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ii. Walker M, Hull A. Preterm labor and birth. In: Taeusch HW, Ballard RA, eds. Avery's Diseases of the Newborn. Philadelphia: WB Saunders, 1998: 144,153.

iii. Hagström H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017; 67: 1265-73. doi: 10.1016/j.jhep.2017.07.027.

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http://globalfamilydoctor.com/publications/new/november/09.htm
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# Fat graft survival inside pocket for silicone implant

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ABSTRACT

Objective: The aim of this study was to investigate the survival potential of the fat grafts inside the implant capsule in an experimental setting.

Materials and Methods: Twenty male Wistar albino rats were used. A two-staged surgical procedure was performed. In the first stage, silicone sheets were placed in the subcutaneous plane on the left side of each rat. On day 60, fat grafts injected into the silicone capsule either by removing the silicone sheaths or leaving the silicone sheaths in their place. In both groups, the same amount of the fat grafts was injected into the right side of the dorsal subcutaneous plane of the rats and they served as their own controls. The findings were evaluated according to the histopathological criteria.

Results: There was no statistically significant difference in the inflammatory cell infiltration, fibrosis, and necrotic adipocytes among the groups. Although, the fat viability rate was higher in control groups, there was no statistically significant difference compared to the capsule or silicone groups ($p>0.05$).

Conclusion: Our study results suggest that implant capsule is a hospitable environment and resection of the capsule is unnecessary, if silicone implants are expected to be removed following fat injection.

Keywords: Fat graft, Lipofilling, Adipocyte, Capsule, Silicone implant, Prosthesis

## 1. INTRODUCTION

The fibrous tissue capsule formation surrounding silicone implants is the natural consequence of inflammatory mechanisms and wound healing processes [1-3]. Silicone implants are widely used in aesthetic and reconstructive breast surgery and are associated with complications, which give rise to many discussions. Despite the debate, an implant capsule is applied as a local flap, a graft material, or even as a vascular carrier which enable the graft to take over itself thanks to its natural, well-vascularized tissue layer [4].

Inrecent years, fat grafting has been increasingly used in aesthetic and reconstructive breast surgery, as it yields symmetry and natural consistency of the breast tissue with the ability of camouflaging the irregularities [5-12]. Tissue layers between the capsule and skin is the favorable plane of injection for the fat grafts [13]. However, there is a relatively limited space for injection without excessive increase in the pressure of the recipient compartment, leading to a higher amount of graft loss. Despite the well-vascularized nature of the implant capsule and a considerably larger space inside the implant pocket, fat injection is practically avoided. In addition, there is a limited number of data regarding the survival of the fat grafts inside the implant pocket, which offers an ample space and well-vascularized bed for fat grafts.

In the present study, we aimed to investigate the survival potential of the fat grafts inside the pocket for the silicone implant in an experimental setting.

## 2. MATERIALS and METHODS

### *Study population*

All experimental protocols were approved by the Local Ethics Committee (Date: 04.01.2016/No.004.2016.mar) on Animal Experiments at Marmara University, School of Medicine and were under the National Institute of Health guidelines for the Care and the Use of Laboratory Animals. All surgical procedures were performed at the Experimental Animal Laboratory of Marmara University, School of Medicine.

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A total of 20 male Wistar albino rats with a mean weight of 500 (range, 450 to 550) g were used. All subjects were fed with a standard diet and were sedated using ketamine (Ketalar® Pfizer, Turkey) and xylazine (Rompun® Bayer, Turkey) [14,15]. Dorsum of the rats were shaved with an electric razor and prepared for surgery. A non-sterile, but clean surgical technique was used. A two-staged surgical procedure was adopted in all subjects. In the first stage, 2x1-cm silicone sheets were placed in the subcutaneous plane on the left side of each rat through a 1-cm incision (Figure 1). On day 60, the second stage of surgery was performed by harvesting the fat grafts from the inguinal fat pad on both sides of the subjects. The collected specimen was gently minced with scissors and filled into 2-cc syringes. The implant pockets on both sides of the rat were, then, exposed.

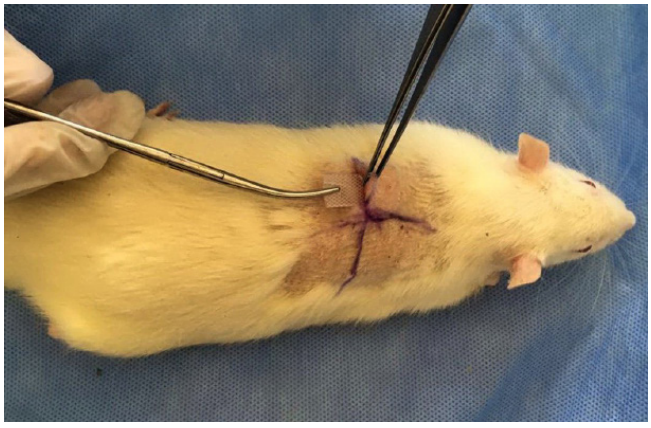

**Figure 1.** Silicone sheet placement in the subcutaneous plane on left side through a 1-cm incision.

All subjects were divided into four groups according to the presence of the silicone sheath inside the implant pocket. In the first group (n=10), silicone sheaths were removed and 1 cc of the fat graft was injected into the implant pocket (Figure 2). In the second group (n=10), the same amount of the fat graft was injected into the left implant pocket, leaving the silicone sheaths in place. The pockets were, then, closed with three separate absorbable sutures.

In both groups the same volume (1 cc) of the fat graft was implanted into the right side of the dorsal subcutaneous plane of the rats through a separate incision and they served as their own controls. As a result, two study groups were divided into two subgroups as follows:

Group 1 (Left side – Capsule Group) – Fat grafts inside the silicone implant pocket without an implant.

Group 1 Control (Right side – Capsule Control Group) – Subcutaneous fat grafts.

Group 2 (Left side – Silicone Group) – Fat grafts inside the silicone implant pocket with an implant.

Group 2 Control (Right side – Silicone Control Group) – Subcutaneous fat grafts.

All subjects were caged separately and sacrificed at the end of four months. The capsule and fat grafts were identified macroscopically through a midline incision and excised with surgical safety margins. Finally, fat grafts were sent to histological examination in formaldehyde solution.

**Figure 2.** 1-cc of fat graft injection into the implant pocket following silicone sheath removal through previous incision.

### *Histological examination*

Adipose tissues which were fixed in 10% formaldehyde solution were dehydrated in ascended alcohol series, clarified in xylene, and embedded in paraffin. A 5-μm-thick paraffin sections were stained with hematoxylin & eosin (H&E) for histopathological evaluation. In each section, five similar areas were evaluated at x200 magnification through light microscope (Olympus BX-51; Olympus Life Science, Tokyo, Japan) by two blinded histologists and photographed with a digital camera (Olympus DP72, Olympus Corp., Tokyo, Japan). The modified histopathological criteria were inflammatory cell infiltration, presence of cyst formation, fibrosis, fat necrosis, and viable fat tissue [16]. Each criterion was scored as none (0), mild (1), moderate (2), and extensive (3), being a maximum score of 15.

### Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 15.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), or number and frequency. The Kruskal-Wallis test (nonparametric analysis of variance [ANOVA]) was used to analyze significant differences among the groups. A $p$ value of <0.05 was considered statistically significant.


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## 3. RESULTS

### *Macroscopic findings*

Significant vascularity was observed around the capsules filled with fat grafts (Group 1) which had regular borders and a globular shape (Figures 3-5). In the control group, fat grafts were shaped irregularly.

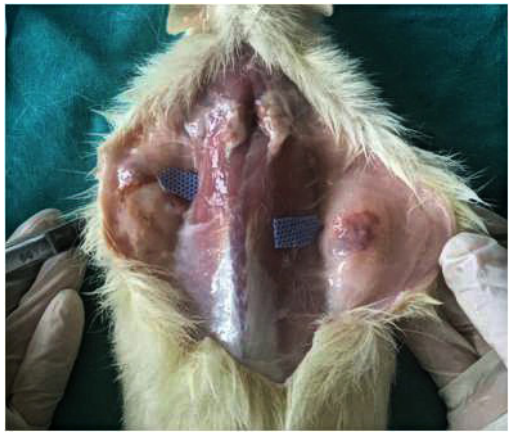

**Figure 3.** Fat grafts in capsule group on left side and capsule control group on right side.

**Figure 4.** Fat grafts in silicone group on left side and silicone control group on right side.

**Figure 5.** A circular shaped fat graft of capsule group on left side and an irregular-shaped fat graft of capsule control group on right side group are seen.

### *Microscopic findings*

Histopathological results showed a cyst formation with vascular congestion, inflammatory cell infiltration, mast cells adjacent to the blood vessels, fibrosis, and viable and necrotic adipocytes in both study groups and controls (Figure 6). There was no statistically significant difference in the inflammatory cell infiltration, fibrosis, and necrotic adipocytes among the groups (0.9931, 0.2882, 0.8621). However, the number of viable adipocytes was higher in the control groups (Table I). Increased degranulated mast cells, vascular congestion, and large cyst formation were moderate in capsule and its control group.

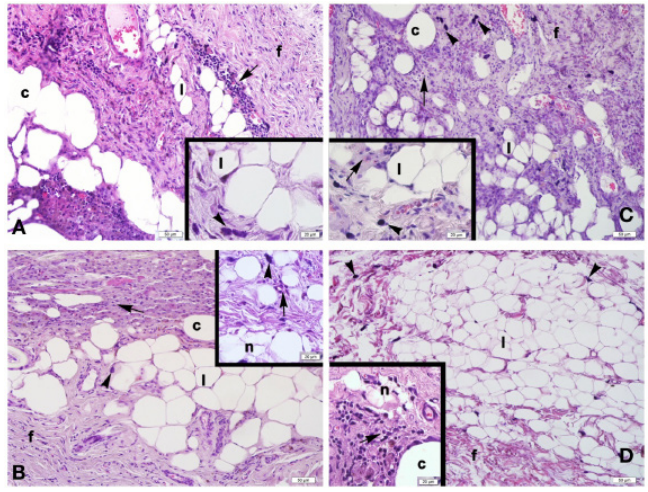


**Figure 6.** Representative light micrographs seen in experimental groups. Cyst formation (c), inflammatory cell infiltration (arrow), mast cells (arrow head), fibrosis (f), viable (l) and necrotic (n) adipocytes are seen in all groups under H&E staining (x200); insets (x400. a) Capsule group; b) Capsule control group; c) Silicone group; and d) Silicone control group.

Inflammation scores were similar in all subgroups. Although the fat viability was higher in the control groups, there was no statistically significant difference compared to the capsule or silicone groups (p=0.2336). The cyst formation scores were also similar in both subgroups, indicating no statistically significant difference (p=0.2711) (Table I). Histopathological results showed cyst formation, vascular congestion, inflammatory cell infiltration, mast cells close to the blood vessels, fibrosis, viable and necrotic adipocytes in all groups. Inflammatory cell infiltration, fibrosis and necrotic adipocytes were similar in all groups. Viable adipocytes were more extant in lipid and silicone control groups. Increased and degranulated mast cells, vascular congestion and large cyst formation were moderate in the lipid experiment group.


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**Table I.** Modified histopathological criteria scores

| | Inflammation | Cyst | Fibrosis | Viable fat | Necrotic fat | Total |
|---|---|---|---|---|---|---|
| Capsule group | 2.25 (0.67) | 2.8 (0.34) | 2.15 (0.88) | 1.9 (0.73) | 1.4 (0.87) | 10.5 (1.77) |
| Capsule control group | 2.2 (1.13) | 2.5 (0.97) | 2.3 (1.15) | 2.1 (0.84) | 1.3 (0.94) | 10.4 (3.2) |
| Silicone group | 2.25 (0.75) | 2.31 (0.88) | 1.75 (0.65) | 1.25 (0.53) | 1.5 (0.92) | 9.06 (1.78) |
| Silicone control group | 2.13 (0.79) | 1.75 (0.88) | 2.5 (0.92) | 2.13 (0.95) | 1.75 (0.88) | 10.25 (1.90) |
| **p value** | p=0.9931 | p=0.2711 | p=0.2882 | p=0.2336 | p=0.8621 | |

Data are given in mean and standard error (SEM) in brackets, unless otherwise stated.

## 4. DISCUSSION

Fat grafting, which has been performed for more than one hundred years, Coleman [17] first refined the technique in 1997. Since then, autologous fat grafting as a reliable natural filler has been increasingly adopted with more consistent results. Currently, it is used for various purposes in aesthetic and reconstructive breast surgery with most common indications being the aesthetic or reconstructive augmentation of the breast with or without silicone implants, correction deformities and asymmetries of the breast, and the refinement of the soft tissues covering the breast implants [18,19]. However, the reabsorption rate of fat grafts widely varies ranging from 0 to 44% and often undergo fat necrosis [20].

A fibrotic capsule surrounding the silicone implants is the natural result of wound healing processes which aggravates within two months [1-3,21,22]. It acts as a barrier between the tissue and the implant. The capsule is a vascular fibrous tissue which receives a significantly higher blood flow than the surrounding soft tissues [23]. Although, it may also serve as an ideal recipient surface for graft harvesting, pericapsular soft tissue is the preferred recipient bed for fat grafts in the clinical practice, and fat injection inside the implant pocket is avoided [13]. On the other hand, data regarding the outcome of the injected fat grafts inside the pocket are scarce. The present study was, therefore, designed to investigate the outcome of fat grafts inside the implant pocket. Our study results showed that fat grafts survived inside the implant pocket in a similar size to the environment following the removal of the implant. Fat survival score of the capsule group was not significantly different than in the control groups. However, this finding is not consistent with the results of Yazawa et al., who reported poor survival of fat grafts inside their pocket for silicone implants without the treatment of basic fibroblast growth factor (bFGF) [24]. In our study, on the other hand, no growth factors or substitutes were available to enhance the vascularity. We used ordinary silicone implants which is compatible with the clinical setting. The discrepancy between the results of Yazawa et al. , and our results can be attributed to the distinct properties of the implanted object in their study. These authors used silicone implants coated with a photoreactive gelatin containing bFGF [24]

It has been well-established that the presence of a foreign body in a physiological environment promotes ongoing stimulation for inflammatory mechanisms which does not offer a well-disposed bed for graft survival [2,26]. In our study, fat grafts survived inside the implant pocket even in the presence of implants. However, the survival rate of fat grafts in the silicone group was significantly lower than in the controls. This decline can be explained either with the ongoing foreign body reaction, which increases the resorption rate of the fat grafts, or with the possible pressure effect of the implant. This finding is likely to support the clinical practice which avoids the arrangement of fat grafts inside the implant pockets.

Fibrosis is an indication of fat graft loss due to an unfavorable recipient bed. Another interesting finding of the present study is the lower fibrosis rate in the capsule and silicone groups, compared to relevant control groups. Although, increased neutrophil and fibroblast infiltration into the implant capsule has already been reported in the literature [1,27] , extensive collagen deposition might have isolated the fat grafts from the surrounding tissues as a barrier to reduce the fibroblast migration into the grafts.

The geometric effect of the implant capsule on fat graft survival is another major theme. Fat grafts in the capsule group had well-defined borders with a spherical shape. The silicone capsule served as a three-dimensional scaffold for the fat grafts and might have provided surgeons with another reconstructive option with fat grafts to achieve the desired shape and size.

Nonetheless, there are some limitations to this study. The low sample size might have contributed to the bias. In our experimental design, each subject served as its own control to reduce the amount of error in a limited sample size. Geometry of the implant pockets can be considered another limitation. Fibrous capsule pockets in our study were formed by the implantation of flat silicone sheaths offering a better contact surface for the fat grafts to survive. However, in the relevant clinical scenario, the implant pockets would be more extensive and rounder. Therefore, the viability of graft lobules at the core of the injection bulk would be questionable.

### Conclusion

In conclusion, to the best of our knowledge, this is the first controlled study to investigate the outcome of the fat grafts inside the silicone implant pockets without using any intervention for vascularity enhancement. Our study results indicate that a pocket


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for the silicone implant is a hospitable environment for fat grafts following the removal of the implant. In addition, resection of the capsule seems to be unnecessary, if silicone implants are expected to be removed following fat injection. Although, our results in the experimental setting demonstrate that the survival rate of fat grafts inside the implant pocket confirms a satisfactory three-dimensional shape, further large-scale studies with higher volumes of fat grafting in larger pockets are required to establish its clinical relevance.

### Compliance with Ethical Standards

**Funding:** The study was not supported by any funds.

**Conflict of interest:** The authors have no conflicts of interest to declare.

**Ethical approval:** The study protocol was approved by the Local Ethics Committee (Date: 04.01.2016/No.004.2016. mar) on Animal Experiments at Marmara University, School of Medicine and were under the National Institute of Health guidelines for the Care and the Use of Laboratory Animals. All surgical procedures were performed at the Experimental Animal Laboratory of Marmara University, School of Medicine.

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# The impact of child abuse and neglect training on knowledge and awareness in university students

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ABSTRACT

Objective: Child abuse and neglect are considered public health issues by authorities such as the World Health Organization (WHO). This study evaluated the effectiveness of the trainings given to university students.

Materials and Methods: In this study, we trained university students at Gazi University who are likely to deal with child abuse cases after graduation. By developing two scales, Child Abuse and Neglect Awareness Scale (CANA-S) and Child Abuse and Neglect Knowledge Test (CANK-T), to assess students' knowledge and awareness levels regarding child abuse and neglect, we evaluated the training's impact.

Results**:** We assessed the knowledge and awareness levels of 43 students before and after training by using our scales, The knowledge level has improved significantly in all groups regardless of age, sex, and department. Similarly, the awareness level has also risen significantly, except regarding the physical abuse subscale.

Conclusion: Overall awareness after education was significant among students from the health and social sciences departments. Total awareness scores did not increase significantly among law students. Measuring and disseminating the effectiveness of these trainings through proper prevention programs will be effective in reducing child abuse in the future.

Keywords : Awareness, Child abuse and neglect, Training program for university students, Knowledge, Scale

## 1. INTRODUCTION

The World Health Organization (WHO) defines child abuse and neglect as "all physical and/or emotional ill-treatment, sexual abuse, neglect or negligence and commercial or other exploitation, which results in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power" [1]. WHO found that 20% of women and 5%-10% of men were sexually abused as children, and 25%–50% of all children were physically abused [2]. In 2012, public institutions and child protection centers in the US received 3.4 million applications for abused and neglected children [3]. Authorities such as the WHO and the American Centers for Disease Control and Prevention (CDC) consider the abuse and sexual exploitation of children as public health issue [4, 5]. Many organizations have focused on training programs for the prevention of child abuse and neglect [6]. Public health policies should include the pre-emptive prevention of child abuse and neglect, as well as support for children's healthy development, which can be achieved through primary methods of prevention and maintaining existing approaches to ameliorate the effects of child abuse and neglect [6].

During the 1980s, "Child-oriented prevention" was a primary prevention method. This school-centered empowerment program for the prevention of child sex abuse has the following general goals: 1) to help children recognize potential situations of abuse and become aware of exploiters, 2) to support children's rejection of sexual requests, 3) to teach children to resist by avoiding exploiters, 4) to encourage children to report previous or current abuse to trusted authority figures, and 5) to explain to children that inappropriate touching and secrets are not their responsibility [7]. Attending such programs has been shown to increase children's awareness concerning protective behaviour against sexual abuse, but how well such programs prevent sexual abuse remains unclear [8, 9]. A primary prevention method, the "parent-oriented prevention method" instructs the adults surrounding the child, such as his/her parents and teachers [10]. The "community-oriented prevention method" works to increase public awareness by focusing on not only the child

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and the adults in his or her immediate surroundings, but also on the rest of the community through public trainings, and media campaigns (television, radio, newspaper, posters, and announcements) [11].

With the increase in child abuse cases in Turkey the need for the prevention of child abuse, as well as the demand for trained, sensitive, and educated individuals working in career fields focused on children has increased. Since 2005, university students have been trained by various departments on child abuse and neglect resulting from the collaboration of the Division of Social Pediatrics of Gazi University, School of Medicine and the Turkish Society for the Prevention of Child Abuse and Neglect (TSPCAN). Implemented trainings and programs on the prevention of child abuse must be grounded on a firm scientific foundation, with reliable data and evidence of significant benefits.

This study evaluated the impact of the training using the Child Abuse and Neglect Awareness Scale (CANA-S) [12] and the Child Abuse and Neglect Knowledge Test (CANK-T) [13] on the awareness of child abuse and neglect. We also evaluated whether this training increased the relevant knowledge levels of the participants or not.

## 2. MATERIALS and METHODS

### *Assessment Tools*

***Child Abuse and Neglect Awareness Scale*:** The CANA-S comprises four subscales (physical abuse, sexual abuse, emotional abuse, and neglect); of the 20 questions, 11 were phrased negatively and 9 positively. All items were presented as Likert scales, with five answer choices (ranging from "not appropriate at all" to "definitely appropriate"). Items were prepared and the reliability and validity were tested during and after the pilot study. Factor analysis was completed for construct validity, and experts were consulted to obtain content validity. In the reliability analysis, Cronbach's alpha value was 0.768 and the correlation coefficient was r = 0.204. The test–retest analysis found was to be significant p = 0.045 [12].

***Child Abuse and Neglect Knowledge Test*:** The CANK-T had 50 multiple choice questions with 5 answer choices each. Reliability and validity testing were completed during and after the preparation of items. The knowledge test was validated by preparing a table of specifications for each lesson and by creating common goals based on the Bloom Taxonomy for all lessons that concerned the child abuse and neglect and expected behaviour education according to the Bloom Taxonomy. The Kuder Richardson-20 reliability coefficient and Pearson's correlation test were used to measure the reliability of the information test. The Kuder Richardson-20 reliability coefficient was calculated separately for test–retest and resulted in 0.943 and 0.918, r=0.443, and p=0.011; the information test was found reliable [13].

### *Application and Population of the Study*

The CANA-S and CANK-T forms were distributed, to the participants before the training began. Just after the last lesson of the 12-week training program, the forms were again distributed to the participants under supervision.

The study population was created by voluntary response sampling and comprised of 145 voluntary college students from medicine, social services, law, psychology, child development, guidance and psychological counseling, sociology, education, midwifery, and nursing departments. The training was advertised before it started both on the website of the Turkish Society for the Prevention of Child Abuse and Neglect and social media.These students had participated in trainings on child abuse and neglect with the collaboration of Turkish Society for the Prevention of Child Abuse and Neglect and the Division of Social Pediatrics of Gazi University, School of Medicine during the 2014–2015 academic year. All in all, 48 students participated in the training for 8 weeks or more; 44 students took both the pre-test and post-test, but the research group consisted of 43 students because one student had been removed as per the exclusion criteria.

### *Exclusion Criteria*

Those who participated in the training for less than 8 weeks were not included in the study as they missed most of the topics addressed, which would have had an impact on the measure of the success of the training.

### *Study Duration and Setting*

Approval for the study was obtained from the Turkish Society for the Prevention of Child Abuse and Neglect and Division of Social Pediatrics of Gazi University, Scool of Medicine and the Gazi University Ethics Committee (number 77082166-604.01.02-18605).

The study was conducted in the Divisions of Social Pediatrics and Medical Education of Gazi University, School of Medicine between 01.01.2014 and 30.05.2014.

### *Training Application and Scope*

The training that has been underway since 2005 was created in collaboration with the Division of Social Pediatrics of Gazi University, School of Medicine and Turkish Society for the Prevention of Child Abuse and Neglect, and the trainings were provided by the above mentioned society instructors for voluntary students on child abuse and neglect for 12 weeks, once a week for 2 hours.

### Statistical Analysis

We examined whether continuous variables were distributed according to normal distribution by using a Kolmogorov–Simonov test and the homogeneity of the variances through a Levene test. Descriptive statistics are shown in the form of median minimum–maximum (min–max) values for continuous variables and as number of observations and (%)


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for nominal scaled data . By using the Wilcoxon signed-rank test, we investigated whether the groups underwent statistically significant changes before and after training according to the CANK-T and CANA-S subscales and total scale points.

Also we evaluated the importance of the extent of difference among the departments of the participants before and after training on the CANK-T, CANA-S subscale and total scales using the Kruskal–Wallis test.

A Spearman correlation test determined whether the correlation between the change in level of knowledge with age before and after training and the change in the subscale of awareness and the total points was statistically significant. For $p<0.05$ the results were considered statistically significant. In this study, Kuder Richardson-Formula 20 test was intrumentalized for the reliability test of CANK-T and the program SPSS for Windows 11.5 was used for data analysis.

