0.81
2. One must be empathetical when a medical error has been reported.	3.18	1.04
Approach to Medical Errors		
3. Medical errors and their causes should be discussed openly with employees.	4.24	0.80
8. I am in favor of reporting any mistakes which have been made.	4.10	0.78
10. I avoid reporting medical errors I have made.	2.12	0.73
11. Managers should take an approach that supports learning from mistakes.	4.10	0.77
12. Medical errors and their causes should be discussed among the managers.	4.18	0.72
13. If a medical error is prevented before it occurres, it does not need to be reported.	2.98	1.20
14. Medical errors should be explained to the patient/patient relative..	3.19	0.81
Medical Error Reasons		
4. Medical errors result from a lack of communication of the person who makes the mistake.	3.07	0.99
5. Medical errors are caused by system deficiencies.	3.42	0.87
6. Medical errors result from the lack of knowledge of the person who makes the mistake.	3.56	0.98
7. The high number of patients receiving care increases the number of medical errors.	4.15	0.94
9. Long working hours increase medical errors	3.96	0.97
15. Many medical errors are actually caused by preventable situations.	3.91	0.82
16. Reporting medical errors improves patient safety	4.06	0.77

ın this sub-dimension, nurses' awareness of the importance of perceiving medical error was found to be low. Studies conducted using the same assessment tool in relation to the subject also concluded that attitude was negative in the perception of medical error [22,25,29]. This finding means that nurses in this study had low awareness of the importance of medical errors and error reporting.

Attitudes toward reporting medical errors are among the primary practices for preventing medical errors. Unlike this study and other research results, Akın Korhan et al., reported positive perceptions of medical errors in their study to determine nurses' attitudes toward medical errors with 151 nurses [21]. It is thought that the variability of these findings may be due to the approach of hospital managers toward their employees and medical policies regarding medical errors.

In this study, a significant difference was found only between the year of work experience in the unit and average medical error perception score. The medical error perception of nurses with less years of work experience in the unit was found to be more negative. This result shows that the less experienced nurses who participated in the study had a lower level of awareness of the importance of medical error compared to the nurses with more work experience.

Results of a study in the literature are similar to those of this study [22,30]. In another study conducted on nurses in our country, as the years of work experience increased, error reporting decreased. Nurses who participated in that study believed that they could handle medical errors among themselves (28.9%), reporting medicine-relatederrors is perceived as a personal failure (8.8%), and they are concerned about putting their jobs at risk (4.4%) [31].

It can be concluded that nurses with less years of experience in the unit have more negative attitude toward medical errors because of different professional training, personal characteristics, difficulties experienced while adapting to the unit, and the possibility of being blamed for errors. Almost half of the nurses (47.6%) who participated in the study of Yiğitbaş **et al.** stated that experience was the reason for medical errors [32].

Knowing the factors that cause errors, discussing them to produce solutions and having managers take the solutions into consideration are important in the resolution of medical errors and reduction of frequency of occurrence. In this study, it has been found that nurses are quite aware of the importance they show in the approach to medical error. Analysis of items in approaches to medical error sub-dimension revealed the following first three expressions with the highest mean scores according to the responses: "Medical errors and reasons must be discussed openly", "Commited medical errors and their causes should be discussed among executives", and "I abstain from reporting all medical errors I made" (Table 3). In light of these statements, it can be said that nurses are in favor of reporting medical errors made. Similarly, in a study conducted by Güven et al, it was determined that the statement with the highest average score in this sub-dimension was "Medical errors and reasons must be discussed openly" [22].

The statement "I abstain from reporting all medical errors I made" received the lowest average score in this sub-dimension. Barriers perceived by nurses to reporting drug management errors were fear of losing the trust of the patient and family, fear of the manager's use of error report as evidence for negative evaluation, and fear of causing patient-nurse disputes [33]. Other reasons for nurses not reporting errors include "the patient was notharmed", "no other person knew about the error", "complexity of the reporting process", and "anxiety about legal punishment" [25,33]. It is important to identify a problem, accept its existence, and develop a method to solve it in preventing medical errors in health services. Therefore, sharing the errors with clinical nurses and administrators and strengthening cooperation while finding solutions regarding medical errors were believed to be effective in minimizing harm to the patients.

The adoption of institutional culture by administrative nurses and their approach to

nurses are important in detecting and solving medical errors. Some important factors affecting employees' approach to medical errors are directing them to give accurate reports, encouraging them to take lessons from errors, providing education, and supporting colleagues [25]. In his study with nurses, Delacroix [34] emphasized that the causes of medical errors should be investigated, and the development of professional competence at a personal and institutional scale in preventing medical errors should be discussed.

In this study, no significant difference was found between the approach to medical error average sub-dimension score and sociodemographic characteristics. Similar results were obtained in other studies in the literatüre [11,35]. In another studies [18,36] conducted on nurses a significant difference was found between gender, the clinic they worked in, years of work experience, and approach to medical error sub-dimension. It should be noted that attitudes toward the explanation of medical errors differ significantly between institutions and cultures.

In this study, it was determined that nurses were aware of the importance they showed against the sub-dimension of the cause of medical errors. The statement "High number of care taking patients increases the medical error number" received the highest average score in this sub-dimension. Caring for too many patients can lead to distraction, loss of concentration, and extreme fatigue. These are the factors that will increase the possibility of error by healthcare professionals. Additionally, the number of patients who are cared for, the number of nurses working, working with inadequate personnel, stress of the work environment, feelings of boredom and burnout are among the causes of medical errors [22,25,35,37].

According to the study conducted by Yiğitbaş et al, fatigue (65.3%), heavy workload (63.7%) and stress (58.9%) are the first three factors that cause medical errors [32]. In addition, other studies stressed that the presence of dysfunctional protocols and procedures, absence of any procedures, lack of communication, work outside the job description, and excessive workload may increase the tendency for medical errors [24,37]. In a study conducted by Er and Altuntaş to determine nurses' perception of medical errors, more than half of the participants (67.9%) stated that nurses who undertake non-nursing duties (secretariat) as the cause of medical errors [38].

Causes of medical errors also include inexperience and lack of knowledge. Experiences in the field of work lead to professional maturity and therefore positively affect the way nurses approach the patient. In a study conducted by Er and Altuntas in determining the opinions of nurses about the causes of medical errors, nurses' inexperience and inadequate professional knowledge and skills are among the reasons for medical errors [38]. In this study, it was determined that nurses with lower years of work experience (one to five years) had high attitude toward the causes of medical errors. Nurses with more years of work experience witnessed more medical errors during their professional life and this might make them get used to medical errors. In the literature, it has been stated that nurses' medication dispensing errors occur in the first five years of working, and that possibility of making medical errors is higher in nurses with less work experience [36,38].

Many medical errors are actually caused by preventable conditions. At this point, the best way to prevent medical errors is to create an institutional culture based on patient safety. In the prevention of medical errors, recognition of errors in advance, and reporting the event help develop strategies for not repeating the errors. By doing so, potential problems, threats, and dangers that may occur in the future can be prevented in the early stages.

Conclusion

Within the scope of quality studies in health institutions, the development of "patient safety" culture should be supported by the development of nurses' attitudes toward medical errors. Furthermore, it is suggested that wide-ranged studies be done with larger nurse groups, especially in clinics where observation-based behavior evaluations can take place. Although nurses' attitudes toward medical errors are generally positive, their low response to the item

"The person who made the medical mistake is not guilty" in the medical error subdimension reveals flaws in their understanding and perception of what medical errors.

In this study, the differences in the nurses' definitions of what constitutes a medical error show differences in the identification and naming of medical errors. Therefore, nurses should be encouraged to develop and use critical thinking skills.

This study has provided some insights on medical errors and factors affecting these errors. The information obtained from this study can contribute to educational programs that support the recognition of medical errors for quality patient care.

