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## Hand hygiene as an incomplete challenge for developing countries: discussions based on knowledge and perceptions of nurses in North Cyprus example and published studies

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#### ABSTRACT

Objective: In the contemporary nursing era, nurses play important roles in terms of patient care and the prevention of healthcare associated infections. Here, we aimed to discuss recommendations for developing countries by describing the level of knowledge and perceptions of hand hygiene among nurses in Northern Cyprus as an example to developing countries.

Materials and Methods: Adapted questionnaires of World Health Organization (WHO) were used for data collection and obtained data were analyzed using biostatistical methods.

**Results**: Among the nurses, 5.6% had good hand hygiene knowledge. "Country of education" and "in-service education" factors were found to affect the knowledge level significantly. Positive perception level was demonstrated by 83.2% of the participants. Availability of alcohol-based hand-rub and promotion of hand hygiene by leaders were perceived as most useful actions.

Conclusion: Our study results highlighted the importance of hand hygiene education both in occupational and in-service education. Improvements are suggested in the existing continuing education programs in countries where WHO-Multimodal hand hygiene improvement strategy is not implemented.

Keywords: Hand hygiene, Clean Hands, Clean Care is Safer Care, WHO

#### **1. INTRODUCTION**

Healthcare-associated infections (HCAIs) are major public health problem throughout the world. HCAIs threatens the patient safety and quality of care by causing prolonged hospital stays, long-term disability, increased resistance of microorganisms to antimicrobials, high costs and increased mortality. Thus, surveillance, development and application of new preventive strategies are crucial for a safer health care. According to World Health Organization (WHO), 7% and 10% of hospitalized patients in developed countries and developing countries respectively, will acquire at least one health-care associated infection [1].

There are more than one mechanisms associated with the dissemination of HCAIs but hands of health care workers (HCWs) are the most risky sites for transmission of HCAIs [2]. "Savior of mothers", Ignaz Semmelweis who was one of the pioneers of antiseptic procedures suggested washing hands with chlorinated lime solutions between different operations [3]. This is widely accepted as the introduction of hand disinfection standards in 1847. Since then, many guidelines on hand hygiene (HH) practices have been published by different organizations

to increase the knowledge and awareness of health care workers[4-6]. In this content, healthcare education plays a key role for the establishment of a sustained change in the behaviors of individuals and institutions, and also for the improvement of HH practices when designing novel interventions.

Knowledge is one of the major factors which gives shape to the perceptions of an individual and determines how she/he will act in terms of HH practices. Globally, tremendous efforts are put in to counteract low knowledge or malpractice regarding HH, but it appears that, in some parts of the world, the lack of policies has led to a lack of information on the significance of HH.

So far, the epidemiological basis of HCAIs in Cyprus has not been studied. Furthermore,WHO Multimodal HH Improvement Strategy is not implemented in Northern Cyprus. Hence, exploring HH knowledge plays a crucial role in bridging the gap between theory and practice. Herein, we describe the level of knowledge and perceptions of HH among nurses in N. Cyprus as an example of developing countries, with tailored recommendations for improvements.

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### 2. MATERIALS and METHODS

#### Design, Setting, Sample

This descriptive cross-sectional study was conducted in 2017, in two public hospitals in Northern Cyprus. Based on the most recent national statistical yearbook, there were 722 nurses working in public hospitals. Sample size has been calculated to be n=184 by using the online sample size calculator Openepi [7], where hypothesized % frequency of the outcome factor in the population is considered to be 80% based on the survey results in the Eastern Mediterranean Region [8]. Sample group of this study included nurses working in two state hospitals who volunteered to participate.

#### Ethical considerations

Ethical approval of this study was obtained from Health Subcommittee of Eastern Mediterranean University Research and Publication Ethics Board with decision number 2017/40-58 and written informed consent was requested from participants before filling out the questionnaires. Only volunteer nurses who signed the informed consent form and answered the questionnaires were included in the study.