## 3. RESULTS

### *Demographic Findings*

Based on their departments, the students were categorized into three groups: Healthcare Sciences, Law, and Social Sciences. The demographic findings are shown in Table I.

**Table I**. Demographic characteristics of the students

| Students | n = 43 |
|---|---|
| **Age (average ± standard deviation)** | 21.1 ± 6.2 |
| **Gender** | |
| Female | 40 (93.0%) |
| Male | 3 (7.0%) |
| **Department** | |
| ***Health Sciences*** | 11 (25.6%) |
| Medicine | 1 (2.3%) |
| Social Services | 9 (21.0%) |
| Nursing–Midwifery | 1 (2.3%) |
| ***Law*** | 5 (11.6%) |
| ***Social Sciences*** | 27 (62.8%) |
| Psychology | 9 (21.0%) |
| Guidance and Psychological Counseling | 11 (25.6%) |
| Sociology | 1 (2.3%) |
| Child Development | 6 (13.9%) |

### *Awareness Subscale before and after Training and Total Points for All Students*

The percentage of change before and after training scores for all students reflected in the total awareness scale points were found statistically significant (Table II). The awareness point before having the training was 85 out 100 which showed us that they had already gained some knowledge concerning the issues covered in the training. By perfoming studies with various groups, the effectiveness of the scale would be better understood. Whereas points regarding the neglect, sexual abuse, and emotional abuse subscales rose significantly for all students after having the training, the physical abuse subscale did not increase significantly (Table II).

**Table II.** Pre and post-training awareness subscales and total scores for all students

| Awareness subscales | Before-Training Median (min–max) | After-Training Median (min–max) | p value[a] |
|---|---|---|---|
| **Neglect** | 23 (13–25) | 23 (19–25) | **0.018** |
| **Physical Abuse** | 23 (19–25) | 24 (16–25) | 0.275 |
| **Sexual Abuse** | 21 (16–24) | 22 (17–24) | **<0.001** |
| **Emotional Abuse** | 19 (14–24) | 20 (16–24) | **0.030** |
| **Total** | 85 (75–95) | 89 (75–95) | **<0.001** |

[a]Wilcoxon Signed Rank Test; values in bold indicate statistical significance

### *Awareness Subscales and Total Results before and after Training According to Departments*

After having the training, the scores for the neglect subscale rose significantly among the social sciences students, while they did not increase among the health sciences and law students (Table III). For the sexual abuse subscale, the scores after having the training increased significantly among health and social sciences students, whereas they did not rise for law students (Table III).

**Table III.** Pre and post-training awareness subscales and total scores of students according to their departments

| Variable | Before-Training Median (min–max) | After-Training Median (min–max) | p value[a] | p value[b] |
|---|---|---|---|---|
| **Neglect** | | | | 0.613 |
| Health Sciences | 23 (19–25) | 24 (19–25) | 0.862 | |
| Law | 24 (18–25) | 24 (24–25) | 0.285 | |
| Social Sciences | 22 (13–25) | 23 (20–25) | **0.028** | |
| **Physical Abuse** | | | | 0.315 |
| Health Sciences | 23 (21–25) | 24 (20–25) | 0.089 | |
| Law | 24 (23–25) | 24 (23–25) | 1.000 | |
| Social Sciences | 24 (19–25) | 24 (16–25) | 0.737 | |
| **Sexual Abuse** | | | | 0.420 |
| Health Sciences | 20 (16–24) | 23 (19–24) | **0.021** | |
| Law | 21 (17–21) | 21 (19–22) | 0.593 | |
| Social Sciences | 21 (17–24) | 22 (17–24) | **0.003** | |
| **Emotional Abuse** | | | | 0.928 |
| Health Sciences | 19 (16–23) | 20 (17–22) | 0.101 | |
| Law | 19 (16–21) | 20 (19–21) | 0.414 | |
| Social Sciences | 19 (14–24) | 19 (16–24) | 0.159 | |
| **Total** | | | | 0.835 |
| Health Sciences | 87 (75–91) | 91 (75–95) | **0.028** | |
| Law | 88 (79–90) | 91 (86–91) | 0.279 | |
| Social Sciences | 85 (76–a95) | 89 (75–94) | **0.024** | |

[a]percent of change (pre-post) before and after training within different departments, Wilcoxon signed rank test; values in bold indicate statistical significance

[b]Increase in awareness scores before and after training within departments, Kruskal-Wallis test; values in bold indicate statistical significance


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On the other hand, the scores of emotional and physical abuse subscale did not step-up significantly for any student after the training (Table III).

The total awareness scores increased among the health and social sciences students after having training although they did not rise among law students (Table III).

### *Test Scores before and after Training on the Knowledge Test for All Students According to Major*

The knowledge test scores after having the training increased in all students regardless of their departments. (Table IV).

In this study, the reliability of CANK-T was measured as 0.584 before the training and 0.636 after the training.

**Table IV.** Scores for the knowledge test before and after training according to major

| Variables | Before-Training Median (min–max) | After-Training Median (min–max) | p value[a] | p value |
|---|---|---|---|---|
| **Department** | | | | 0.077[b] |
| Health Sciences | 35 (26–41) | 39 (36–45) | **0.005** | |
| Law | 33 (30–34) | 40 (38–43) | **0.042** | |
| Social Sciences | 35 (25–41) | 39 (25–46) | **<0.001** | |
| **Overall** | 34 (25–41) | 39 (25–46) | **<0.001** | |

[a]percentage of change (pre-post) before and after training., Wilcoxon signed rank test; values in bold indicate statistical significance

[b]percentage of change (pre-post) before and after training increase in awareness scores within departments, Kruskal–Wallis test

## 4. DISCUSSION

Child abuse and neglect is a significant issue, that can be transferred from one generation to another. It negatively affects childhood as well as adult life. A preventive method is providing an education on child abuse in order to increase the awareness of parents and individuals who deal with children and society as a whole.

The method for studying cognitive awareness requires learning how to learn, focusing on one's attention, planning what needs to be done step by step, evaluating each step of the learning process, and correcting and organizing [14]. We used the CANA-S to observe how individuals perceive child abuse and neglect, and also learn their level of comprehension , their knowledge and ideas on the topic.

In our literature review, we found school-oriented prevention programs for kindergartens, elementary and middle schools, and a few high schools. However, there were no such programs for college students [9, 15].

In the majority of studies we reviewed, we observed that school-based prevention training programs significantly increased children's knowledge and behaviour [16, 17]. When students actively participated in the training, an increase in both knowledge and protective behaviour scores was found higher among different age groups [18]. Standardized scales, short stories, and certain images were used before and after the training in kindergartens, elementary and middle schools so as to evaluate the knowledge at school-based trainings. High school students were assessed using only question-based knowledge tests such as The Sexual Attitudes Survey and its four subscales [19]. In our study, we administered the CANK-T twice, once before and once after the 12-week child abuse and neglect training. After the 12 week-training, the scores for knowledge were higher. In some studies, in order to evaluate the level of information recall, assessments were conducted only 3-12 months after the training, but we found no consensus on the ideal waiting period [9]. A study investigating the information recall found no difference between 6 months and 12 months after training [20]. In our study, the knowledge assessment was conducted right after the 12-week training, since it would have been difficult to reach voluntary students at any subsequent time. Furthermore, since the primary purpose of the study was to evaluate how much of the information had been understood, there was no need for a scale using long-term reminder.

Our study demonstrated that the 12-week child abuse and neglect training was an efficacious one achieving an increase in the total awareness and knowledge levels of all students participating in the training.

When the scores before the training and after the training were compared for the physical abuse subscale, no statistically significant increase was found. This is attributable to the already high before-training awareness scores, suggesting that physical abuse may be easier to identify from other types of abuse as the former often has visible indications.

The significant high scores for the total awareness of this issue among health and social sciences students when compared with those of law students may stem from students who are likely to work in child-related occupations in the future have a great interest in child abuse and neglect training than others. Additionally, it can also be explained by the low rate of law students who attended the training. There was no statistical difference between the increase in awareness in the emotional abuse and physical abuse subscales in terms of students' majors. This suggested that emotional abuse was difficult to understand and prove. Why the physical abuse awareness did not increase can be explained by all three majors having high awareness scores on entering the training that had little room for meaningful increase.

In some studies, an important link has been found between age and rise in knowledge through education [21, 22]. On the other side, in a study where elementary school students aged 5–7 and 8–13 year olds were compared, it was observed that the older students learning was faster and more thorough than in the younger ones [23]. Yet, some studies did not find any difference for age, regarding learning and increasing knowledge on this issue[16-18, 24]. In previous studies, the groups that received trainings comprised of high school or younger students, while our study group consisted of university students of similar age. For this reason, it was not possible to comment on age and increase in knowledge regarding our study.

The reliability of CANK-T used in our study was found low according to the scale we implemented which might stem from the absence of the voluntary students in trainings.

When scores in knowledge and awareness based on gender has been evaluated, as the women made up 93% (n=40) of the study population, no valued statistical comparison could be made. Work to increase male students' participation in future trainings must be put forward. If more male students were more informed about this topic, their awareness and participation could have increased.

As we demonstrated in our study, CANK-T and CANA-S [12,13] scales developed by us, authors of this study, are applicable during trainings on the child abuse and neglect issue.

### Limitations of the Study

The limitations include the number of drop-outs which is inevitable in view of the voluntary nature of participation in the study and the low number of students who took the final test. Because Turkish Society for Prevention of Child Abuse and Neglect trainings will continue in the future, this limitation may be overcomed by adjusting future trainings.

Child abuse prevention trainings and programs must be implemented with a strong scientific basis, reliable data, and proof of significant benefit.

### Compliance with Ethical Standards

**Funding:** The study was not supported by any funds.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Ethical approval:** Approval for the study was obtained from the Turkish Society for the Prevention of Child Abuse and Neglect and Division of Social Pediatrics of Gazi University, Scool of Medicine and the Gazi University Ethics Committee (number 77082166-604.01.02-18605).

**Informed consent:** Informed consent was obtained from all individual participant included in the study.

**Authors' Contrubition:** Concept and Design – HA, FSD, IIB; Supervision – FSD, IIB; Resources – HA, FSD, IIB; Materials – HA, FSD, IIB; Data Collection and Processing – HA, IIB; Analysis and Interpretation – IIB, HA; Literature Search – HA; Writing Manuscript – HA; Critical Review – FSD, IIB

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Original Article

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# The effects of pneumoperitoneum and patient position on the perfusion index and pleth variability index during laparoscopic bariatric surgery

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ABSTRACT

Objective: Limited data are available on the use of the perfusion index (PI) and the pleth variability index (PVI) during laparoscopic bariatric surgery. We investigated the effects of pneumoperitoneum and the reverse Trendelenburg position on these indices.

Materials and Methods: PI, PVI, heart rate (HR), blood pressure, $SpO_2$ and ventilation parameters were recorded before anaesthesia induction (T0), 5 min after endotracheal intubation (T1), immediately before surgery, after the patient had been in the reverse Trendelenburg position for 5 min (T2), after inflating the abdomen with $CO_2$ in reverse Trendelenburg (T3), after the abdomen had been deflated (T4) and 5 min after extubation (T5).

Results: General anaesthesia induced an increase in the PI (P<.001), and a decrease in the PVI (P=.002). The PI and PVI values were not affected during T2 or T3. Pneumoperitoneum caused an increase in mean arterial pressure (MAP) and a decrease in HR. PVI and MAP decreased during T4, but the PI and HR remained unchanged. PVI, HR and MAP increased during T5.

Conclusion: Our data suggest that the reverse Trendelenburg position and pneumoperitoneum did not affect the PI or PVI values, whereas deflation decreased the PVI in morbidly obese patients under general anaesthesia.

Keywords: Anaesthesia, Morbid obesity, Pleth variability index, Perfusion index, Bariatric surgery

## 1. INTRODUCTION

The prevalence rates of overweight and obesity are increasing worldwide, such that anaesthesiologists are encountering morbidly obese patients more frequently than before. Obesity produces a variety of hemodynamic, respiratory and metabolic changes that predispose patients to serious perioperative complications [1-4]. Hemodynamic monitoring and optimal fluid therapy are the cornerstones of therapy to improve outcomes and allow patients to tolerate the surgical procedure [5].

The perfusion index (PI) is defined as the pulsatile and non-pulsatile tissue ratio of absorbed light. The pleth variability index (PVI) is a completely non-invasive index that can be used to automatically and continuously monitor variations in the PI during the respiratory cycle, and thus has the ability to predict fluid responsiveness, and facilitate fluid management, via dynamic variables. Optimising tissue and organ perfusion through goal-directed fluid therapy based on dynamic predictors of fluid responsiveness improves clinical outcomes [6,7]. However, there are limitations and drawbacks to the PI and PVI that restrict their use depending on the patient's position, pneumoperitoneum and use of norepinephrine, for example [8-11]. The effects of these variables have mainly been assessed in healthy individuals and non-morbidly obese patients undergoing laparoscopy [10,12]. Moreover, few studies have used the PI and PVI to predict fluid responsiveness during laparoscopic bariatric surgery [7]. To facilitate patient management and improve outcomes, anaesthetists must understand the advantages and limitations associated with the use of hemodynamic parameters to guide perioperative care in obese patients.

Therefore, we investigated the effects of pneumoperitoneum and the reverse Trendelenburg position on the PI and PVI in patients undergoing laparoscopic bariatric surgery.

## 2. MATERIALS and METHODS

The Clinical Research Ethical Committee of Marmara University, School of Medicine approved this study ( protocol no: 09.2018.737). Written informed consent was obtained from 70

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patients at two hospitals, who were enrolled in this prospective observational cohort study from June 2018 to December 2019 and scheduled for elective laparoscopic bariatric surgery. The inclusion criteria were American Society of Anesthesiologists (ASA) grade II–III, age > 18 years and body mass index (BMI) > 35 kg/m$^2$.

The exclusion criteria were a history of uncompensated cardiac disease (cardiac ejection fraction ≤ 30%, arrhythmias), severe respiratory disease (mechanical ventilation ≥ 8 ml/kg tidal volume) and chronic renal dysfunction.

Three patients were excluded due to conversion to open surgery, or because their PVI values could not be obtained for technical reasons, such that 67 patients were included in the final analysis.

### *Anaesthetic procedure and monitoring*

After an overnight fast, received no premedication. Following preoxygenation, anaesthesia was induced with propofol (2–2.5 mg/kg) based on the adjusted body weight, remifentanil (1 µg/kg) was administered based on adjusted body weight, and rocuronium (0.6–1.2 mg/kg) was administered based on total body weight; through endotracheal intubation, patients were maintained on desflurane and remifentanil according to clinical observations. Ventilation was adjusted to a tidal volume of 8–10 ml/kg based on ideal body weight, with an I:E ratio of 1:2 and positive end-expiratory pressure (PEEP) of 5 cm$H_2O$. Respiration frequency and other ventilation parameters were used to guide maintenance of normocapnia ($PaCO_2$: 35–45 mmHg) during the perioperative period. Heart rate (HR), non-invasive blood pressure, peripheral oxygen saturation, capnography, inhaled gas concentration and temperature were continuously monitored in all patients. The PI and PVI values were measured using a Masimo Radical 7 pulse oximeter probe (Masimo Radical 7; Masimo Corp., Irvine, CA, USA) attached to the right ring finger.

### *Study protocol*

The PI and PVI values were obtained immediately before inducing anaesthesia (T0) and after baseline hemodynamic variables were obtained. The hemodynamic and mechanical ventilation parameters were obtained 5 min after endotracheal intubation (T1). Immediately before surgery, the patient's position was changed to the reverse Trendelenburg position (head-up tilt to ~25°), all parameters were recorded after a 5-min stabilisation period (T2), and surgery commenced. Hemodynamic and ventilation parameters were measured at 3–5 min intervals after inflating the abdomen with $CO_2$ (12–15 mmHg, as measured by the insufflator) (T3), at the end of surgery when the abdomen was deflated (T4) and 5 min after extubation (T5) (Figure 1). The PI, PVI, hemodynamic parameters (HR, blood pressure and $SpO_2$) and ventilation parameters ($EtCO_2$, tidal volume, PEEP and peak airway pressure [Ppeak]) were recorded at each time point. In addition, demographic characteristics, volume of bleeding, volume of fluid administered, anaesthesia and operating times, and reverse Trendelenburg angle were recorded.

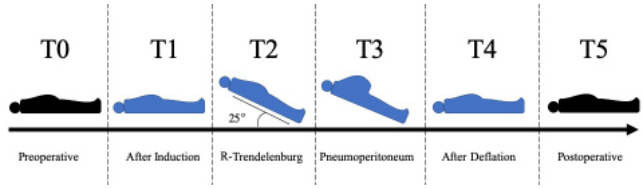


**Figure 1.** Illustration of the protocol of the study. T0: before endotracheal intubation; T1: 5 min after endotracheal intubation; T2: 5 min after reverse Trendelenburg; T3: 5 min after pneumoperitoneum; T4: after the termination of pneumoperitoneum; T5: 5 min after endotracheal extubation.

### Statistical analysis

The required sample size was determined based on the data of Siswojo et al. [13]. The minimum number of samples required to determine a 2% change in the PVI values was determined to be 67, with an alpha of 0.05 and power of 0.90. However, we enrolled 70 patients considering the possibility of dropouts. The descriptive characteristics are expressed as frequencies and percentages for categorical variables, and as means, standard deviations and medians for numerical variables. Skewness and kurtosis values were used to assess the normality of the data. The parameters were analysed by repeated measures-analysis of variance (ANOVA). The Friedman rank-sum test was used to analyse parameters that did not meet the ANOVA assumptions. The Wilcoxon rank-sum test was used for post-hoc analysis. Because the reliability of the dynamic parameters would decrease during spontaneous breathing, comparisons of the T1–T4 measurements were made under mechanical ventilation and general anaesthesia; the T0, T1 and T5 measurements were also compared to determine the effect of general anaesthesia on the parameters. The data were analysed using R software (3.6.2; (R Development Core Team, Vienna, Austria). A p-value < .05 was considered significant.

## 3. RESULTS

Data for the demographic characteristics (age, gender, BMI, weight, height and ASA score), duration of anaesthesia and surgery, pneumoperitoneum, and angle of the reverse Trendelenburg position are presented in Table I, along with the volume of intraoperative fluid therapy (crystalloids and colloids), surgical bleeding and urine output data.

The results of the interventions are presented in Table II. General anaesthesia (T1) induced an increase in the PI (P< .001), and decreases in the PVI (P= .002) and mean arterial pressure (MAP) (P < .001). A decrease in MAP (P = .004) was seen in the reverse Trendelenburg position (T2) but the PI (P = .788) and PVI (P = .131) values were unaffected. Neither the PI nor the PVI changed significantly after pneumoperitoneum (T3) (P = .078 and P = .397, respectively). Neither the PI nor the PVI changed significantly after pneumoperitoneum (T3) (P = .078 and P = .397, respectively).


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**Table I.** Distribution of the study population in terms of demographics and baseline characteristics

| | n | Mean ± SD |
|---|---|---|
| Age (years) | | 39.2 ± 10.9 |
| Gender (M/F) | 12/55 | |
| BMI (kg/m$^2$) | | 46.7 ± 6.0 |
| Weight (kg) | | 125.8 ± 20.6 |
| Height (cm) | | 163.9 ± 8.1 |
| ASA score II/III | 44 / 23 | |
| Duration of anaesthesia (min) | | 162.2 ± 47.4 |
| Duration of surgery (min) | | 122.8 ± 45.8 |
| Duration of pneumoperitoneum (min) | | 102.1 ± 42.6 |
| The angle of reverse Trendelenburg (°) | | 24.5 ± 4.3 |
| Intraoperative crystalloids (ml) | | 1534 ± 418 |
| Intraoperative colloids (ml) | 7 | 450 ± 84 |
| Bleeding (ml) | | 80 ± 86 |
| Urine output (ml) | | 246 ± 140 |

ASA: American Society of Anaesthesiologists physical status, BMI: body mass index, n: number of patients

**Table II.** Values of perfusion index (PI), pleth variability index (PVI), heart rate (HR), mean arterial blood pressure (MAP), arterial oxygen saturation measured using a pulse oximeter (SpO2), end-tidal pressure of CO2 (EtCO2), peak airway pressures (Ppeak), positive end-expiratory pressure (PEEP), and tidal volumes at six time points

| Parameters | T0 | T1 | T2 | T3 | T4 | T5 | P-value |
|---|---|---|---|---|---|---|---|
| **PI, %** | 2.12 ± 1.58 | 4.32 ± 2.38 | 4.60 ± 2.74 | 3.64 ± 2.29 | 3.24 ± 2.52 | 2.58 ± 2.36 | <.001 |
| **PVI, %** | 20.76 ± 8.83 | 15.76 ± 6.65 | 15.15 ± 9.36 | 14.80 ± 6.74 | 12.33 ± 6.99 | 17.70 ± 7.12 | <.001 |
| **HR, beats/min** | 84.73 ± 14.00 | 85.15 ± 13.40 | 83.06 ± 13.44 | 72.91 ± 12.99 | 69.26 ± 12.35 | 92.36 ± 16.07 | <.001 |
| **MAP, mmHg** | 97.64 ± 14.34 | 86.59 ± 18.00 | 76.62 ± 14.22 | 86.74 ± 16.36 | 78.65 ± 11.20 | 101.65 ± 14.71 | <.001 |
| **$SpO_2$, %** | 98.74 ± 1.77 | 98.77 ± 1.54 | 98.12 ± 2.00 | 97.76 ± 1.79 | 98.79 ± 1.35 | 97.60 ± 3.32 | <.001 |
| **$EtCO_2$, mmHg** | | 34.23 ± 4.47 | 32.66 ± 3.70 | 34.91 ± 3.47 | 37.97 ± 3.13 | | <.001 |
| **Ppeak, $cmH_2O$** | | 25.98 ± 5.27 | 25.02 ± 4.61 | 31.02 ± 4.47 | 27.12 ± 4.24 | | <.001 |
| **PEEP, $cmH_2O$** | | 6.02 ± 1.43 | 6.82 ± 1.97 | 8.06 ± 2.05 | 8.80 ± 2.38 | | <.001 |
| **Tidal Volume, ml** | | 511.77 ± 58.10 | 519.32 ± 52.02 | 517.32 ± 54.16 | 514.60 ± 54.25 | | .988 |

Data are presented as the mean ± standard deviation. T0: before endotracheal intubation; T1: 5 min after endotracheal intubation; T2: 5 min after reverse Trendelenburg; T3: 5 min after pneumoperitoneum; T4: after the termination of pneumoperitoneum; T5: 5 min after endotracheal extubation, when appropriate

Pneumoperitoneum caused an increase in MAP (P = .001) and a decrease in HR (P = .013). The PVI (P = .028) and MAP (P = .007) decreased, whereas the PI (P=.788) and HR (P = .960) were unchanged, after pneumoperitoneum compared to the start (T3) and termination (T4) periods. A significant decrease in the PVI was observed after release of the pneumoperitoneum (T4) compared to T1 (P = .003) but the PI (P=.078) remained unchanged (Figures 2 and 3). After extubation of the trachea (T5), the PVI (P < .001), HR (P < .001) and MAP (P < .001) increased, but the PI (P = .078) did not change significantly. Significant differences were observed in the $SpO_2$ values measured at T3 (P < .001) and T5 (P = .014) compared to the preoperative value (T0). $EtCO_2$ increased gradually towards the end of the operation after inflating the abdomen with $CO_2$. A significant difference in the EtCO2 was detected after deflation (T4) (P < .001) compared to the other time periods (T1–T3). Pneumoperitoneum (T3) caused an increase in Ppeak (P = .001) and PEEP (P = .001). After deflation (T4), Ppeak decreased slightly (P = .090), but PEEP (P = .001) remained high, compared to the other time periods (T1 and T2). No significant difference in tidal volume was observed during the intraoperative period (P = .988). Mean tidal volume per ideal body weight of all patients was calculated to be 9.3 ± 1.6 ml/kg. A tidal volume ≥ 8 mL/kg increased the reliability of the measured dynamic parameters.