Key points for policy, practice and/or research

- Nurses' attitudes toward medical errors are formed mainly by systematic problems rather than characteristics of nurses, except for a few sociodemographic features. Although nurses' attitudes toward medical errors are generally positive, their low response to the item "The person who made the medical mistake is not guilty" in the medical error sub-dimension reveals flaws in their understanding and perception of what medical erroris.
- In this study, the differences in the nurses' definitions of what constitutes a medical error show differences in the identification and naming of medical errors. Therefore, nurses should be encouraged to develop and use critical thinking skills.
- This study has provided some insights on medical errors and factors affecting these errors. The information obtained from this study can contribute to educational programs that support the recognition of medical errors. In addition, our findings may help in taking the necessary measures to reduce or eliminate barriers to reporting medical errors. In doing so, desired quality of patient care can be provided.

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Conflict of Interest

The authors declares that there is no conflict of interest.

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ORIGINAL ARTICLE

Elderly expectation toward their family, society, and government: A cross-sectional observational study

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Abstract

The elderly face very challenging situations due to their mental and physical conditions. Like the other country in the world, Bangladesh Government has enacted laws to protect the elderly rights. However, the law does not seem to represent what the elderly actually needs. Therefore, 385 elderly people, aged between 60 and 90 years were surveyed to understand their expectations from family, society, and government. There were 57.1% men and 42.9% women. Most of the elderly (80%) were educated. Just over half (53.5%) had ordinary mental and physical health, while a quarter (31.4%) had good status. More than half (53%) of the participants required 2000–5000 BDTK (Bangladeshi Taka) equivalent to $20-50 to cover monthly treatment expenditures. The majority (67.3%) felt government Old Age Allowance should be increased to BDT 5,000 ($50). Of 13.8% of individuals experienced harsh discourse from family because of the cost of therapy. However, 16.9% of people choose not to respond to this question. More than half (57.4%) of the respondents' thought caregivers were insufficient. One-third felt that legislation should be changed to take care of parents (33.5%) and One-third felt that children should take care of more (33.5%). Some (3.6%) thought that children should act as they did in their childhood respectively. Almost half (44.2%) of respondents did not know that the elderly should receive a separate senior citizen card for preferential treatment, yet 51.9% thought this. Some (44.7%) felt the elderly should get priority in any queue and discounts in Bus/Uber/Rickshaw. Results also showed that expectation is more than the service provided. Further, a one-stop elderly care clinic is required to provide integrated care and support for the quality of life of the elderly.

Keywords: Ageing, geriatric, older, expectation, health status

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Introduction

The term older typically refers to a generation that includes all citizens of the country who are 60 years of age or older according to the National Policy on Aging [1]. Currently, there are 720 million individuals in the world who are old and that will increase to 1.5 billion by 2050 [2]. Presently, Bangladesh has approximately 15 million people who are 60 years of age or older which is 7% of the total population. However, by 2050, that figure will grow to double (36 million), almost 22% of the country's population [3]. Governments and social systems face significant challenges by the growing number of ageing and the shortage of workers to care for the elderly. The emergence of cutting-edge technologies like AI (artificial intelligence), IATs (intelligent assistant technologies), and information technology opens up new technological possibilities and prospective solutions to ease the strain of elderly care and raise the standard of care of old home [4]. A proper understanding of the need and expectations of elderly people to be assessed before formulating their care plan. Due to a lack of appropriate community supports, and the family are the main caretaker usually for an elderly person who has a major physical and mental illness [5]. However, over the last two decades, the conventional supportive family structure has been crumbling even in low and moderate-income nations [5]. Healthcare for the aged has become a vital problem as a result of the Spanish flu pandemic, and the growing number of medical issues that affect the old population [6]. A commitment of the government of Bangladesh has been reflected in its announcement to work toward attaining UHC (Universal Health Coverage). UHC comprises health services and financial risk protection under SDGs (Sustainable Development Goals) with target no SDG 3.8.1 and SDG 3.8.2 [7]. Bangladesh has made incredible strides in recent years to increase access to crucial public basic healthcare like immunisation [8]. Though it needs to be mentioned that elderly health care is still a challenge for this nation. However, Bangladesh has implemented a limited number of programmes for the elderly, including a pension system, retirement benefits, and Old Age Allowance (OAA), Allowances for the Widow, Deserted and Destitute Women, and the Vulnerable Group Development (VGF) under the Social Safety Net (SSN) [9].

Regrettably, a large section of the senior population is still not adequately served by these services. The Bangladesh government started paying the elderly 100 BDT (where 100 BDT=$1.08) per month under the OAA programme in 1997–1998. At first, 0.4 million aged people registered for this programme. Currently, 5.701 million senior citizens receive a raise amount to 500 BDT ($6 approx.) per month [10]. The difficulty is that the sum given is minimal, and obtaining a registrar a huge impediment. Despite the information and technology ministry and technology's best efforts to gather all data with the assistance of the IT industry, the majority of the senior people are ignorant of this service because lack of formal education. Additionally, corruption makes it more difficult to provide this service to the elderly and vulnerable demographic [11].

Demography, aged care and fragility have been the key themes of research on the elderly. Bangladesh's government has enacted laws that are focused on the elderly. As a result, the law does not accurately represent how the old are seen and treated. The expectation of the elderly is a crucial factor in properly tailoring the strategy to meet their requirements and enhance their quality of life and well-being. This article discusses the demography of elderly in Bangladesh. We also figure out the health status of elderly and evaluate the expectation of elderly toward family, society, and government as well.

Materials and Methods

In order to understand how elderly people, view on their family, society and government, a cross-sectional observational study was conducted on 385 elderly persons between January and June 2022 at the Bangladesh Bioethics Society. This study also points out the health status of the elderly. The sampling method was intended. Selected three research areas in Mirpur, Dhaka City, were elderly folks. Ethical Review Committee of the Bangladesh Bioethics Society reviewed and accepted the research protocol.

No. ERC/BBS/26/2022 for ethical clearance. Informed consent was obtained before the start of the study.

Data were collected by a structured questionnaire with 40 questions. It took participants 15 to 20 minutes to complete. Because older people (those 60 and older) are more susceptible to COVID 19, several interviews have been conducted over the phone if the interviewees are reluctant to talk to strangers. The conversations were taped. After the information was added to the statistics database, the phone record was deleted. No participant's voice was saved for identification purposes as a result. Yet, the majority of the participants underwent thorough face-to-face interviews while adhering to all safety precautions. For their protection, face masks, hand sanitizers, face shields, and PPEs were made available.

Statistical analysis: Raosoft analysed the sampling procedure's statistical underpinnings by accounting for the response distribution's 50%, the margin of error's 5%, and the confidence interval's 95%. The evaluation of demographic and other factors was done using frequency and percentage distributions. Comparison between gender and abuse with treatment cost was done by Chi-square test. SPSS software version 22.0. was used for statistics.

Result

Socio-demography

The demographics of the elderly are shown in Table 1. The median age ±SD was 69.12±7.82 and the age range was between 60 and 90 years. Of 42.9% of people were women and 57.1% were men. Most of the (80%) elderly population of our study were educated, above Secondary School Certificate (SSC), where Bachelor degree (27.0%), Higher School Certificate (21.8%), SSC (11.9%), and Master degree (6.5%). Some (20%) studied up to class 5-10, however, only 12.7% had no formal education. In our study, elderly male people were more than female though the gender difference was not significant (not shown in table).

Health Status

Just over half (53.5%) had ordinary mental and physical health, while a quarter (31.4%) had good status. Cumulatively, 84.5% of all respondents

Table 1. Socio-demographic information (n=385).

