# Knowledge, attitude, and perception of Libyan pharmacists towards pharmacogenomics services: A cross sectional prospective study

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Received: 11 June 2024 / Revised: 20 August 2024 / Accepted: 22 August 2024

ABSTRACT: Pharmacogenomics is the study of how person's genes affect their response to drugs and could be used to personalize drug therapy and improve patient outcomes. Pharmacists are increasingly involved in the application of Pharmacogenomics services, as they are well-positioned to educate patients about their genetic risks and help them select the best medications for their individual needs. To evaluate the knowledge, attitude, and perception of Libyan pharmacists towards Pharmacogenomics services, a cross-sectional study was conducted among pharmacists in Libya using a validated, pilot-tested, and self-administered online questionnaire between August 2023 and September 2023. Descriptive statistics and multivariate logistic regression models were used to describe the results of the study. Most of the participants were female (73%), community pharmacists (56%), and from the eastern part of Libya (73.8%). The respondents have a low knowledge score in Pharmacogenomics and 75.2% of them expressed interest in attending Pharmacogenomics training in the future. Additionally, the participants showed positive attitude and perception towards Pharmacogenomics services (total mean attitude score = 2.9 out of 4 and total median perception score = 32.0 out of 35). They agreed upon barriers for the implementation the Pharmacogenomics services, such as were lack of reimbursement, knowledge, and guidelines. Overall, the survey revealed that pharmacists are interested in learning more about Pharmacogenomics and are positive about the potential benefits of this technology. Despite the low knowledge of pharmacists in Pharmacogenomics, they showed a positive attitude and perception. Therefore, there is a high need for training and improving the Pharmacy curriculum by involving more Pharmacogenomics courses to ensure the proper application of Pharmacogenomics.

KEYWORDS: Knowledge; attitude; perception; pharmacogenomics; pharmacists; Libya.

## 1. INTRODUCTION

At the forefront of personalized medicine, pharmacogenomics (PGx) revolutionizes healthcare by tailoring drug therapy to each individual's unique genetic profile, optimizing medication effectiveness, and minimizing adverse effects, ushering in a new era of precision treatment [1, 2]. In other words, by identifying the specific genes that may contribute to adverse drug reactions, health professionals may eventually be able to tailor medication regimes to suit the genetic makeup of patients, leading to increased efficacy, safety, and adherence [3]. Hospitals pioneered the implementation of PGx-tailored drug therapy, laying the foundation for its broader application in healthcare settings [4] and pharmacists serve as key drivers in expanding the reach and effectiveness of PGx services within healthcare facilities [5, 6]. As public understanding of PGx testing grows, testing costs decline, and direct-to-consumer options emerge, community, hospital, and clinical pharmacists have a unique opportunity to spearhead the integration of PGx services into patient care [7].

However, PGx is not yet widely practiced in pharmacotherapy, even by healthcare professionals such as pharmacists. One reason for this is that PGx testing is still relatively new and expensive [5, 6, 8]. Additionally, there is a lack of awareness of PGx among healthcare professionals. In developing countries like Libya, where resources are limited, PGx is even less likely to be practiced. Another reason that

How to cite this article: Mohamad KA, Alshami HA, Hussein MSE, Elshintiri NE. Knowledge, attitude, and perception of Libyan pharmacists towards pharmacogenomics services: A cross sectional prospective study. J Res Pharm. 2025; 29(4): 1507-1515.

necessitates the need for the activation of PGx practice in developing countries is that there are regional genetic variations that affect drug response. This means that the way people respond to medications can vary depending on where they live. For example, studies have shown that people in Africa are more likely to have genetic variants that make them more susceptible to the side effects of certain medications [6, 7]. A WHO report suggests that pharmacists are the world's third-largest healthcare professional group, following physicians and nurses [9]. They also may be the first point of contact for the public for PGx testing services [10, 11]. The successful implementation of PGx testing and services in pharmacy settings has been supported by available evidence [12, 13]. The American Pharmacists Association values the optimization of medications for each patient and endorses these services as a vital responsibility for pharmacists [12, 13].