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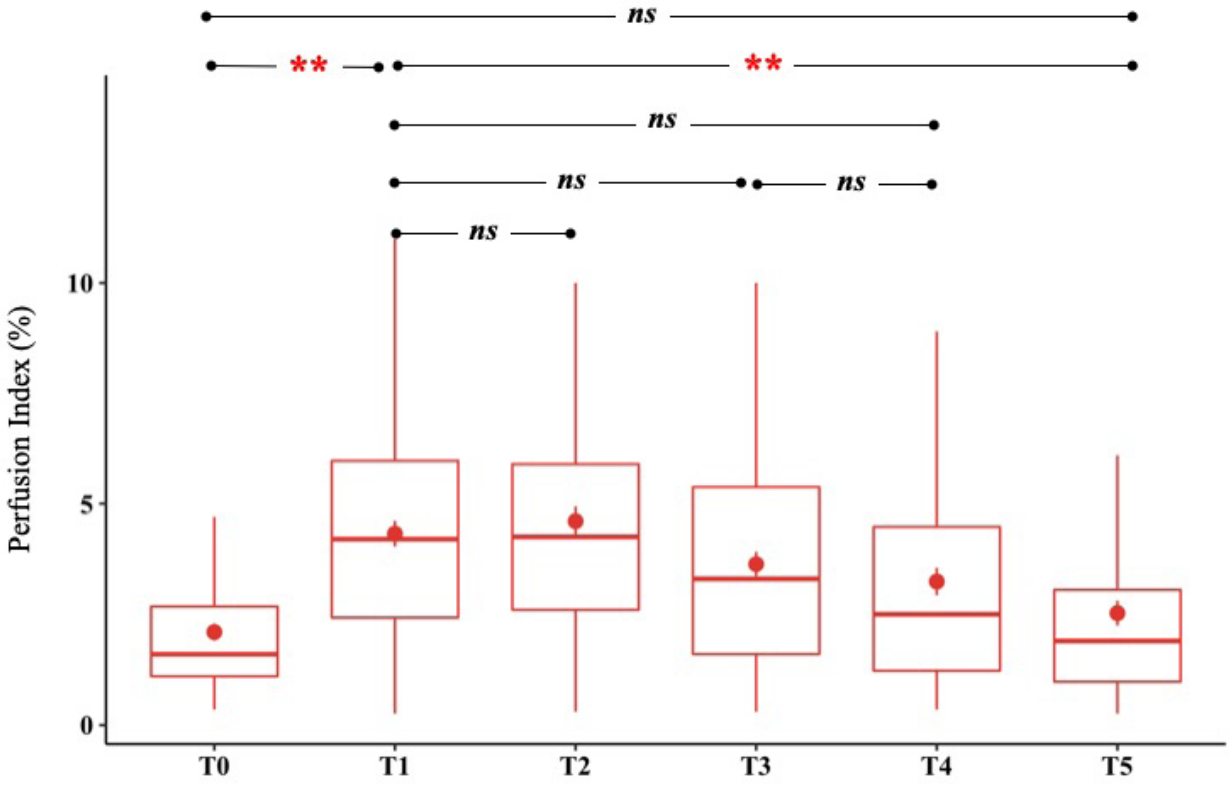


**Figure 2.** The values of perfusion index (PI) at six time points.** p < 0.001, ns: no significant difference between time points.

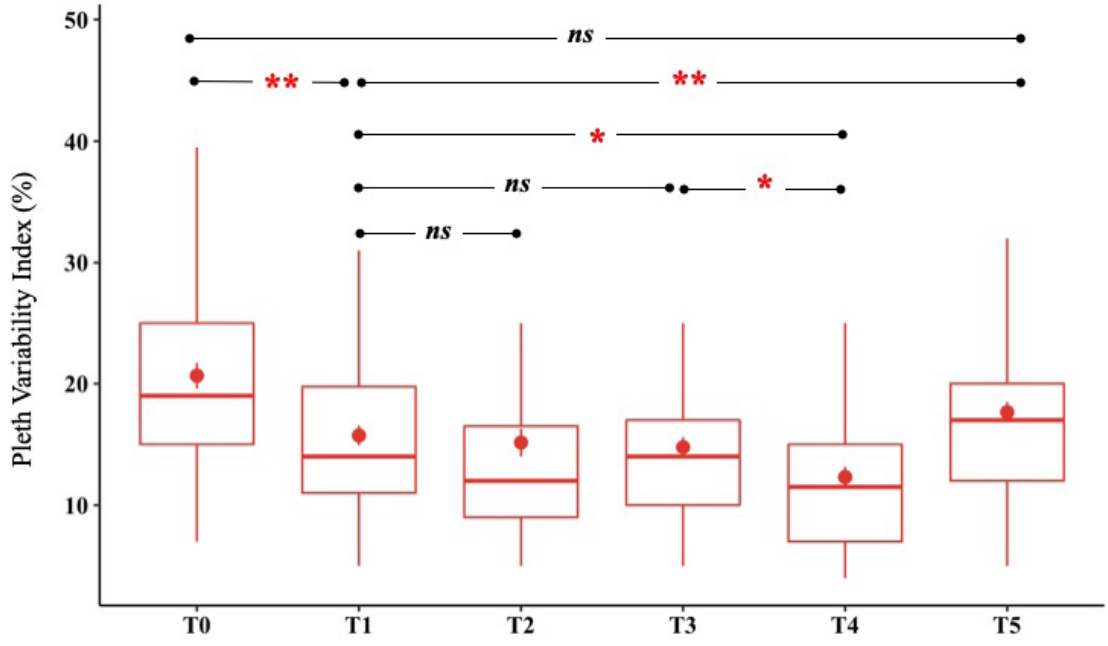


**Figure 3.** The values of pleth variability index (PVI) at six time points. * p < 0.05, ** p < 0.001, ns: no significant difference between time points.


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## 4. DISCUSSION

The main findings of our study are that the reverse Trendelenburg position and pneumoperitoneum did not affect the PVI or PI, whereas deflation decreased the PVI, but not the PI. In addition, the PI increased, and the PVI decreased, under general anaesthesia. Therefore, the PI and PVI can be used to guide laparoscopic bariatric surgery in patients under general anaesthesia, but not under conditions of deflation.

Our findings are consistent with an observational study, in which general anaesthesia was induced using anaesthetic agents and opioid analgesics increased the PI, but decreased the PVI [14]. These results are similar to those of our recently published article on laparoscopic cholecystectomy [9]. Administration of general anaesthetic agents and opioid analgesics causes significant changes in peripheral vascular physiology and sympathetic tone. After inducing general anaesthesia, an increase in the PI and a decrease in the PVI reflect peripheral vasodilation and decreased sympathetic tone [14]. In addition, respiratory parameters (tidal volume, ventilation rate and type [spontaneous or controlled]) also affect the PI and PVI [14-16]. The decrease in PI and increase in PVI seen during the postoperative period may be related to variations in respiration during spontaneous ventilation, residual effects of intravenous or volatile anaesthetic agents and opioid analgesics, or increased sympathetic activity due to postoperative pain [16]. Therefore, we assumed that the hemodynamic parameters measured 5 min after endotracheal intubation (T1) could be used as baseline values when evaluating the effects of patient position and pneumoperitoneum on the PI and PVI.

The reverse Trendelenburg position can cause hemodynamic changes due to venous pooling, which can in turn lead to severe hypotension [17]. These physiological effects are similar to those associated with the seated position [17]. Bapteste et al., evaluated the utility of the PPV and PVI for predicting fluid responsiveness during general anaesthesia in the sitting position [18]. They demonstrated that, when measured with a finger sensor, the PVI was unable to predict fluid responsiveness in the sitting position. However, when measured with an ear sensor, the PVI predicted fluid responsiveness with a sensitivity of 83% and specificity of 91% [18]. We recorded the PVI using a finger sensor; our findings in the reverse Trendelenburg position might have been different if we had used an ear sensor.

Tapar et al., tested changes in the PI after patients were switched from the supine to the reverse Trendelenburg position (head-up tilt to 45°). They reported that the reverse Trendelenburg position decreased the PI significantly, which was explained by the decrease in venous return and increase in systemic vascular resistance [8]. In our hospital, the reverse Trendelenburg angle used during bariatric surgery is approximately 25°. In the present study, the reverse Trendelenburg position induced a decrease in MAP, but the PI and PVI values did not change; these findings were associated with the angle of the reverse Trendelenburg position and use of general anaesthesia. Tapar at al. used a head-up tilt of 45° in awake participants, whereas in our patients the mean angle was 24.5 ± 4.3° under general anaesthesia; this may explain the discrepant results [8].

Intra-abdominal pressure is increased to 10–15 mmHg by $CO_2$ insufflation in patients undergoing laparoscopic bariatric surgery. Pneumoperitoneum can induce haemodynamic changes, which are expressed as decreases in stroke volume, cardiac output and venous return, and an increase in systemic vascular resistance [19]. Dynamic parameters, such as the PVI and stroke volume variation (SVV), may also be affected by changes in intra-abdominal pressure. Several animal and clinical studies have investigated the effects of pneumoperitoneum and/or intra-abdominal pressure on dynamic parameters [10,20–23]. These experimental studies showed that the PPV and SVV were affected by increased intra-abdominal pressure, but neither the PPV nor SVV predicted fluid responsiveness [20]. When a threshold value is used, higher than normal intra-abdominal pressure may be indicative of fluid responsiveness [21]. The results of Høiseth et al. [22] and Lui et al. [23] showed that the PVI increases and the PI decreases after pneumoperitoneum. Furthermore, the SVV increases, according to Liu et al. [23], although Høiseth et al. found that SVV was unchanged after pneumoperitoneum [22]. Wajima et al.[10] reported that pneumoperitoneum did not change the PVI, but decreased the PI and increased the SVV. These discrepancies regarding the effects of pneumoperitoneum may be related to differences in study design. For example, the anaesthesia methods (general anaesthesia or combined epidural), anaesthetic drugs (midazolam, propofol, rocuronium or cisatracurium) and opioids (remifentanil or fentanyl) used differed among studies, as did the patient characteristics (height and weight), mechanical ventilation strategies (tidal volume or PEEP). In our study, the PVI did not change after the pneumoperitoneum, similar to the results of Wajima et al. They suggested that the most likely mechanism underlying this outcome was that remifentanil and epidural analgesia block noxious stimuli and sympathetic activity in the fingertips [10]. We only administered remifentanil as an opioid to our patients; epidural anaesthesia was not used, which blocks sympathetic activity and vasoconstriction resulting from pneumoperitoneum or surgery. Høiseth et al. [12] and Lui et al. [23] used fentanyl to maintain general anaesthesia. In our study, the PI tended to decrease after pneumoperitoneum. In the study of Wajima et al. [10], the PI decreased significantly, while MAP was unchanged, after pneumoperitoneum, whereas in our study the PI tended to decrease after pneumoperitoneum, while MAP increased significantly and the HR decreased. The reason for the discrepant results is unclear, but we assume that it relates to differences in patient characteristics, and to the fact that we did not administer epidural analgesia. Unlike these previous three studies, our patients were morbidly obese; the various metabolic and neurohormonal changes commonly associated with morbid obesity may have contributed to the abnormalities in cardiac morphology and function [24].

In the present study, the PVI and MAP decreased, but the PI and HR were unchanged, after the pneumoperitoneum was released. We believe that this may be the result of the attenuation


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of sympathetic activity caused by increased intra-abdominal pressure.

Our study had some limitations. First, the study cohort consisted of morbidly obese patients (mean BMI = 46.7 kg/m$^2$), and it is well known that intra-abdominal pressure is correlated with BMI [25]. Moreover, the intra-abdominal pressure was uniformly assumed to be 0 mmHg before pneumoperitoneum, because the actual values were unknown. However, we believe that repeated-measures design overcame this limitation. The second limitation of our study was that intra-abdominal pressure was induced by $CO_2$ insufflation over a short period of time, which might differ from the actual conditions secondary to intra-abdominal hypertension in critical patients. Changes in the PI and PVI with increased intra-abdominal pressure must be determined in further studies.

In conclusion, our data suggest that the reverse Trendelenburg position and pneumoperitoneum did not alter the PI or PVI, whereas deflation decreased the PVI, but did not change the PI, in morbidly obese patients under general anaesthesia. Furthermore, we reconfirmed that the PI increased, while the PVI decreased, under general anaesthesia. Thus, the PI and PVI were both useful as hemodynamic parameters in patients under general anaesthesia for laparoscopic bariatric surgery, where a dose of remifentanil sufficient to block noxious stimuli was used except after release of the pneumoperitoneum.

### Compliance with Ethical Standards

**Funding**: The authors received no financial support for the research, authorship, and/or publication of this article.

**Ethics Statement:** The Clinical Research Ethical Committee of Marmara University, School of Medicine approved this study ( protocol no: 09.2018.737).

### Conflict of Interest

The authors declare that they have no conflict of interest.

### Authors' Contibutions:

RA designed the study, carried out the experiments, gathered experimental data, performed the statistical analysis and drafted the manuscript. MKA designed the study and helped its coordination, carried out the experiments, gathered experimental data, performed the statistical analysis and revised the manuscript. GTA conceived the study, carried out the experiments, gathered experimental data, and revised the manuscript. PCD carried out the experiments, gathered experimental data and revised the manuscript. All authors read and approved the final manuscript.

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# Evaluation of individual health literacy among inpatients of different types of hospitals in Istanbul

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ABSTRACT

Objective: The objective of our study is to evaluate the individual health literacy level among patients who received health services from different types of hospitals in Istanbul.

Materials and Methods: This cross-sectional study was conducted among inpatients of a public, private and university hospital in Istanbul. Data were collected by the application of a questionnaire to 1500 adult inpatients who were discharged between February-July 2017. The study questionnaire included questions to determine the health literacy competency and sociodemographic characteristics of patients. Rapid Estimate of Adult Literacy in Medicine (REALM) scale was used to measure the health literacy level.

Results: The mean REALM score was higher among females than males ($p<0.013$). Health literacy mean score was lowest among public hospital inpatients and highest among university hospital inpatients ($p<0.001$). Primary-school graduate patients had significantly lower scores ($p<0.001$) than the other groups. The findings of the REALM test were in agreement with the health literacy competencies.

Conclusion: Males, patients older than 35 years old, primary-school graduates, and public hospital inpatients had lower levels of health literacy.

Keywords: Health Literacy, Health Services, Patients, Inpatients

## 1. INTRODUCTION

Health literacy is defined as "people's knowledge, motivation and competences to access, understand, appraise, and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course" [1]. It is a life-long activity that needs to be continuously improved.

Health literacy has become an important concept in the healthcare sector because it increases the effectiveness and efficacy of the services and reduces health expenditures. Studies show that the success of the health services and achievement of desired outcomes are related to the health literacy level of the service-taker [2 – 4].

Education, socioeconomic status, cultural, social and environmental factors affect the health literacy level and therefore, health outcomes and costs are also affected [5, 6]. Today, it is easy to access the health information. Beside the healthcare providers such as physicians, nurses, pharmacists, the information can be obtained from media, internet and community advice. While facing this variety of information, the ability to understand is dependent on the health literacy level of the person [7].

In a report of Social Determinants Commission of the World Health Organization, health literacy has been recognized as a critical determinant for mitigating health inequalities. The report emphasizes the value of improving health literacy [8].

Health literacy has begun to gain attention by the end of the 20th century in the United States (US) and after in the European Union (EU) [9]. Multiple studies from the US demonstrated the effect of health literacy in quality, cost, organization, and management of the health services. In a study conducted in eight EU countries, it has been shown that the health literacy level of the European people was inadequate. Recognizing the importance of health literacy, the EU has begun to implement various policies on this issue. Researches show that 29-62% of the population in the EU and 26% in the US do not have a sufficient level of health literacy [10].

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According to a report published by UNESCO in 2009, 776 million adults were not health literate at primary level [11]. It is known that insufficient health literacy causes increase in the rate of hospitalization and amount of the health expenditures, gives rise to accessibility problems in health services, the use of the wrong medicines and the deterioration of health status [5].

In Turkey, a study conducted by Health and Social Service Workers' Union, showed that 64.6% of the population had inadequate or problematic health literacy. The results of this study revealed that approximately 12.5% of health expenditure in a year was spent due to insufficient or problematic health literacy [5].

This study aims to measure individual health literacy levels of patients who received healthcare at different types of hospitals in Istanbul, Turkey.

## 2. MATERIALS and METHODS

This is a cross-sectional study conducted in three hospitals a public hospital, private hospital and university hospital in Istanbul. Each of these was accredited hospitals in terms of their quality. Individual health literacy data were collected from inpatients who were over 15 years old, hospitalized in a period between February and July 2017 and accepted to participate in the study. The sample size for each hospital was calculated separately. To estimate a proportion for the unlimited population at 95% confidence level with 5% sampling error and anticipated 50% proportion, 384 people for each hospital was found to be required as a sample. While taking into account the losses that may occur during the data collection, it is planned to collect data from 500 people for each hospital, 1,500 people in total.

Data were collected by a questionnaire during face-to-face interviews. The questionnaire included questions about socio-demographic characteristics, health literacy level and health literacy competencies of the study group.

Rapid Estimate of Adult Literacy in Medicine (REALM) scale was used for measuring the health literacy level. REALM test has been developed by Davis et al. [12]. It is based on people's ability to read, pronounce and understand 66 medical words. Total application time of the test lasts for 3-5 minutes while the total evaluation score is interpreted as health literacy level, such as 0-18 points for a 3rd grader or lower, 19-44 points for 4-6th grader, 45-60 points for 7-8th grader and 61-66 points indicate the high schooler level of health literacy. The evaluation can be made by a categorical grouping of the points taken, as well as by comparing the mean scores of the different groups. Turkish version of the REALM was prepared and found to be valid and reliable by Özdemir et al. [13].

Beside the REALM test, participants were also asked if they have these three health literacy competencies: reading the medical brochures, understanding the medical documents and filling the forms by themselves in health institutions.

These competencies will be mentioned as reading, understanding and filling competencies for the convenience hereafter.

### Statistical Analysis

Data analysis and statistical evaluation of the results was made via SPSS 23.0 software. Descriptive statistics such as mean, standard deviation, percentage and significance tests were used to compare various groups of people. According to the type of data and number of groups, comparisons between groups were evaluated by significance tests such as the t-test, ANOVA, Chi-square test and 0.05 was considered as the significance threshold for p-value. Post-hoc analysis of significant ANOVA results was done by Tukey test. Multiple linear regression analysis was used to control the effect of confounding factors.

Ethical approval was obtained from the Medipol University Non-Invasive Clinical Research Ethics Committee on October 9th, 2015. Official permissions were obtained from the hospital administrations before the study was conducted.

## 3. RESULTS

Table I presents the comparison of mean REALM scores and frequencies of reading, understanding and filling competencies of patients by gender groups. A statistically significant difference was found between the mean health literacy scores of males and females (t=2.500, p=0.013). Females' mean health literacy score was higher than males'. Reading (p=0.373) and filling (p=0.174) competencies did not show a significant difference between gender. However, there was a statistically significant difference between the two groups in terms of understanding competency (p=0.019).

**Table I.** Mean REALM scores and reading, understanding and filling competencies of patients by gender groups.

| | REALM Score | Filling forms | | Understanding documents | | Reading brochures | |
|---|---|---|---|---|---|---|---|
| **Gender** | **Mean ± SD** | **n** | **%** | **n** | **%** | **n** | **%** |
| Male (n=675) | 55.36 ± 9.52 | 496 | 80.4 | 454 | 69.8 | 566 | 86.5 |
| Female (n=764) | 56.56 ± 8.79 | 556 | 78.4 | 567 | 76.2 | 655 | 87.8 |
| Total (n=1439) | 56.00 ±9.16 | 1052 | 79.3 | 1021 | 76.9 | 1221 | 92.1 |
| | t=2.500, p=0. 013 | $\chi2$=3.498, p=0.174 | | $\chi2$=7.891, p=0.019 | | $\chi2$=1.972, p=0.373 | |

Rapid Estimate of Adult Literacy in Medicine (REALM)

Table II presents the comparison of mean REALM scores and frequencies of reading, understanding and filling competencies of patients by age groups.


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There was no statistically significant difference between the mean health literacy scores of different age groups (p=0.087). However, the percentage of the people with reading, understanding and filling competency decreased as age increased and these differences were statistically significant (p<0.001 in each). This difference was mainly due to high levels of health literacy in younger (25-34 and 15-24) age groups.

**Table II.** Mean REALM scores and reading, understanding and filling competencies of patients by age groups

| | REALM Score | Filling forms | | Understanding documents | | Reading brochures | |
|---|---|---|---|---|---|---|---|
| **Age Group** | **Mean ± SD** | **n** | **%** | **n** | **%** | **n** | **%** |
| 15-24 (n=205) | 55.04 ± 8.81 | 156 | 80.0 | 157 | 78.5 | 182 | 91.0 |
| 25-34 (n=485) | 56.51 ± 8.79 | 390 | 85.9 | 371 | 77.8 | 436 | 91.4 |
| 35-44 (n=345) | 56.09 ± 8.79 | 253 | 80.3 | 244 | 72.6 | 295 | 87.3 |
| 45-54 (n=200) | 55.07 ± 10.95 | 142 | 78.5 | 125 | 66.5 | 158 | 82.7 |
| 55-64 (n=119) | 54.79 ± 10.29 | 71 | 67.0 | 78 | 67.2 | 90 | 77.6 |
| >64 (n=94) | 57.32 ± 8.22 | 42 | 51.9 | 47 | 57.3 | 63 | 75.0 |
| Total (n=1448) | 55.92 ± 9.23 | 1054 | 79.1 | 1022 | 73.1 | 1224 | 87.1 |
| | t=1.925, p=0.087 | χ2=69.634, p<0.001 | | χ2=36.066, p<0.001 | | χ2=41.310, p<0.001 | |

Rapid Estimate of Adult Literacy in Medicine (REALM)

Table III presents the comparison of mean REALM scores and frequencies of reading, understanding and filling competencies of patients by the type of hospital. The mean REALM scores of the patients differed significantly by hospital types (p<0.001). The difference was caused by low health literacy level of the patients in the public hospital and high health literacy level of the patients in the university hospital. A statistically significant difference was found in filling competency by the hospital type (p<0.05). Because the percentage of patients who can filled the forms themselves was significantly lower in the private hospital than others. There was also a significant difference in understanding competency between the groups (p<0.001). It was observed that this difference was mainly due to the group of the university hospital. However, significant differences were found between each group. There was no statistically significant difference in reading competency between patients of different hospital types (p=0.090).

**Table III.** Mean REALM scores and reading, understanding and filling competencies of patients by type of hospital

| | REALM Score | Filling forms | | Understanding documents | | Reading brochures | |
|---|---|---|---|---|---|---|---|
| **Hospital Type** | **Mean ± SD** | **n** | **%** | **n** | **%** | **n** | **%** |
| University (n=491) | 58.34 ± 6.95 | 374 | 80.4 | 385 | 80.5 | 438 | 89.4 |
| Private (n=486) | 56.79 ± 8.99 | 337 | 77.5 | 322 | 74.2 | 391 | 87.5 |
| Public (n=482) | 52.58 ± 10.55 | 351 | 79.4 | 313 | 68.5 | 403 | 84.1 |
| Total (n=1459) | 55.92 ± 9.26 | 1062 | 79.1 | 1020 | 74.5 | 1232 | 87.0 |
| | t = 5 3 . 8 4 7 , p<0.001 | χ2=12.937, p=0.012 | | χ2=18.073, p<0.001 | | χ2=8.048, p=0.090 | |

Rapid Estimate of Adult Literacy in Medicine (REALM)

Table IV presents the comparison of mean REALM scores and frequencies of reading, understanding and filling competencies of patients by their educational level. Mean REALM scores showed a significant difference by education level (p<0.001). The low mean score of the "primary school" group and the high mean scores of "middle-high school" and "university" groups caused this difference. Statistically significant differences were found in filling competency, understanding competency and reading competency between the educational levels (p<0.001 in each). Post-hoc analysis revealed that differences between each educational level were significant for each competency. As the educational level advanced, the percentages of all competencies increased. For reading competency, it was understood that this difference was primarily due to "primary school" level.