Gender	Male	220 (57.1%)
	Female	165 (42.9%)
Age	Maximum	90 years
	Minimum	60 years
Marital status	Single	21 (5.5%)
	Married	229 (59.5%)
	Unmarried	6 (1.6%)
	Widow/widower	129 (33.5%)
Religion	Muslim	362 (94.0%)
	Hindu	23 (6.0%)
Educational qualification	No education	49 (12.7%)
	Up to class 5	40 (10.4%)
	Class 6-10	37 (9.6%)
	SSC	46 (11.9%)
	HSC	84 (21.8%)
	Bachelor	104 (27.0%)
	Higher	25 (6.5%)
Place	Government Shelter Home, Mirpur	216 (56.1%)
	Health Science (BUHS), Hospital, Mirpur, Dhaka	102 (26.5%)
	Child and Old Age Care Centre, Kalayanpur, Private Home, Mirpur	67 (17.4%)
Dependency status	Self-dependent	159 (41.3%)
	Dependent on Family Members	223 (57.9%)
	Dependent on others	3 (0.8%)

were healthy overall. More than 10 percent were in poor physical and mental health. Of 1% of people were sad and bedridden (Table 2). More than half (53%) of the participants required 2000–5000/= BDT ($20-50) to cover monthly treatment expenditures. However, less than a fifth (18.7%) required between 5000 and 10,000 BDT ($50-100). Half (51.2%) of the cases, the son paid for the treatment, and in one-third (36.4%) of the cases, the old person paid for the treatment themselves. Of 13.8% of respondents were harassed because of the cost of therapy. 16.9% of people choose not to respond to this question (Table 2). More than half (54.5%) routinely took medications, although fewer than half (45.5%) were unable to do so because they could not afford the medications (18.4%) or forgot to take them (22.9%) (Table 2).

Expectations of Elderly Toward Family and Society

In response to the query, who provided care during illness? In the event of illness, respondents were cared for by their daughter (23.6%), son (22.3%), daughter-in-law (19.7%), and spouse (15.1%) respectively (Table 3). More than half (57.4%) of the respondents' thought caregivers were insufficient, nevertheless. Less than half (48.3%) require special attention when eating, drinking, or receiving medical treatment. However, one-third (33.5%) of participants thought that the legislation should be changed to take care of parents. Of 33.5% the elderly felt children should take care of more and some (3.6%) thought that kids should act as they did as kids (Table 2). In a question on how much care they received. Just fewer than ten percent of people believed that their family members were providing adequate care for them (Table 3). A little less than half of the respondents (44.7%) felt that elderly should get priority in any queue. Few wanted sitting places for the elderly, and few felt there should be discounts in Bus/uber/rickshaw for elderly.

Table 2. Heath of elderly (n=385).

Physical health status	Very good	6 (1.6%)
	Good	121(31.4%)
	Average	206 (53.5%)
	Poor	48 (12.5%)
	Bed ridden	4 (1.0%)
Mental health status	Very good	7(1.8%)
	Good	119 (30.9%)
	Average	193 (50.1%)
	Poor	62 (16.%)
	Depressed	4 (1.0%)
Treatment cost per month	<2000	100 (26.0%)
	2000 to 5000	204(53.0%)
	5000 to 10,000	72 (18.7%)
	10,000 to 20,000	7(1.8%)
	20,000-30,000	2(0.5%)
Who bear the cost of treatment	Self	140 (36.4%)
	Son	197 (51.2%)
	Daughter	24 (6.2%)
	Grandchild	6(1.6%)
	Relative	5(1.3%)
	Brother	6(1.6%)
	Spouse	7(1.8%)
Abused due to treatment cost	Yes	53 (13.8%)
	No	267(69.4%)
	Don't want to answer	65(16.9%)
Takes medicine regularly	Yes	210 (54.5%)
	No	175(45.5%)
Cause of not taking medicine regularly	Can't afford	71(18.4%)
	Forget	88(22.9%)
	Don't feel like	18(4.7%)
	Not applicable	208 (54.0%)

Expectation of Elderly from the Government

The large majority of respondents (73.8%) believed that Bangladesh should have geriatric hospitals in each district. Less than half (44.2%) of respondents did not know that the elderly should receive a separate senior citizen card for preferential treatment, yet 51.9% thought this (Table 4).

Though, 67.3% of respondents thought the government's Old Age Allowance was not enough, and the majority (61.0%) thought it should be increased to $5,000 per month (Table 4). Less than a quarter of the elderly expect the government and society should improve their conditions and Government should take responsibility to protect elderly rights (19.5%), Government support should be available and adequate (21.8%), establish free treatment facility and easy entrance to Community Health service centres aside from Government Hospitals (20.8%), establish more numbers of hospitals for the elderly (18.4%), Governments should adopt a Comprehend the Elderly Act (19.5%). (Table 4).

Discussion

Demography

The mean age ± SD age of our participants was 69.12±7.82, ranged between 60 to 90 years. The majority (41%) belonged to the age between 60–65 years, however, the age group between 60 and 69 year respondents were 56.9%. This result was consistent with Nepal. More than a quarter (27.9%) of the Nepalese population was between the ages of 60 and 64 years. Their mean age of them was 68.8 ±7.1 [12]. In comparison to Nepal, the Bangladeshi elderly population has more young elderly, and makes them more active and independent than other age group. On the other hand, the life expectancy of UK population (62.4 years for men and 60.2 years for women) is much lesser than Bangladesh [13]. According to report of 2022, the life expectancy of Bangladesh was 74.3 years (male 73 years and female 75.6 years) [14]. So, it may be concluded that even in the developed world, health inequality persists for the elderly population. Moreover, in our study, more them half (57.9%) were dependent on family members. However, less than half (41.3)

Table 3. Expectation of the elderly toward family and society (n=385).

Who takes care during illness	Spouse	58 (15.1%)
	Son	86(22.3%)
	Daughter	91(23.6%)
	Daughter in law	76(19.7%)
	Grand child	22(5.7%)
	Relatives	46 (11.9%)
Has adequate caregivers	Yes	164(42.6%)
	No	221(57.4%)
Types of special provision	Feedings	9(2.3%)
	Rest and refreshment	51 (13.2%)
	Health care	44 (11.4%)
	All of these	87 (22.6%)
	Not applicable	194 (50.4%)
Thoughts on health care Society should do toward elderly	Taking care properly	113 (29.4%)
	Should take care more	129 (33.5%)
	Law should be done to take care of parents/elderly	129 (33.5%)
	Should do what we did at their childhood	14 (3.6%)
Society should do toward elderly	Get priority of elderly in any line or queue	172 (44.7%)
	Sitting place	18 (4.7%)
	Discount in Bus/uber/rickshaw	23 (6.0%)
	Supportive attitude	1 (0.3%)

were still self-dependent (Table 3) and more than a quarter (36.4%) are active and bore themselves (Table 2). The dependency status among the Indian elderly population (70.7%) is much higher than in Bangladesh [15]. Considering the age group, life expectancy, and dependency of the elderly population, the Bangladesh government may consider increasing the retirement age from 60 years to 65 years. It may reflect the positive image of elderly toward their family and society [16].

The vast majority of the (80%) elderly population of our study were educated, above SSC, with Bachelor degree (27.0%), HSC (21.8%), SSC (11.9%), and Master degree (6.5) respectively. Only 12.7% had no formal education. Our result is consistent with the result of other in Bangladesh [1]. In their study those who lived in urban area were more educated (11.4% SSC, 25.5% HSC, 37.8% above primary education) then rural. Only 12.6% were illiterate [1].

Our study population consists of a little more males than females. Similar gender difference has been found in Bangladesh, where 45% were females and 55% were males [17] which is consistent with our study. Though a study also found that they had 72% of female elderly [18]. They found more female old people as they collect data from old home care only. However, we consider old home and also a hospital for the

Table 4. Expectation of the elderly toward government (n=385).

Government is doing enough for elderly population	Yes	86 (22.3%)
	No	236 (61.3%)
	Don't want to answer	63 (16.4%)
Bangladesh needs geriatric hospital in every district	Yes	284 (73.8%)
	No	20 (5.2%)
	Don't know	81(21.0%)
Elderly population should have special senior citizen card for special attention	Yes	200 (51.9%)
	No	15 (3.9%)
	No idea	170 (44.2%)
Senior citizen allowance given by the government is enough	Yes	60 (15.6%)
	No	259 (67.3%)
	Don't want to answer	66 (17.1%)
How much allowance should be the better?	Ok with existing amount	58 (15.1%)
	5,000/month	235 (61.0%)
	10,000/month	92 (23.9%)
Getting any government support	Yes	103 (26.8%)
	No	282 (73.2%)
Getting any non-government support	Yes	29 (7.5%)
	No	356 (92.5%)
Expectation from government and society to enhance the conditions of the elderly	Government should take responsibility to protect elderly rights	75 (19.5%)
	Government support should be available and adequate	84 (21.8%)
	Governments should adopt a comprehensive health policy	65 (16.9%)
	Establish more numbers of hospitals for the elderly	71 (18.4%)
	Establish free treatment facility and easy entrance to Community Health service centres besides Government Hospitals	80 (20.8%)
	Establish more number of old homes at district levels	10 (2.6%)
Thoughts on governments responsibility regarding health of elderly	OK	126 (32.7%)
	Should take more initiative	178 (46.2%)
	Law should be done like USA	80(20.8%)
	Increase financial support	1(0.3)

inclusion of general old people. Nevertheless, in many countries geriatric population has a higher ratio for female [12].