Pharmacists could have a vital role in delivering a wide range of services related to PGx. These services include conducting tests, providing counselling, interpreting test results, and optimizing drug therapy by making necessary adjustments to medication dosage. By utilizing the information obtained from PGx, pharmacists can personalize drug therapy for each patient, thereby ensuring the best possible treatment outcomes [5, 6]. Furthermore, patients widely recognize pharmacists as suitable healthcare providers to deliver PGx services. This perception is rooted in the demonstrated interest and willingness of patients to seek these services in spite of the extra cost. The recognition of pharmacists as trusted professionals in the field of PGx further strengthens their position as key contributors to personalized medicine, enhancing patient care and treatment efficacy [2, 11, 14, 15].

To further promote the participation of community and hospital pharmacists in PGx, it is crucial to explore their awareness and perception towards these services.

There is a lack of evidence describing the knowledge, attitude, and perception towards PGx services among pharmacists in Libya. In addition, pharmacists are still relatively unfamiliar with PGx and its applications in clinical practice. The aim of the study was to explore the knowledge, attitude, and perception of pharmacists towards PGx, and the barriers to apply PGx in the Libyan health settings.

## 2. RESULTS

## 2.1. Demographic characteristics of the respondent

Table 1 summarizes the demographic characteristics of the respondents. The majority (73%) of the participants were female and 90.8% aged less than 40 years old. Interestingly, while pharmacists hailed from across Libya, a significant portion (74%) originated from the eastern region. A greater number of the participants were bachelor's degree holders (64.5%) and community pharmacists with a total of 158 pharmacists. Regarding years of experience, the majority of the respondents (76.6%) had less than 10 years of experience.

## 2.2. The knowledge of pharmacists towards PGx:

The study found that the majority of participants, over 70%, had an understanding of the impact of an individual's genetic makeup on the way medications are processed and their effectiveness (Table 2). Furthermore, they recognized that PGx can be utilized to predict the safety and efficacy of medications and realized that genetic variation is responsible for variation in drug response. In terms of recognizing the reasons for requesting genetic testing, almost 80% of the respondents pursued genetic testing to understand why conventional treatments were ineffective. In addition, the data reveals that 28.4% (80 participants) of those surveyed underwent genetic testing to gain insights into their genetic predispositions for adverse reactions. In contrast, a significant proportion of participants, 57.4% (162 individuals), sought genetic testing to determine the most appropriate treatment options based on their genetic profiles.

Variable	Categories	Frequency (%)
Condon	Female	205 (73%)
Gender	Male	77 (27%)
	20-30	132 (46.8%)
Age group	31-40	124 (44%)
	41-50	20 (7.1%)
	Above 51	6 (2.1%)
Part in Libya	East	209 (74%)

**Table 1.** The demographic characteristics of the respondents.

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	West	53 (18.8%)		
	Middle	12 (4.3%)		
	South	8 (2.9%)		
	Bachelor's	182 (64.5%)		
Highest Academic Qualification	Diploma*	20 (7.1%)		
	Pharm D	30 (10.6%)		
	Masters	38 (13.5%)		
	PHD	12 (4.3%)		
	Community pharmacist	158 (56%)		
<b>D</b> 1 1 1 1	Academic	54 (19.1%)		
Role as a pharmacist	Clinical pharmacist	42 (14.9%)		
	Hospital pharmacist	28 (9.9%)		
	Less than 5 years	130 (46.1%)		
	5-10	86 (30.5%)		
Years of experience	11-15	46 (16.3%)		
	More than 15 years	20 (7.1%)		

\*Diploma: a certificate given to bachelor's degree holders after the completion of 6-9 months of specialized study in areas such as pharmacogenomics, clinical pharmacy, pharmacology or pharmaceutical industry.

Additionally, more than half of the respondents incorrectly identified medications that require PGx testing, such as paroxetine, simvastatin, clopidogrel, and pantoprazole. However, the knowledge and awareness regarding the impact of genetic variability on warfarin were relatively moderate, with only 50.4% of participants being aware. The study also assessed the overall knowledge score of the participants, which was found to be 9.944 ± 0.21 out of 19. This score indicates a low level of knowledge regarding PGx.

## 2.3. Attitudes of pharmacists towards PGx services:

According to the survey results, 47.8% expressed their readiness to receive and interpret PGx testing results (Table 3). Meanwhile, approximately 80% of the respondents expressed an immediate interest in activating the PGx services in Libya. Furthermore, a majority of pharmacists (over 80%) expressed their readiness to advise patients on treatment choices based on patients' PGx testing results as well as advise physicians to request pharmacogenomic testing. Overall, the average attitude score was 2.9  $\pm$ 0.17 out of 4.0, indicating a positive attitude towards PGx services.