**Table IV.** Mean REALM scores and reading, understanding and filling competencies of patients by level of educational

| | REALM Score | Filling forms | | Understanding documents | | Reading brochures | |
|---|---|---|---|---|---|---|---|
| **Educational Level** | **Mean ± SD** | **n** | **%** | **n** | **%** | **n** | **%** |
| Primary School (n=341) | 51.39 ± 10.92 | 185 | 61.3 | 168 | 52.3 | 239 | 73.8 |
| High School (n=676) | 55.75 ± 8.80 | 503 | 80.9 | 491 | 74.8 | 590 | 89.4 |
| University (n=418) | 59.83 ± 6.52 | 363 | 91.2 | 356 | 86.0 | 391 | 94.7 |
| Total (n=1435) | 55.90 ± 9.30 | 1051 | 79.5 | 1015 | 73.0 | 1220 | 87.3 |
| | t=86.842, p<0.001 | χ2=98.417, p<0.001 | | χ2=107.628, p<0.001 | | χ2 =80.438, p<0.001 | |

Rapid Estimate of Adult Literacy in Medicine (REALM)


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Table V presents the comparison of mean REALM scores and frequencies of reading, understanding and filling competencies of patients by their insurance type. There was a significant difference between the groups in mean REALM scores ($p<0.001$). There was also a significant difference between groups in the percentage of filling competency. This was caused by the differences between Social Security Insurance (SSI) – Working Plan and Private Insurance groups from other groups. There was a significant difference between the groups in the percentage of understanding competency ($p<0.05$). High percentages of understanding competency in SSI – Working Plan and Private Insurance groups were responsible for this difference. There was a statistically significant difference between the groups in the percentage of reading competency ($p<0.001$) and this difference was primarily due to the high percentage of reading competency of SSI – Working Plan group than others.

**Table V.** Mean REALM scores and reading, understanding and filling competencies of patients by insurance types

| | REALM Score | Filling forms | | Understanding documents | | Reading brochures | |
|---|---|---|---|---|---|---|---|
| **Insurance Type** | **Mean ± SD** | **n** | **%** | **n** | **%** | **n** | **%** |
| SSI Working (n=746) | 56.11 ± 8.92 | 575 | 83.7 | 545 | 75.0 | 662 | 90.7 |
| SSI Retired (n=228) | 56.90 ± 8.60 | 137 | 67.8 | 145 | 67.8 | 179 | 82.9 |
| Private (n=193) | 57.22 ± 10.00 | 146 | 83.4 | 142 | 78.5 | 156 | 85.7 |
| Other (n=257) | 53.61 ± 9.74 | 179 | 73.1 | 172 | 67.7 | 209 | 82.3 |
| Total (n=1424) | 55.93 ± 9.24 | 1037 | 79.2 | 1004 | 73.0 | 1206 | 87.3 |
| | t=7.687, p<0.001 | $\chi2$=35.570, p<0.001 | | $\chi2$=17.409, p=0.008 | | $\chi2$ =21.091, p=0.002 | |

Rapid Estimate of Adult Literacy in Medicine (REALM), Social Security Insurance (SSI)

Table VI presents the comparison of mean REALM scores and distribution of reading, understanding and filling competencies of patients by their occupational categories. Mean REALM scores showed a statistically significant difference ($p<0.001$). Health literacy scores of health professionals and civil servants were significantly high and the score of housewives group was significantly low. While analyzing the reading, understanding and filling competencies, unemployed and retired groups were combined due to their low observed values.

Also, the health professionals group was excluded from the analysis due to null values in two cells of the analysis table. It was found that the patients' filling competencies differed significantly by their profession ($p<0.001$). It was seen that this difference was primarily due to the housewife group. Percentage of housewives who filled the forms on their own was significantly lower than other groups. The percentages of patients with understanding competency showed a significant difference by the occupational groups ($p<0.001$). It was observed that this difference was due to retired and self-employed groups. There was also a significant difference ($p=0.002$) between the reading competency by occupational groups because of the high percentage in the public servants group.

**Table VI.** Mean REALM scores and reading, understanding and filling competencies of patients by their occupational categories

| | REALM Score | Filling forms | | Understanding documents | | Reading brochures | |
|---|---|---|---|---|---|---|---|
| **Occupation** | **Mean ± SD** | **n** | **%** | **n** | **%** | **n** | **%** |
| Student (n=93) | 55.86 ± 7.44 | 78 | 86.7 | 77 | 83.7 | 85 | 92.4 |
| Housewife (n=416) | 54.58 ± 9.57 | 274 | 72.5 | 289 | 71.5 | 341 | 84.0 |
| Self-employed (n=285) | 54.85 ± 10.67 | 214 | 80.8 | 188 | 67.9 | 244 | 87.8 |
| Worker (n=380) | 56.33 ± 8.66 | 277 | 80.1 | 270 | 73.8 | 314 | 85.6 |
| Public Servant (n=115) | 60.12 ± 4.91 | 103 | 92.0 | 94 | 83.2 | 110 | 97.3 |
| Health Professional (n=36) | 62.76 ± 4.17 | 35 | 100.0 | 31 | 86.1 | 36 | 100.0 |
| Unemployed or Retired (n=95) | 55.40 ± 9.70 | 59 | 69.4 | 55 | 61.1 | 74 | 81.3 |
| Total (n=1420) | 55.90 ± 9.23 | 1040 | 79.3 | 1004 | 72.9 | 1204 | 87.1 |
| | t=8.719, p<0.001 | $\chi2$=37.220, p<0.001 | | $\chi2$=21.647, p<0.001 | | $\chi2$ =21.091, p=0.002 | |

Rapid Estimate of Adult Literacy in Medicine (REALM)

Multiple linear regression analysis results are presented in Table VII. REALM scores of females, individuals who attended university hospitals and university graduates were significantly higher than the other groups. REALM scores significantly increased by age. Insurance type and occupation did not seem to be significant predictors of health literacy.


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**Table VII.** Linear regression results: factors associated with individual health literacy

| | B | SE | b | t | p |
|---|---|---|---|---|---|
| **Constant** | 43.727 | 1.827 | | 23.937 | <0.001 |
| ***Independent variables*** | | | | | |
| **Gender** *0: Male 1: Female* | 1.495 | 0.482 | 0.079 | 3.102 | =0.002 |
| **Age** | 0.065 | 0.18 | 0.100 | 3.554 | <0.001 |
| **Hospital type** *1: University 2: Private 3: Public* | -2.150 | 0.288 | -0.190 | -7.467 | <0.001 |
| **Education level** *1: Primary 2: Secondary-High 3: University* | 3.706 | 0.314 | 0.329 | 11.809 | <0.001 |
| **Insurance type** *1: SSI Working 2: SSI Retired 3: Private 4: Other* | -0.199 | 0.149 | -0.033 | -1.341 | =0.180 |
| **Occupation** | 0.198 | 0.157 | 0.036 | 1.261 | =0.207 |

The unstandardized beta (B), the standard error for the unstandardized beta (SE B), the standardized beta (β), the *t* test statistic (t), and the probability value (p), Social Security Insurance (SSI)

## 4. DISCUSSION

The mean REALM score of the study group was 56.0 ± 9.16. In a similar study conducted by Özdoğan, the mean was found as 55.8 ± 11.2 which was similar to ours' [14]. In comparison between genders, females' mean health literacy score (56.56 ± 8.79) was significantly higher than those of males (55.36 ± 9.52) in our study. When genders were compared in terms of the competencies, females were found to understand the documents given in healthcare institutions better than males. While, in a similar study, it was found that females undestood such documents less than males [10]. However, it may be due to lower general literacy among females as it was mentioned in that study. There was no statistically significant difference in the competency of filling the forms between genders. Both groups often filled the forms themselves. According to Özdoğan's research, 45% of the patients answered as "I always read-and-fill myself" and 54% of the participants stated that they ask other people to read-and-fill the given forms [14]. In our study, 79.3% of the patients said that they always filled the given forms themselves. There was no significant difference between the gender groups in the competency of reading the brochures. Aslantekin also could not find any significant relationship between gender and competency of reading the written documents such as scientific publications about their diseases [10].

When individual health literacy scores of patients were compared among age groups, no significant difference was observed. However, the percentage of people who filled the forms on their own, understood the texts written in documents and read the brochures, decreased as the age increased. These percentages decreased in the age group who were older than 25-34 years. Aslantekin's research could not find any statistical significance in the relationship between the age variable and competency of understanding the written documentation about diseases, such as informed consent forms [10]. This may be because our study sample was larger than Aslantekin's.

There was a significant difference between health literacy scores by the hospital type. Mean health literacy score was low in the public hospital and high in the university hospital. In a similar study conducted by Uğurlu, the health literacy scores of the patients who admitted to the public hospital were significantly lower than the university hospital patients [15]. When they investigated reading, understanding and filling competencies, they found that the percentage of competency among university hospital patients was higher than the percentages of other hospital types. Patients who received healthcare from the university hospital might have more contact with health professionals and information previously or might have higher awareness because of their presumably more complex health problems. But, further studies are required to determine the cause of this difference.

When individual health literacy scores of patients were compared between educational levels, the mean score increased as the educational level increased. A similar result was found in the study of Çopurlar [16]. Likewise, the percentages of people with reading, understanding and filling competencies increased with the educational level. Aslantekin also found a significant relationship between the understanding of written documents (such as informed consent forms) and educational background. 20% of the literate level people stated that they understood the documents, while 86.4% of participants were not a graduate of a university [10].

Some differences were observed in the individual health literacy status between groups of different health insurance types and occupational categories in univariate analyses but multiple regression analysis revealed that these differences were not statistically significant.

Patients' individual health literacy scores which were measured via the REALM scale and the reading, understanding and filling competencies demonstrated similar results when investigated under different classifications like age, hospital type, education, and occupation. These findings indicated that the REALM alone might be sufficient to measure health literacy. According to our study findings patients older than 35 years, primary school level education, unemployed or retired, receiving health services

from the public hospital seemed to be less health literate. Actions should be taken for these groups to increase the level of health literacy.

Since the data of this study were collected from the limited number of hospitals in Istanbul, the results could not be generalized to any population.

### Compliance with Ethical Standards

**Ethical Approval:** Ethical approval was obtained from the Medipol University Non-Invasive Clinical Research Ethics Committee on October 9th, 2015. Official permissions were obtained from the hospital administrations before the study was conducted.

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

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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 knowledge-related 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 ≥ 75, moderate if the score was between 50 and 74, and poor if the score was ≤ 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 (± standard deviation) of the participants was found to be 35.67 ± 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 ±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 ± 6.44, and the average length of time they spent on a patient was 6.64 ± 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 ± 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 ± 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).


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

| | Categorical Variable | Frequency | Mean ± SD | p value |
|---|---|---|---|---|
| [1]Knowledge Scores | **Duration of practice** | | | |
| | 3-11 years | 69 (55.2%) | 15.26 ± 2.25 | 0.157** |
| | 12-20 years | 38 (30.4%) | 14.76 ± 2.07 | |
| | 21-29 years | 18 (14.4%) | 13.94 ± 2.48 | |
| | **Gender** | | | |
| | Male | 13 (10.4%) | 14.62 ± 2.69 | 0.493* |
| | Female | 112 (89.6%) | 14.96 ± 2.22 | |
| | **Department** | | | |
| | Urology | 20 (16%) | 15.55 ± 2.58 | 0.135** |
| | Pediatrics | 19 (15.2%) | 15 ± 2.69 | |
| | Surgery | 17 (13.6%) | 14.24 ± 1.48 | |
| | Cardiology | 17 (13.6%) | 15.53 ± 1.84 | |
| | Gynecology | 16 (12.8%) | 15.19 ± 2.93 | |
| | Emergency | 12 (9.6%) | 15.58 ± 1.73 | |
| | Neurosurgery | 9 (7.2%) | 14.22 ± 2.22 | |
| | Neurology | 5 (4%) | 13.2 ± 1.3 | |
| | Orthopedics | 5 (4%) | 12.8 ± 1.1 | |
| | In room service | 4 (3.2%) | 15 ± 1.41 | |
| | Pulmonary diseases | 1 (0.8%) | 15 ± 0 | |
| | **Country of Education** | | | |
| | NorthernCyprus | 62 (49.6%) | 14.26 ± 2.29 | **0.001*** |
| | Turkey | 63 (50.4%) | 15.57 ± 2.05 | |
| | **Taking training on HH in the last three years** | | | |
| | Yes | 122 (97.6%) | 14.98 ± 2.25 | **0.037*** |
| | No | 3 (2.4%) | 12.33 ± 1.15 | |
| | **Daily hand rub use** | | | |
| | Yes | 117 (93.6%) | 15.09 ± 2.23 | **0.001*** |
| | No | 8 (6.4%) | 12.5 ± 0.93 | |
| | **Ward** | | | |
| | Medical | 58 (46.4%) | 15.12 ± 2.11 | 0.179* |
| | Surgical | 67 (53.6%) | 14.75 ± 2.39 | |
| | **Clinic** | | | |
| | Outpatient | 48 (38.4%) | 15.33 ± 2.17 | **0.048*** |
| | Inpatient | 77 (61.6) | 14.66 ± 2.3 | |
| [2]Perception Scores | **Duration of practice** | | | |
| | 3-11 years | 69 (55.2%) | 82.25 ± 8.38 | 0.358** |
| | 12-20 years | 38 (30.4%) | 82.1 ± 9.68 | |
| | 21-29 years | 18 (14.4%) | 84.43 ± 12.69 | |
| | **Gender** | | | |
| | Male | 13 (10.4%) | 83.65 ± 5.27 | 0.916* |
| | Female | 112 (89.6%) | 82.38 ± 9.82 | |
| | **Department** | | | |
| | 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 | |

[1]Knowledge scores (out of 25) based on different categories. [2] 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'.

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


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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' 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. | Impact of HCAIs on patient outcome (high/very high) | 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 ≥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) |


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## 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 cross-transmission 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


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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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**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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**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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# The impact of training of peer educator on sexual and reproductive health: An interventional study

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ABSTRACT

Objectives: This study aims to reveal the knowledge and attitude change that a well-structured sexual and reproductive health (SRH) peer educator training creates in volunteer preclinical students from Marmara University School of Medicine.

Materials and Methods: Participants (n=29) were given 28 hours of training on 13 subjects by professionals. Those who attended and completed all sessions were certified as "peer educator" (Group 1,n=12). Group 2 (n=17) participated only in the first 8 sessions. SRH attitudes and knowledge levels of participants were evaluated. Data was analysed in SPSS-11.0 programme.

Results: Females constitute 51.7% of the participants. All participants had the similar level of "egalitarian" point of view (p:0.859). SRH final attitude score of Group 1 was higher than preliminary attitude score (p:0.008) and SRH final attitude score of Group 2 (p:0.033). The mean SRH knowledge score of Group 1 was 38.3±4.65, while that of Group 2 was 26.76±4.16 (p:0.0001).

Conclusion: It has been shown that a well-structured peer educator training can increase the knowledge of volunteer medical students and make a positive attitude change. After the implementation of the "Health Transformation Programme" in Turkey, adolescents were ignored. So, with peer educator trainings, trained educators will be able to help those adolescents and offer unprejudiced and egalitarian services to their patients when they become physicians.

Keywords: Adolescent health, Attitude, Gender roles, Contraception

## 1. INTRODUCTION

Adolescence is both an important period in which new behaviours are acquired and the most effective intervention period in preventing adult risk taking behaviours [1]. Even though, the adolescent group, which constitutes approximately 17% of the world population, is the most vulnerable group in terms of sexual and reproductive health (SRH), they are unable to access and make demand for health services [2].

Although, the lack of information about SRH of adolescents has been recognized in 1994 and studies have begun, the problem remains today [3]. According to a study done with 141 students studying in a public high school during the 2016-2017 academic year in Istanbul, the level of students' SRH knowledge was found to be inadequate [4]. A similar situation has been identified in medical schools too. A study, conducted in 2014 with 857 students from Trakya University School of Medicine in Edirne, Turkey has shown that only 23.5% of first and second-year students, and 23.1% of third and fourth-year students correctly knew how to prevent sexually transmitted infections (STI) [5].

Because most of the young people acquire knowledge and behaviour from their friends and share these with their friends, it has been shown that reaching young people with their own peers is a more appropriate approach [6]. Peer education is shown as one of the most effective educational tools to reach adolescents [7].

Peer education is an approach that aims sharing of information, skill or attitude between people who are involved in the same group in terms of age, sex, education or status [8]. Young people are more likely to internalize messages and thus, change their attitude and behaviour when they think that the person, they are talking to is like them and carries the same concerns [9]. Peer education is one of the most effective methods frequently used for SRH, which is one of the most difficult subjects for young people to talk about.

Well-structured SRH peer education has been shown to create changes in knowledge, attitudes and behaviour in both peer educators (PE) and peers/students trained by PE [10]. It has

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also been shown that the self-esteem of students who receive peer educator training has increased, and their leadership and communication skills are improved [11].

In this study, it is aimed to show that a well-structured SRH peer educator training programme changes the knowledge and the attitude of voluntary medical school students.

## 2. MATERIALS and METHODS

This is an interventional study. The intervention is the training given to the students.

For the study, the ethics permission was obtained from Marmara University School of Medicine Clinical Research Ethics Committee (with the protocol number 09.2017.255 and the date 7 April 2017). All participants were informed and their consent was obtained.

The population of the study was the pre-clinical students who study at Marmara University School of Medicine (MUSM). After presented the project in social media, applications have been accepted with an online form for a period of two weeks (n=35). In this project, those who attended and successfully completed the 13 sessions (28 hours) were certified as "peer educator".

The purpose of the training is to ensure that volunteer students can inform their peers at SRH issues and support them in solving their SRH problems. As well as sessions that provided information on basic SRH subjects, sessions aimed at providing a positive change of attitude in the areas related to SRH were also given during the training. To communicate positively with their peers and to be able to transfer their knowledge in effective ways, communication and presentation skills and contraceptive counselling were also included in the training programme.

Table I presents the curriculum of the training programme (28 hours on 13 topics).

**Table I.** Curriculum of training programme

| No | Subject | Duration(hours) |
|---|---|---|
| | ***a. Introduction and SRH Rights*** | |
| 1 | Introduction to Sexual and Reproductive Health: Basic Concepts | 1 |
| 2 | Sexual and Reproductive Health Rights | 6 |
| | ***b. Breast Cancer*** | |
| 3 | Breast Cancer Awareness and Breast Self-Examination | 3 |
| | ***c. HIV / AIDS and STI*** | |
| 4 | Sexually Transmitted Infections and The Ways of Prevention | 3 |
| | ***d. Basic Concepts in SRH I*** | |
| 5 | Social Norms in Sexual and Reproductive Health | 1 |
| 6 | Sociological Aspect of HIV/AIDS and Stigmatisation | 2 |
| 7 | LGBTI + Identities and Misunderstandings | 2 |
| 8 | Litigation of LGBT Individuals and Legal Discriminations | 2 |
| | ***e. Basic Concepts in SRH II*** | |
| 9 | Sexual and Reproductive Health Status of Youth in Turkey | 1 |
| 10 | Gender | 1 |
| 11 | Male Sexual Health Issues | 1 |
| 12 | Contraceptive Methods, Emergency Contraception | 3 |
| 13 | Communication and Presentation Skills | 2 |
| **TOTAL** | | 28 |


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### *Intervention Event (Training)*

#### *a. Introduction to SRH and SRH Rights*

The purpose of the first part was to briefly introduce the anatomy and physiology of male and female reproductive systems to the participants.

In the second half of the day, the legal status of SRH rights in the World and in Turkey was explained with a presentation.Then to consolidate this knowledge, a case study was applied.

#### *b. Breast Cancer*

The aim was to teach "breast self-examination" skills, which is a breast cancer awareness and preventive action, considering the age group of the PE and peers.

#### *c. HIV/AIDS and STI*

Together with informing about STI and HIV/AIDS, training has been provided for developing sensitivity and attaining a positive attitude. In addition, the use of male and female condoms on the models was demonstrated.

#### *d. Basic Concepts in SRH I*

In order for youth to be able to recognise and express their own norms and values regarding the sexuality; "SRH Social Norms" topic has been mentioned.

In the next session, the social aspect of HIV/AIDS and the acts of stigmatisation in Turkey were discussed. In the following sessions; description of lesbian, gay, bisexual, transgender and intersex (LGBTI+) identities, the prejudices and attitudes these people encounter in the world; the problems encountered in the justice system by the transgender individuals in Turkey were explained and the proposed solutions were discussed.

#### *e. Basic Concepts in SRH II*

In the first session, nationwide research findings on adolescents in Turkey were shared, and local adolescent problems were discussed. The concept of gender on health and social life was generally mentioned.

In the third session, men's sexuality and the most common sexual health problems specific to adolescents were discussed.

A long session about contraception was held to prevent adolescent pregnancies and STIs.

During the last session of the day and the year, a session about communication and presentation skills was held to enable peers to transfer their knowledge and skills effectively and successfully to their friends.

The data related to the study was obtained with the information forms taken at the beginning of the training and after. The study was evaluated using two kinds of data that was gathered from the participants: their socio-demographic standing, and their SRH knowledge, attitude and ideas about cultural gender roles. The latter was gathered using standard measures.

### *Assessment of Training, Data Collection Tools*

The first data was collected with a form for socio-demographic-information, the gender roles attitude scale (GRAS,Zeyneloglu-Terzioglu,2011) and the SRH attitudes scale (SRHAS). After the training, data was collected for evaluating the knowledge of SRH and SRHAS.The evaluation of the training is based on four-stage "Kirkpatrick Model" [12].

#### *I. Reaction*

At the end of each session, feedbacks were gathered from the participants anonymously and these feedbacks were put into practice in the further stages of the training and at the end of the training. Feedbacks were taken using the "Course Evaluation Form".

#### *II. Learning*

Participants' SRH knowledge was assessed by a questionnaire consisting 15 questions. There were 13 multiple choice and 2 true-false questions. Each of correct answer was given one point; 4 points for physiology of reproductive system, 3 points for STI, 12 points for correct condom usage and 29 points for contraceptive methods (max: 48 points, min:0 points).

Participants' general SRH attitudes were assessed twice with "SRH Attitude Assessment Scale [13]" before and after training. The scale includes 30 statements with five Likert-type scale responses. Answers to questions 1-7, 10-14, 18, 21-24 are a linear scale between strongly disagree:1 and, strongly agree:5, on the other hand answers to questions 8-9, 15-17, 19-20, 25-30 are a linear scale between strongly agree:1 and strongly disagree:5 (max:150, min:30). The scores obtained from each question are added to obtain a "total attitude score".

The "Gender Roles Attitude Scale [14]" was used to assess participants' gender attitudes. The scale includes five subsections with 38 items. The subsections consist of egalitarian gender role", "female gender role", "gender role in marriage", "traditional gender role", and "male gender role". Responses were collected on a five-point Likert-type scale. The answers were scored as 5 points for 'completely agree', 4 points for 'agree', 3 points for 'undecided', 2 points for 'disagree', and 1 point for 'absolutely disagree'. The scores obtained from each question were added to obtain the "total score" (max:190, min:38). If the total score is less than 95, it is interpreted as having "traditional attitude" and if it is greater than 95, it is interpreted as having "egalitarian attitude".

### Statistical Analysis

The collected data was evaluated in the SPSS 11.0 programme and analysed with normality tests, Spearman/Pearson correlation, Mann-Whitney-U, Student-T, and Sign tests. The statistical significance level was considered as $p<0.05$.

## 3. RESULTS

Twelve of the 29 volunteer students who participated in 13 different sessions, fully participated in all the trainings and after being successful in evaluation, completed the training as "SRH Peer Educator (Group 1)". Seventeen students only participated in the first eight sessions of 13 sessions and were not certified as PE (Group 2).

Females constituted 51.7% of the participants (n=15). The mean age of the participants was 20.31±1.03 (median:20.0, min:19, max:23). Distribution of participants' demographic information by groups is given in Table II.

According to the GRAS, all participants had the same level of "egalitarian" attitude (mean:173.6±14.0, median:177.0, min:144.0 max:190.0) (p:0.859). Mean SRHAS score of the participants (n=29) was 131.58±13.42 (median:135.0, min:108, max:150) before the SRH training, and was 138.72±11.59 (median:143.0, min:108, max:150) after it (p:0.001).

The mean score of participants' SRH Knowledge Scale was 31.55±7.21 (median:30.0, min:19, max:44).