#### Data collection

'Perception Survey for Health-Care Workers', and 'HH Knowledge Questionnaire for Health-Care Workers' prepared by WHO and revised in 2009 [9] were used in this study. 25 knowledgerelated questions with multiple choice, yes-no or true-false answers were applied; while perception of the participants was measured via three questions with 4-point likert scale and twelve questions with 7-point likert scale answers. Both of the surveys were cross-culturally and conceptually translated. Adaptation to Turkish language included the following steps: (i) Forward translation, (ii) Expert panel Back-translation, (iii) Pre-testing and cognitive interviewing and (iv) Finalization. In addition; a demographic form was also prepared to obtain information regarding participants' age, gender, duration of practice, facility, ward and service, country of education, average number of patients (daily), and average time allocated for a patient. A count of 200 self-administrated questionnaires were proportionally distributed to the wards of the aforementioned two hospitals for voluntary participation of nurses with informed consent.

#### Data analysis

After data were obtained, scores for knowledge and perception were calculated for each participant by assigning one point to every correct answer in knowledge-related questions, and by summing up the scores of perception-related likert scale questions. In calculation of knowledge scores, every one of the 25 statements had the same weight, and no penalty has been applied for wrong answers. As a result, a knowledge score out of 25 have been calculated for each participant, and then it was multiplied by 4 in order to report the knowledge score out of 100. In order to calculate the perception score for each participant, weights of the questions were assigned based on the number of likert points (1-4 in four 4-point likert scale questions, and 1-7 in twelve 7-point likert scale questions). The sum of those weights out of 96 were then converted to a perception

score out of 100. Similar to the previous studies [9, 12], the levels of knowledge and perception were determined as good if the score was  $\geq$  75, moderate if the score was between 50 and 74, and poor if the score was  $\leq$  50 upon 100.

#### Statistical analysis

Data management was done using Microsoft EXCEL 2010 software. IBM SPSS version 21 (SPSS Inc., Chicago, IL, USA) were used for statistical analyses including calculation of the scores, descriptive analysis and hypothesis tests. In order to determine the factors affecting knowledge and perception scores, firstly normality tests were conducted for determining if parametric or nonparametric comparison tests should be applied. Since knowledge and perception scores were not normally distributed, Mann-Whitney U tests were applied for factors with two categories, and Kruskal-Wallis tests were conducted to compare scores with factors of over two categories. p-value less than 0.05 were considered significant.

## **3. RESULTS**

Among the 200 nurses, 125 participated in our study with a response rate of 62.5%. The mean age ( $\pm$  standard deviation) of the participants was found to be 35.67  $\pm$  6.68 years. 112 (89.6%) of the participants were females, and 13 (10.4%) were males. The departments of the respondents are given in Table I. Answers of participants to the questions regarding whether they received a formal training in HH within the last three years and information about the country of institution they graduated from (i.e. from a university in Northern Cyprus or Turkey) are also given in Table I.

The calculated mean of the occupation duration of the nurses participating in this study was 12.22  $\pm$ 7 years, with a minimum of three and maximum of 28 years. Based on the practical experience of the participants in hospitals; they stated that the average number of patients they were dealing with every day was 17.74  $\pm$  6.44, and the average length of time they spent on a patient was 6.64  $\pm$  3.24 minutes.

Based on the answers of nurses participating in the study, knowledge scores were calculated on a scale of 25. The knowledge scores ranged between eight and 20, with a mean of  $14.92 \pm 2.26$ . The calculated knowledge scores were then converted as out of 100; and "good, moderate and poor knowledge" frequencies were found as: 5.6% (7 of 125 nurses) of the participants had good knowledge, while 80.8% had moderate knowledge, and 13.6% had poor knowledge. The participants' knowledge scores based on different categories are given in Table I.

HH perception scores were calculated for each participant by summing up the scores of questions related to HCAI's and actions to improve HH permanently in their institutions. Obtained totals were converted to a scale out of 100. The mean perception score was found to be  $82.52 \pm 9.44$ , with a median of 82.29 (min=42.71, max=97.92).

The level of perception about HH was also calculated. Among the nurses, 83.2% (n=104) had good perception, while 16% had moderate perception, and 0.8% had poor perception. Descriptive measures and comparisons of perception scores based on demographics were variable (Table I).