Health Status

In our study, the bulk of research participants had in good health. Only 10 percent were in poor physical and mental health and 1% of people were sad and bedridden. Another study projected that of 74% elderly had poor to very poor health as the study population of them was from rural Bangladesh and illiterate [11]. Moreover, 40% of rural elder people have limited access to water, sanitation and health [19] and suffered from chronic malnutrition [20].

However, more than half (53%) of our study respondents required monthly treatment costs ranging from 2,000 to 5,000 BDT, and a quarter needed between 5,000 and 10,000 BDT. Research has shown almost similar results. An average of BDT 1,586 to 1,689 was paid by Bangladeshi elderly for healthcare from out of pocket, in conditional healthcare payment varied between BDT 2,106.6 to 2,241 [8].

However, in our study, more than half of the cases, the son paid for the treatment, and in one-third of cases, respondents paid their treatment cost by themselves. In addition, in our study, of 13.8% of individuals experienced harsh discourse because of the cost of therapy. Of 16.9% participants wished not to respond to such a question. If we consider, those who did not wish to answer this question, may have the same suffering as above, Therefore, total 30.7% of respondents were harassed because of the cost of therapy. This outcome remains the same elsewhere in Bangladesh [21]. Majority (61.0%) of the out study participants felt that the government's OAA was not enough, and they thought it should be increased to BDT 5,000 per month. If the government increases the OAA, elderly harassment may be lessened. However, we did not research the root cause of the harassment of the elderly in our research.

Expectations from the Family and Society

According to 57.4% of our study population, they were not adequately cared by their family members. More than one-third (33.5%) of our study participants thought that the legislation should be changed to take care of parents and the elderly and some thought that children should act as they did as kids (3.6%). However, aging is a natural process, but it is not easy for elderly people to lead happy life without support [22]. Therefore, retrospective support should come from family, society and at large from the government.

However, the problem is more pronounced in the urban elderly population now a day. As their children have a good educational background, they try to migrate to foreign countries keeping their parents alone at home. So they suffer from loneliness and feel neglected [23]. To combat this problem, the 'Parents care act 2013 was formulated. The law states that, children shall "take good care of their parents and provide them with food and shelter. Each of the children will have to pay 10% of their total income regularly to their parents if they do not live with their parents. In violation of the law, there is the provision of BDT 200,000 as fine and, in default, six months' jail" [24]. The biggest drawback is that it is implemented yet. Parent's Care Act 2013 should implement for retrospective care of the elderly.

Expectation from Government

In our study maximum (73.8%) of the study population considers every district in Bangladesh should have a geriatric hospital. As they mainly suffer from many age-related health issues and it makes more complicated when they face the challenges related to non-communicable diseases [18].

A little over half (51.9%) of the study population consider they should have senior citizen preferential health system card. A little less than half of the respondents (44.7%) felt that the elderly should get priority in any queue. Few wanted for sitting place for the elderly, and few felt there should have discount in Bus/Uber/Rickshaw for elderly. So, it may be concluded that there

is significant gap between elderly people expectation and care provided by the government. An integrated care approach is required to provide better support to the elderly population.

Limitation

There were undoubtedly some restrictions in the current investigation. The results of this survey, which was based on a questionnaire, were dependent on the responses that were given. Respondents only came from one part of Dhaka city only; therefore, we cannot speak for all of Bangladesh.

Conclusion

Most of the participants in our study were educated, belonged to the middle-income class and had good health. Men participants scored not significantly higher than women. Most (41%) were between the ages of 60 and 65. More than half (53%) of the participants required 2,000–5,000 BDTK to cover monthly treatment expenditures. Of 13.8% of individuals experienced harsh discourse because of the cost of therapy. However, 16.9% of people choose not to respond to this question. The majority (67.3%) felt government Old Age Allowance should be increased to BDT 5,000. One-third (33.5%) of participants thought that the legislation should be changed to take care of parents. Some felt that children should take care of more (33.5%) and some (3.6%) thought that children should act as they did as in their childhood. The Parent's Care Act 2013 should implement for retrospective care of the elderly. The maximum (73.8%) respondents wished for a geriatric hospital in every district in Bangladesh. Half (51.9%) of respondents thought that the elderly should receive a separate senior citizen card for preferential treatment. Almost half of the respondents (44.7%) felt that the elderly should get priority in any queue. Some elderly preferred sitting place for the elderly, and some for discounts on Bus/Uber/Rickshaw. So, it shows expectation is more than the services provided. Though the National aging policy is in place by the government, however, many people especially in rural area are not aware of these benefits. Further monitoring and an integrated care approach by a one-stop elderly care clinic are required to provide better support to the elderly population.

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Conflict of Interest

Authors declared any conflict of interest of this writing.

Data Availability Statement

Datasets for this article have been included in the article. Data can be also available from the corresponding author on reasonable request.

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ORIGINAL ARTICLE

Changes in hepatic thiol contents and regulation of glutathione S-transferase by high-fructose diet: Effects of kefir and some probiotic bacteria

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Abstract

In this study, thiol/disulfide homeostasis in the liver tissues of high-fructose-fed rats was investigated in conjunction with the changes in the main hepatic detoxification enzyme, glutathione S-transferase (GST). Additionally, the effects of well-known probiotics namely Kefir, *Lactobacillus helveticus,* and *Lactobacillus plantarum* supplementation on the thiol/disulfate contents and GST activity and gene expression levels were analyzed. Fructose, administered as a 20% solution in drinking water for 15 weeks, developed an animal model of metabolic syndrome in male Wistar rats. Kefir, *L. helveticus,* and *L. plantarum* supplementations were given by gastric gavage once a day during the final 6-weeks. The changes in hepatic GST were determined with kinetic-optimized spectrophotometric enzyme assays and qRT-PCR. Total thiol, native thiol, and disulfide levels were analyzed using (5,5-dithio-bis-(2-nitrobenzoic acid) as a chromogenic agent. High-fructose consumption reduced total and native thiol contents while increasing disulfide levels in the liver tissues of rats. Kefir and *L. plantarum* normalized the thiol levels and all probiotics reduced disulfide contents. High fructose augmented total GST activity but reduced the GST-Mu isoform. *L. helveticus* and *L. plantarum* normalized the total and GST-Mu activity, respectively. These results demonstrated a shift toward disulfide formation in the hepatic tissues of rats fed with high fructose. A possible reason would be the increase in total GST activity that uses the free glutathione, the main native thiol source in cells, as a substrate. Besides, probiotics such as Kefir, *L. helveticus,* and *L. plantarum* have an improving effect on thiol/disulfide homeostasis as well as main detoxification enzymes.

Keywords: Kefir, *Lactobacillus plantarum*, *Lactobacillus helveticus*, glutathione S-transferase, thiol/disulfide balance, fructose

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Introduction

Today, fructose is widely utilized in processed foods because it has a longer shelf life, dissolves quicker, and is sweeter than other carbohydrates [1]. Numerous studies have demonstrated that a high-fructose diet develops metabolic syndrome with insulin resistance, hypertriglyceridemia, endothelial dysfunction, oxidative stress, and hepatic steatosis [2-4]. As a result of hepatic stress caused by the load of fructose metabolism, it also showed hepatic oxidative damage and altered lipid metabolism [5].

Prooxidant and antioxidant imbalance might contribute to the onset of metabolic syndrome even though its etiology is extremely complex and not yet fully understood [6]. In comparison to healthy individuals, patients with metabolic syndrome have reduced plasma antioxidant enzyme activity and greater levels of oxidative damage indicators [7]. By encouraging the development of inflammation, thrombosis, and atherosclerosis and affecting vascular function, increases in oxidative stress have been linked to metabolic syndrome's pathogenesis [8].

