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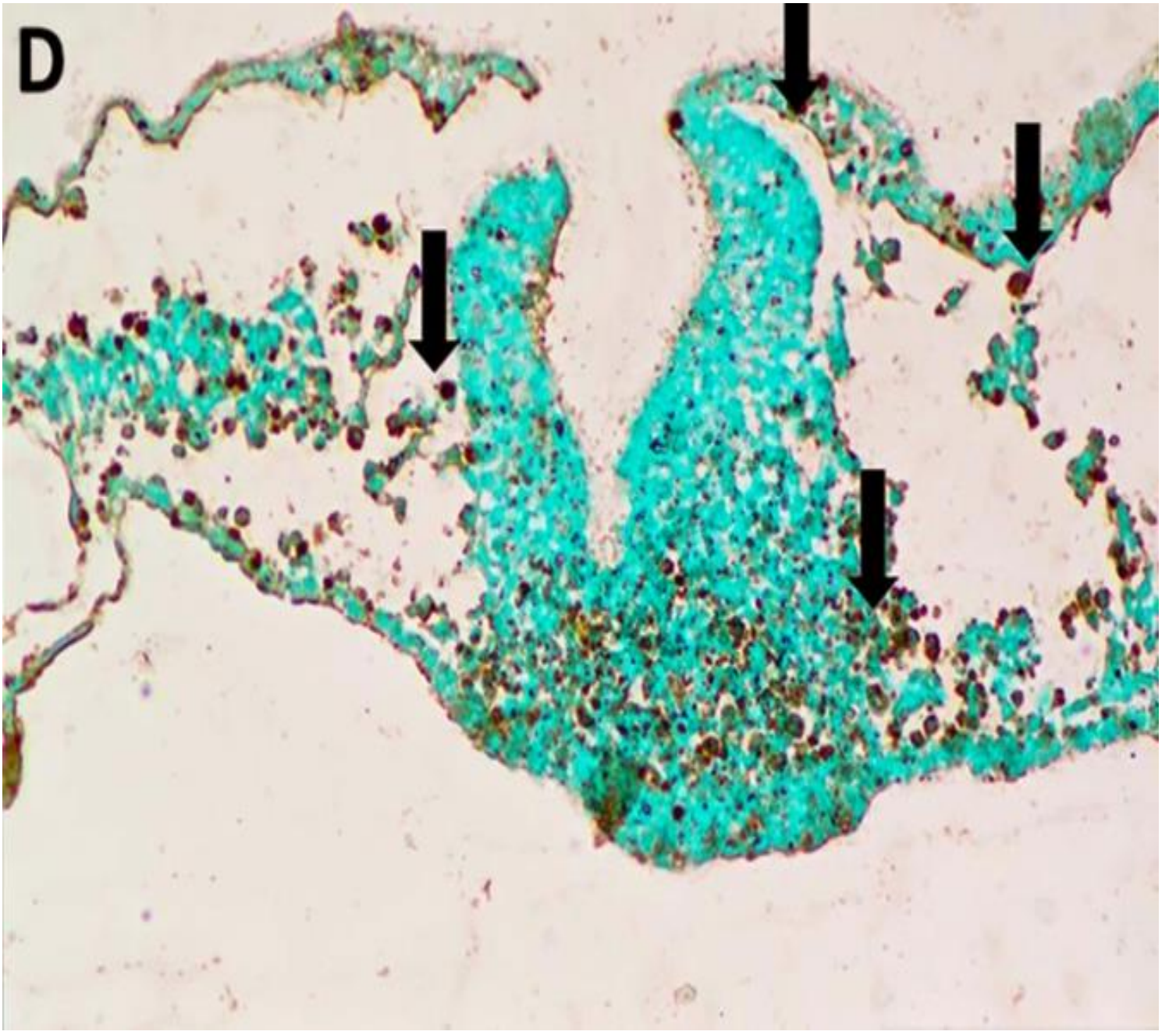

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Contents

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Uterosacral Ligament Dissection during McCall Culdoplasty to Prevent Ureteral Kinking, and Round Ligament Fixation to Support Vaginal Vault: A New Surgical Technique

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ABSTRACT

Objective: This study aims to describe a new surgical technique to prevent ureteral kinking via dissection uterosacral ligament from parietal peritoneum before McCall culdoplasty suture placement, and vaginal cuff fixation to round ligament to prevent apical vaginal vault prolapse after vaginal hysterectomy.

Materials and Methods: At the initial step of vaginal hysterectomy, a circumferential incision was done on vaginal tissue, which covers the uterine cervix. Then posterior cul-de-sac was entered. Bilateral uterosacral ligament was identified, separately clamped, cut and sutured. Classical vaginal hysterectomy was completed up to the round ligament, which was separately grasped, cut and sutured. After the vaginal hysterectomy, the uterosacral ligament dissected from cardinal ligament and parietal peritoneum to prevent ureteral kinking during McCall Culdoplasty suture placement. Two internal McCall sutures with non-absorbable sutures and one external suture with absorbable sutures were place on the uterosacral ligament. Then bilateral apical lateral vaginal walls were fixated to ipsilateral round ligament to further support to vaginal vault.

Results: I have applied the new technique to my patients with pelvic organ prolapse for about one year. Ureteral kinking has not occurred in any patient. Early complications such as hemorrhage, bladder and ureter injury did not observed.

Conclusion: Ureteral kinking is a challenging problem for gynecologists during suture placement on the uterosacral ligament. Dissection of the uterosacral ligament from the cardinal ligament and parietal peritoneum yielded the surgeon to safe suture passage during McCall Culdoplasty suture placement and eliminated the requirement of cystoscopy evaluation to check ureteral competency.