**Table II.** Distribution of socio-demographic characteristics of Group 1 and 2

| Socio-demographic characteristics | Group I | | Group II | | Total | | p |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| **Sex** | | | | | | | |
| Female | 6 | 50.0 | 9 | 52.9 | 15 | 51.7 | 1.000 |
| Male | 6 | 50.0 | 8 | 47.1 | 14 | 48.7 | |
| **Age** | | | | | | | |
| 19-20 | 9 | 75.0 | 10 | 58.8 | 19 | 65.5 | 0.449 |
| ≥21 | 3 | 25.0 | 7 | 41.2 | 10 | 34.5 | |
| **Education Level of Mothers** | | | | | | | |
| High school and below | 6 | 50.0 | 7 | 41.2 | 13 | 44.8 | 0.716 |
| University and above | 6 | 50.0 | 10 | 58.8 | 16 | 55.2 | |
| **Education Level of Fathers** | | | | | | | |
| High school and below | 4 | 33.3 | 5 | 29.4 | 9 | 31.0 | 1.000 |
| University and above | 8 | 66.7 | 12 | 70.6 | 20 | 69.0 | |
| **Monthly Family Income** | | | | | | | |
| ≤6000 TLY | 7 | 58.3 | 12 | 70.6 | 19 | 65.5 | 0.694 |
| >6000 TLY | 5 | 41.7 | 5 | 29.4 | 10 | 34.5 | |
| **Living with parents** | | | | | | | |
| Yes | 10 | 83.3 | 10 | 58.8 | 20 | 69.0 | 0.234 |
| No | 2 | 16.7 | 7 | 41.2 | 9 | 31.0 | |
| **Self-evaluation of Health Status** | | | | | | | |
| Very Healthy/Healthy | 11 | 91.7 | 14 | 82.3 | 25 | 86.2 | 0.622 |
| Uncertain/Sick/Very sick | 1 | 8.3 | 3 | 17.7 | 4 | 13.8 | |
| **Total** | 12 | 100.0 | 17 | 100.0 | 29 | 100.0 | |

On 05.06.2017 the rate of U.S. Dollar to Turkish Lira (TYL)=3.50


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Table III presents the distribution of the scores of Group 1 (n=12) and Group 2 (n=17).

Group 1's SRH final attitude assessment score (median:146.5) was higher than preliminary attitude assessment score (median:139.5) (p:0.008). A positive, strong, and statistically significant correlation was found between these scores (r:0.746, p:0.005).

Group 2's final attitude assessment score (134.9±12.7) was higher than preliminary attitude assessment score (127.4±13.4) (p:0.018). A positive, moderately strong and statistically significant correlation was found between these scores (r:0.601, p:0.011).

**Table III.** Overall score statistics for both groups

| Assessment Type | n | Mean | Standard Deviation | Median | Min | Max | p |
|---|---|---|---|---|---|---|---|
| Gender Roles Attitude Score | 12† | 173.8 | 10.7 | 171.5 | 160.0 | 190.0 | 0.859 |
| | 17‡ | 173.5 | 16.3 | 177.0 | 144.0 | 190.0 | |
| SRH Preliminary Assessment Score | 12 | 137.9 | 11.3 | 139.5 | 115.0 | 150.0 | 0.041 |
| | 17 | 127.4 | 13.4 | 127.0 | 108.0 | 149.0 | |
| SRH Final Assessment Score | 12 | 144.2 | 7.1 | 146.5 | 127.0 | 150.0 | 0.033 |
| | 17 | 134.9 | 12.7 | 137.0 | 108.0 | 149.0 | |
| SRH Knowledge Score | 12 | 38.2 | 4.7 | 40.0 | 29.0 | 44.0 | 0.0001 |
| | 17 | 26.8 | 4.2 | 27.0 | 19.0 | 34.0 | |

†:Group 1 (n=12), ‡: Group 2 (n=17) SRH: sexual and reproductive health

The mean SRH knowledge score of Group 1 was 38.3±4.65, while that of Group 2 was 26.76±4.16 (p:0.0001). The knowledge scores of Group 1 were found to be higher than the scores of Group 2 in the subjects of STI (p:0.043), general contraception (p:0.0001), emergency contraception (EC) (p:0.0001) and correct condom usage (p:0.015). The knowledge about physiology of reproductive system was similar in both groups (p:0.028). (Table IV).

To the question that asks for other emergency contraceptive methods that can replace hormonal contraceptives, while 83.3% of Group 1 gave the answer as contains the copper–bearing intrauterine device (Cu-IUD), only %11.7 of Group 2 chose this answer (p:0.0001).

**Table IV.** Distribution of SRH knowledge scores according to groups

| SRH Knowledge Scale | n | Mean | Standard Deviation | Median | Min | Max | p |
|---|---|---|---|---|---|---|---|
| Reproductive System Physiology Knowledge Score | 12† | 3.8 | 0.6 | 4.0 | 2.0 | 4.0 | 0.088 |
| | 17‡ | 3.6 | 0.56 | 4.0 | 3.0 | 4.0 | |
| STI Knowledge Score | 12 | 3.0 | 0.0 | 3.0 | 3.0 | 3.0 | 0.043 |
| | 17 | 2.5 | 0.9 | 3.0 | 0.0 | 3.0 | |
| General Contraception Knowledge Score | 12 | 11.2 | 2.0 | 11.0 | 7.0 | 13.0 | 0.0001 |
| | 17 | 6.4 | 1.5 | 6.0 | 4.0 | 9.0 | |
| Emergency Contraception Knowledge Score | 12 | 9.0 | 2.3 | 9.0 | 4.0 | 12.0 | 0.0001 |
| | 17 | 4.2 | 1.88 | 4.0 | 1.0 | 8.0 | |
| Correct Condom Usage Knowledge Score | 12 | 11.3 | 1.2 | 12.0 | 9.0 | 12.0 | 0.015 |
| | 17 | 10.1 | 1.5 | 10.0 | 7.0 | 12.0 | |

†:Group 1 (n=12), ‡: Group 2 (n=17) SRH: sexual and reproductive health, STI: sexually transmitted infections

## 4. DISCUSSION

In this study, it was aimed to show the impact of a well-structured peer educator training on changing the SRH knowledge and the attitude of voluntary medical school students, who want to provide unprejudiced and egalitarian service to their patients. Also, authors would like to suggest a model curriculum to researchers that are interested in SRH matters.

According to the Report of the International Conference on Population and Development (ICPD), adolescence is defined


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as one of the important age groups in SRH [15]. It is both the riskiest group and the group in which positive behaviours begin to be acquired in the field of SRH. Also, they are the group that can be affected most positively by interventions. To increase the accessibility and quality of SRH services for adolescents in Turkey, which were never offered before 1994, and to ensure the use of these services, the European Union supported 55 million Euro budgeted the Reproductive Health Programme was implemented in Turkey as one of the signatories of the ICPD. However, in 2003, when the "Health Transformation Programme" was implemented by making radical changes in the health care system in Turkey, Youth Friendly Reproductive Health Centres were not included in the new organizational chart, so the situation returned to what it was before 1994 [16, 17].

After the inception of the programme in 1994, it was decided that all students should be given 40 minutes of SRH training in schools until end of the 11th year of basic education. For this purpose, training materials were prepared [18], high school teachers were trained and school trainings were started. Parallel to the implementation of the "Health Transformation Programme", school curricula changed and the SRH trainings came to an end.

A great deal of experience and knowledge was gained through implementation of the programme. But with the change of the health system, adolescents were once more ignored again. To meet the needs of the information source and counselling with "peer education", which has proven its effectiveness, it was aimed to do SRH peer educator training by choosing volunteers from the first – and second-year students of MUSM in 2016-2017 education period. Twenty-nine people participated in trainings on 13 different subjects that lasted 28 hours in total. Twelve of them have participated in all trainings and have been certified as "Peer Educator" by getting a high grade in the knowledge evaluation. To meet the existing information and consulting needs, this study will not be left as a project only. New peer educator trainings, plans and follow-ups of PE's trainings are planned in the future to ensure sustainability. Briefly, to be able to train 12 PE at the end of the study, which was planned and maintained with totally voluntary participants and trainers to meet the need emerging with the new health system, is one of the strongest aspects of our study. And to be able to plan this in 2016 while realizing that different projects should be carried out for the provision of SRH needs and rights for adolescents as Chandra-Mouli et al [19] stated in 2017 is another strong point of ours. Up to now, authors could reach few articles in English similar to this study's topic.

The trainings in this project were inevitably done in the time periods outside of school hours and/or at the weekend, as the participants were full-time university students. Although, this research has an important limitation that 100% participation in the trainings in the programme could not be achieved, the sensitivity of the subjects and the participation on the basis of volunteering did not make this possible. The training programme has been planned and implemented together with educators and PE candidates. It was aimed to create a model curriculum for people who are interested in SRH. And those who aim to organize training can put into practice this curriculum by adapting subjects and durations according to their own goals. Moreover, the long-term effects of peer education were not among the aims of this article. We recommend that the results of the research should be interpreted and evaluated according to this perspective. And future studies should be planned to evaluate the issue.

In our study, the socio-demographic characteristics of Group 1 and Group 2 were similar, such as sex, age, parent educational status, income level, place of residence, and thoughts on their own health status. It was determined that the participants had an egalitarian gender perception. We think that this may be due to the fact that our participants are a homogeneous group of volunteers and motivated people who are interested in SRH, studying at the same school and are in the same age group. In another study conducted at MUSM with 394 preclinical students on the same dates as our research, it was found that most of the students had an "egalitarian attitude" [20]. In an earlier research conducted with 507 students from Erzurum Atatürk University (2010-2011), health science students were found to be more egalitarian in their gender attitudes than the rest [21]. The fact that our participants who will serve in the healthcare field in future have "egalitarian gender" perception and will be able to provide services without gender discrimination made us happy in terms of showing that we reached one of the objectives of our study.

Although, the gender attitudes of Group 1 and Group 2 were "equal" and similar to each other, Group 1's "SRH attitudes", which were assessed on a different scale, were more positive than Group 2 before and after the training. However, both groups were able to make positive changes in SRH attitude. The reason for the positive development in both groups may be the attitude-focused nature of the first 8 education subjects that both groups participated in. Similar to our findings, in a study conducted in Ohio and Kentucky in the USA in 1995-96, which is one of the few studies investigating the effects of peer educator training on educators, an increase in attitudes of PE was found with HIV and alcohol prevention based peer educator training done with 845 9th grade students from 17 high schools. But the data reported that they could not achieve meaningful results due to problems with collecting data [22].

It was determined that Group 1, whose knowledge levels were significantly increased with training, had better SRH knowledge than Group 2. Group 1 was better in the subjects of STI, general and EC and condom use because the last sessions of the training focused on SRH knowledge. The reason that there was no difference in knowledge about the physiology of the reproductive system may be due to the fact that reproductive system physiology was mentioned during the first session of the training which both groups attended. Also, the vast majority of Group 1 were aware of the fact that Cu-IUD could be used for emergency contraception such as hormonal contraceptive methods, but the vast majority of Group 2 did not. Parallel to our results, an increase in HIV/AIDS and STI knowledge levels has been shown in a peer educator training programme conducted

with 30 university students in the USA in 1999 [23]. In another peer educator training programme with 70 university students at Stanford University, a positive change in SRH norms and STI knowledge level was shown [24].

Young people who are inadequately informed about SRH may be prone to unsafe behaviour and may be at risk. With this type of trainings, risky behaviours can be avoided by increasing SRH knowledge [25]. It is also possible to break down the medical barrier in front of adolescents which is an issue that Chandra-Mouli et al., also emphasize [19], by providing positive attitude development as it is in our educational programme and understanding the sexual and reproductive rights, besides increasing the knowledge of young people and especially those studying in the medical school.

In this study, we showed that the volunteers who participated in the training programme had increased knowledge of SRH and their attitudes improved in a positive way. We completed the first step of our project in SRH. The next step is to ensure that PE have a positive attitude and behaviour by reaching out to peers and increasing their knowledge. For this reason, we aim to create knowledge and attitude change in the peers by providing information transfer in the most appropriate way in our future work. As researchers, we need to pay attention to the fact that the actual effects of the studies that start with the same goal do not reach the desired level [26, 27]. So, we will consider the problems that occurred in the studies done before, and plan the training and the role of PE [28]. We hope that problems will end in this way, and not only the PE but also those who they will reach out to, can also benefit from our study [4].

In conclusion, our research has shown that a well-structured peer educator training programme can increase the knowledge of medical students who volunteer to become PE and can result in a positive attitude change. Trained PEs will be able to help themselves and the people they reach, to be healthy in the field of SRH with the achievements they received. Moreover, when they become physicians, they will make a positive contribution to patients for life, and offer unprejudiced and egalitarian services.

We tried to contribute to the SRH training with our local trainers. And we will continue to work until the day that provision of easily accessible and young friendly SRH counselling and services to the adolescents without prejudice will take place in the new health system.

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### Compliance with Ethical Standards

**Ethical Approval:** This study was approved by Marmara University School of Medicine Clinical Research Ethics Committee (with the protocol number 09.2017.255 and the date 7 April 2017).

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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.

**Author Contributions:** Concept – ANO, AC, BB, NK; Design – ANO, AC, BB, NK; Supervision – ANO, AC, BB, NK Materials – ANO, AC, BB, NK; Data Collection and/or Processing – AC, BB, NK; Analysis and/or Interpretation – ANO, AC, BB, NK; Literature Search – ANO, AC, BB, NK; Writing Manuscript – ANO, AC, BB, NK; Critical Review – ANO; Final Approval – ANO, AC, BB, NK.

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# The prognostic importance of double-expressor subgroup and AID, UNG and mismatch repair protein expressions in diffuse large B-cell lymphomas

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ABSTRACT

Objective: The cases of diffuse large B-cell lymphoma, (DLBCL not otherwise specified (NOS)) which immunohistochemically exhibit MYC and BCL2 expressions are defined as double-expressor lymphomas (DELs). This study aimed to assess the prognostic impact of DEL and the expressions of other proteins that may have role in tumorogenesis.

Materials and Methods: In this study, 90 tumor samples from patients diagnosed with DLBCL NOS were evaluated retrospectively. Immunoexpressions of MYC, BCL2, activation-induced cytidine deaminase (AID), uracil-DNA glycosylase (UNG) and DNA mismatch repair proteins including MLH1, MSH2, MSH6 and PMS2 were analyzed.

Result: Eleven cases (12.2%) which exhibited ≥40% MYC and ≥50% BCL2 immunexpressions were classified as DEL DLBCL. Patients with MYC positivity displayed lower overall survival rate than MYC negative cases. A trend of lower overall survival was observed in the double-expressor lymphoma group, however, this was not proven to be statistically significant. Significant relationship between AID, UNG and p53 immunexpressions with double-expressor lymphoma or overall survival was not detected. The correlation between immunexpressions of p53 and MYC was observed. The loss of expression of mismatch repair proteins was not observed in any cases.

Conclusion: In this study, a relationship between low overall survival and MYC expression is detected. However, our result does not demonstrate that double-expressor lymphoma can be associated with poor outcomes.

Keywords: Diffuse large B-cell lymphoma, Double-expressor lymphoma, MYC, BCL2, AID, Mismatch repair proteins

## 1. INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive B-cell lymphoma and a heterogenous group of diseases in terms of morphologic appearances, immunhistochemical phenotypes and molecular aberrations.

Several studies have been made with a great effort to subtype DLBCL at all levels to predict clinical outcomes and determine suitable treatment regimes. The main treatment for DLBCL not othervise specified (NOS) is the use of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). The disease recurs in nearly half of patients. In order to predict the clinical course, the National Comprehensive Cancer Network-International Prognosis Index (NCCN-IPI) score system has been established with clinical and laboratory data [1-3].

It has been reported that double-expression of MYC and BCL2 in DLBCL is a prognostic factor by earlier studies of Johnson et al. and Green et al. Numerous studies have contributed to our knowledge about these cases. DLBCL cases which show overexpression with both MYC and BCL2 antibodies with the cut-off values of 40% and 50% respectively, have been mentioned as double-expressor lymphoma (DEL), according the last World Health Organization (WHO) lymphoma classification update [3]. It is advised to identify these cases because of the fact that DEL subset in DLBCL may have the role in prognostic significance [4-8].

Translocation mutations have an important role in the lymphomagenesis process in the majority of lymphomas. It is thought that DNA fractures that occur during physiological somatic hypermutation and isotype switching in normal B-cell activation related to the formation of these mutations may play a role. Activation-induced cytidine deaminase (AID), uracil-DNA glycosylase (UNG), mismatch repair proteins (MLH1,

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MSH2, MSH6, PMS2) and p53 proteins have roles during somatic mutation and isotype switching [9-14].

The aim of this study is to assess the prognostic impact of double-expression with MYC, BCL2 antibodies and the expression of other proteins that may have role in tumorogenesis.

## 2. MATERIALS and METHODS

### *Case Selection and Clinical Data*

Tumor samples from patients who were diagnosed with DLBCL NOS between January 2007 and June 2015 and treated with R-CHOP regimen, were searched retrospectively. The samples were obtained from Pathology archive of Marmara University Hospital. Ninety cases among 187 cases were identified who met the inclusion criteria. The inclusion criteria were: to have formalin-fixed paraffin-embedded (FFPE) tumor block and have enough tumor volume in it (more than 100 cells), samples without artefact and have the survival data. Tumors that developed as secondary to low-grade lymphoma and were primarily located at the mediastinum, central nervous system, skin, intravascular and the body cavity were exluded.

The database of 90 eligible cases was collected from clinical records of the hematology department. Age, sex and tumor location of the all cases were recorded while Ann-Arbor stage, revised (R)-IPI/NCCN-IPI scores were obtained from 58 and 52 patients, respectively.

Hematoxylin and Eosin stained pathology slides were re-reviewed by one hematopathologist and one general pathologist on the basis of morphology and immunohistochemistry for the purpose of confirmation of diagnosis according to the last 2016 WHO classification [15].

This study was approved by Marmara University Clinical Research Ethics Board (Protocol number: 09.2016.578). All methods were performed in accordance with the relevant guidelines regulations.

### *Immunohistochemistry*

Sections with a thickness of 4 µm per tumor were obtained from formalin-fixed paraffin-embedded (FFPE) tumor blocks for immunohistochemical analysis. Immunohistochemical staining with MYC, BCL2, BCL6, CD10, MUM1, p53 and Ki67 antibodies was performed using standard methods on the Ventana platform (Roche, Basel, Switzerland). The proper external control tissues were used for each antibody as recommended. The percentage of cells that demonstrated staining for each antibody was recorded. The intensity of staining also was recorded and moderate or strong intesity of immunoexpression were accepted as positive staining, while weak immunoexpression was not. According the last WHO recommendation, thresholds for immunoexpression of tumor cells with MYC and BCL2 antibodies are accepted as 40% nuclear staining and 50% cytoplasmic staining, respectively [15]. The cases that were stained with MYC and BCL2 antibodies greater than these percentages were defined as DEL. Fluorescence in situ hybridization (FISH) analyses for MYC and BCL2 were not performed.

Cell of origin (COO) was determined according to Hans algoritm with CD10, BCL6 and MUM1 antibodies and cases were grouped as germinal center B-cell like (GCB) DLBCL and non-germinal center B-cell like (non-GCB) DLBCL [16]. Ki67 proliferation index recorded in the area of tumor showed maximum percentage of staining. Cases grouped according the percentage of staining as below 50%, between 50-90 and more than 90%. Nuclear staining of tumor cells for p53 antibody was evaluated and then cases were grouped as below or above 50% staining according to p53 immunoexpressions. Immunhistochemical staining with AID, UNG and DNA mismatch repair proteins including MLH1, MSH2, MSH6, and PMS2 antibodies were also studied. Cut-off percentages for staining were accepted as 15% and 20% for AID and UNG respectively. The loss of staining with MLH1, MSH2, MSH6, and PMS2 antibodies were recorded for each tumor.

### Statistical Analysis

Fisher's exact test and Pearson $\chi^2$ tests were used for group comparison of categorical variables. Overall survivals were calculated from the date of diagnosis to death or last follow up and were estimated using the Kaplan-Meier curves. The log-rank test was used to compare overall survival (OS) between subgroups. Prognostic factors that would affect OS were analyzed by using univariate and multivariate Cox proportional hazard regression models adjusting for confounding variables. The statistical significance level was considered as $p<0.05$. All statistical analyses were performed by using Statistical Package for Social Sciences (IBM, Chicago, USA).

## 3. RESULTS

### *Patient Characteristics and Clinical Datas*

Data from 90 patients were analyzed. Median age at diagnosis was 59 years. Forty-two patients (53%) were older than 60 years of age. Forty-four (49%) of all patients enrolled to this study were male 46 (51%). Female and sex ratio (M/F) was 0.96. Median follow-up time was 31 months (range, 1 to 104 months). Forty-eight tumor samples were taken from lymph nodes and forty-two from extranodal sites. Twelve of the tumors were taken from the gastrointestinal system, 11 from Waldeyer's ring, 11 from the bones, two from the lungs and the remaining tumor samples each was from other organ sites. Forty-four of 58 cases (76%) had high Ann-Arbor stage (III-IV). Twenty seven of 52 cases had poor R-IPI score and 31 of 52 cases had high or high/intermediate NCCN-IPI scores.

No significant OS difference was observed when the cases grouped according to gender. Patients who were older than 60 years had significantly worse OS rates ($p=0.001$). No significant OS difference was detected for tumors taken from lymph nodes or extranodal sites ($p=0.222$), although, slightly better clinical course was observed in extranodal tumors. OS was better for low Ann-Arbor stages, R-IPI and NCCN-IPI scores that was statistically significant ($p=0.026$, $p<0.001$, $p<0.001$, respectively).


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### *Immunohistochemical Analysis Results*

Of the 90 cases enrolled in the study, 19 cases showed MYC positivity and 53 cases showed BCL2 positivity. Among them 11 cases (12.2%) were double-expressor lymphoma that stained both antibodies. It was also observed that there was no overexpression with either MYC or BCL2 antibodies in 20 patients that were defined as double-negative cases (Figures 1 and 2). The demographic, clinicopathologic and immunhistochemical data of DEL subgroup are summarized in Table I. Patients with MYC positivity displayed poorer OS than MYC negative cases (p=0.018), whereas no significant difference was determined for BCL2 antibody (p=0.073). Double-expressor lymphoma cases staistically did not show any OS difference when compared with other cases (p=0.169), albeit, these cases tended to show poor OS (Figure 3).

a) b)

**Figure 1.** MYC <40% (a), and ≥40% (b) immunoexpression(200X).

a) b)

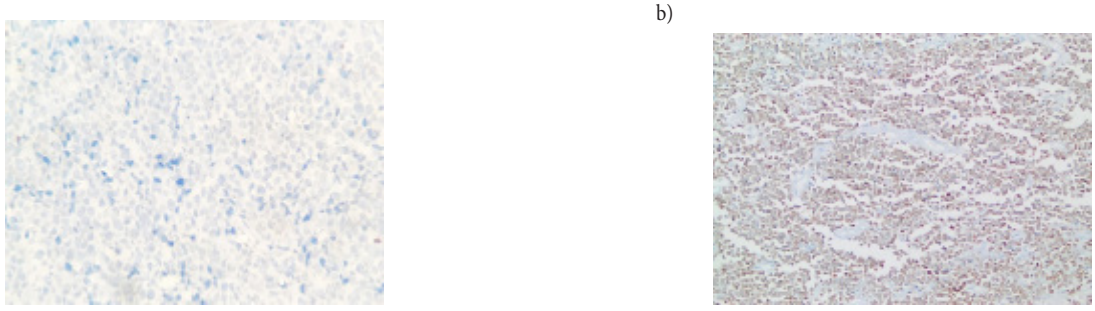

**Figure 2.** BCL2, <50% (a), and ≥50% (b) immunoexpression (200X).

a) b)

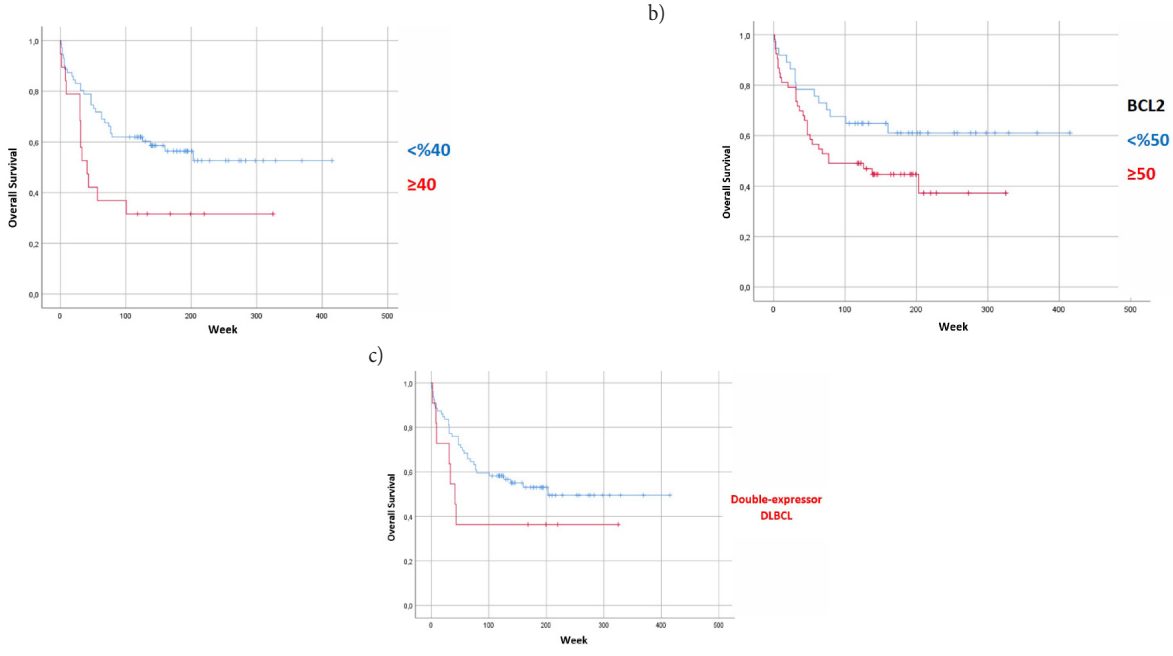


**Figure 3.** MYC expression-Overall survival (a), BCl2 expression-Overall survival (b), Double expressor lymphoma-Overall survival (c).