## 2.4. Perceptions of pharmacists towards PGx services:

Overall, the median perception score was 32.0 out of 35.0 (range: 0–35) and this indicates a good/positive perception towards PGx services while none (0%) of the respondents. As documented in Table 4, the majority of the respondents (96.5%) indicated strongly agreed/ agreed that the pharmacists in Libya need training in PGx. Similarly, 92.9% and 91.5% indicated strongly agreed/ agreed that pharmacists are well-placed within the healthcare system to provide PGx services and PGx testing will prevent patients from taking the inappropriate medicine or the wrong dose respectively. Moreover, 90.8% of the respondents showed a positive perception towards the incorporation of pharmacogenetic screening into medication therapy management to optimize pharmacotherapy. Most of the respondents (87.2%) strongly agreed/agreed that the pharmacist is able to apply genetic pharmacy and becomes one of the basics of caring for the patient in the future. In addition, more than two-thirds (70.3%) of the respondents indicated that PGx testing services are feasible in Libya.

Item	Yes	No	I don't know
Pharmacogenomics is the study of genes	118 (42%)	164 (58%)	0
Interest in attending pharmacogenomics training in future	212 (75.2%)	70 (24.8%)	0
Genes affect the drug efficacy	236 (83.7%)	6 (2.1%)	40 (14.2%)
The safe use and efficacy of medication can be predicted by gene testing	200 (70.9%)	12 (4.3%)	70 (24.8%)
Genetic determinants of drugs response may change over a person's lifetime	162 (57.4%)	28 (9.9%)	92 (32.6%)
Genetic variants are responsible for variability in drug effect	220 (78%)	12 (4.3%)	50 (17.7%)
Genetic testing results used to change drug therapy	202 (71.6%)	16 (5.7%)	64 (22.7%)

Table 2. The knowledge of pharmacists towards PGx

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Genetic testing results can be used for dose adjustment to suit	1(( (50.00/)		04 (00 00())			
patient	166 (58.9%)	22 (7.8%)	94 (33.3%)			
Genetic testing results can be used as indicator to stop	174 (61.7%)	28 (9.9%)	80 (28.4%)			
treatment	171 (01.770)	20 (9.970)	00 (20.170)			
<b>Reasons for requesting Genetic testing</b>						
Failure of therapy	224 (79.4%)	· · · ·	46 (16.3%)			
Preventing side effect	80 (28.4%)		94 (33.3%)			
Guide for Initiation of therapy	162 (57.4%)	20 (7.1%)	100 (35.5%)			
Which of the following medications need Genetic testing:						
Paroxetine	106 (37.6%)	26 (9.2%)	150 (53.2%)			
Simvastatin	80 (28.4%)	70 (24.8%)	132 (46.8%)			
Cefuroxime	78 (27.7%)	60 (21.2%)	144 (51.1%)			
Pantoprazole	38 (13.5%)	118 (41.8%)	126 (44.7%)			
Clopidogrel	112 (39.7%)	48 (17.0%)	122 (43.3%)			
Ibuprofen	30 (10.6%)	110 (39.0%)	142 (50.4%)			
Warfarin	142 (50.4%)	30 (10.6%)	110 (39.0%)			
Total mean knowledge score = 9.944 ± 0.21 out of 19 (52.34% below 60%)						

## 2.5. Knowledge, attitude and perception of the participants based on demographic characteristics:

Statistical analysis revealed no significant differences in participants' knowledge, attitudes, or perceptions based on their gender, role, age, or years of experience (Table S1, Table S2, Table S3, and Table S4). However, pharmacists from eastern Libya exhibited significantly different perceptions compared to their counterparts in other regions (Table S5 and Table S6). Interestingly, participants with a diploma in pharmacy demonstrated significantly higher knowledge levels than those with bachelor's or PharmD degrees (Table S7 and Table S8).