Keywords: McCall Culdoplasty, Pelvic organ prolapse, Round ligament, Uterosacral ligament, Vaginal hysterectomy

INTRODUCTION

Development vaginal vault prolapse after pelvic organ prolapse surgery is still challenging issue to the surgeon. To prevent vaginal vault prolapse performing McCall Culdoplasty provides additional apical support to the vaginal vault. After the operation of McCall Culdoplasty, cystoscopic evaluation of ureteral flow is necessary to observe ureteral kinking does not occur. Dissection of the uterosacral ligament (USL) from the cardinal ligament and parietal peritoneum provides isolation of ligament, prevents ureteral kinking, and eliminates cystoscopy requirement after operation. Fixation of the lateral vaginal fornixes with the cardinal ligament to the round ligament provides additional support to the vaginal apex.

The aim of the article is to describe a new surgical technique to prevent vaginal vault prolapse after pelvic organ prolapse (POP). The presented new surgical technique prevent ureteral kinking during McCall Culdoplasty suture placement and provide opportunity to the surgeon to eliminate cystoscopy requirement after McCall Culdoplasty. Additionally fixation of the apical lateral vaginal wall with cardinal ligament to the round ligament provides additional apical support.

Short Communication

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MATERIAL AND METHODS

The study was performed in Antalya Training and Research Hospital, Clinic of Obstetrics and Gynecology. The local ethics committee approved the study and it was performed in accordance with the ethical standards described in Declaration of Helsinki. Informed consent was obtained from the patient to use information, pictures, and video presentation.

In the initial of the vaginal hysterectomy, a circumferential incision was done vaginal tissue that covers the uterine cervix. Bladder tissue was dissected from the uterine cervix. The posterior cul-de-sac was entered with sharp dissection. Left and right side vaginal tissue, which cover the uterine cervix, were dissected from the uterosacral ligament (USL) and the cardinal ligament. The left USL was identified, grasped with a Heaney clamp, cut, and sutured with number 1 vicryl (an absorbable suture polyglactin 910) (**Figure1**).

Figure 1: Grasping, cutting and suturing the left uterosacral ligament.

The free end of the thread was held with a clamp. After that, the cardinal ligament was grasped with a clamp, cut, sutured, and the free end of the thread was held. The same surgical procedure was performed on the right side of the uterus. Anterior visceral peritoneum opened with sharp dissection. Following this, the left broad ligament and the uterine artery were clamped, cut, and sutured as classical hysterectomy. When the surgical procedure reached to the uterine fundus, the round ligament was identified, separately clamped, cut, sutured, and separated from the broad ligament. The free end of the suture thread was held with a mosquito forcep. After this, the utero-ovarian ligament and the fallopian tube were clamped together with Heaney clamp, cut, sutured, and ligated. The free end of the suture thread was held. The same surgical procedure was done right side of the uterus, and vaginal hysterectomy was completed. After vaginal hysterectomy, to repair of anterior vaginal wall prolapse (cystocele), the vaginal tissue was incised vertically and dissected from bladder fascia. This surgical maneuver allows the surgeon to better visualization of the pelvic region. Then surgery turned to the pelvic phase. Bilateral retrograde salpingo-oophorectomy was done as described by Kaba (1) in eligible patients, in which there was no contraindication.

To perform McCall Culdoplasty, the USL was pulled medially and inferiorly, the cardinal ligament pulled laterally, and superiorly withheld threads. The parietal peritoneum between them was dissected with scissors to separate the USL from the cardinal ligament. Then the uterosacral ligament was separated from the parietal peritoneum and loose connective tissues up to spina ischiadica. At the level of spina ischiadica, the ureter could be palpated in the dissected region. The separation of the USL serves the surgeon to the security of the ureter during McCall suture placement, prevents ureteral kinking, and eliminates cystoscopy requirements after operation. The same procedure was done on the right USL. To place first internal McCall suture, the needle was passed approximately 2 cm near to the spina ischiadica with non-absorbable 2-0 polypropylene suture on the left USL (**Figure2**).

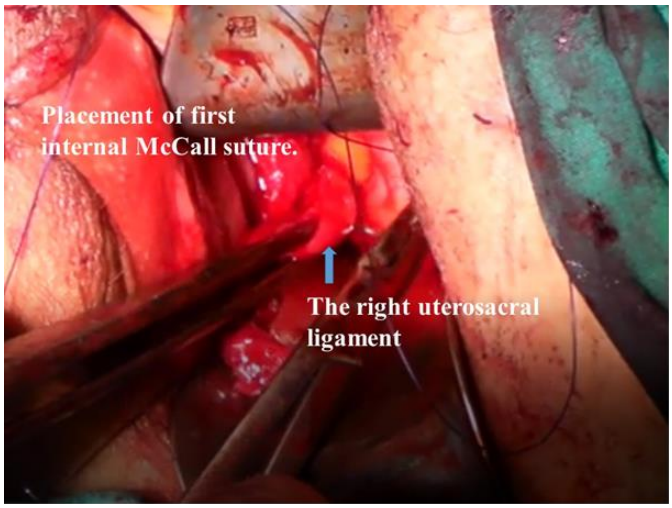

Figure 2: Placement of first internal McCall suture.

Then the needle was passed cul-de-sac peritoneum, and to the right USL. The second suture was placed approximately two cm distal of the first suture similarly. To place external McCall suture, a number 1 vicryl suture was passed through the posterior vaginal wall, the parietal peritoneum, left side uterosacral ligament, cul-de-sac peritoneum, right uterosacral ligament, the parietal peritoneum and vaginal wall. All three sutures were held with mosquito clamps. Later a number 1 vicryl suture was passed left lateral posterior vaginal wall, the free-end of the cardinal ligament. After that, the round ligament was pulled outward, and the needle was passed through the body of ligament approximately 2 or 3 cm away from free-end of the ligament, and then the anterior lateral vaginal wall (**Figure3**). The free-end of the thread was held. The same suture placement was done to the right side of vaginal apex.