When cases grouped as only MYC positive, only BCL2 positive, double-expressor lymphoma and double negative lymphoma; double negative cases showed markedly better OS than other three groups (p=0.015). There was no significant association between double-expressor lymphoma and the factors including sex, age and tumor localization, Ann-Arbor stage and R-IPI/NCCN-IPI scores were distrubuted independently (Table I).

**Table I.** The demographic, clinicopathologic and immunohistochemical data of DEL subgroup

| Characteristics | | DEL (n=11) | Non-DEL (n=79) | All | p value |
|---|---|---|---|---|---|
| **Gender** | Male | 4 | 40 | 44 | 0.375 |
| | Female | 7 | 39 | 46 | |
| **Age** | ≤60 | 4 | 38 | 42 | 0.229 |
| | >60 | 7 | 41 | 48 | |
| **Tumor location** | Nodal | 4 | 44 | 48 | 0.229 |
| | Extranodal | 7 | 35 | 42 | |
| **AID** | >%20 | 1 | 15 | 16 | 0.421 |
| | ≤%20 | 10 | 64 | 74 | |
| **UNG** | >%50 | 3 | 14 | 17 | 0.449 |
| | ≤%50 | 8 | 65 | 73 | |
| **p53** | >%50 | 8 | 40 | 48 | 0.169 |
| | ≤%50 | 3 | 39 | 42 | |
| **Cell origin** | GCB | 7 | 34 | 41 | 0.199 |
| | Non-GBC | 4 | 45 | 49 | |

DEL: Double-expressor lymphoma, AID: Activation-induced cytidine deaminase, UNG: uracil-DNA glycosylase, GBC: Germinal center B-cell

Cell of origin subtype was determined for all patients according to Hans algorithm. Forty-one cases (46%) were GCB and 49 cases (54%) were non-GCB subtypes. There was no significant prognostic difference among patients with GCB or non-GCB subtypes (p=0.707).

Cases were classified into two groups according to the cut-off value for AID antibody that was accepted as 20% staning of tumor cells. Sixteen cases showed immunreactivity for AID antibody in more than 20% of tumor cells, whereas 74 cases did not show any immunoreactivity for AID antibody. Cases were divided into two groups as: immunexpression for UNG antibody more or less than 50% of cells. Immunostaining in more than half of the neoplastic cells was observed in 17 cases (18.9%). No significant difference was observed between groups for both antibodies in terms of overall survival (p=0.330 and p=0.559). In 42 cases (46.7%), more than 50% of the neoplastic cells had p53 immunexpression and in 48 cases (53.3%), less than 50% neoplastic cells had p53 immunexpression. There was no difference between these groups in terms of overall survival (p=0.740). The loss of expression with MLH1, MSH2, MSH6 and PMS2 was not observed in any tumor sample.

Multivariate analysis demonstrated that age, MYC expression and Ki67 expression were independent prognostic factors.

## 4. DISCUSSION

It was first reported that double-expressions of MYC and BCL2 in DLBCL were prognostic factors by earlier studies of Johnson et al. and Green et al. [5-6]. Numerous studies have contributed to our knowledge about these cases. DLBCL cases that show overexpression with both MYC and BCL2 antibodies with the cut-off values of 40% and 50% respectively, are defined as double-expressor lymphoma, according the last WHO lymphoma classification update [3,15]. It is advised to identify these cases because of the fact that DEL subset in DLBCL may be related with poor prognosis. Our study focused on immunohistochemical overexpression of MYC and BCL2 in DLBCL. Even though, there were differrent threshold values at earlier papers, 40% and 50% cut-off values are accepted widely nowadays. Thereby, we determined DEL cases as parallel to the WHO suggestion. Incidence of the DEL subset in DLBCL was reported as between 20%-35% in previous studies with different cut-off values but the incidence of DEL cases in our study was 12.2% [15].

It has been stated that DEL subset is associated with a poor prognosis in DLBCL in many studies. Firstly, Johnson et al. and Green et al., reported that double-expressions of MYC and BCL2 were prognostic factors independent of genetic rearrangement of MYC and BCL2 genes [5,6]. However, our study showed that the association regarding the role of DEL may not be reliable. Our results suggested that DEL cases showed poor clinical courses, but these were not independent predictors of poor survival. Although, inadequate sample size and limited number of DEL cases may have limited our ability to detect significant prognostic differences, there are some other publications that support our data. Therefore, the role of DEL as prognostic subgroup is still controversial. In this study, we found that MYC expression in more than 40% of tumor cells detected by immunohistochemistry were associated with shorter OS in DLBCL irrespectively of the NCCN-IPI scores and Ann-Arbor stage. In multivariate analysis, we confirmed that MYC overexpression was an independent prognostic factor in DLBCL. On the other hand, BCL2 expression more than 50% of tumor cells showed no significant association with poor OS. Although, many studies support poor prognostic role of DEL subset, it will be better to confirm the role of DEL with further studies with large data-sets or meta-analyses. The other limitation of our analysis was the lack of FISH analysis, thus double-hit lymphoma subgroup which was associated with poor prognosis could not be determined. This made study population heterogeneous in terms of cell origin.

The affect of primary localization of tumor to OS is controversial, because of several reasons including classification problems and difficulties of determination of tumor location [17]. It is still a controversial issue whether Waldeyer's ring tumors are nodal or not. Some tumors may be located at or invade both nodal and extranodal sites and it is not easy to detect actual origin of the

tumor. In this study, we detected the localization according to biopsy site and extranodal tumors, especially Waldeyer's ring and the bones tended to show better clinical course but that was not statistically significant. In the literature, studies do not have consensus about prognostic importance of primary tumor location. However, better outcomes in the head and neck DLBLCs are seen in some studies [18-21]. Patient age, Ann-Arbor stage and NCCN-IPI scores were important predictors of OS in our study as parallel to studies in literature [22-28]. Meanwhile, in our study, not reaching all IPI scores and stages of patients were also considered as a limitation.

The cases in our study were examined in two groups as GCB and non-GCB according to gene expression profiles. They were determined by immunohistochemical Hans algorithm methods [29]. There was no significant difference in overall survival between GCB and non-GCB groups in our study. Although, the Hans algorithm has an acceptable application validity, it is reported that its efficacy is limited in terms of identifying 10-15% of the cases, which cannot be classified by gene expression profiles, repeatability problems, application errors, and weak prognostic value [30-35].

AID and UNG are DNA base excision repair proteins that have important role during B-cell maturation. They create DNA breaks and mutations in physiological processes as somatic hypermutations and class switch recombination [36]. Since, these proteins take role in the formation and repair of DNA breaks, which cause translocations and may have a role in lymphoma etiopathogenesis. Immunostaining of the AID protein has been reported in several lymphomas, especially in DLBCL and Hodgkin's lymphoma. There are studies showing that AID immunostaining may be associated with poor prognosis in patients with chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL / SLL) and follicular lymphoma. We have limited knowledge about the expression of UNG in DLBCL [9, 37-42]. The loss of UNG and mismatch repair proteins in murine patients have been shown to increase the rate of mutation and cause DLBCL-like disease, while only loss of UNG is shown to be protective [42]. In our study, there was no relation between the expression of AID/UNG proteins and overall survival or DEL status. Few publications indicate that the loss in the immunexpressions of mismatch repair proteins in DLBCL cases is not expected [43,44]. Consistently, we did not see any loss of these proteins in our study.

It is reported that overexpression of p53 protein may be associated with mutations in the p53 gene and lymphomagenesis [45]. There are reports that show relationship between p53 expression and MYC protein expression and / or MYC gene translocation in DLBCL [10, 46-48]. In some studies, increased p53 immunoexpression has been reported to be a poor prognostic factor in DLBCL [46,47,49,50]. In our study, there was no correlation between p53 expression and overall survival or DEL subgroup. The correlation between immunexpressions of p53 and MYC were solely observed.

In conclusion, our result did not demonstrate that double-expressor lymphoma was associated with poor outcomes, although, we showed a relationship between low overall survival and MYC expression. We did not detect any significant relation between AID, UNG and p53 immunexpressions with double-expressor lymphoma and overall survival. It had been concluded that mismatch repair proteins did not play a significant role in the pathogenesis of DLBCL due to the lack of loss of immunoexpression.

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### Compliance with Ethical Standards

**Ethical Approval:** This study was approved by Marmara University Clinical Research Ethics Committee (Protocol number: 09.2016.578). All methods were performed in accordance with the relevant guidelines regulations.

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# A study exploring the autism awareness of students attending the department of pre-school teacher education of a public University in Istanbul, Turkey

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ABSTRACT

Objectives: Early detection of autism might largely depend on pre-school teachers' awareness and their prompt referral of these children to health authorities for accurate diagnosis. The purpose of our study was to assess the awareness about childhood autism among students attending the Department of Pre-school Teacher Education of a public university.

Materials and Methods: This descriptive study was carried out on 181 out of 218 students.

Results: The best known characteristic of a child having autism was "having a hard time in social relations" (90.1%). The majority (85.6%) of the study group believed that autism was curable and thought that a child having autism could pursue a family life in the future with his/her spouse (51.3%). Around 60.7% of all participants were of the opinion that a child with autism cannot participate in conversations.

Conclusion: The idea of a child with autism disturbing the teaching environment (50.8%) exists which might be a very important obstacle for his/her education; thus interfering with his/her treatment. Autism awareness of respondents could be considered to be relatively good among the senior students.

Keywords : Autism, Awareness, Pre-school Teaching, University Students

## 1. INTRODUCTION

Autism disorder was first described in 1943 by the American child psychologist, Leo Kanner [1]. Autism is considered as a neurodevelopmental condition interfering with the person's ability to communicate and relate to others [2]. Prevalence rates have been rising sharply and are estimated to be one in 50 amongst children [3, 4].

Many studies show that early diagnosis enables prompt initiation of appropriate therapy and early intervention aiding in their development and improving their communication and social skills [5-10]. Diagnosis at younger ages plays a crucial role in prognosis and developmental outcomes [8, 10]. Interventions may have diminished effectiveness in older children [8]. However, the length of time from a parent's first notice of symptoms to the time of diagnosis is reported to be relatively long, leading to delayed diagnosis and intervention [10]. Outside of parents and care-givers, pre-school teachers are the group most likely to spend the longest time and the closest relations with small children having autism in the early years of life [5, 8]. Early identification might largely depend on pre-school teachers' knowledge and awareness about autism and their attitudes towards interventions [5-10]. Their ability to pick out children with autism in the classroom is beneficial in the long term [5]. The Illinois Weselan University greatly emphasizes the role of teacher training in not only identification but also management of autism spectrum disorders in infancy [5]. Furthermore pre-school teachers must be able to not only identify children with developmental problems but also refer them to appropriate health authorities [7]; from thereon they can take a role in family support services [10].

To this end, the purpose of the current study was to assess the awareness of childhood autism among students attending

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the Department of Pre-school Teacher Education of a public university in a metropolitan city, Istanbul, Turkey.

## 2. MATERIALS and METHODS

### *Participants*

This descriptive study was conducted on students attending the Department of Pre-school Teacher Education of a public university in Istanbul, Turkey, in April 2015. A population of 192 out of 218 first grade and fourth grade students who gave informed consent to be a participant were admitted to our study.

This study was approved by Marmara University Ethics Committee. All procedures performed in this study were in accordance with the ethical standards.

### *Instrumentation*

Data was collected using a self-administered questionnaire. Out of 192 questionnaires, 11 questionnaires were excluded due to missing answers. Finally, 181 were found adequate to be included in the current study. This study was composed of 100 students attending first grade and 81 students attending the fourth grade. Nineteen autism awareness assessment questions were present in the questionnaire being made up of true (1 point) and false/do not know (0 points).

Questions about "autism awareness" were prepared referring to The Validity and Reliability of the Social Communication Skills Scale for Pre-school Children (Turkish version) study carried out by Öner et al. [11]; besides "Using the modified checklist for autism in toddlers in a well-child clinic in Turkey: Adapting the screening method based on culture and setting" prepared by Kara et al. [12] and also using "Knowledge About Childhood Autism among Health Workers (KCAHW)" questionnaire developed by Bakare et al. [13].

Since, we were unable to find a scale/questionnaire inquiring The Autism Awareness of Pre-school Teachers we had to prepare our own questionnaire. After deep review of the current literature, we believed that the above-mentioned three questionnaires/scales/checklists would be the best to prepare such a questionnaire. Questions that are more decisive in recognizing autism spectrum disorder and important for pre-school teachers to know were chosen and included in the questionnaire. The questions were evaluated based on the frequency of correct answers to each question without determining the cut-off point. In other words no cut-off point was used. True answer was the correct response for each question. This might be considered as a limitation of our questionnaire.

### Statistical Analysis

Descriptive analyses were presented using tables of frequencies for the ordinal variable. The Chi-square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups. A p-value of less than 0.05 was considered to show statistically significant result.

## 3. RESULTS

This descriptive study was conducted on 100 first grade and 81 fourth grade students attending the Department of Pre-school Teacher Education of a Public University in Istanbul, Turkey. Of all respondents, 156 students (86.2%) were females and 25 students (13.8%) were males. The mean age of the total of 181 students was 21.04 ± 2.89 (min 19, max 44).

The best-known characteristic of a child having autism was "having a hard time in social relations" with a percentage of 90.1%; not distributed statistically significantly between the grades (Table I; $p>0.05$). Based on other results presented in Table I, we can observe that 158 (87.3%) of the respondents were aware that a child having autism can have language delay ($x^2=2.773$; $p>0.05$). A total of 98 (54.1%) students were aware that children having autism cannot express themselves using gestures, showing statistically significant difference between the grades ($x^2=13.272$; $p<0.001$). Similarly, a statistically significant difference was observed between the fourth grade (46.0%) and the first grade students (30.0%), as far as the characteristic of a child with autism using echolalia-reverse usage of pronouns was concerned ($x^2=5.458$; $p<0.05$). Overall, 37.6% of all respondents were aware of the echolalia speech in the current study.

Around 60.7% of all participants were of the opinion that a child with autism cannot participate in conversations. Approximately, 70.4% of the fourth grade students and 53.0% of the first grade students gave correct answer to this question, causing a


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**Table I.** Distribution of Correct Response Rates Given to Autism Awareness Assessment Questions according to grades

| | Correct response rate | | | | | | Chi-square Significance |
|---|---|---|---|---|---|---|---|
| | First grade students(n=100) | | Fourth grade students(n=81) | | Total(n=181) | | |
| | n | % | n | % | n | % | |
| Language delay | 91 | 91.0 | 67 | 82.7 | 158 | 87.3 | $x^2$=2.773 p=0.096 |
| Impairment establishing eye-contact | 80 | 80.0 | 76 | 93.8 | 156 | 86.2 | **$x^2$=7.187 p=0.007*** |
| Staring at spinning objects, TV, particularly advertisements | 74 | 74.0 | 77 | 95.1 | 151 | 83.4 | **$x^2$=14.351 p=0.0006*** |
| Autism is curable | 82 | 82.0 | 73 | 90.1 | 155 | 85.6 | $x^2$=2.401 p=0.121 |
| Likes puzzles, sports, music, arts, math etc. | 54 | 54.0 | 45 | 55.5 | 99 | 54.7 | $x^2$=0.044 p=0.834 |
| They might be aggressive from time to time | 53 | 53.0 | 57 | 70.4 | 110 | 60.8 | **$x^2$=5.664 p=0.017*** |
| Seen more frequently in males | 25 | 25.0 | 43 | 53.1 | 68 | 37.6 | **$x^2$=15.051 p=0.0001*** |
| Have hard time in social relations | 88 | 88.0 | 75 | 92.6 | 163 | 90.1 | $x^2$=1.053 p=0.304 |
| Might have abnormal eating habits | 49 | 49.0 | 51 | 62.9 | 100 | 55.2 | $x^2$=3.528 p=0.060 |
| Cannot express themselves using gestures | 42 | 42.0 | 56 | 69.1 | 98 | 54.1 | **$x^2$=13.272 p=0.0003*** |
| Cannot participate in conversations | 53 | 53.0 | 57 | 70.4 | 110 | 60.7 | **$x^2$=5.664 p=0.017*** |
| Cannot play imaginative plays | 12 | 12.0 | 20 | 24.7 | 32 | 17.7 | **$x^2$=4.952 p=0.026*** |
| Can imply a meaning by creating verbal expressions | 6 | 6.0 | 9 | 11.1 | 15 | 8.29 | $x^2$=1.538 p=0.215 |
| Spins around himself/ jumps repetitively/walks on toes | 52 | 52.2 | 45 | 55.5 | 97 | 53.6 | $x^2$=0.227 p=0.633 |
| Can harm himself by biting/hitting his head | 42 | 42.0 | 52 | 64.2 | 94 | 51.9 | **$x^2$=8.833 p=0.003*** |
| Is involved with parts of objects/toys | 70 | 70.0 | 66 | 81.5 | 136 | 75.1 | $x^2$=0.315 p=0.075 |
| Attracts others' attention by their voices/ behaviors | 48 | 48.0 | 32 | 39.5 | 80 | 44.2 | $x^2$=1.309 p=0.596 |
| Echolalia/reverse usage of pronouns | 30 | 30.0 | 38 | 46.0 | 68 | 37.6 | **$x^2$=5.458 p=0.019*** |
| Can use someone else's hand to reach things | 36 | 36.0 | 35 | 43.2 | 71 | 39.2 | $x^2$=0.976 p=0.323 |

* Statistically significant p<0.05

statistically significant difference between the grades ($x^2$=5.664; p<0.05).

Nearly, 86.2% of all participants were aware that a child with autism can have impairment in establishing eye-contact; 93.8% of the fourth grade students and 80.0% of the first grade students gave correct answers to this question, creating a statistically significant difference between the grades ($x^2$=7.187; p<0.05).

Similarly, a statistically significant difference was calculated between the fourth grade (95.2%) and the first grade students (74.0%) as far as 'staring at spinning objects, television, particularly advertisements, was considered as a characteristic of a child with autism ($x^2$=14.351; p<0.05). This item was correctly answered by the majority of the whole group (83.4%). One of the characteristics not distributed statistically significantly between the grades (p>0.05), but known by the majority of all participants (75.1%) was "He is involved with parts of objects/toys".

In addition, there was a statistically significant difference in knowing that a child with autism cannot play imaginative games. This was marked by 17.7% of all students; 24.7 % of fourth grades, 12.0% of first grades ($x^2$=4.952, p<0.05).

As far as the strengths of a child having autism was questioned "Likes puzzles, sports, music, arts, mathematics, etc"was marked by 54.7% of all participants.

Ninety-two of the students (50.8%) thought that a child having autism could disturb the teaching environment in the class (Table II). Of the fourth grade students, 70.4% thought that children having autism might be aggressive from time to time, this percentage was 53.0% among the first grade students, the difference being statistically significant ($x^2$=5.664; p<0.05). Of all students, 51.9% thought that a child having autism can harm himself by biting or hitting his head, this percentage was 64.2% among the fourth grade and 42.0% among the first grade students; the difference being statistically significant ($x^2$=8.833; p<0.01).


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**Table II**. Distribution of responses of students to general questions about autism

| General questions about autism † | Percentage of 'YES' responses (%) |
|---|---|
| 1.Marking World Autism Day true as April 2nd | 78.6 |
| 2.Having attended a conference/project on autism before | 12.7 |
| 3.Having an acquaintance with autism | 10.5 |
| 4.Having shared an indoor setting with an individual having autism. | 33.1 |
| 5.Thinking that a child having autism could pursue a family life in the future with his/her spouse | 51.3 |
| 6.Thinking that a child having autism could have healthy children in the future | 46.4 |
| 7.Thinking that a child having autism could disturb the teaching environment in the class. | 50.8 |

†There was no statistically significant difference in the percentage of YES responses among the first grade and fourth grade students (p>0.05)

The majority (85.6%) of the study group believed that autism is curable, the difference not demonstrating significance statistically between the grades (p>0.05).

Furthermore, there was a statistically significant difference in knowing that the autism is seen more frequently in males (53.1 % in fourth grades, 25.0% in first grades; $x^2$=15.051, p<0.001).

Around half of the participants (55.2%) were aware that a child with autism might have abnormal eating habits, the difference not showing significance statistically between the grades (p>0.05).

The majority 140 (78.6%) of the participants were found to mark World Autism Day true as April 2nd ; furthermore 23 (12.7%) of the participants stated that they had attended a conference/ project on autism before. Nineteen (10.5%) students admitted that they had an acquaintance having autism. Sixty (33.1%) students declared that they had shared an indoor setting with an individual having autism (Table II). Around 94.5% of all students felt a lack of confidence in being able to meet the needs of pre-school children having autism in their class.

The mean autism awareness scores were compared between the first grade students (9.1 ± 3.7) and the fourth grade students (11.2 ± 3.9). The difference was found to be statistically significant (t=3.75; p<0.05).

## 4. DISCUSSION

In the current study, among all students of the Department of Pre-school Teacher Education of the public university, the best-known characteristic of a child with autism was "having a hard time in social relations". The leading features of childhood autism were found to be "social interaction difficulties and lack of social responsiveness" in several studies [4, 6, 7, 9, 14-18]. "Making friends" is reported as a challenging issue for the children having autism [3,14]. In a review article by Gray and Tonge, the early features of autism were reported as "lack of interest in other children", lack of seeking to share own environment", "failure to develop peer relations", " failure to join in activities of others", and "lack of social play" [15]. In the London study, it is reported that children with autism actually seek friendships with others, but they do not have the skills to maintain them [19]. In Durand-Zaleski's study the elementary school teachers characterising autism as a social communication problem, resembled the findings of our study [20]. In Wang et al's study conducted on caregivers of pre-school children having autism in China, poor ability to communicate was the best-known characteristic of childhood autism [10]. A child with autism having difficulty in communicating and in social interactions was mentioned as the top – ranking characteristic of autism by primary school teachers in Pakistan in Arif et al's study [5]. Similar results appeared in Lian et al's study conducted on pre-school teachers in Singapore [7] and in Liu et al's study also carried out on pre-school teachers in China [8].

In our study, the majority of the respondents were aware that a child having autism can have language delay. More than half of them were of the opinion that a child with autism cannot participate in conversations. Approximately one third of all respondents were aware of the echolalia speech-reverse usage of pronouns in the current study. Delay in speaking was reported to be one of the signs of childhood autism.[7,9,17, 18, 21-24]. Actually, Heidgerken et al. imply that even if children falling within the lower end of the spectrum can often achieve adequate functioning in language and social behavior, they can still retain some persistent speech and behavioural pecularities [23]. Some children with autism can sometimes never speak; they can use words in different meanings, they can misuse the pronouns, they can have echolalia, they cannot start or continue a conversation [15, 22, 24]. In Arif et al's study, individuals with autism are stated to exhibit varying verbal abilities, ranging from being nonverbal to having advanced speech [5]. The questions inquiring language delay, initiating or responding to conversation and other speech problems like echolalia were better known by the participants of our study as compared to the participants of Karabekiroğlu et al's, Wang et al's, Arif et al's and Liu et al's studies [5,8,10,25]. Being aware of language delay appeared with similar percentages in our study as in Lian et al's study [7].