Antioxidant defense is greatly aided by dynamic thiol-disulfide homeostasis, which is also engaged in critical processes like apoptosis, signal transmission, and enzyme activity regulation [8]. Organic molecules with a sulfhydryl group (-SH) are defined as thiols that compromise the majority of the body's non-enzymatic antioxidants. Intracellular and extracellular total thiol pool includes either free or oxidized (disulfide) forms or thiols attached to proteins. The reversible formation of mixed disulfides between two separate thiol-containing molecules might emerge from their oxidation. Covalent disulfide linkages that are produced when thiols undergo an oxidation reaction might be reduced via other antioxidant systems [9]. Thiols that are found in proteins as well as thiols that have a low molecular weight, such as cysteine, homocysteine, and glutathione make up the majority of the intracellular thiol pool and their levels decrease under conditions of high oxidative stress to neutralize free radicals, and the sulfhydryl groups of thiols play a crucial role in this process.

Among the several detoxification enzymes present in the liver, glutathione S-transferases (GSTs) play a vital role in the detoxification of xenobiotics and endobiotic compounds. To make electrophilic molecules more hydrophilic and less hazardous, they conjugate intracellular thiol-containing reduced glutathione (GSH) to the electrophilic substance. Therefore, GST activity fundamentally controls glutathione homeostasis, and the redox state of glutathione is crucial for several biological processes. Besides several foreign compounds and metabolites of oxidative stress are detoxified by the cytosolic GSTs, namely the Mu isoenzyme, which is particularly concentrated in the liver [10].

Probiotics are living bacteria that, when administered in sufficient doses, have a beneficial effect on a host. Their dietary supplements have been employed in the prevention and treatment of a number of illnesses, including gastrointestinal disorders, allergies, and diseases that are inflammatory in nature [11]. They have considerable antioxidant properties both in vivo and in vitro [12] and are naturally present in fermented dairy products including kefir, yogurt, cheese, and others. One of the key elements of the human microbiota, *Lactobacillus* species, has been shown to limit hyperinsulinemia, dyslipidemia, and hyperglycemia in high-fructose or high-fat-fed rats [13-15]. *L. plantarum* supplementation has been demonstrated to increase insulin resistance and antioxidant enzyme capacity, as well as to reduce pro-inflammatory cytokines [16]. Recently, we showed that supplementing with *L. plantarum* and *L. helveticus* mitigated the negative effects of dietary fructose on antioxidant enzymes such as superoxide dismutase and catalase [17]. Several lactic acid and acetic acid bacteria, as well as yeasts, are lodged in the polysaccharide matrix known as kefiran in the fermented milk product kefir, which have also possible health benefits in a variety of illness models [18,19]

Limited information in the literature exists regarding how probiotic therapy affects metabolic syndrome brought on by high fructose consumption. Therefore, the goal of the current investigation was to determine if supplementing fructose-fed rats with Kefir, *L. helveticus*, and *L.*

plantarum enhances thiol-disulfide equilibrium and modifies the primary detoxification enzymes namely glutathione S-transferase in the liver tissues of rats.

Materials and Methods

Animals and Diets

Three-week-old male Wistar rats were housed in climate- and humidity-controlled environments with a 12-hour light/dark cycle. The protocol to use animals was authorized by the Afyon Kocatepe University Ethical Animal Research Committee (approval number: 49533702-117). Standard rat chow, consisting of 62 percent starch, 23 percent protein, 4 percent fat, 7 percent cellulose, common vitamins, and salt, was fed to the rats.

The rats were randomly separated into five groups of eight rats each after one week of accommodation and the groups were as follows; Control, Fructose (F); Fructose + Kefir (F+K); Fructose + *L. plantarum* (F+LP) and Fructose + *L. helveticus* (F+LH). For 15 weeks, rats were fed a 20 percent (w/v) solution of fructose (Danisco Sweeteners OY, Kotka, Finland) in drinking water. During the last six weeks, rats were also administered to 1×10^9 CFU per 100 g of body weight of *L. plantarum* and *L. helveticus* (Horsholm, Denmark; ATCC: 14917 and ATCC: 15009, respectively) which were cultured in our laboratory through gastric gavage once a day. The rats were also gastric gavaged with kefir once daily for the final six weeks (1 ml per 100 g of animal weight). The kefir grains were obtained commercially (Sevdanem, Danem Kefir, Isparta, Türkiye) and fermented in our lab daily with pasteurized milk. Rats were sedated with a ketamine-xylazine cocktail (100 and 10 mg/kg, *i.e.*, respectively) at the end of the observational period and then decapitated. Liver tissues were dried, frozen in liquid nitrogen, and stored at -85 °C for further molecular analyses.

Preparation of Cytosolic Fractions from Rat Liver Tissues

After being washed with the ice-cold homogenization mixture (50 mM KH_2PO_4, 1.15% KCl, 0.5 mM PMSF, 5 mM EDTA, pH:7.0), the bladed homogenizer (Tissue Ruptor™, Qiagen, USA) was used to slice and homogenize rat liver tissues. The samples were then centrifuged at 1,500 g for 15 minutes to separate the nuclear component from the non-degradable cells. Supernatants were put into Eppendorf tubes and stored for subsequent use at -85°C. The Lowry technique [20] was used to determine the homogenates' total protein content.

Determination of Kinetic Parameters of Total and Mu Isoform of Glutathione S-transferase Activity

Total GST enzyme activity is quantified using 1 chloro-2,4 dinitrobenzene (CDNB), a common substrate for all GST isoforms, and reduced glutathione (GSH) as substrates. GST-Mu activity is differentiated from total by using l,2-dichloro-4-nitrobenzene (DCNB) instead of CDNB [21]. To begin, the kinetic characteristics of the liver GST enzymes were analyzed to find the most effective ways to measure their activity. This was accomplished by studying the GST enzymatic activity depending on GSH by maintaining a constant concentration of CDNB. In addition, variations in CDNB-dependent GST activity were tracked at constant GSH concentrations. The same experiments were also repeated with DCNB instead of CDNB as substrate. After calculating Km and Vmax values for the substrates of GST, the following optimized protocol was conducted to determine hepatic GST activities.

In a UV-transparent 96-well plate, 15 µl of 2 mg protein-containing homogenates were thoroughly mixed with 250 µl of phosphate buffer (50 mM, pH:7.0), 20 µl of GSH (50 mM), and 15 µl of CDNB (50 mM) or DCNB (20 mM). The changes in absorbance were then measured for 2 minutes at 340 nm using a spectrophotometric microplate reader (MultiScan GO™, Thermo Scientific, USA). Total GST and GST-Mu isoform activities were determined as the amount of product formed by The homogenate containing 1 mg protein per minute using the extinction coefficient of 9.6 $mM^{-1}.cm^{-1}$ for total GST and 8.5 $mM^{-1}.cm^{-1}$ for DCNB-dependent GST activities [22].

Determination of Total and Native Thiol Contents, Disulfide Amounts

Total thiol, native thiol, and disulfide contents of liver homogenates were measured using Ellman's reagent (5,5-dithio-bis-(2-nitrobenzoic acid)) as a chromogenic reagent [23]. For the measurement of total thiol contents, 120 µl of homogenates or different concentrations of GSH standards (0.10-0.25-0.50-0.75-1, 2, 4 mM) were mixed with 40 µl of 20% (w/v) TCA and centrifuged at 10,000 *g* for 20 minutes. Then, in a 96-well microplate, 220 µl of EDTA (10 mM, prepared in 500 mM Tris pH: 8.2), 20 µl of supernatant (or standards), and 20 µl of DTNB (10 mM, dissolved in methanol) were added. After 10 min incubation, absorbances at 415 nm were measured and the total thiol contents were calculated from the GSH standard calibration curve. Thiol contents of liver tissues were calculated as nmol thiol/mg protein [24,25].