After these, anterior vaginal wall incision was closed with 2-0 vicryl following Kelly's plication. Then the two internal McCall sutures were ligated. The apical vaginal wall was closed with number 1 vicryl by the locked manner. Finally, the two apical lateral vaginal round ligament fixation sutures and external McCall sutures were ligated. Surgery was completed with posterior colporrhaphy.

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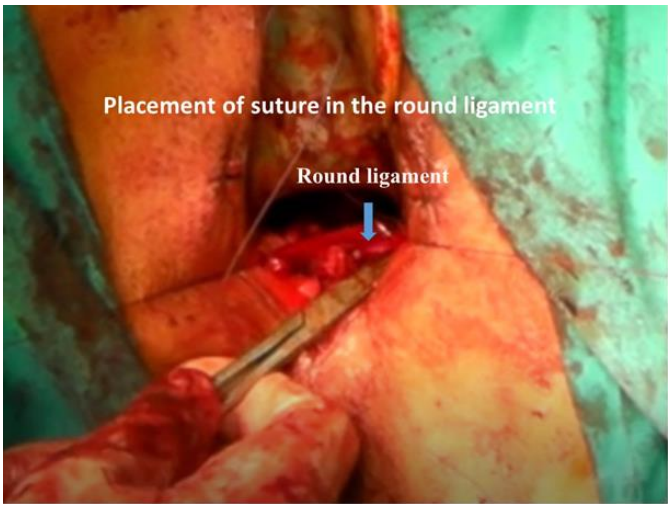

Figure 3: Placement of suture in the round ligament

RESULTS

I have performed the new surgical technique on my patient with pelvic organ prolapse. The technique was repeatable and suitable for all patients. Renal pelvic anatomy and ureteral curses were evaluated with ultrasonography to check pelvic dilatation and ureteral kinking at the second day after the operation. No early surgical complications such as ureteral kinking, or hemorrhage, which needed to reoperation, were developed.

Until now, no patient has applied to the clinic with vaginal vault prolapse or any other complication related to operation. In the presented case/video pelvic organ prolapse was not observed four months after operation (**Figure4**).

Figure 4: No vaginal vault prolapse was seen at fourth month control of patient.

DISCUSSION

The new surgical technique has performed to all patients without complication. Dissection of the USL supplied better visualization and safe suture placement, prevent ureteral kinking, and eliminate cystoscopy requirement after the operation. Fixation of the lateral vaginal wall to the round ligament supplies additional apical vaginal support.

Further studies are needed to evaluate the repeatability and effectiveness of this new surgical technique.

Acknowledgments: I want to thank Gokhan Pekdemir for helping the video editing process without getting any financial benefit.

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Author Contributions: MK: Study design, Literature review, Data collection and processing, Surgery **MK:** Writing, Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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The Role of Educational Interventions in Improving the Quality of Life of Cancer Patients: Review the Literature

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ABSTRACT

Objective: Being diagnosed with cancer can be very distressing for patients and may have an impact on the emotional and physical aspects of their lives, both at the time of diagnosis and throughout their treatment. Studies have shown that reduced quality of life has a detrimental effect on disease progression and is related to feelings of hopelessness and helplessness. Educational interventions, for example, self-care education or educating the 'caregiver's family were related to an improved quality of life after cancer treatment. The objective of this article is to review the clinical research articles focused on implementing educational interventions as a means to improve the ""Quality of Life"" [QoL] of cancer patients.

Material and Methods: The data in this study were collected from Scopus, Med line, Science Direct and Hinari databases. An in-depth search and advanced search of keywords ``Quality of life"", "Cancer Patients", "education ", “Oncology Patients", “Patients with Cancer“, “Quality of life”, “Intervention” was executed based on Inclusion and exclusion criteria. A total of 291 articles were identified. The final 13 articles were included in the review.

Results: All analyzed studies have included some educational component in their intervention plan, during or after the cancer treatment. Patient education included different aspects like nutrition counseling, diet plan, and prevention of side effects related to cancer treatment in patients by patient self-care and education. Muscular progressive relaxation techniques were used to counteract nausea and emesis. Music was used to distract the patients throughout the whole chemotherapy treatment as well as before and after. One of the main elements of the self-care education was training about nutrition. Educational techniques such as instructing to perform abdominal massage, abdominal exercises to manage emesis and constipation associated with treatment, educational interventions also included daily text-messeges and web based education. Out of 13 studies analyzed, 10 showed a positive outcome.

Conclusion: We can conclude that educational interventions may be useful in maintaining and improving cancer patients` quality of life.

Keywords: Quality of life, Cancer, education, Oncology , Intervention

Review Article

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INTRODUCTION

With an increasing incidence of both cancer and survival rates worldwide, due to early screening options available and with the advancement of cancer treatment in many countries, there is also a requirement to focus not only on the pharmacological treatment of cancer, but also to consider the patient's quality of life after their treatment. Being diagnosed with cancer can be very distressing for patients and may impact emotional and physical aspects of their lives, both at the time of diagnosis and throughout their treatment (1). Patients may worry about the effect of the disease on their body, treatment options and the side effects of treatment, such as nausea, vomiting, and diarrhea; all of which can cause anxiety, fatigue, loss of appetite, constipation, Insomnia, and emotional changes (2, 3, 5, 6). Symptoms and their severity vary from patient to patient (4). Maintaining and improving the quality of a patient’s life not only benefits the patient but can additionally decrease the burden on their caregivers (7). Over the years, the quality of life(QoL) has been an assessment of the patient’s health-related quality of life(QoL), and it is changing to encompass all aspects which can be proven to affect a patient’s physical and mental health (8).