Table 3. Attitudes of pharmacists towards PGx services

Variable	Yes	No	Not sure			
Are you interested to activate the pharmacogenomics in Libya?	226 (80.1%)	14 (5%)	42 (14.9%)			
Are you willing to receive and interpret the pharmacogenomics testing results of your patients?	135 (47.8%)	90 (32%)	57 (20.2%)			
Do you advise physician to request pharmacogenomic testing?	244 (86.5%)	10 (3.5%)	28 (9.9%)			
Would you advise your patient on a treatment choice based on patient's pharmacogenomics testing result?	232 (82.3%)	18 (6.4%)	32 (11.3%)			
Total mean attitude score = $2.9 \pm 0.17$ out of 4 (72.5% >60%)						

#### 2.6. Barriers to implementation of PGx services:

As shown in Table 5, various factors that impact the implementation of PGx have been identified. This study highlighted the lack of reimbursement (258; 91.5%) as a major barrier to the implementation of PGx into routine practice. Additionally, pharmacists also face other obstacles such as limited knowledge (244; 86.5%), absence of guidelines or evidence (196; 69.5%), ethical considerations regarding ownership of genetic data (188; 66.7%), and the lack of acceptance by patients (136; 48.2%).

Table 4. Perceptions of pharmacists towards PGx services

Variables	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
You expect that the pharmacist is able to apply genetic pharmacy and becomes one of the basics of caring for the patient in the future	128 (45.4%)	118 (41.8%)	36 (12.8%)	0 (0%)	0 (0%)

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Knowledge, attitude, and perception of pharmacists towards pharmacogenomics services				Research Article			
Pharmacists are well-placed within the	150	112		<b>2</b> (2 <b>2</b> 0)	2 (22)		
healthcare system to provide pharmacogenomics services	(53.2%)	(39.7%)	18 (6.4%)	2 (0.7%)	0 (0%)		
Pharmacogenomics testing services are feasible in Libya	98 (34.8%)	100 (35.5%)	74 (26.2%)	8 (2.8%)	2 (0.7%)		
Pharmacists in Libya need training in pharmacogenomics	242 (85.82%)	30 (10.64%)	10 (3.54%)	0 (0%)	0 (0%)		
Pharmacogenomics testing will prevent your patient from taking the inappropriate medicine or the wrong dose	182 (64.5%)	76 (27%)	22 (7.8%)	2 (0.7%)	0 (0%)		
Incorporation of pharmacogenetic screening into medication therapy management will optimize pharmacotherapy	186 (66%)	70 (24.8%)	20 (7.1%)	6 (2.1%)	0 (0%)		
Pharmacogenomics-guided treatment is cost-effective	136 (48.2%)	90 (31.9%)	52 (18.4%)	2 (0.7%)	2 (0.7%)		
Total median perception score = 32.0 out of 35 (range: 0-35) (91.4% >60%)							

Data expressed as Frequency (%)

Table 5. Barriers to implementation of PGx services

Variables	Strongly Agree agree		Neutral	Disagree	Strongly disagree	
Lack of reimbursement	198 (70.2%)	60 (21.3%)	22 (7.8%)	2 (0.7%)	0 (0%)	
Limited knowledge	192 (68.1%)	52 (18.4%)	28 (9.9%)	8 (2.8%)	2 (0.8%)	
Absence of guidelines or evidence	140 (49.6%)	56 (19.9%)	56 (19.9%)	24 (8.5%)	6 (2.1%)	
Ethical considerations regarding ownership of genetic data	110 (39%)	78 (27.7%)	86 (30.5%)	6 (2.1%)	2 (0.7%)	
Lack of acceptance by patients	60 (21.3%)	66 (23.5%)	98 (34.9%)	38 (13.5%)	5 (1.8%)	
Lack of time	54 (19.1%)	36 (12.8%)	96 (34%)	78 (27.7%)	18 (6.4%)	
Resistance from other healthcare professionals	68 (24.1%)	58 (20.6%)	106 (37.6%)	42 (14.9%)	8 (2.8%)	
Data expressed as Frequency (%)						

Data expressed as Frequency (%)

## **3. DISCUSSION**

The knowledge, attitude, and perception of healthcare providers play a vital role in the capability of implementation of PGx. This study was the first study conducted to investigate the knowledge, attitude, and perception of pharmacists towards PGx services and covered many cities in Libya.

In spite of 53.9% of the participants have >5 years of experience, they have a low level of knowledge regarding PGx. Such a lack could prevent the effective implementation of PGx. This lack could be attributed to a shortage in the available training and qualified trainers in Libya. The results of the current study are consistent with other studies conducted regionally in the Arab world and Middle East, and internationally as well [16-19]. Nationally, in Zawia, a city in the west of Libya, Beshna and Alahrish reported that community pharmacists have fair knowledge notwithstanding three-quarter of them learned about PGx during their university education by lectures or scientific conferences [20].