#### Table I. Descriptive measures and comparisons of knowledge and perception scores based on different categories.

	Categorical Variable	Frequency	Mean ± SD	p value
Knowledge Scores	Duration of practice			
0	3-11 years	69 (55.2%)	15.26 ± 2.25	0.157**
	12-20 years	38 (30.4%)	$14.76 \pm 2.07$	
	21-29 years	18 (14.4%)	$13.94 \pm 2.48$	
	Gender			
	Male	13 (10.4%)	$14.62 \pm 2.69$	0.493*
	Female	112 (89.6%)	14.96 ± 2.22	
	Department			
	Urology	20 (16%)	$15.55 \pm 2.58$	
	Pediatrics	19 (15.2%)	$15 \pm 2.69$	0.12535
	Surgery	17 (13.6%)	$14.24 \pm 1.48$	0.135**
	Cardiology	17 (13.6%)	$15.53 \pm 1.84$	
	Gynecology	16 (12.8%)	15.19 ± 2.93	
	Emergency	12 (9.6%)	$15.58 \pm 1.73$	
	Neurosurgery	9 (7.2%)	$14.22 \pm 2.22$	
	Neurology	5 (4%)	$13.2 \pm 1.3$	
	Orthopedics	5 (4%)	$12.8 \pm 1.1$	
	In room service	4 (3.2%)	<u>15 ± 1.41</u>	
	Pulmonary diseases	1 (0.8%)	15 ± 0	
	Country of Education			
	NorthernCyprus	62 (49.6%)	$14.26 \pm 2.29$	0.001*
	Turkey	63 (50.4%)	$15.57 \pm 2.05$	
	Taking trair			
	HH in the last t Yes	122 (97.6%)	14.98 ± 2.25	0.037*
	No	3 (2.4%)	14.98 ± 2.25 12.33 ± 1.15	0.037
	Daily hand rub use	3 (2.4%)	12.33 ± 1.15	
	Yes	117 (93.6%)	15.09 ± 2.23	0.001*
	No	8 (6.4%)	$13.09 \pm 2.23$ 12.5 ± 0.93	0.001
	Ward	8 (0.470)	12.5 ± 0.95	
	Medical	58 (46.4%)	15.12 ± 2.11	0.179*
	Surgical	67 (53.6%)	$13.12 \pm 2.11$ 14.75 ± 2.39	0.179
	Clinic	07 (35.070)	11.75 ± 2.57	
	Outpatient	48 (38.4%)	15.33 ± 2.17	0.048*
	Inpatient	77 (61.6)	14.66 ± 2.3	0.010
rception Scores	Duration of practice	// (01.0)	11.00 ± 2.0	
	3-11 years	69 (55.2%)	82.25 ± 8.38	0.358**
	12-20 years	38 (30.4%)	82.1 ± 9.68	01000
	21-29 years	18 (14.4%)	84.43 ± 12.69	
	Gender	10 (11170)	0110 = 1103	
	Male	13 (10.4%)	83.65 ± 5.27	0.916*
	Female	112 (89.6%)	82.38 ± 9.82	
	Department	112 (0)(0)(0)	02100 2 9102	
	Urology	20 (16%)	80.21 ± 6.27	<0.001**,a
	Pediatrics	19 (15.2%)	86.02 ± 9.79	
	Surgery	17 (13.6%)	88.54 ± 5.62	
	Cardiology	17 (13.6%)	82.78 ± 3.5	
	Gynecology	16 (12.8%)	86 ± 6.44	
	Emergency	12 (9.6%)	74.39 ± 6.64	
	Neurosurgery	9 (7.2%)	76.85 ± 16.46	
	Neurology	5 (4%)	82.92 ± 13.49	
	Orthopedics	5 (4%)	69.58 ± 12.29	
	In room service	4 (3.2%)	86.98 ± 2.62	
	Pulmonary diseases	1 (0.8%)	92.71 ± 0	
	Country of Education			
	NorthernCyprus	62 (49.6%)	84.74 ± 8.25	0.037*
	Turkey	63 (50.4%)	80.32 ± 10.08	
	Ward	,		
	Medical	58 (46.4%)	82.58 ± 8.75	0.915*
	Surgical	67 (53.6%)	82.46 ± 10.07	
	Clinic			
	Outpatient	48 (38.4%)	81.97 ± 8.53	0.399*
	Inpatient	77 (61.6)	82.86 ± 10.01	

<sup>1</sup>Knowledge scores (out of 25) based on different categories. <sup>2</sup> Perception scores (out of 100) based on different categories. \* Mann Whitney U test, \*\* Kruskal-Wallis test, a Significance between categories; Orthopedics-Surgery (p=0.014), Emergency-Gynecology (p=0.035), Emergency-Pediatrics (p=0.003), Emergency-Surgery (p<0.001), Urology-Surgery (p=0.034)

Frequency and percentages of true and false answers to questions related to routes of cross-transmission and HH methodologies

from 'HH Knowledge Questionnaire for Health-Care Workers' are shown in Table II.