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Studies have shown that reduced quality of life has a detrimental effect on disease progression and is related to feelings of hopelessness and helplessness (10). The cancer burden significantly imposes stress not only on the patients, but also on their spouses (9). Educational interventions, for example self-care education or educating the caregiver's family were related to an improved quality of life after cancer treatment (7, 9). One possible reason for a decreasing QoL among cancer patients was unanswered questions and an uncertain future (11). Providing sufficient information about the treatment, along with the side effects and self-care strategies, has proven to decrease some treatment-related complications and psychosocial outcomes (11, 12). Patient education by using verbal, written, or audiovisual formats could help them to understand and manage cancer-related fatigue (13, 14, 15, 16). The objective of this review article is to review the clinical research articles focused on implementing educational interventions as a means to improve the"QUALITY OF LIFE" (QoL) of cancer patients.

MATERIAL AND METHODS

The current article is a review study. The data in this study was collected from Scopus, Med line, Science Direct and Hinari databases. An in-depth search and advanced search of keywords ``Quality of life", "Cancer Patients", `education`` "Oncology Patients", "Patients with Cancer Quality of life", "Intervention", and "Chemotherapy" was executed based on Inclusion and exclusion criteria. Inclusion criteria of article selection included the following: Articles published 2010-2020, Articles in English, Research articles, Full-text Open access, quality of life as primary/secondary outcome, Adult solid cancer patients Educational interventions. A total of 291 articles were identified, out of which: 228 were removed at abstract screening, 28 were removed at title screening, and 21 were removed on full-text screening. The final 13 articles were included in the review (**table1**). The results were broken down and analysed based on the Symptoms and negative effects of cancer treatment addressed, Educational Interventions used, QOL ASSESSMENT TOOLS used. Studies with positive and negative outcomes are analyzed separately. We summarized the finding on the **table 2**. Thirteen articles were obtained after an in-depth and advanced search from different articles and databases from 2010 to 2020 by applying the inclusion and exclusion criteria of our study. All of these articles were clinical trials conducted on patients undergoing cancer treatment to analyze the effect of related treatment side effects on quality of life.

RESULTS AND DISCUSSION

Studies included mostly breasts, CNS, GI, colorectal and lung cancer patients (1, 4, 5, 10, 17). Different symptoms/effects of cancer treatment that may have a detrimental effect on the QoL of cancer patients were addressed in the studies. Breast cancer was the most common studied disease in the studies analyzed (6, 9, 11, 15, 16). Studies have suggested that breast cancer treatment is related to symptoms, such as emesis and constipation, which may affect the patient's quality of life, while using serotonin antagonists as antiemetic treatment may promote constipation (6). Other patients reported lymphedema, pain, restricted range of motion in their shoulders and arms, as well as arm weakness after surgery (1). Nausea and vomiting are the main symptoms reported in GI, breast, and lung cancer patients after receiving chemotherapy, which leads to a decrease in quality of life (1, 4, 10). Fatigue was also one of the self-reported symptoms (1, 5). In a study of colorectal cancer, Late radiotherapy toxicity symptoms such as flatulence, abdominal distension, and diarrhea were also addressed, affecting the quality of life mainly in nutrition deteriorated patients (17). Lung cancer patients were noted to have fatigue, loss of appetite, shortness of breath, cough, pain, and bloody sputum, which are distressing to the patient (10) Gynecological cancer patients receiving chemotherapy also reported a decrease in their quality of life in terms of physical and social activities (18). Patients who are treated with chemotherapy frequently have a sarcopenic weight gain, which also has a deleterious effect impact on quality of life (10). Quality of life is further worsened by concomitant depression and anxiety, which are very common in patients at the time of diagnosis, as well as after the treatment (19)

Educational Interventions

Various kinds of interventional methods were used to reduce the side effects of the treatment received by the patient. The interventional methods included patient health education, physical training, nutritional counseling, different self-care techniques, psychological support, physiotherapy to improve the patient's overall quality of life(QoL,) (4, 5),.and also providing caregivers and spousal support for better handling of the situation, to cope with the stress and thereby improve quality of life of the patient., (7, 9). All studies analyzed have included some educational component in their intervention plan, during or after the cancer treatment. Patient education included different aspects like nutrition counseling, diet plan, and prevention of side effects related to cancer treatment in patients by patient self-care and education.

Table 1: Searched literature sources

	Medline	Scopus	Hinari	Science Direct	Summary
Total records identified	25	83	90	93	291
Records removed at abstract screening	21	66	73	66	226
Records removed at title screening	2	4	9	13	28
Records removed at full-text screening	1	4	5	11	21
Studies included in systematic review	1	6	3	3	13

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Table 2: Literature Samples

#	Authors	Title	Diagnoses	Intervention	QOF assessment Tools	outcomes
1	Jun Xie1 , Tingli Zhu2* ,Qun Lu	The effects of add-on self-care education on quality of life and fatigue in gastrointestinal cancer patients undergoing chemotherapy	GI cancer	Visual aids, muscular progressive relaxation techniques, nutritional training	EORTC quality of life questionnaire QLQ-C30.	positive
2	Chi-Chin Huang1 & Han-Pin Kuo2,3 & Yueh-E Lin1,4	Effects of a Web-based Health Education Program on Quality of Life and Symptom Distress of Initially Diagnosed Advanced Non-Small Cell Lung Cancer Patients: A Randomized Controlled Trial	NSCLC	Web-based health education program	EORTC quality of life questionnaire QLQ-C30.	positive
3	Paula Ravasco, Isabel Monteiro-Grillo, and Maria Camilo	Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy	Colorectal cancer	Individualized nutritional counselling	Median quality-life dimensions scores	positive
4	Akiko Hanai1 • Hiroshi Ishiguro1 • Takashi Sozu	Effects of a self-management program on antiemetic-induced constipation during chemotherapy among breast cancer patients: a randomized controlled clinical trial	Breast cancer	self management program to manage their emesis and constipation	health-related quality of life (HRQOL).	No differences between groups
5	Fabrice Kwiatkowski1, Marie-Ange Mouret-Reynier2, Martine Duclos3,	Long-term improvement of breast cancer survivors' quality of life by a 2-week group physical and educational intervention: 5-year update of the 'PACThe' trial	Breast cancer	daily group supervised training, dietary education, physiotherapy and psychological support	SF36 questionnaire	positive
6	TimóteoMatthies Rico1 & Karina dos Santos Machado2 & Vanessa Pellegrini Fernandes3	Use of Text Messaging (SMS) for the Management of Side Effects in Cancer Patients Undergoing Chemotherapy Treatment: a Randomized Controlled Trial	Various	Text messages about managing side effects of chemotherapy	EORTC quality of life questionnaire QLQ-C30.	positive