The current study found no statistically significant differences in the effect of gender, age, years of experience, and pharmacist's role on the respondents' answers regarding the knowledge of pharmacists in PGx. This finding relates to the effect of demographics on the respondents' responses to the items on the study domains. However, the modest knowledge could be overcome by updating the curricula of all pharmacy programs, undergraduate programs and postgraduate programs as well. In support of this notion, it has been found that PharmD, as the modernist Pharmacy program, students have better knowledge [21]. A prior study conducted in Saudi Arabia revealed that postgraduate qualified individuals knew more about PGx [11]. In our study Diploma holders, that could be related to PGx, have better knowledge than Bachelor's and PharmD degree holders. This suggests that highly qualified pharmacists might encounter PGx material, and research indicates that PGx knowledge among pharmacists increased with modified curriculum [22]. Thus, to prepare aspiring pharmacists for PGx services, PGx education ought to be a part of undergraduate curricula.

Additionally, Adesta et al. and colleagues reported that 90 minutes long training remarkedly elevated the self-efficacy and competency of a diverse group of healthcare professionals in using PGx data,

and eventually led to greater PGx adoption [23]. While community pharmacists' knowledge and confidence in providing PGx services increased after completing an online course and a workshop on the subject [22]. Thus, PGx training modules can be created specifically for working pharmacists and made available as a continuing professional development course. To boost public confidence in community pharmacist-led PGx services, PGx training should be standardized, and community pharmacists should receive a certificate of completion to display in their pharmacies [24]. Therefore, there is a need to make continuous development courses/training obligatory to get/renew the license of healthcare professionals in Libya.

In harmony with previous studies [16, 25], the participants in this study showed an overall positive attitude towards PGx services. Additionally, they are interested in enabling PGx services in the Libyan healthcare system and actively participate in interpreting the results of PGx. However, less than half of the participants are ready to help patients explain the PGx testing results, this could be attributed to the lack of knowledge resulting in low confidence. Previously, Hundertmark and colleagues have concluded that pharmacists with higher education (postgraduate or training) are more ready to implement and interpret PGx tests [26]. Thus, it seems to be crucial to provide training to Pharmacists (since they are the third largest healthcare providers) to provide better healthcare services or incorporate more PGx courses into the curriculum of the Pharmacy programs, as it was reported that previous training enhanced the attitude of physicians after attending a short duration PGx education program [27].

Similar to attitude, the participants exhibited a positive perception, in harmony with regional and international studies [10, 17, 28, 29], towards PGx services. This could be imputed to the benefits of PGx implementation, including patient-optimized and cost-effective pharmacotherapy and prevention of irrational medication prescribing or dosing as well. Furthermore, the study spotted agreement among respondents on the ability of the Libyan pharmacists, after receiving training, to be a cornerstone in the implementation of PGx due to the reputability of the pharmacy and pharmacists within the health system and society.

Despite the willingness among pharmacists to integrate PGx services into practice and patients' interest in the services, there are several barriers hindering the PGx application in patient care. Besides low knowledge and self-confidence among pharmacists, the feasibility of providing PGx services in community and hospital pharmacies could also prevent PGx implementation [14, 16]. Additionally, resistance from other health professionals and a lack of clear compensation rules have also posed challenges [11, 16]. In North Africa and the Middle East, the application of PGx in patient care is very limited due to a paucity of data, which can be attributed to a lack of manpower, funding, and equipped laboratories [15, 21]. Regionally, some Arab countries started to implement PGx like Saudi Arabia and United Arab Emirates [30, 31], while resource limitations and lack of genomic studies prevent others, like Syria [16]. However, paving the way for healthcare providers to fully implement the PGx in Libya will not be easy; the participants agreed that there are some barriers, including lack of reimbursement and knowledge, absence of guidelines or evidence, ethical considerations regarding ownership of genetic data and the lack of acceptance by patients. However, it is worth mentioning that these barriers are conquerable, as with the right strategies in place and pharmacists with appropriate training interpreting PGx test results, the implementation of PGx services in pharmacists.

## 4. CONCLUSION

Libyan pharmacists have a low level of knowledge about PGx. They have a positive attitude towards PGx and believe that it has the potential to improve patient care. However, they are not confident in their ability to provide PGx services. Most of Libyan pharmacists need training in PGx and keen to attend PGx training. The major barriers to the implementation of PGx services among pharmacists in Libya were that pharmacists are not reimbursed for providing PGx services and lack of knowledge and guidelines. The study concluded that there is a need to address these barriers in order to promote the use of PGx services by pharmacists in Libya. This will help to improve the quality and reduce the cost of healthcare. The study highlights the need for more training and education on PGx for Libyan pharmacists. The study also highlights the need for guidelines and reimbursement for PGx services in pharmacy settings.