Table II. Frequency and percentages of true and false answers to questions related to routes of cross-transmission and HH methodologies from 'HH
Knowledge Questionnaire for Health-Care Workers'.

Descript	ion	Correct Answer	Frequency	Percentage
	Health-care workers' hands when not clean	true	104/125	83.2%
Main route of cross-transmission of potentially	Air circulating in the hospital	false	7/125	5.6%
harmful germs between patients in a health-care	Patients' exposure to colonized surfaces	false	6/125	4.8%
facility	Sharing non-invasive objects between patients	false	8/125	6.4%
	The hospital's water system	false	0/125	0%
Most frequent source of germs responsible for	The hospital air	false	16/125	12.8%
health care-associated infections	Germs already present on or within the patient	true	24/125	19.2%
	The hospital environment (surfaces) false	85/125	68%	
	Before touching a patient	yes	125/125	100%
HH actions preventing transmission of germs to the	Immediately after a risk of body fluid exposure	no	37/125	29.6%
patient	After exposure to the immediate surroundings of a patient	no	35/125	28%
	Immediately before a clean/aseptic procedure	yes	100/125	80%
	After touching a patient	yes	107/125	85.6%
HH actions preventing transmission of germs to the	Immediately after a risk of body fluid exposure	yes	113/125	90.4%
health-care worker	Immediately before a clean/aseptic procedure	no	32/125	25.6%
	After exposure to the immediate surroundings of a patient	yes	59/125	47.2%
	Handrubbing is more rapid for hand cleansing than handwashing	true	108/125	86.4%
Knowledge on when using alcohol-based hand rub	Handrubbing causes skin dryness more than handwashing	false	17/125	13.6%
and handwashing with soap	Handrubbing is more effective against germs than handwashing	true	91/125	72.8%
	Handwashing and handrubbing are recommended to be performed in sequence	false	29/125	23.2%
	20 seconds	true	78/125	62.4%
Knowledge on minimal time needed for alcohol-	3 seconds	false	0	0%
based hand rub to kill most germs on your hands	1 minute	false	41/125	32.8%
	10 seconds	false	5/125	4%
	Before palpation of the abdomen	rubbing	80/125	64%
	Before giving an injection	rubbing	63/125	50.4%
Knowledge on the required HH method specific	After emptying a bedpan	rubbing	43/125	34.4%
situations	After removing examination gloves	rubbing	66/125	52.8%
	After making a patient's bed	rubbing	60/125	48%
	After visible exposure to blood	washing	59/125	47.2%
	Wearing jewellery	yes	108/125	86.4%
Avoided cosmetics, as associated with increased	Damaged skin	yes	123/125	98.4%
likelihood of colonization of hands with harmful germs	Artificial fingernails	yes	118/125	94.4%
0	Regular use of a hand cream	no	86/125	68.8%

Frequency, percentage, and 95% Confidence Intervals of high/ very high answers (from a 4-point likert scale) and selection of answers  $\geq 6$  (from a 7-point likert scale) for questions related to HCAIs and HH effectiveness from 'Perception Survey for Health-Care Workers' are shown in Table III.

Table III. Frequency, percentage, and 95% Confidence Intervals of high/very high answers from a 4-point likert scale and selection of answers ≥6 from
a 7-point likert scale for questions related to HCAIs and HH effectiveness from 'Perception Survey for Health-Care Workers'.