Native thiol contents (GSH) were measured using the total thiol methodology with the exception that sodium borohydride ($NaBH_4$) was used to pre-reduce dynamic disulfide linkages (-S-S-) in the sample to free functional thiol groups [26]. Briefly, 600 µl of homogenate was mixed with 150 µl of reaction solution (3.5 M NaBH4 and 1.5 M NaOH, prepared absolute methanol) and incubated for 20 min at room temperature. After adding 70 µl of 12 M HCl, the samples were centrifuged at 10,000 *g* for 20 minutes. The thiol contents of the supernatant were determined by the abovementioned protocol as described. After the total thiol and native thiol measurements were completed, half of the difference between total and native thiols was calculated as disulfide contents as described previously [27].

Determination of gstm1 Gene Expressions by qRT-PCR

Total RNA was extracted from liver tissues by following the manufacturer's instructions for the Rneasy total RNA extraction kit (Qiagen, Hilden, Germany). Quantity and quality were determined using 260/280 nm spectrophotometer readings and agarose gel electrophoresis (Thermo Scientific, Waltham, MA, USA). One microgram of total RNA was converted to cDNA by reverse transcription using a Thermo Scientific kit (Thermo Scientific, Waltham, MA, USA). Gene expressions of *gstm1* isoform and internal standard *gapdh* were determined by qRT-PCR using the primer pairs for *gstm1* forward: 5′- AGAAGCAGAAGCCAGAGTTC and *gstm1* reverse: 5′-GGGGTGAGGTTGAGGAGATG, *gapdh* forward: 5′-TCCTTGGAGGCCATGTGGGCCAT and *gapdh* reverse: 5′-TGATGACATCAAGAAGGTGGTGAAG as we described previously in detail [28].

Statistical Analysis

Each experiment was carried out at least three times. The results are presented as mean ± standard errors of the mean (SEM). The enzyme kinetics module of GraphPad (version 8.0, GraphPad Software, La Jolla, CA, USA) software was used to determine Km and Vmax values from double reciprocal graphs. One-way ANOVA followed by the Bonferroni post-hoc test was used to conduct statistical comparisons using the same software. When the P values were less than 0.05, the differences in the groups were accepted as significant.

Results

The Changes in Metabolic Parameters

Our recent research [15,29] presented data on the metabolic indicators of the same animals, involving body weight, caloric consumption, plasma levels of insulin, glucose, and triglyceride levels. The use of high-fructose or probiotics did not affect the body weight of rats. All probiotics had no effect on the plasma glucose rise caused by a high-fructose diet. Fructose increased serum and liver fructose levels, as well as lipopolysaccharide contents, whereas the kefir intervention dramatically decreased fructose levels in rat hepatic tissues. Increased plasma insulin and triglyceride levels were normalized with kefir, *L. plantarum,* or *L. helveticus* supplementations. Herein, we used the same animal tissues to investigate the biochemical and molecular effects of fructose and probiotics on the liver.

Kinetic Parameters (Km and Vmax) of GST Enzymes

In this study, firstly we figured out the kinetic parameters of both the total and Mu-type

isozymes of GST enzymes using CDNB and DCNB as substrates in addition to GSH which is a common substrate of all GST isozymes. For this, the effect of CDNB on the enzyme activity of GST was studied by keeping the amount of GSH constant. Figures 1A and 1B show the Michaelis-Menten plot and the Lineweaver-Burk plot for the CDNB-dependent GST activity. Furthermore, GSH-dependent GST activity was investigated at constant CDNB levels, and variations in GST activity were tracked. The Michaelis-Menten plot (Figure 1C) and the Lineweaver-Burk plot (Figure 1D) show that the maximum velocity of total GST activity was calculated to be 481.80 ± 6.44 U/mg, and the Km value for GSH and CDNB was found to be 12.94 ± 0.71 mM and 8.85 ± 1.18 mM, respectively.

The kinetic characteristics of DCNB-specific GST-Mu activity were also established. The DCNB-dependent enzymatic activity of GST-Mu was investigated by maintaining the concentration of the GSH constant. Figures 2A and 2B show Michaelis-Menten and Lineweaver-Burk plots for DCNB-dependent GST activity. GSH-dependent GST-Mu activity was also investigated at constant DCNB levels, and fluctuations in GST-Mu activity were tracked. According to the Michaelis-Menten (Figure 2C) and Lineweaver-Burk (Figure 2D) plots, the maximum velocity of GST-Mu activity (Vmax) was calculated as 8.01±0.34 U/mg, Km value for GSH and DCNB were determined as 15.15±2.19 mM and 2.97±0.49 mM, respectively.

The Changes in Hepatic Total GST and GST-Mu with a High-fructose Diet and the Effects of Probiotics

Glutathione S-transferases catalyze glutathione conjugation to electrophilic molecules, mostly external xenobiotics but also endogenous chemicals. Glutathione conjugation is the initial stage and an essential detoxification mechanism. In addition to conjugation processes, some isoforms of this enzyme, such as Mu kinds, have peroxidase-like activity toward hydroperoxides [30] and hence could play a role in stress metabolism. Our results demonstrated a general increase in total GST activity in fructose-fed rats which was decreased by *L. helveticus* administration (Fig. 3A). On the contrary to total

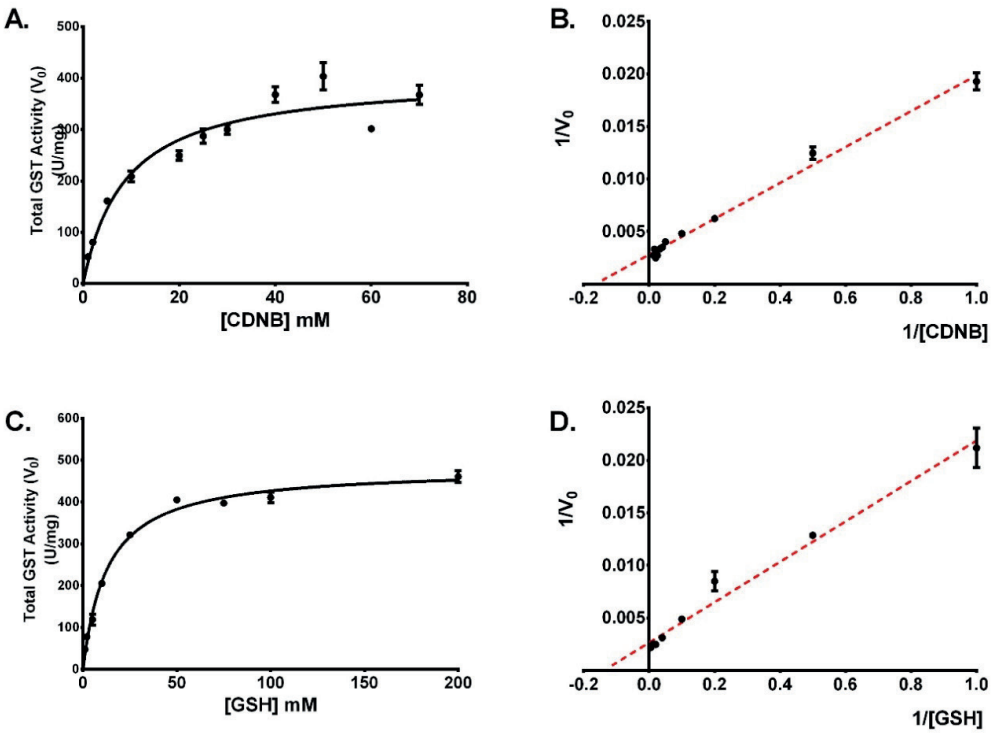

Figure 1. Michaelis-Menten and Lineweaver-Burk plots for CDNB-dependent GST activities (A and B), and GSH-dependent GST activities (C and D), respectively.

GST activity, GST-Mu enzyme activity and its gene expression levels were suppressed with fructose (Fig 3B and 3C). None of the probiotics have significant effects on gene expression levels but only *L. plantarum* upregulated GST-Mu activity towards the control group.