## **5. MATERIALS AND METHODS**

## 5.1. Study design

A prospective cross-sectional survey was conducted among pharmacists practicing in Libya. A selfadministered questionnaire was used to collect data on the pharmacists' knowledge, attitude, and perception of PGx services. The ethical approval was obtained from the Ethical Research Committee of the Libyan International Medical University (reference no: PHR-2024-00201). The questionnaire was developed after a review of previous literature and was validated by three lecturers with expertise in PGx and pharmacy practice research. The questionnaire consists of 32 items and 4 sections:

Demographic section: This section includes questions about the pharmacists' age, gender, educational level, and years of experience.

Knowledge of PGx: This section includes questions about the pharmacists' understanding of the basic concepts of PGx, such as how genes affect drug response.

Attitudes: This section includes questions about the pharmacists' feelings towards PGx, such as whether they believe it is a valuable tool for improving patient care.

Perceptions: This section includes questions about the pharmacists' beliefs about the potential benefits and challenges of PGx services.

The knowledge, attitude, and perception domains of the questionnaire were assessed using a 5-point Likert scale, with 1 being "strongly disagree" and 5 being "strongly agree." The questionnaire was pre-tested among 10 pharmacists. To ensure the reliability of the values, the Cronbach's alpha coefficient was calculated (0.630, 0.845, and 0.732 for knowledge, attitude, and perception domain, respectively).

## 5.2. Sample size

The sample size for the study was calculated using the Raosoft Sample Size Calculator. The margin of error and confidence interval were set at 5% and 95%, respectively. Based on the total number of pharmacists in Libya, the estimated participants, using Raosoft Sample Size Calculator, was 253 pharmacists. The study was able to collect data from 282 pharmacists.

### 5.3. Data collection

The researchers could not access an official list of pharmacies in Libya. Therefore, they used a snowball sampling technique. This method based on starting with a small set of community and hospital pharmacists who then referred colleagues to participate in the study.

The study's researchers shared the hyperlink to the electronic survey with the community pharmacists and hospital pharmacists. Also, eligible pharmacists were invited to take part in this survey using social media invitations like Messenger, WhatsApp, and Telegram. After a few days, a reminder was sent to the targeted respondents who did not respond. The respondents were allowed to submit only one response, informed that participation in the study was voluntary, and assured that responses were anonymous, and their information is confidential. The respondents were notified that their submission of responses was considered as consent to participate in the survey. The data was collected from August 2023 to September 2023. A total of 282 pharmacists participated in the study.

## 5.4. Data analysis

The data was analysed using the Statistical Package for Social Sciences (SPSS) for Windows, version 22.0. Descriptive analysis was used to describe the data, such as the mean, median, and standard deviation of the scores. Inferential analysis was used to test the hypothesis that there is a relationship between the independent variables (socio-demographic variables) and the dependent variables (knowledge, attitude, and perception). Independent samples t-test, one-way ANOVA, and the least significant difference (LSD) test were used to test the difference in knowledge, attitude, and perception basing on the demographic characteristics of the respondents.

The knowledge section of the questionnaire was scored using a 0-1 scale, with 1 being a correct answer and 0 being an incorrect answer. The attitude section of the questionnaire was scored using a 0-2 scale, with 0 being "no/not sure," 1 being "yes, but after having had training on the subject," and 2 being "yes, straight away." The perception section of the questionnaire was scored using a 1-5 scale, with 5 being "strongly agree" and 1 being "strongly disagree."

The total knowledge score was categorized using Bloom's cutoff points into good (80% to 100%), moderate (60% to 79%), and low (below 60%). For attitude and perception, scores greater than 60% and less than 60% of the total score were considered as good/positive and poor/negative attitude and perception, respectively.

**Author contributions:** Concept – H.A, M.H.; Design – H.A., K.M.; Supervision – M.H.; Resources – N.E; Data Collection and/or Processing – H.A., K.M., M.H; Analysis and/or Interpretation – H.A., K.M.; Literature Search – H.A., K.M.; Writing – K.M., H.A., M.H, N.E.; Critical Reviews – K.M., H.A., M.H, N.E.

Conflict of interest statement: The authors declared no conflict of interest.

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