Description	Question	Frequency	% (95% CI)
Questions related to HCAIs and HH effectiveness based on answers high/very high (3/4) from a 4-point likert scale.		103/125	82.4% (76, 88.8)
	HH effectiveness in preventing HCAIs (high/ very high)	116/125	92.8% (88, 96.8)
	Importance in the ward of hand hygiene with respect to all patient safety issues (high/very high)	65/125	52% (43.2, 61.6)
Questions related to actions to improve HH and other components of HH management based on the selection of answers with scores $\geq 6$ from a 7-point likert scale.	Leaders and senior managers support and openly promote HH	118/125	94.4% (90.4, 97.6)
	Alcohol-based handrub always available at each point of care	119/125	95.2% (90.4, 98.4)
	Hand-hygiene posters are displayed at point of care as reminders	107/125	85.6% (79.2, 91.2)
	Each healthcare worker receives education on HH	117/125	93.6% (88.8, 97.6)
	Clear and simple instructions for HH are made visible for every healthcare worker	113/125	90.4% (84.8, 95.2)
	Healthcare workers regularly receive feedback on their HH performance	111/125	88.8% (83.2, 94.4)
	You always perform HH as recommended (being a good example for your colleagues)	114/125	91.2% (85.6, 96)
	Patients/parents are invited to remind healthcare workers to perform HH	113/125	90.4% (84.8, 95.2)
	Importance that the head of the ward places on the fact that HCWs perform optimal HH (high/ very high)	83/125	66.4% (57.6, 75.2)
	Importance that your colleagues places on the fact that HCWs perform optimal HH (high/ very high)	61/125	48.8% (40, 57.6)
	Importance that the patients/parents places on the fact that HCWs perform optimal HH (high/ very high)	28/125	22.4% (16, 29.6)
	Effort required to perform good HH when caring for patients (high/very high)	28/125	22.4% (15.2, 29.6)

## 4. DISCUSSION

This study demonstrates low rates of "good HH knowledge," despite in – service education among nurses in NorthernCyprus. Therefore, the quality and effectiveness of in – service education activities should be re-evaluated and standardized. Also, our analysis shows that poor HH knowledge is strongly associated with educational background and interestingly with the country of education. Even though, the perception of HH effectiveness in patient safety was high, it was the least important among other safety issues for nurses participating in our study. Our study participants perceived promotion of HH by leaders/senior managers as the most useful action to improve adherence to HH practices along with alcohol-based hand-rub use.

World Health Organization's "Clean Care is Safer Care" was launched in October 2005 as the first Global Patient Safety Challenge, aimed at reducing HCAI worldwide. Global promotion of HH was one of the most important actions within "Clean Care is Safer Care" campaign [6]. In order to provide a safer care for patients, healthcare workers must have good HH knowledge and follow the HH guidelines. There are studies which demonstrate the necessity of a high level of knowledge for good HH practices, despite the fact that practices may not always reflect their knowledge [10-13]. As a limitation, practices were not observed in our study, but our results did not show an adequate level of HH knowledge (5.6% had good level HH knowledge) leaving less chance for proper practices. The risk for patients to develop HCAIs in developing countries is significantly higher than in developed countries [6]. Good HH practices in developed countries have a crucial role in the prevention of infection in patients. Different studies using WHO instruments have reported a moderate level of HH knowledge scores, but a low level of good knowledge scores (ranging from 4.3 to 9), especially in developing countries, corresponding to our results [11,14–16]. These results highlight that raising the knowledge level of HCWs should be the primary goal for reaching global patient safety, especially in developing countries.

Our participants graduated from two different educational backgrounds, namely; North Cyprus and Turkey. Interestingly, the group of participants who were educated in Turkey had significantly higher HH knowledge scores. In Turkey, it was reported previously that nurses' knowledge level for infection prevention was above the average, but transfer of knowledge to practice was problematic [17]. Another study from Turkey, also reporting low knowledge of HH and noncompliance to HH practices and suggesting in-service HH educations as a significant factor to improve HH practices among health care personnel including the nurses [16]. Also, poor knowledge of hand washing techniques among nurses was reported with suggestions referring to the need to improve present the undergraduate nursing education program in Turkey [18,19]. On the other hand, there is no data referring to HH or infection prevention knowledge in North Cyprus. With this regard, our study results may question the need of revision in the nursing education programs of both countries. Furthermore, our results suggest country of education as a factor to be taken into consideration for improving HH practices.

As expected, we found that "in-service education" is significantly related to the overall HH knowledge scores. This aligns with other studies indicating a positive association between different styles of continuous training activities with HH knowledge [20-23]. Thus, more emphasis needs to be given to regularly update the HH knowledge of nurses, as this may enhance HH practices.

Apart from that, in-service education can help nurses to keep their knowledge up to date. Only 19.2% of our respondents answered correctly when asked about the most frequent source of germs responsible for HCAIs. In a study from India, which used same instruments as ours; 27% of nurses answered the question about the most frequent source of germs leading to HCAIs, correctly [15]. In another study among nursing students in Sri Lanka, this rate was found to be 26.9% [24]. The level of knowledge for this specific question was far from being adequate and is lower but comparable with other developing countries like Sri Lanka or India. Moreover, the duration of practice was negatively correlated with the knowledge of the most frequent source of germs responsible for HCAIs. The rate of correct answers given for questions regarding routes of crosstransmission and HH methodologies were average (Average Knowledge Scores were 58.8% and 60.21% respectively), which correlates with the literature.[15,24].