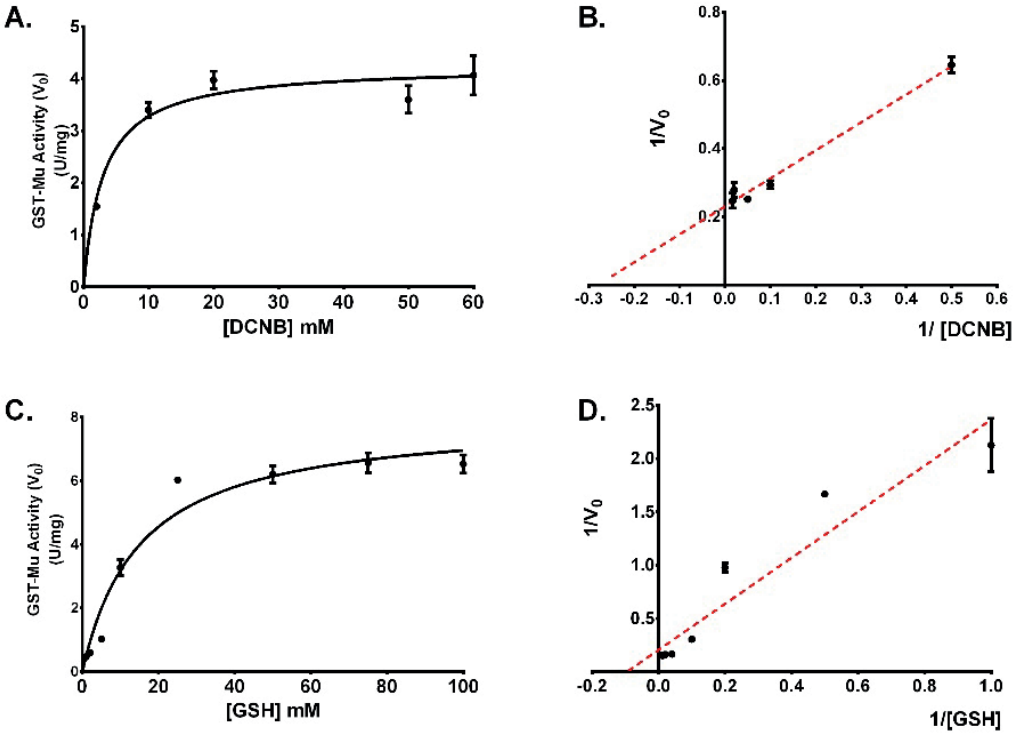

Figure 2. Michaelis-Menten and Lineweaver-Burk plots for DCNB-dependent GST-Mu activities (A and B), and GSH-dependent GST-Mu activities (C and D), respectively.

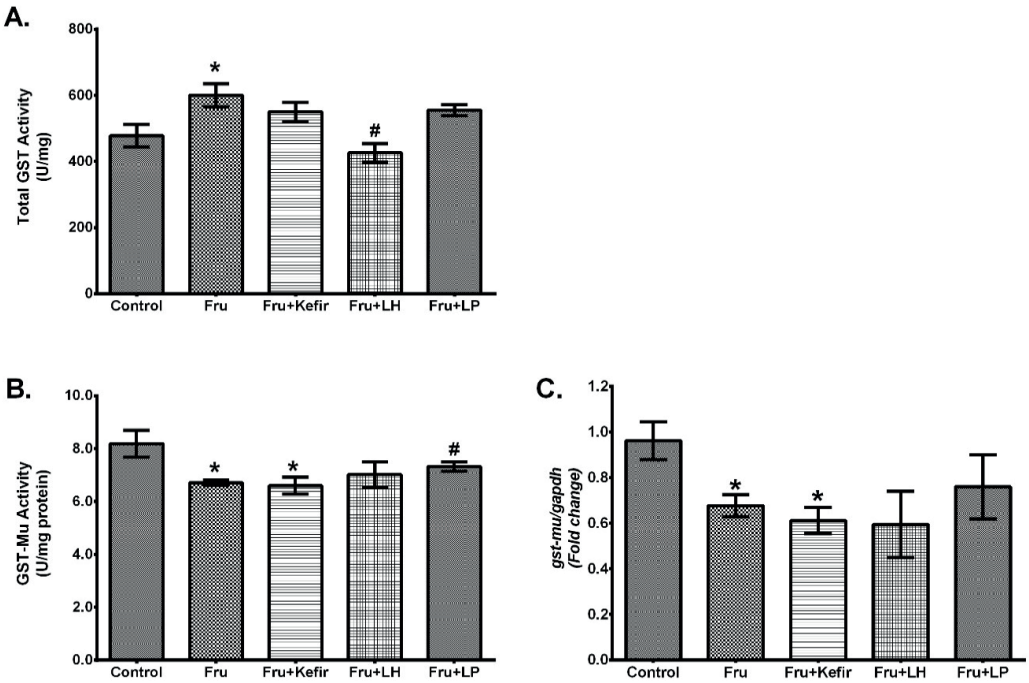

Figure 3. Effects of high-fructose diet and probiotics on hepatic total GST activities (A), hepatic GST-Mu activities (B), and GST-Mu gene expression levels (C). Differences from control (*) and fructose (#), $P < 0.05$. Results are given as mean ± SEM (n = 6–8). Fru: Fructose, LH: *Lactobacillus helveticus*, LP: *Lactobacillus plantarum*

Changes in Total Thiol, Native Thiol, and Disulfide Contents

Native, total and oxidized thiol levels in hepatic tissues were evaluated in this study to highlight dynamic variations in the thiol metabolism. In addition, the ratio of extant native thiol and disulfide concentrations to total thiols was evaluated to identify oxidative alterations thoroughly. Results clearly demonstrated the suppression of total and native thiol contents by high-fructose (Fig. 4A and 4B). However, oxidized forms of thiols, that is disulfide levels, were augmented with fructose (Fig. 4C). Kefir and *L. plantarum* have modulatory action on native thiol contents in such a way that they normalized the thiols up to the control group. In addition, the considerable elevation of disulfide content was identified in the liver tissues of rats fed a high-fructose diet. All probiotics significantly restored the disulfide levels ($P < 0.05$), indicating the suppression of oxidative stress-induced changes in thiol metabolism.

Discussion

High consumption of processed foods with excess fructose levels, reportedly has a