In our study, the majority of all participants were aware that a child with autism can have impairment in establishing eye-contact. Around half of the participants were aware that children having autism cannot express themselves using gestures. These children are most of the time reported to have difficulty with not only verbal but also with nonverbal communication such as lack of eye-contact, lack of gesture, lack of facial expression, lack of social responsiveness, disliking social touch with almost no social smile [4,7,15,17,18,24]. Resembling the findings of our study, in another Turkish study carried out in elementary school teachers, around half of the respondents stated that children with autism have difficulty maintaining eye-contact [25]. Yasar and Cronin's study conducted on College of Education Students in Ankara and Trabzon in Turkey, similar findings emerged [26]. Poor eye-contact, gesture, and social responsiveness were stated in similar ratios to our study in Arif et al's, Liu et el al's, Wang


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et al's and Lian et al's studies [5,7,8,10]. The characteristics of childhood autism namely "staring at spinning objects, televison, particularly advertisements" and "being involved with parts of objects/toys" were marked by the majority of the respondents in our study. Gazing at objects, staring into space for long periods of time, being occupied with parts of objects can be seen as characteristics of small children with autism [15,18,21,27,28]. As far as the characteristic of "staring at spinning objects, television, particularly advertisements" was concerned, the awareness percentage of our participants showed similarity with Karabekiroğlu et al's study from Turkey [25]. A characteristic of childhood autism less known by our participants was "cannot play imaginative games". Some of the small children having autism are reported as not using toys appropriately, such as lining them up rather than imaginative or pretend games and also that they prefer not to imitate other children during play [7,9,15,17,18,21,24,27,28].

As far as the strengths of a child having autism was questioned "Likes puzzles, sports, music, arts, math etc"was marked by around half of all participants in our study. This percentage was higher in the current study as compared to Wang et al's study [10]. It is recommended by Yasar and Cronin that not only families but also educators must be aware of these strengths for the social and intellectual development of these children and for them to be better accepted by the community in Turkey [26].

Among the emerging pessimistic thoughts in our study was that nearly half of the respondents' believed that a child having autism could disturb the teaching environment in the class. Furthermore, approximately half of the respondents thought that children having autism might be aggressive from time to time and also that a child having autism can harm himself by biting or hitting his head. In severe forms of autism, aggressive behaviors like severe temper tantrums and/or frequent minor tantrums; hurting others by biting, hitting, kicking; hurting self by biting the hand or banging the head may be seen [28]. Impatience when waiting for needs to be met; often being frightened or very anxious: being oblivious to dangerous situations, might also present in severe forms according to Krug et al. [28]. However, these problematic situations exist in a minority of these children; besides, they exist in trivial degrees in children having mild to moderate forms of autism [6-9,17,26]. Most of the time, after behavioral and social training conducted at early ages, they might often be easy to manipulate [6-9,17,26]. In McConkey and Bhlirgri's study, the most difficult problems the pre-school teachers found hard to deal with were temper tantrums [9]. In countries where children broadly attend pre-school from an early age like in Sweden, Early Intensive Behavioral Intervention (EIBI) programmes in young children with autism are largely delivered by regular pre-school staff [6, 29]. These EIBI methods are also being recommended by Liuet et al., Lian et al., McConkey and Bhlirgri, Stichter et al. and Yasar and Cronin [7-9,17,26]

It is stated that children with autism are also at risk of being harmed, ignored or nagged in the classroom, for example they are more likely to be bullied [30,31]. In Humprey and Symes's study, the respondents felt that the key benefits mainstream pupils without autism would gain from a child with autism integrated into mainstream was increased understanding and tolerance of people different to themselves [30]. In McConkey and Bhlirgri's study, it is reported that not only the children having autism would benefit from inclusion but also their normally developing peers [9].

The majority of the study group believed that autism is curable. One of the recent review articles written by Ratajczak and Sothern discuss autism's being no longer considered as incurable [32]. In this article, non-categorical pre-school classes, individual speech therapy, applied behavioral analysis, together with other behavioral and social interventions are discussed, as well as the effects of sulforaphane, malariotherapy, fever and various other therapies in the treatment of autism [32]. A considerable ratio of the early detected children with autism were reported to have optimal outcome, that is losing all symptoms in addition to the diagnosis [32]. Similarly, a study carried out by Mukaddes et al., in Turkey, after Early Intensive Behavioral Intervention (EIBI), Pivotal Response Training (PRT) and comprehensive naturalistic behavioral programme, a group of children having autism recovered [33]. In Mukaddes et al's study, collaboration between Families, Nursery Teachers, Speech Therapists and Special Educators were among the determinants for achieving recovery [33].

As far as the overall findings of our study are concerned, the general awareness of pre-school teaching students concerning childhood autism was better than the participants of the Wang et al's, Arif et al's and Liu et al's studies [5, 10]. However, around the majority of the participants declared that they did not feel confident in being able to meet the needs of pre-school children having autism in their class. Similar feelings were reported in Liuet et al's, Humprey and Symes' and McConkey and Bhlirgri's studies [8, 9, 30]; whereas in Sweden, pre-school teachers felt more secure about their approach to the children having autism in Andersson et al's study [29]. In Yasar and Cronin's study conducted on College of Education students in Turkey, students admitted that they had basic knowledge about autism, but they needed more inclusive and in-depth knowledge [26].

Few of the students in our study admitted that they had an acquaintance having autism. Around one third declared that they had shared an indoor setting with an individual having autism. In Yasar and Cronin's study, most of the students stated that they did not know any individual with autism and they had never experienced teaching a child with autism during their practicum hours [26].

Inclusive education began in Turkey in 1983 with the regulation regarding children with special needs. In Turkey, even though there are legal requirements about special education services and inclusive education, there is a scarcity of trained educators to provide those services and there are no well-designed educational environments for inclusive education [26].

In 2006, all teacher training programs in Turkey were required to add special education and inclusion classes to their programs [26]. However, few of the Universities in Turkey have a program which can educate teachers and specialists for students with


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autism, because there are not enough university professionals who can prepare the teachers who will serve students with autism in special education and inclusive settings as Yasar and Cronin stated in their article [26]. To this end, Turkey needs professionals who can work on autism, and also academic staff who can develop college training programs [26].

Diagnosis of autism at younger ages plays a crucial role in prognosis and developmental outcomes. Outside of parents and care-givers, pre-school teachers are the group most likely to spend the longest time and the closest relations with small children having autism in the early years of life. The role of pre-school teachers is not only timely recognition and referral of these children; but also their intellectual, social and behavioural management; together with parent support in cooperation with health authorities.

In the current study, around half of the respondents thought that a child having autism could disturb the teaching environment in the class. Those problematic situations actually exist in a minority of these children; besides, they exist in trivial degrees in children having mild-moderate forms of autism. Most of the time after behavioral and social training conducted at early ages, they might often be easy to manipulate. However, around the majority of the participants of our study declared that they did not feel confident in being able to meet the needs of pre-school children having autism in their class. To this end, after this study, we believe that our study group needs further training on timely picking up these children in the classroom, on their intellectual, social and behavioural management; manipulation of problematic behaviour and also being a role model for the normally developing children for their attitutes towards their peers with autism.The most important of all is that they must not discriminate the children with autism and prevent discrimination within the classroom. In Turkey, although all teacher training programs are required to add special education and inclusion classes to their programs, most of the time they do not have well-designed educational environments for inclusive education. Furthermore, few of the Universities in Turkey have a program which can prepare teachers and specialists for students with autism, because there are not enough university professionals who can prepare the teachers who will serve students with autism in special education and inclusive settings.

### *Limitations*

Several questions relating to childhood autism were not covered in our study. Besides, the results of this study cannot be generalized to Istanbul Province or to Turkey as a whole. Nevertheless, it can serve as a guide to further studies. This study using a self-administered questionnaire can also present the limitation of reporting bias and desirability for providing right answers.

## Conclusion

The autism awareness of the respondents of our study could be considered to be relatively good. The respondents can be interpreted as belonging to a group of people between the general public and educators. Therefore, this study is important for the early detection of autism and early intervention, and also for decreasing any discrimination present in the community. Autism spectrum disorders could be integrated into the curricular or extracurricular theoretical and practical courses of all colleges of education; particularly pre-school teaching, awareness of educators can be raised to very high levels. This is almost essential, keeping in mind the fast increase in autism prevalence.

Adequate knowledge and awareness about childhood autism among educators would ensure early detection of children with autism in the community and this in turn would allow early intellectual, social and behavioural interventions.

## Compliance with Ethical Standards

**Ethical Approval:** This study was approved by Marmara University Ethics Committee. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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**Conflict of Interest**: The authors declare that they have no conflict of interest. **Informed Consent:** Informed consent was obtained from all participants. **Authors' Contributions**: Concept and Design – SH, NEM; Supervision – MK; Resources – SH, NEM; Materials – SH, MK; Data Collection and Processing – SH, NEM, MK; Analysis and Interpretation – SH, ŞGK; Literature Search – SH, NEM; Writing Manuscript – MK; Critical Review – AK, MK

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# The role of diffusion tensor imaging for the assessment of liver fibrosis and inflammation in chronic viral hepatitis: A preliminary study

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ABSTRACT

Objective: To evaluate the role of magnetic resonance (MR) diffusion tensor imaging (DTI) in the assessment of liver fibrosis and inflammation in chronic viral hepatitis by measuring apparent diffusion coefficient (ADC) and fractional anisotropy (Fa) values.

Material and Methods: Twenty-seven patients (5 women and 22 men;mean age39.8±11.3) with hepatic fibrosis were included in our study. The relationship between ADC, Fa values and histological activity index (HAI) score were evaluated using Spearman's correlation coefficient. Patients were subgrouped as group A (fibrosis score 1) and group B (fibrosis score 3). The mean ADC and Fa values of groups A and B were compared using Student's t-test. To evaluate the use of ADC and Fa values in distinguishing group A from group B, ROC analysis was applied; sensitivities and specificities were calculated.

Results: Fa values correlated with HAI scores significantly (r=0.397, p<0.05) The difference was significant between the mean ADC values (group A:1.46± 0.191x103mm2/s; group B:1.105± 0.141x10-3 mm2/s; p<0.001) and Fa values (group A: 0.473±0.091; group B: 0.643± 0.007; p<0.001) between the groups. For distinguishing group A from group B, ADC had a sensitivity of 81.8% and a specificity of 93.8%. The sensitivity and specificity of Fa were 90.9% and 100%, respectively.

Conclusion: Diffusion tensor imaging may play a role in the evaluation of fibrosis and HAI scores in patients with liver fibrosis.
Keywords: Hepatitis, Liver fibrosis, Diffusion tensor imaging.

## 1. INTRODUCTION

The detection of hepatic fibrosis and inflammation in patients with chronic viral hepatitis is crucial for planning the treatment and follow-up strategies which will affect the long-term prognosis [1]. Anti-viral treatment can eradicate the infection, increase patient survival and reduce the need for liver transplantation [1]. Antiviral treatment is indicated in patients with moderate to advanced stages of fibrosis. The score of fibrosis and HAI scores are determined by histopathologic evaluation obtained after liver biopsy. However, liver biopsy has some limitations such as its complication rate [1-5%] and high cost [2, 3]. Thus, noninvasive methods are needed to diagnose and score the liver fibrosis.

Over the last years, investigations on magnetic resonance (MR) diffusion weighted imaging (DWI) have been carried out to provide a noninvasive way of detection and quantification of liver fibrosis [1, 4-10]. The microscopic mobility of the water protons is the aspect that DWI relies on. Apparent diffusion coefficient (ADC) indicates the movement of water molecules in a tissue [4]. The fibrotic changes cause architectural distortions of the liver parenchyma and lead to the diffusion restriction of water molecules. As expected, ADC value decreases as the degree of fibrosis increases in the tissue [1,4-10].

Unlike DWI, diffusion tensor imaging (DTI) can be helpful for evaluating anisotropic properties of tissues since, it allows the analysis of diffusion along multiple directions [11]. By employing DTI, not only ADC but also fractional anisotropy (Fa) values can be calculated. Fa values reveal the fraction of anisotropic diffusion to total diffusion. There is very limited research on the utility of DTI in staging of fibrosis. To our knowledge, only one study has examined the usefulness of DTI in regard to liver fibrosis [1].

Our hypothesis is that the fibrotic and inflammatory changes encountered during the course of chronic hepatitis will not only cause restricted diffusion, but will also cause an increase in the fraction of anisotropic diffusion which will lead to a decrease in ADC and increase in Fa values obtained by DTI.

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The objective of this study is to test the hypothesis by correlating both ADC and Fa values with the degree of fibrosis and histological activity index (HAI) scores in patients with chronic viral hepatitis.

## 2. MATERIALS and METHODS

### *Patients and Histopathologic Analysis*

Institutional review board approval was obtained for this retrospective single-institution study. The data bank of the gastroenterology clinic was searched to find patients who had liver biopsy due to either chronic hepatitis B or C. Among those patients, the ones who underwent MR-DTI were included in the study between April 2009 and June 2010. There were a total of 27 patients (5 women and 22men; mean age=39.8±11.3). The mean time interval between biopsy date and imaging was 177.2±232.4 days. Twenty-two patients had chronic hepatitis B and five patients had chronic hepatitis C. The HAI score and scores of fibrosis were documented for each patient according to histopathology reports of the liver biopsies. In 1981, HAI scoring system was described by Knodell et al. In this scoring system, necroinflammatory activity of the liver biopsy specimens are formulated and scored between 0 and 18, by combining periportal necrosis and inflammation score (between 0 and 10), lobular necrosis and inflammation score (between 0 and 4), and portal inflammation score (between 0 and 4) [12,13]. In our study, 26 patients had HAI scores calculated according to Knodell system; median HAI score was 7 (range:2-11) (one patient had a fibrosis score, but no HAI score was calculated according to his liver biopsy report ).

Fibrosis in the HAI system is scored as 1, 3, or 4, with 1 indicating portal fibrosis only, 3 indicating bridging fibrosis, and 4 indicating cirrhosis [13]. This discontinuous scale (2 is missing) is used to allow a clear separation of mild (score 1) from extensive (score 3) fibrosis [13]. In our study, 16 patients had fibrosis score 1, and 11 patients had fibrosis score 3 (one patient had a fibrosis score, but no HAI score was calculated according to the HAI system). We were not able to include any patients with fibrosis score 4 (cirrhosis) in this retrospective study; the gastroenterologists at our institution were reluctant to refer cirrhotic patients (who were diagnosed according to clinical, laboratory and liver imaging findings) to liver biopsy due to high risk of biopsy-related complications.

### *MR Imaging*

All MR imaging examinations were performed using a 1.5Tesla Scanner (GE Healthcare, Waukesha, WI ). In addition to the conventional MR imaging protocol, an axial breath-hold, single-shot gradient echo planar DTI sequence covering the whole liver was acquired using the following parameters: Matrix: 256x160, Acquisition time: 3:04 (min:sec), TE: 89.4 msec, TR: 6125.0 msec, Bandwith: 31.25 kHz, number of excitations: 4.0, field of view: 48, Slide thickness: 8.0 mm, Spacing: 1.0 mm, b-value: 1000 sec/mm2, number of diffusion directions: 6. Spectro Spatial RF pulse was used to reduce chemical shift artifacts. Whereas atypical conventional DWI sequence employs three diffusion gradients in three orthogonal directions (frequency-encoding (x), phase-encoding (y), and section-select (z), our DTI sequence employs six directions (x, y, z, xy, yz and xz) as described previously [1].

### *Image Analysis*

Two radiologists who were blinded to fibrosis scores and HAI scores reviewed all images, independently. ADC and Fa maps were calculated on a remote Workstation (GE, Advantage Windows Workstation, Milwaukee, WI). Three regions of interest (ROIs) with equal diameters (approximately 1 cm) were placed in the right lobe of the liver away from intrahepatic vasculature.

### Statistical Analysis

The reports of two radiologists who measured ADC and Fa values were evaluated using Bland-Altman statistic. For further analysis, their measurements were averaged. The mean ADC and Fa values were calculated first for all patients and then separately for groups A (fibrosis score 1) and B (fibrosis score 3).

The relationship between ADC and Fa values in our patients was evaluated using Pearson's correlation. The relationship between HAI scores and ADC or Fa values in the whole group was evaluated using Pearson's correlation. Correlation coefficients ≥0.7, >0.5 to <0.69, >0.3 to <0.49, >0.1 to <0.29, and >0.01 to <0.09 were interpreted as indicators of very strong, substantial, moderate, low, and negligible associations, respectively [14]. P values <0.05 were considered statistically significant.

Then, patients were subgrouped as group A (fibrosis score 1) and group B (fibrosis score 3) according to the results of histopathological analysis obtained by liver biopsy. The mean ADC, Fa ages and values of patients in group A (fibrosis score 1) and B (fibrosis score 3) were compared using Student's t-test. Regarding the gender and the hepatitis type, groups were compared using Fisher exact test. P values <0.05 were considered statistically significant.

To evaluate the use of ADC and Fa values in distinguishing patients with fibrosis score 1 (group A) from those with fibrosis score 3 (group B), a ROC analysis was applied. The areas under the curve and cut-off values were calculated. Sensitivities and specificities with 95% confidence intervals (CIs) were calculated accordingly.

## 3. RESULTS

There was a good agreement between the two radiologists for measuring both ADC and Fa values according to Bland-Altman analysis (Figure1). Figure 2 demonstrates representative MR images of a patient with score 3 fibrosis and a HAI score of 10.


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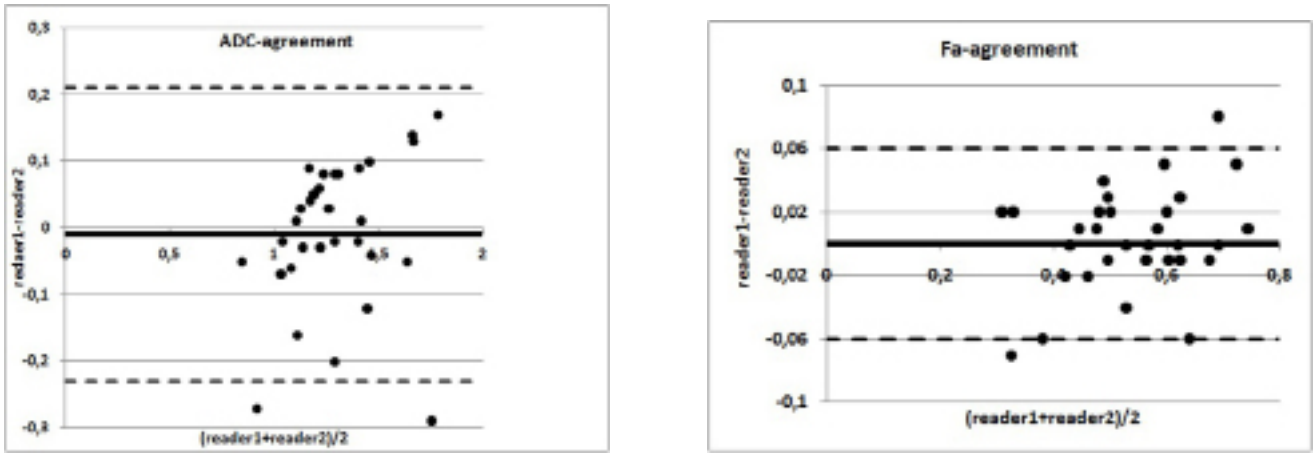
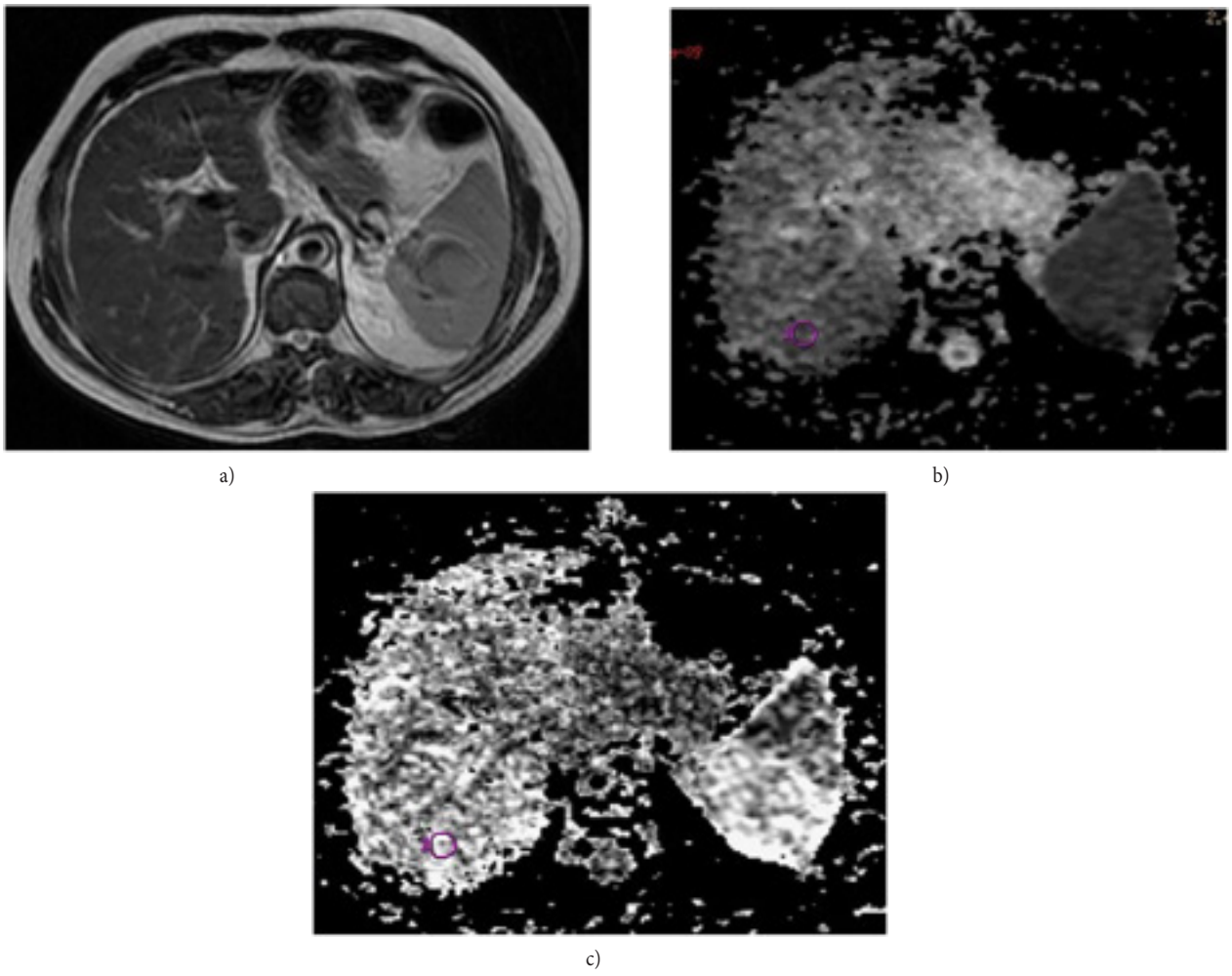



**Figure 1.** Graphs show results of Bland-Altman test regarding the interobserver agreement on ADC (a) and Fa (b) measurements. The solid line represents mean difference, and the dashed lines represent limits of agreement (d ± 2SD).



a) b)

c)

**Figure 2.** T2-weighted image (a), ADC map (b) and Fa map (c) of a patient with score 3 fibrosis. His HAI score was 10.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In the whole group , mean ADC and Fa values were 1.31±0.24 x$10^{-3}$ $mm^2$/s and 0.54±0.12, respectively. There was a negative, very strong and significant (r=-0.864, p<0.00000001) correlation between ADC and Fa values (Table I).