Our participants' perceptions were significantly different across different departments. Nurses who worked in the emergency departments had significantly lower HH perceptions compared to those working in gynecology, pediatrics and surgery. Likewise, orthopedics and urology nurses had significantly lower perceptions compared to nurses working in surgery departments. Interestingly, a higher perception was observed in nurses educated in North Cyprus in contrast to those educated in Turkey, despite a lower level of HH knowledge. Also, we noted higher perceptions through increasing working years. Among the nurses, 16.8% had poor to moderate levels of perception whereas the remaining 83.2% had a good perception towards HH. Santosaningsih et al. reported the rate of positive perceptions in different groups to be in a range between 69.1 to 98.7% in a hospital in Indonesia [25]. In Korea, HCWs' mean score of HH perception was 75.2 whereas it was 82.52 in our study [26]. We know that, improved HH compliance is associated with the change of perception toward HH among medical personnel [27]. Although, mean score is found to be 82.52 in our study, it is still far from the levels in developed countries, which indicates a lack of HH compliance in our country. To sum up, educational background, working years and high work load seem to be the factors influencing the perceptions of nurses participating in our study. However, different factors and their roles can be considered in further studies.

Our participants perceived HH to be less important among other patient safety issues. The importance placed on the HH by colleagues, patients/parents was perceived poorly among 48.8% of our participants with 95% CI [40, 57.6] and 22.4% with 95% CI [16, 29.6] respectively. Moreover, leaders/senior managers also had a poor perception of HH. Thus, initially the leaders/senior managers must be trained concerning the importance and effectiveness of alcohol-based hand-rub to improve HH compliance. The availability of alcohol-based hand-rub and promotion of HH by leaders/senior managers for the improvement of perception, knowledge and practice in HH plays an essential role [28]. Furthermore, it is important to note that, in addition to the healthcare professionals, patients and parents also play a critical role in their own safety by reminding HCWs to wash their hands as an effort to increase HH compliance in real life [29,30].

Standardization of in-service education activities will contribute to the quality and effectiveness of healthcare, HH and HCAI prevention. For this reason, implementation of WHO-multimodal hand hygiene improvement strategies in the developing countries should be considered. Suggested improvements in HCAI prevention strategies in developing countries where WHO guidelines are not implemented, would be (i) organization of educational activities, (ii) implementation of new practices and (iii) evaluation of compliance to HH practices among nurses and (iv) planning of future works can be beneficial in the transition period.

Improvements on HH compliance among nurses should start with the proper education of nurses. Moreover, HH awareness among leaders of health care facilities as well as nurses should be raised. Continuous education which will frequently remind nurses to wash their hands in a proper way is essential. Apart from that, periodical observation activities for HH practices should be performed.

Our study results are comparable with other studies especially from developing countries. Possibility of (i) a sampling bias as participation to the study was carried out on a voluntary basis, (ii) tendency to over score socially desirable behavior and (iii) unrealistic estimation of their behaviors can be listed as the limitations of this study.

This is the first study in Northern Cyprus documenting the level of knowledge and perceptions towards HH among nurses. To conclude based on our results, the suggested improvements in HH compliance among nurses would be to educate and raise the HH awareness among leaders of health care facilities and the nurses. Following this study, contacting relevant administrators to organize a campaign and trainings on HH methodologies would be beneficial to raise the awareness of HH compliance. Follow-up study could be conducted after two years to monitor the success rate of the outcome.

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## **Compliance with Ethical Standards**

**Ethical Approval:** The study was reviewed and approved by Health Subcommittee of Eastern Mediterranean University Research and Publication Ethics Board with decision number 2017/40-58.

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**Conflict of Interest**: The authors declare that they have no conflict of interest.

**Informed Consent**: A written informed consent was obtained from each participant.

**Authors' Contributions:** M.G. and N.I.A. conceived and planned the study, N.I.A performed the analytic calculations. M.G. and N.I.A. wrote the article. Both authors contributed to the final version of the manuscript. M.G. supervised the project.

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