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Table 2: Literature Samples

#	Authors	Title	Diagnoses	Intervention	QOF assessment Tools	outcomes
7	Rita Rezaee1, Nasrin Shokrpour2, Maryam Rahimi	The effect of peer education on the self-efficacy and mental adjustment of breast cancer patients undergoing chemotherapy	Breast cancer	Peer education groups with one session, mental adjustment and self efficacy.	EORTC quality of life questionnaire QLQ-C30.	positive
8	Jolien M. Admiraal, MSc, Annette W.G. van der Velden, MD, Jenske I. Geerling, MANP	Web-Based Tailored Psychoeducation for Breast Cancer Patients at the Onset of the Survivorship Phase: A Multicenter Randomized Controlled Trial	Breast cancer	ENCOURAGE program which relies on automated problem solving strategies, and services for presenting problems.	EORTC quality of life questionnaire QLQ-C30 and breast cancer specific Quality of Life Questionnaire (QLQ-BR23).	No differences between groups
9	Marcela dos Reis Bigatão1, Fernanda Maris Peria2, Daniela P. C. Tirapelli1	Educational program on fatigue for brain tumor patients: possibility strategy?	CNS	Study introduced a leaflet based on four types of contents: informational, energy conservation, physical exercise (walking) and sleep management.	The FACIT-F questionnaire	No differences between groups
10	F. KwiatkowskiM.A. Mouret-ReynierM. Duclos	Long term improved quality of life by a 2-week group physical and educational intervention shortly after breast cancer chemotherapy completion. Results of the 'Programmeof Accompanying women after breast Cancer treatment completionin Thermal resorts' (PACThe) randomised clinical trial of 251 patients	Breast cancer	physical training, dietary education and physiotherapy.	SF36 questionnaire	positive
11	María JoséYusteSánchezaMaríaTorresLacombaaBeatrizSánchez Sánchez	Health related quality of life improvement in breast cancer patients: Secondary outcome from a simple blinded, randomised clinical trial	Breast cancer	physiotherapy intervention combined with a therapeutic education program;	EORTC quality of life questionnaire QLQ-C30 and breast cancer specific Quality of Life Questionnaire (QLQ-BR23)	positive
12	lBénédicteBelgacemab Candy AuclairabMarie-ChristineFedor	A caregiver educational program improves quality of life and burden for cancer patients and their caregivers: A randomised clinical trial	Various	The caregiver educational programme	SF36 questionnaire	positive
13	SaadetÇömezÖzgülKarayurt	The effect of web-based training on life quality and spousal adjustment for women with breast cancer and their spouses	Breast cancer	Breast Cancer and Quality of Life website	Functional Assessment of Cancer Therapy-breast cancer scale and the Dyadic Adjustment Scale.	positive

Patient education about self-management of symptoms by muscle relaxation techniques was performed, which has been shown to be useful for preventing nausea and vomiting in GI cancer patients (4) The patients were first instructed using visual aids regarding the management of their conditions. Muscular progressive relaxation techniques were used to counteract nausea and emesis. Music was used to distract the patients throughout the whole chemotherapy treatment as well as before and after. One of the main elements of the self-care education was training about nutrition (4) Nutritional counseling, including dietary supplements and avoidance of fatty foods in the diet for breast and non-small cell lung cancer, educating patients to prevent anti-emetic induced constipation and prevent fatigue in brain tumors by implementing energy conservation methods (5, 6). Educational techniques such as instructing to perform abdominal massage, abdominal exercises to manage emesis and constipation associated with treatment (6), and Interventional therapy in hydrothermal centers in breast cancer patients included daily group supervised training, dietary education, physiotherapy, and psychological support (20). Providing information to reduce fatigue in brain tumor patients through physical exercise, managing their daily activities to conserve energy with the help of occupational therapy sessions and sleep management (5). Intervention for breast cancer patients includes physiotherapy, physical training, dietary education, nutrition counseling and group support provided to them to improve side effects of the treatment and help to maintain the quality of life in those patients in the long-term (21). Non-small cell lung cancer patients were offered a web-based health education program in Chinese teaching them about the thorough details of their lung cancer, including basics such as vital signs and symptoms to the anatomy and pathophysiology and all associated lab tests. Patients were also taught in regards to their treatment protocols as well as symptomatic management (10). In other studies - Breast, colon, and lung cancer patients received text messages about the side effects of chemotherapy and its management. Patients in the intervention group received text messages about managing side effects of chemotherapy from the beginning of treatment to cycle 4 that they attested to have read daily. The messages were delivered via the specially designed program- cHEmotHErApp (2). Web-based educational counseling was also provided to the caregivers and spouses about the patient's diagnosis, and treatment (7, 9).The caregiver educational program was based on the teaching of care classified into four categories: meal support, nursing care, welfare care, and symptom management (7).