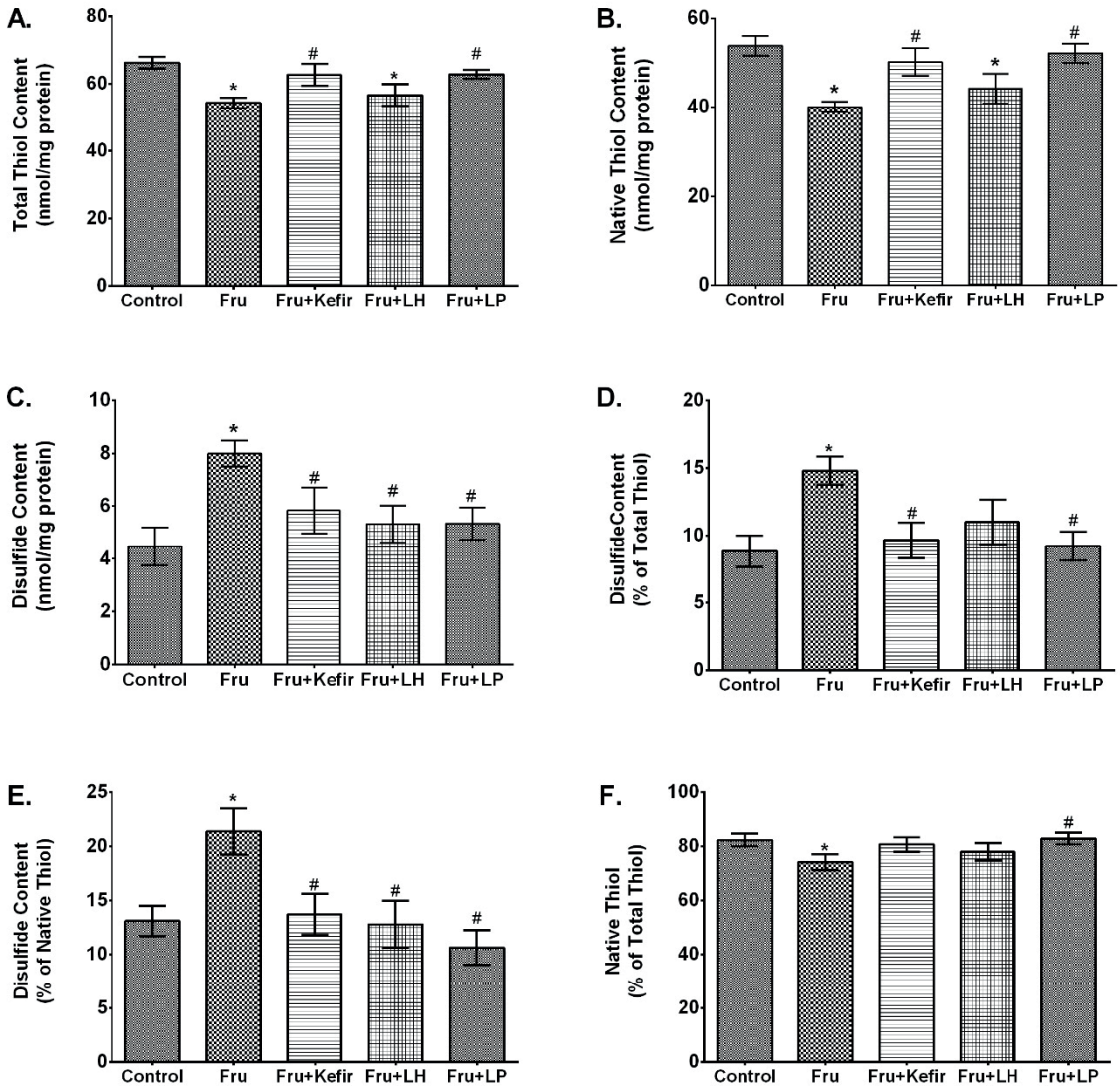

Figure 4. The changes in total thiol (A), native thiol (B), disulfide content (C), percent disulfide content against total thiol levels (D), percent disulfide content against native thiol levels (E), percent native thiol content against total thiol levels (F) in hepatic tissues of fructose- and probiotic-fed rats. Differences from control (*) and fructose (#), $P < 0.05$. Results are given as mean ± SEM (n = 6–8). Fru: Fructose, LH: *Lactobacillus helveticus*, LP: *Lactobacillus plantarum*

connection to the rising prevalence of insulin resistance, obesity, and metabolic syndrome [2]. On the other hand, the mechanism by which high-fructose consumption contributes to the development and worsening of metabolic disorders is still up for debate. One of the detrimental consequences of dietary fructose is the deterioration in the oxidant/antioxidant balance [31] and experiments have revealed that high-fructose ingestion causes oxidative stress in a variety of tissues and organs [32].

In cells, there exist specific oxidized/reduced ratios of free thiols and thiol-containing compounds such as cysteine, glutathione, and thiol proteins. This pool of cellular thiols is controlled by the mechanisms linked to their inherent antioxidative activity, as well as their dynamic synthesis and removal from cells via glutathione redox cycles and xenobiotic conjugation [33]. Dynamic thiol/disulfide homeostasis in organisms governs cellular antioxidant systems and signaling processes [34], and therefore, plays a vital role in maintaining the intracellular oxidation-reduction potential balance. GSTs, a major thiol metabolizing enzyme, react differentially under both normal and pathological situations to a number of chemicals and oxidative stress [35]. Both in vivo and in vitro studies have shown that GSTs are controlled by reactive oxygen species, including superoxides, hydrogen peroxide, and the byproducts of membrane lipid peroxidation [36,37]. The cytosolic Mu isoenzyme of GSTs is particularly high in the liver, and in addition to its involvement in the detoxification of various external substances and oxidative stress byproducts, it also plays a role in the regulation of gene expression [35]. Herein, we looked at how a high-fructose diet affects the hepatic thiol/disulfide balance and the major detoxification enzyme, glutathione S-transferase, which utilizes the cellular thiol pool for its function. Furthermore, we also investigated the effects of dietary kefir supplementation in conjunction with individual probiotic bacteria, *L. plantarum*, and *L. helveticus,* on thiol homeostasis and the main hepatic detoxification enzyme.

Our results showed that high-fructose consumption reduced hepatic total and native thiol levels by acting as an oxidative stress source in the liver tissues. The increased hepatic oxidative burden was further demonstrated by the increased disulfide concentration. The decrease in native thiol contents in the liver tissues most probably is the result of its increased utilization due to oxidative stress and enhanced total GST activities which use glutathione for its function. In contrast to overall GST activity, high-fructose diet decreased Mu-type GST isozyme expression and activity levels. The reduction in GST-Mu mRNA expressions suggests that its transcription is being controlled. The drop might possibly be related to a decrease in mRNA half-lives since increased oxidative stress can lead to mRNA instability [38].

Kefir, one of the well-known probiotics has been shown to exert anti-inflammatory, antiviral, and anti-allergic effects [39]. Its protective activities have also been established against metabolic diseases caused by fructose [19]. Recently, we have demonstrated favorable effects of kefir on the hepatic and intestinal abnormalities caused by excessive fructose consumption [29]. The expression of inflammatory markers and major lipogenic genes in the liver were both suppressed with kefir supplementation. In addition, kefir therapy enhanced insulin signaling elements and fructose transporters. Herein, while kefir did not significantly affect the activity or expression of GST enzymes, it did raise total and native thiol levels within the normal range. It also reduced the disulfide levels drastically in high-fructose-fed rats, which indicates that the oxidative pressure is being relieved in favor of a more reduced atmosphere.

Another recent study we performed also demonstrated the reduction of plasma insulin levels and improvement in the kidney antioxidant parameters with probiotic bacteria, *L. plantarum* and *L. helveticus* which were supplemented to the high-fructose-fed rats [17]. Hepatic weight, lipid content, and fatty acid synthase expression were all reduced in high-fructose-fed rats when *L. plantarum* was supplemented into the diet. *L. helveticus* had also a restorative impact on lipid accumulation by lowering fatty acid synthase expression and modulating insulin receptor substrate-1 [14]. According to the findings of this research, the effectiveness of *L. plantarum* in

restoring cellular total and native thiol contents and disulfide levels was comparable to that of kefir. *L. helveticus* was similarly efficient in reducing the increased levels of disulfide in rats that had been given fructose. *L. helveticus* is the only microorganism that significantly affects GST enzyme levels, decreasing total GST activity in the direction of the control group. Neither kefir nor *L. plantarum* substantially altered GST activity or expression levels. Taken together, the bases of the antioxidant effects of probiotics as indicated in this study would be the maintenance of cellular thiol contents in their reduced form. Previously, probiotic supplementation in rats has been shown to boost glutathione production in pancreatic cells [40] and to activate the transcription of genes involved in glutathione manufacture in the intestinal mucosa [41]. Additionally, supplementation with *L.casei*, *L. acidophilus*, and *Bifidobacterium lactis* was also effective in restoring glutathione levels in rats after oxidative stress [42]. These researches back up our hypothesis that probiotic bacteria would boost reduced glutathione and other thiol-containing substances in the presence of oxidative stress which is induced by high-fructose diet.

Overall, this study shows that high-fructose diet modulates the activities of total hepatic glutathione-dependent detoxification enzymes, mainly glutathione S-transferases. Because acute fructose intake causes a quick but transitory burst of damaging reactive oxygen species, this would have to be considered as a defensive reaction. The upregulation of the total GST enzyme activities by fructose observed in this study reduced free thiol levels and leads the formation of oxidized thiols (*i.e.*, disulfides). Because of this, the redox equilibrium that exists inside the liver tissues will ultimately become disrupted. Although more research is needed to explore the probable processes involved, the current study demonstrates the efficacy of chosen probiotics in the prevention of oxidative stress, particularly in terms of thiol/disulfide homeostasis. In this manner, antioxidant probiotic strains can be identified and studied as prospective candidates for the prevention and treatment of a variety of free radical-related disorders such as obesity, diabetes mellitus or metabolic syndrome.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Data Availability Statement

All data within this study has been presented and there is no other data for public repositories.

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