**Table I.** Gender, mean age, number of the patients according to the type of the chronic viral hepatitis, mean ADC and Fa values are given for fibrosis score 1 (group A) and fibrosis score 3 (group B) patients.

| | Fibrosis Score 1 (group A) | Fibrosis Score 3 (group B) | p Value |
|---|---|---|---|
| **Gender** | 2 female, 14 male | 3 female, 8 male | >0.1 |
| **Mean age ± SD (years)** | 35.75 ± 10.74 | 45.64 ± 8.60 | <0.05 |
| **Hepatitis type** | 14 hepatitis B, 2 hepatitis C | 8 hepatitis B, 3 hepatitis C | >0.1 |
| **Mean ADC value ± SD** | 1.46 ± 0.191x$10^{-3}$ $mm^2$/s | 1.105 ± 0.141x$10^{-3}$ $mm^2$/s | <0.001 |
| **Mean FA value ± SD** | 0.463 ± 0.08 | 0.644 ± 0.07 | <0.001 |

The correlation between ADC values and HAI scores was negative, moderate and not significant (r=-0.34, p=0.088). The correlation between Fa values and HAI scores was positive, moderate and significant (r=0.397, p=0.045). The mean ADC values in patients with fibrosis score 1 (group A) and in patients with fibrosis score 3 (group B) were 1.46±0.191x$10^{-3}$ $mm^2$/s and 1.105±0.141x$10^{-3}$ $mm^2$/s , respectively (Student's t-test, p<0.001). The mean Fa values in patients with fibrosis score 1(group A) and score 3 (group B) were 0.463±0.08 and 0.644±0.07, respectively, (Student's t-test, p<0.001). ADC value had an area under the curve of 0.949. Using 1.22x$10^{-3}$ $mm^2$/s as the cut-off value, the sensitivity was 81.8% (9/11; 95% CI= 52.3%-94.9%) and the specificity was 93.8% (15/16; 95% CI=71.7%-98.9%). Fa value had an area under the curve of 0.969. Using 0.59 as the cut-off value the sensitivity was 90.9% (10/11; 95% CI= 62.3%-98.4%) and the specificity was 100% (16/16; 95% CI=80.6%-100%).

## 4. DISCUSSION

In our preliminary study, we aimed to find a correlation between Fa values, obtained by DTI with HAI scores and/or fibrosis scores obtained by histopathologic evaluation of liver biopsy specimens of patients with chronic viral hepatitis.We found out that Fa values correlate moderately and significantly with HAI scores. Since, severe degrees of inflammatory activity predict worsening of hepatic fibrosis and constitute an indication for therapy independent of the current level of fibrosis [13], this finding may play an important role in the follow-up of patients with chronic hepatitis. In distinguishing patients with fibrosis score 1 from those with fibrosis score 3, Fa and ADC values can be used successfully. The performance of Fa values was slightly better as reflected in Az values obtained through ROC analysis. This is also important, since a clear separation of patients with fibrosis score 1 from those with fibrosis score 3 is crucial in terms of clinical decision making [13,15].

Although, the normal liver parenchyma exhibits anisotropic diffusion, our hypothesis was that the inflammation and fibrotic process encountered during the course of chronic hepatitis would cause further anisotropy. Our results show that this hypothesis might be true. Thus, in addition to ADC values, Fa values can also be used in the follow-up of the patients with hepatic fibrosis due to chronic hepatitis. Our results show that Fa values can be employed especially to monitor the histopathological activity.

There are studies trying to correlate ADC values with HAI scores and fibrosis scores using DWI [7, 10]. In these studies, a negative correlation was reported between ADC values and fibrosis scores and HAI scores. Our results are parallel to the results of those studies. Nevertheless, the major difference between our study and the former ones is the employment of DTI instead of DWI. There are a few studies trying to employ DTI in the diagnosis of liver fibrosis and inflammation [1, 16]. Taouli et al., in their pioneer study, reported a sensitivity of 78.3% and a specificity of 69.2% in distinguishing patients with fibrosis stage1 from the patients with a higher fibrosis stage using an ADC value of 1.36 as cut-off [1]. They also reported that they did not take the advantage of calculating anisotropy with DTI, since it was previously shown that the liver has a near isotropic diffusion. Very recently, Tosun et al., reported in their study that ADC values showed a trend toward lower values and Fa values showed a trend toward higher values with increasing fibrotic stage, however, without statistically significant correlation [16]. They also reported that ADC values showed a trend toward lower values and Fa values showed a trend toward higher values with increasing inflammatory score. Although, our results are parallel to those of Tosun et al's., we need to note that the histopathological evaluation method we employed was different. We determined HAI scores and fibrosis scores according to Knodell et al, although Tosun et al. used METAVIR system.

Furthermore, we tried to correlate HAI scores with ADC and Fa values, not the inflammation scores. Our results showed that using Fa values in the diagnosis of liver fibrosis and inflammation might have an additional advantage. In our study, using a Fa value of 0.59 as cut-off value, the sensitivity and specificity of DTI in distinguishing patients with fibrosis score 1 from the patients with fibrosis score 3 were 90.9% and 100%, respectively. Although, liver biopsy is the gold standard in the diagnosis and the most valuable method used in the management of patients with chronic hepatitis, being an invasive procedure it may have minor to major complications. Furthermore, it may not be easily accepted by patients. Therefore alternative non-invasive and reliable approaches to diagnose and follow-up of liver fibrosis are needed. In our understanding DTI might be a promising tool in this regard. ADC and Fa values are biomarkers that need to be further evaluated.

Nevertheless, our study has several limitations. First, it is a retrospective study that has intrinsic shortcomings. On the


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contrary of a prospective study, the medical management was not changed according to neither Fa nor ADC values for none of the patients. Second, as mentioned before, because this is a retrospective study, there was a relatively long time interval between the histopathological evaluation of the liver biopsies and the MR imaging of the patients. Despite this fact, we could still get statistically significant results. Third, we were not able to include any patients with fibrosis score 4 in this study. Nevertheless, as we mentioned above, a clear separation of patients with fibrosis score 1 from those with fibrosis score 3 is crucial in terms of clinical decision making [13, 15]. Patients with score 4 fibrosis (cirrhosis) are typically diagnosed using laboratory and conventional imaging findings and do not constitute a real diagnostic challenge for gastroenterologists. Fourth, our study population was relatively small. However, we still reached statistically significant results.

In conclusion, Fa and ADC values obtained by employing DTI might be promising quantitative biomarkers that can be used in the management of patients with liver fibrosis due to chronic hepatitis. Prospective studies with larger patient populations are needed to support our preliminary results.

### Compliance with Ethical Standards

**Ethical Approval:** This study was approved by Şişli Etfal Training and Research Hospital Ethics Committee. (Protocol number:401). All methods were performed in accordance with the relevant guidelines regulations.

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

**Authors' Contribution**: Concept: OYU, ASM and SME, Data collection and planning: MSB, Data collection and analysis: CA, BYO, YA, Analysis and evaluation: AO, MB, Literature review and planning: HO, Critical review: SME, Final approval: all the authors.

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# Comparison of the effects of intraoperative morphine, fentanyl or paracetamol administration on postoperative pain level and analgesic consumption in patients with synchronous intraoprative remifentanil infusion

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ABSTRACT

Objective: We aimed to compare the effects of morphine, fentanyl or paracetamol applied for anesthesia induction and at the end of the surgery for postoperative pain control and analgesic consumption in patients who have undergone pelvic and lower abdominal surgery.

Material and Methods: Patients with the American Society of Anesthesiologists (ASA) score I-II and aged between 18-70 years were given intravenous remifentanil intraoperatively. Fentanyl was administered in doses of 1.5 mcg / kg during anesthesia induction and 10 min before the end of the surgery. In fentanyl group, morphine was administered in doses of 0.1 mg / kg during induction and 0.5 mg/kg 30 min before the end of the surgery and paracetamol was administered in doses of 10 mg/kg during induction and 5 mg/kg 30 min before the end of the surgery. Morphine was administered for patient-controlled analgesia.

Results: The mean verbal pain scores of the paracetamol group were significantly higher when compared to the pain scores of the other groups at the 0, 1, 2, 3, 4, 8, 12, and 16 hours ($p < 0.01$ , $p = 0.02$). Postoperative morphine consumption in the paracetamol group was significantly higher ($p = 0.02$).

Conclusion: The addition of intraoperative paracetamol to the remifentanil infusion, may not be sufficient in postoperative analgesia in gynecologic cancer surgery.

Keywords: Morphine, Paracetamol, Fentanyl, Postoperative pain.

## INTRODUCTION

Postoperative pain is an acute form of pain that begins with surgical trauma and ends with tissue healing. In the postoperative period, many physiological responses including various systems develop with acute pain. In this respect, pain relief provides metabolic and endocrine stress response, reduction of thromboembolic complications, preservation of cognitive functions, shortening of mobilization and rehabilitation period, reduction of hospital stay and cost, and prevention of chronic pain.

Nowadays, opioids, non-opioids and local anesthetics are used in the treatment of postoperative pain. Opioids are the primary drugs used for this purpose. Systemic opioids should be used preoperatively, intraoperatively and postoperatively for effective postoperative analgesia management.

Remifentanil is a short-acting opioid. Intraoperative use of remifentanil has no effect on pain control in the postoperative period. Morphine is a strong, natural, μ receptor agonist opioid, commonly used in postoperative pain management. Fentanyl is a synthetic opioid with strong analgesic activity than morphine. Paracetamol inhibits prostaglandin synthesis via central cyclooxygenase (COX) inhibition in the central nervous system, and also shows analgesic activity by its indirect effects on serotoninergic system. It was introduced into clinical use in 2002 and has been shown to be effective in the treatment of postoperative pain in various clinical studies [1].

In our study, we aimed to compare the effects of morphine, fentanyl or paracetamol administered in addition to remifentanil infusion at anesthesia induction and postoperative use on pain control and analgesic consumption in the postoperative period on patients who have undergone pelvic and lower abdominal surgery with vertical incision due to gynecological cancer (endometrium or ovarian cancer).

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## PATIENTS and METHODS

The study was approved by the Istanbul University Cerrahpasa Ethics Committee (C-002) on 12 January 2010. Sixty patients aged between 18-70 years with the American Society of Anesthesiology (ASA) score I-II were included in the study. Informed consent was obtained from the patients. Patients with a history of alcohol and drug addiction, pregnant women and obese patients with a body mass index above 35 kg / m2, suffering from chronic pain, who were undergoing revisional surgery and who had radiotherapy previously were excluded from the study.

After the patients were taken to the operating room, standardized monitoring was performed including heart rate (HR) and electrocardiography (ECG), non-invasive systolic blood pressure (NIBP), diastolic blood pressure (BP) and peripheral oxygen saturation (SpO2). Lactated ringer infusion was started at a rate of 4 ml / h by opening a 20 G intravenous vascular access through the left hand. Sixty patients were randomly divided into 4 groups by closed envelope method. Midazolam 2 mg was administered intravenously (iv) to the patients. During anesthesia induction 1 mcg / kg iv remifentanil in the remifentanil group (Group R), 1.5 mcg / kg iv fentanyl in the fentanyl group (Group F), 0.1 mg/ kg morphine in the morphine group (Group M) and 10 mg / kg paracetamol in the paracetamol group (Group P) were administered. At the end of the surgery 1.5 mcg/kg fentanyl 10 minutes before surgical closure in Group F, 0.05 mg/kg morphine 30 minutes before surgical closure in Group M, 5 mg/kg paracetamol 30 minutes before surgical closure in Group P were administered as additional doses. All groups received iv remifentanil at the infusion rate of 0.1 mcg / kg / min intraoperatively. Age, ASA score, weight, height and body mass index (BMI) of the patients and operation time were recorded.

During anesthesia induction, 2 mg / kg propofol was given to the patients and neuromuscular block was provided with 0.8 mg / kg rocuronium bromide and orotracheal intubation was performed. After tracheal intubation, anesthesia was maintained with 50% 02-air mixture (0.5-1 MAK) with desflurane. Mechanical ventilation was performed with tidal volume 6-8 ml / kg and respiratory rate 10-14 / min (ETC02 35-40 mm Hg). Intermittent 10 mg of rocuronium bromide was given as a bolus dose if needed to ensure neuromuscular block. Hypotension was evaluated as systolic arterial pressure <80 mm Hg or a decrease more than 20% at baseline value, and was treated with 5 ml / kg iv fluid infusion, 20% reduction in inhalation anesthesia, decrease of remifentanil infusion rate and 5 mg ephedrine bolus administration respectively. Bradycardia was evaluated as heart rate <50 beats / min and corrected with 0.5 mg atropine iv injection. Intraoperative tachycardia and hypertension were evaluated as superficial anesthesia after exclusion of other causes and iv 1 mcg / kg bolus remifentanil was administered.

In the postoperative period, patient controlled analgesia (PCA) method was prepared with 1 mg / ml morphine, and 1 mg PCA dose was administered with a lock time of 5 minutes. Postoperatively, all patients were observed in the Post-Anesthesia Care Unit (PACU) for 24 hours. A 4 h limit dose of 300 mcg/kg was applied to the patients during iv PCA usage.

In PACU, each patient's BP, HR, and SpO2 were recorded once per hour. Preoperative pain scale called verbal rating scale (VRS) numbered 0 to 4 was described to the patients [1]. This assessment was recorded once as soon as the patients were extubated and admitted to PACU, and at 1, 2, 3 and 4 hours after arriving PACU and every 4 hours thereafter. After admission to PACU, sedation levels were evaluated according to the number of alertness levels numbered from 1 to 5 [2]. This assessment was recorded once at the 1st, 2nd, 3rd and 4th hours in PACU and every 4 hours thereafter.

Nausea and vomiting were recorded during a 24-hour observation. Nausea and vomiting were treated with 4 mg ondansetron iv. A 24-hour morphine consumption at PACU was recorded.

The primary endpoint of our study was the VRS (2 and below), and the secondary endpoint was postoperative morphine consumption.

### Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows 17.0 was used for statistical analysis. Descriptive statistical methods (Mean, Standard deviation, Frequency, Percent) as well as qualitative data were compared using the chi-square test.

In the comparison of quantitative data; One way ANOVA was used for the comparison of the parameters between the groups. Repeated Measures ANOVA was used for intragroup comparisons of the parameters. P <0.05 was considered as statistically significant.

## RESULTS

There was no significant difference between the groups in terms of age, weight, height and BMI (Table I).

**Table I.** Demographic data according to groups

| Groups | Group P | Group M | Group F | Group R | p |
|---|---|---|---|---|---|
| Age (year±SS)* | 47.5±10.1 | 50.8±13.1 | 49.2±13.3 | 53.9±15.5 | 0.6 |
| BW(kg±SS)* | 70.8±10.2 | 69.4±9.0 | 70.2±14.4 | 68,1±12.5 | 0.9 |
| Height (cm±SS)* | 160.2±6.9 | 158.6±5.3 | 159.1±7.4 | 155.3±7.8 | 0.2 |
| BMI(kg/m$^2$±SS)* | 29.2±4.9 | 29.7±6.3 | 28.0±6.2 | 28.4±7.3 | 0.9 |

BW: Body weight, BMI: Body mass index
*: Data are presented as ± standard deviation

The mean VRS was significantly higher in Group P than in Group M, Group F and Group R at the 0, 1, 2, 3, 4, 8, 12, and 16 h measurements postoperatively (p <0.01, p = 0.02). The difference between the groups in terms of VRS levels was not statistically significant at 20th and 24th hours (p = 0.21, p = 0.09) (Table II) (Figure1).


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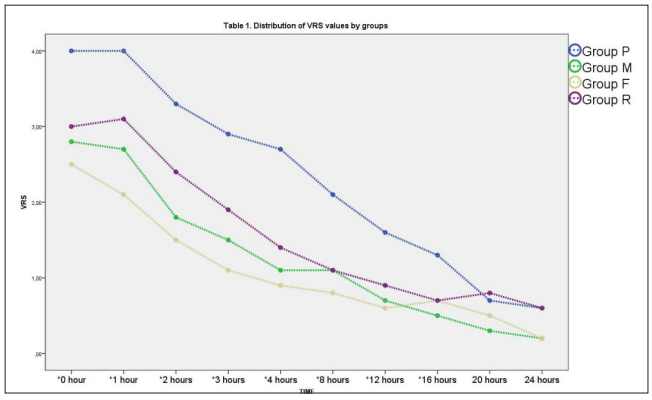


**Figure1.** Verbal rating scale scores according to groups/ Graph of verbal rating scale and timing

**Table II.** VRS scores according to groups

| VRS | Group P | Group M | Group F | Group R | p |
|---|---|---|---|---|---|
| 0 h | 4.0±0.0 | 2.8±0.8 | 2.5±0.8 | 3.0±0.9 | 0.00 |
| 1th h | 4.0±0.0 | 2.7±0.8 | 2.1±0.9 | 3.1±0.9 | 0.00 |
| 2.nd h | 3.3±0.9 | 1.8±0.7 | 1.5±0.9 | 2.4±1.1 | 0.00 |
| 3.rd h | 2.9±0.6 | 1.5±0.6 | 1.1±0.6 | 1.9±1.1 | 0.00 |
| 4.th h | 2.7±0.6 | 1.1±0.6 | 0.9±0.8 | 1.4±0.9 | 0.00 |
| 8.th h | 2.1±0.5 | 1.1±0.8 | 0.8±0.7 | 1.1±0.7 | 0.00 |
| 12.th h | 1.6±0.6 | 0.7±0.5 | 0.6±0.6 | 0.9±0.7 | 0.00 |
| 16.th h | 1.3±0.0 | 0.5±0.6 | 0.7±0.8 | 0.7±0.5 | 0.02 |
| 20.th h | 0.7±0.0 | 0.3±0.7 | 0.5±0.5 | 0.8±0.8 | 0.21 |
| 24.th h | 0.6±0.8 | 0.2±0.4 | 0.2±0.4 | 0.6±0.6 | 0.09 |

VRS: Verbal rating scale
Data are presented as ±standart deviation

Postoperative morphine consumption levels of Group P were significantly higher than Group M and Group F (p = 0.02) (Table III).

**Table III.** Morphine consumption according to groups

| | Group P | Group M | Group F | Group R | p |
|---|---|---|---|---|---|
| Morphine consumption (mg ±SS)* | 45.9±12.6 | 30.1±19.1 | 29.7±20.8 | 35.9±8.9 | 0.02 |

*: Data are presented as ±standard deviation

Intraoperative remifentanil consumption was (mcg/kg/dk) 0.14 (±0.1), 0.12 (±0.5), 0.12 (±0.9), 0.12 (±0.5) in P,M,F and R groups respectively and this was statistically insignificant between groups (p>0.05).

There was no significant difference between the groups in terms of postoperative nausea and vomiting (Table IV).

The mean sedation score was significantly lower in Group R than Group M, Group F, and Group P at the 0th hour (p <0.01). The mean sedation score was significantly lower in Group P than Group M and Group F (p <0.01).

There was no statistically significant difference between the groups in terms of heart rates levels at the 1st, 2nd, 3rd, 4th, 8th, 12th, 16th, 20th and 24th hour measurements (p> 0.05).

The mean arterial pressures between the groups were not statistically significant at the 1st, 2nd, 3rd, 4th, 8th, 12th, 16th, 20th and 24th hour measurements (p> 0.05).

There was no significant difference between the groups in terms of operation and anesthesia time (p> 0.05).

## DISCUSSION

Acute postoperative pain is still a research area among anesthesiologists. Effective postoperative analgesia leads to a reduction in morbidity and hospitalization time due to stress and anxiety. In studies on postoperative analgesia, opioids are used as the main drug of perioperative analgesia. In our study, the mean VRS of patients in Group P was significantly higher compared to Group M, Group F and Group R. In our study, VRS score was 2 or less in Group F patients at the 1st hour and after, and postoperative morphine consumption was similar between Group F and Group M patients.

Previous studies have shown that intraoperative use of fentanyl provides effective postoperative analgesia [3]. In Kochs et al. study, 553 patients who underwent elective major abdominal surgery were given 150 mcg fentanyl or 15 mg morphine 20 minutes before the end of the surgery and they had a sufficient analgesia [4]. The results of our study show similarity with the studies comparing the efficacy of morphine and fentanyl on postoperative pain level. In our study, no significant difference was found between postoperative VRS scores in patients receiving intraoperative morphine or fentanyl.

Claxton et al. used morphine and fentanyl for postoperative analgesia in daily surgical procedures; and reported that the use of morphine and fentanyl for acute postoperative pain treatment in PACU after surgery provided an equivalent level of analgesia, and visual analogue scale scores were higher in the fentanyl group in patients who were referred to the ward after 50 minutes [5]. In addition, patients in the fentanyl group used a higher dose of oral analgesics in the surgical ward. This is a predictable outcome given for the duration of action of fentanyl and morphine. In our study, the difference between postoperative VRS scores in the morphine and fentanyl groups was not statistically significant. The patients in Group F had a VRS score of 2 or less at the postoperative 2nd hour and after, similar to Group M. In our study, we applied postoperative iv morphine PCA for postoperative pain treatment to both groups. Postoperative morphine consumption was similar in both groups. Therefore, in our study, we think that VRS level in Group F lasts as long as Group M, which may be due to morphine use in the postoperative period.

Paracetamol is a non-opioid analgesic with a low incidence of side effects and drug interaction. There are less adverse effects such as platelet dysfunction, nephrotoxicity, gastrointestinal side effects, agranulocytosis and sodium retention compared to NSAIDs. Hepatotoxicity and hepatic insufficiency, which are


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the most important side effects, are not observed unless the recommended doses are exceeded [6]. Previous studies have shown that although opioid is used for induction of anesthesia, paracetamol including abdominal surgery, can provide effective postoperative analgesia in patients undergoing abdominal surgery. In most of these studies, paracetamol was compared to NSAID drugs [7-10]. Some clinical studies have shown that intravenous paracetamol may provide postoperative analgesia similar to morphine and is tolerated more easily [11-13]. These results are not consistent with our study. In these studies, paracetamol was administered as proparacetamol and administered at a dose of 2 g iv [11-13]. Van Aken et al., concluded that the reason for the equivalent effect of paracetamol and morphine in the treatment of postoperative pain was due to the low number of patients and the insuciffiency of the power of in their study [12]. In our study, we did not give opioids to patients in Group P intraoperatively except for remifentanil infusion. We also compared paracetamol with opioids with strong analgesic activity and applied these opioids in the pre-extubation period in addition to anesthesia induction. As a result of our study, we believe that paracetamol may be insufficient to provide effective postoperative analgesia in patients undergoing lower abdominal and pelvic surgery without additional opioid analgesia. However, in the current study patients in Group P had higher VRS scores and morphine consumption compared to Group R. In a previous study, intraoperative remifentanil infusion was found as effective as fentanyl administration and authors declared that remifentanil had any hyperalgesic effect [2]. In the same study, it was presented that remifentanil may have an analgesic effect up to 60 minutes [2]. In addition, another study comparing the analgesic effects of remifentanil and paracetamol, pain scores did not differ significantly between groups [14]. Remifentanil has a more stronger analgesic effect compared to morphine [14]. In accordance with previous studies, Group R provided a sufficient analgesia in our study. We divided an effective paracetamol dose into two; one dose during anesthesia induction another dose at the end of the surgery. We think that the reason why paracetamol was not as effective as remifentanil in our study may be due to the use of a higher dose at the beginning of the surgery. However, the analgesic effect of dividing paracetamol into two doses should be researched in further studies.

Opioids are known to cause nausea and vomiting [4, 8, 15-17]. In our study, we did not find a significant difference between the groups in terms of nausea and vomiting rates. We think that this may be due to insufficient number of patients included in the study.

One limitation of our study was that paracetamol was used only intraoperatively. This may cause a confusion evaluating the effect of paracetamol on postoperative pain treatment. Postoperative analgesic effects of opioids used in the study have long-term effects. However, the routine dose of paracetamol in postoperative pain treatment is administered at 4-6 hour intervals [18].

In the first 16 hours, VRS values were found to be significantly higher in patients receiving paracetamol in addition to remifentanil infusion to provide postoperative analgesia in gynecologic cancer surgery.

As a conclusion; postoperative morphine consumption was significantly higher in patients receiving paracetamol for postoperative pain treatment compared to fentanyl and morphine groups.

In the postoperative period, no complications developed related to the drugs used intraoperatively.

We suggest that intraoperative paracetamol used in addition to remifentanil infusion in gynecologic cancer surgery may not be sufficient to provide postoperative analgesia.

We believe that this issue should be investigated in prospective, clinical, randomized studies in the future.

### Compliance with Ethical Standards

**Ethical Approval:** This study was approved by Istanbul University Cerrahpasa Ethics Committee (C-002) on 12 January 2010.

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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.

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