QoL ASSESSMENT TOOLS

The most commonly used tool was the Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30 (1, 23, 5, 10, 3) which was developed by The European Organization for Research and Treatment of Cancer – QL group as a combined assessment system composed of a generic core questionnaire, EORTC QLQ-C30, which evaluates issues common to different cancer sites and treatments, and a range of supplementary modules designed to assess specific issues, according to the type of treatment or disease site, or to dimensions like fatigue (22) Another important used questionnaire was the 36-Item Short Form Survey. The SF-36 was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 includes one multi-item scale that assesses eight health concepts: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue) general health perceptions (23). Two studies analyzed the QoL of patients using The Functional Assessment of Cancer Therapy (4,6) research (24), the organization offers validated questionnaires for almost all cancer types. Two questionnaires were used during our research - The Functional Assessment of Cancer Therapy - Breast (FACT-B) and The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F). The Functional Assessment of Cancer Therapy - Breast (FACT-B) is a 37-item instrument designed to measure five domains of HRQOL in breast cancer patients: Physical, social, emotional, and functional well-being as well as a breast-cancer subscale (BCS). The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) (4) FACIT is a 40-item measure that assesses self-reported fatigue and its impact on daily activities and function. It is a subset of the longer Functional Assessment of Cancer Therapy – Anemia (FACT-An). This 20-item subscale, referred to as the anemia subscale, comprises 13 items that assess fatigue and anemia. Another interesting QoL assessment tool was the Health-Related Quality of Life Scale (25*) Developed by the Centers for Disease Control and Prevention, the Health-Related Quality of Life (HRQOL-14) scale has 14 items that give a complete overview of a person's health and wellbeing. The scale consists of three modules. The Core Healthy Days module, The Activity Limitations module, and The Healthy Days Symptoms module.

OUTCOMES

In some of the studies, cancer patients undergoing treatment have positive outcomes in terms of improving their overall quality of life by preventing side effects (2, 3, 4, 7, 9, 10, 17, 19, 20, 21). For example, a study of gastrointestinal patients undergoing chemotherapy has beneficial effects with self-care education in improving quality of life such as nausea, emesis, and constipation with patient education, physical therapy, nutritional counseling, and diet plans (4). In studies Implementing methods like patient self-care education to prevent fatigue and side effects of the treatment (4). Another example of web-based health education to teach patients about their diagnosis, explain the pathophysiology of their disease, and about treatment has shown a significant impact on lessening the distress caused by the disease (10). Nutritional therapy and education among colorectal cancer patients have a favorable outcome (17), In breast cancer patients physical training in hydrothermal centers, dietary education, physiotherapy, psychological support, and peer education had an improvement in quality of life both after the treatment and in long term (19, 20, 21). Web-based training not only improved patient care but also had a positive impact on their spouses which helped them to understand the patient’s needs and make adjustments according to the patients’ needs (9). Caregiver education in terms of patient care, welfare, meal support, and symptom management has also improved patient’s quality of life and decreased

caregiver's burden (7) and it was also reported that patients receiving chemotherapy who received text messages(SMS) to manage their side effects had a favorable outcome in their side effects prevention by better management with the help of intervention method (2).

Other studies showed no benefit from educational intervention or required further research for final results: Self-management techniques for the management of anti-emetic induced constipation and emesis by abdominal massage, exercise, and education about defecation position do not improve patient's symptoms and thereby no improvement in their quality of life(6). There was also no improvement in patient's outcome through the educational program on fatigue prevention in brain tumor patients with the use of non-pharmacological interventions by providing information on energy conservation, physical exercise and sleep management strategies (5). In the breast cancer study patients, no significant difference in the web-based psychoeducation and health-related quality of life changes were noticed between the intervention and control group patients. However, an improvement in quality of life was observed in both groups by alleviating the distress (11). In gynecological cancer patients, chemotherapy causes a decrease in quality of life but Art therapy may help in improving the patient's quality of life QoL during chemotherapy. FACT-G (Functional assessment of cancer therapy-general) assessment does not show significant improvement in QoL Further more studies are required to have more evidence on it (18)

CONCLUSION

Out of 13 studies analyzed, 10 showed positive outcomes (**Table 1**). Studies with positive outcomes showed the improvement in patient's quality of life during or after cancer treatment and educational interventions proved to be beneficial in improving patients' Physical, Emotional, and Social well-being and helping them to cope with the stress and trauma due to the cancer diagnosis and treatment. Self-care education proved effective in improving both quality of life and antifatigue in gastrointestinal cancer patients undergoing chemotherapy. Self-care education could be considered as a complementary approach during combination chemotherapy in gastrointestinal cancer patients.(4)Web-based health education and peer education as well as text messaging, may be a tool for supporting side effect management in cancer patients (2, 9, 19). Daily group supervised training, dietary education, physiotherapy, and psychological support. Therapeutic education, support groups, self-care education, web counseling, DIET and nutritional counseling, sharing the importance of physical exercise or physical activity, and providing information and support to the family, spouse, and other caregivers can help them to know about the patient's condition. They may provide their support in the patient treatment process.Therefore, by acknowledging family, spouse and caregivers needs, we can have better results for patient care and can also decrease their burden. Monitoring and prevention of treatment-related side effects are really important in the care of the patient. We can conclude that educational interventions may be useful in maintaining and improving cancer patients` quality of life.

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Plasma lipids, lipid peroxides and antioxidant system in osteoarthritic patients underwent spa therapy

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ABSTRACT

Objective: The molecular processes underlying degenerative cartilage disease "osteoarthritis, OA" are not fully known.. Although oxidative stress causes cell damage in various tissues, there is not enough evidence for the involvement of oxidative stress in degenerative joint diseases. On the other hand, various spa therapies such as balneotherapy, mud, mineral water, and sulfur bath have long been used for treating osteoarthritis. This study aimed to investigate the effect of spa therapy with balneotherapy on oxidant/antioxidant status and lipid levels.

Material and Methods: This prospective cross-sectional study was conducted on 28 osteoarthritis patients who had spa therapy at Bursa Military Hospital, Turkey. Osteoarthritis patients between 45-70 years who had no contraindications to spa therapy were eligible for inclusion in the study. Spa therapy included balneotherapy with acratothermal water, physical therapy modalities, and mild exercise for 15 days. Blood samples were obtained before and after the treatment cycle to determine the patients' possible changes in oxidant/antioxidant status and lipid profiles. Serum malondialdehyde (MDA), total thiol (T-SH) levels, total antioxidant capacity (TAC), superoxide dismutase (SOD), glutathione peroxidase (GPx) activity, and plasma lipids were measured.

Results: We found a statistically nonsignificant decrease in MDA levels and a significant increase in GPx activity. Whereas plasma lipids, T-SH levels, TAC, and SOD activity remained unchanged.

Conclusion: We may suggest that different mechanisms may play a role in the beneficial effects of spa therapy with balneotherapy in OA besides stimulation of GPx activity.

Keywords: Balneotherapy, Lipids, Osteoarthritis, Spa therapy, Total antioxidant capacity

INTRODUCTION

Osteoarthritis (OA) is a musculoskeletal disease of synovial joints characterized by cartilage degeneration. The final steps in this disease are the progressive loss of articular cartilage and irreversible impairment of joint motion (1, 2). Although mechanical overload is thought to be involved in the degeneration of articular cartilage, molecular mechanisms and the mediators playing a role in the pathogenesis of the disease have not been elucidated yet (2).

Oxidative stress has become a popular area of research in recent years due to its importance in the pathophysiology of OA. Free radical-mediated reactions damage tissues by promoting aging, functional failure, and degenerations if produced uncontrolled (3). In addition, increased oxidative damage due to free radicals has been demonstrated to associate with knee OA (4). On the contrary, antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), were shown to be diminished in OA patients, which indicates the significance of oxidative stress in the pathophysiology of the disease (5).

Researchers are continually looking for new treatment options because there are currently no treatments available to prevent or delay OA. Osteoarthritis treatment consists of pharmacological treatments, non-pharmacological treatments, and surgical treatments. Spa therapy, including mud-pack therapy, hydrotherapy, balneotherapy with mineral and/or thermal waters, physiotherapy, and exercise, has been applied to osteoarthritic patients as the most common non-pharmacological approach (6-9). Balneotherapy has improved the quality of life by targeting pain relief and joint function (10).

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In addition to short-term analgesic, myorelaxant, and the other effects, it has long-term and preventive effects on the body from six months to a year. However, despite its long history and widespread use, the underlying mechanism regarding spa therapy's general effect and preventive aspect have not been clearly understood. Studies have suggested that therapy with hyperthermal baths, drinking cures, and peloid packs reduce oxidative stress and induce antioxidant defense mechanisms (11, 12). However, the beneficial effects of these treatments and the biological mechanisms of action are still under investigation.

There are few studies regarding the effects of spa therapy on plasma lipids and oxidant/antioxidant status in OA patients. Therefore, in the present study, we aimed to determine whether spa therapy with balneotherapy influences oxidant/antioxidant status and lipid profiles of OA patients.

MATERIAL AND METHODS

Patients

This study included 28 osteoarthritic patients (19 female, 9 male) with a mean age of 59.5 ± 7.0 years. The patients underwent spa therapy comprised of balneotherapy with acratothermal water (at 39-41 oC) for 20 min, mild exercise, and physical therapy for 15 days (with treatment on Saturdays and Sundays) at Bursa Military Hospital, Turkey. The physicochemical properties of thermal mineral water used in balneotherapy are shown in Table 1. Twelve of 28 patients took one analgesic (paracetamol, metamizole) when patients had pain. All patients were fed an identical diet. Anyone from 45-70 ages with osteoarthritis who had no contraindications to spa therapy was eligible for inclusion in the study. The exclusion criteria:The presence of any systemic disease except osteoarthritis, antioxidant and vitamin use, antihypertensive (calcium canal blockers, β blockers), antihyperlipidemic, antidiabetic drug use, alcohol use, and cigarette smoking. In addition, hematological and biochemical analyses were performed at the beginning of the study to exclude systemic disease.

The Ethics Committee approved the study of Istanbul University by following international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013). All subjects received prior information about the study, and written informed consent was obtained from participants.

Measurements

Fasting blood samples were obtained from patients on the study's 1st day and 16th day for measurements. Plasma lipid profiles, malondialdehyde (MDA) levels, total sulfhydryl groups (T-SH), total antioxidant capacity (TAC), glutathione peroxidase activity (GPx), and superoxide dismutase (SOD) activity were assayed.

Plasma total cholesterol, low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were assayed by Roche autoanalyzer using enzymatic kits according to standard laboratory protocols.

Plasma MDA levels, a reactive aldehyde produced by lipid peroxidation of polyunsaturated fatty acids, were measured spectrophotometrically using thiobarbituric acid according to Buege & Aust (13).

Briefly, 1.0 ml plasma was mixed with the mixture of 2.0 ml trichloroacetic acid (TCA), thiobarbituric acid (TBA), hydrochloric acid (HCl), and heated in boiled water for 15 minutes. After cooling, samples were centrifuged 1000 x g for 10 minutes, and the upper phase was obtained. Absorbance was measured by spectrophotometry at 535 nm. MDA concentrations were calculated using extinction coefficient (ϵ =1.56 x 105 $M^{-1}cm^{-1}$) and presented as nmol/ml in plasma. Plasma T-SH levels were determined by the method of Hu (14), using Ellman's reagent [5,5'-dithiobis-(2-nitrobenzoic acid)]. TAC was evaluated by FRAP (Ferric Reducing Antioxidant Power Assay) method (15). FRAP determination was based on spectrophotometric measurement of the intense blue color change at 593 nm wavelength while Fe+3 tripyridiltriazin complex (Fe+3-TPTZ) was reducing to Fe+2 form. Change of absorbance is related to the total reducing power of electron giving antioxidant in reacting mixture. Ascorbic acid standards were used to calculate FRAP values. In addition, 1000 µM ascorbic acid used in the FRAP method equals 2000 µM FRAP value. The TAC value of samples was calculated. Plasma GPx activity was assessed using the method suggested by Paglia & Valentine (16), which measures GPx activity indirectly by measuring the rate of NADPH (nicotinamide adenine dinucleotide phosphate) oxidation to NADP+. NADPH oxidation is accompanied by a decrease in absorbance at 340 nm. Plasma SOD activity has been assayed by a spectrophotometric method based on the inhibition of superoxide-induced NADH oxidation (17). One unit of the enzyme activity is defined as the amount of SOD capable of inhibiting the rate of NADH oxidation of the control by 50 %.

Statistical Analysis

Statistical analysis in this study was made by GraphPad Prism V.8 program. The Kolmogorov-Smirnoff test was used to examine the normality of distribution. In addition to descriptive analysis, paired t-tests have been used to compare before and after treatment of the patient. Data were expressed as mean ± S.D (Standard Deviation). Results were evaluated at a $p < 0.05$ significance level, between 95 % confidence interval.

RESULTS

The study includes 28 patients with a mean age of 59.5 ± 7.0 years (age range: 45–70 years) (Table 2).

The evaluation of BMI before (27.1 ± 2.3) and after (26.9 ± 2.5) spa therapy demonstrated a minor nonsignificant reduction ($p > 0.05$) in all the population (Figure 1).

A statistically insignificant decrease was established in plasma MDA, T-SH levels, and TAC regarding the first measurement ($p > 0.05$). Also, a insignificant increase was observed in plasma SOD activity at the last measurement (Table 3).

The difference between the TAC measurements of the 1st and the 16th days was significant when patients were divided according to gender (Figure 2).

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However, we found statistically significant high plasma TAC values in male patients than in female patients (data not shown). Finally, GPx activity showed a statistically significant ($p < 0.001$) increase in patients having undergone spa therapy (Table 3).

In our study, all patients' blood lipid levels were within normal limits. Data analysis revealed a minor reduction in total cholesterol, LDL-C, and VLDL-C levels and a minor increase in patients' triglyceride levels at the end of spa therapy. However, the changes were not statistically significant. A significant decrease in HDL-C levels was found in patients after the spa therapy (Table 4). Finally, no adverse reactions were seen in participants.

Table 1. Physicochemical properties of water used in balneotherapy

Characteristic		Value
pH		7.1
Hardness (Fr^0S)		28.8
Carbon dioxide (CO_2) (mg/L)		22
Metaboric acid (HBO_2) (mg/L)		1.2
Metasilicic (H_2SiO_3) (mg/L)		40.3
Total mineral (mg/L)		602.1
Anions (mg/L)	Chloride (Cl^-)	6.1
	Bicarbonate (HCO_3^-)	341.6
	Sulfate (SO_4^-)	72.0
	Fluoride (F^-)	0.9
Cations (mg/L)	Sodium (Na^+)	31.7
	Calcium (Ca^{2+})	82.2
	Potassium (K^+)	4.7
	Magnesium (Mg^{2+})	20.1

Analysis was performed at the Balneology and Water Chemistry Laboratory of the Department of Medical Ecology and Hydroclimatology, Istanbul Faculty of Medicine

Table 2. Demographic data of patients studied at baseline

Parameters	All patients (n=28)
Sex	
Male (n, %)	9 (32)
Female (n, %)	19 (68)
Age (years)	59.5 ±7.0
Height (cm)	164.5 ± 8.7
Weight (kg)	74.1 ± 10.2
Body mass index (kg/m^2)	27.1 ±2.3
Disease duration (years)	10.2 ± 7.6

Table 3. Plasma MDA, T-SH, TAC, GPx and SOD activities changes in osteoarthritics before and after the spa therapy

	Before therapy	After therapy
MDA (nmol/ml)	6.47 ± 1.50	5.49 ± 0.80
T-SH (nmol/ml)	377 ± 62	362 ± 46
TAC	949.4 ± 226.4	896.1 ± 238.9
GPx (U/l)	376 ± 95	419 ± 78**
SOD (U/ml)	78.0 ± 21.5	78.4 ± 19.7

** $p < 0.001$ compared to before therapy, MDA malondialdehyde, T-SH total sulfhydryl groups, TAC total antioxidant capacity, GPx glutathione peroxidase, SOD superoxide dismutase

DISCUSSION

Oxidative stress in OA pathogenesis has been documented in numerous studies. Although some investigators have reported that reactive oxygen species (ROS) are involved in the degeneration of articular cartilage (2, 18, 19), there are also a few controversial studies (1). It has been suggested exogenous H2O2 has damaged cultured chondrocytes (2), and superoxide anions cause apoptotic cell death in synoviocytes (18). Mazzetti et al. (1) have found that nitric oxide (NO) rather than ROS may significantly alter chondrocyte functions in OA. DelCarlo and Loeser (20) have reported that NO, not alone but with ROS, plays an essential role in chondrocyte cell death. Although it has been suggested that the continual production of free radicals within the degenerated joint may result in the exhaustion of effective antioxidant control (3), studies related to antioxidant defenses are also conflicting. For example, Kurz et al. (2) have reported that dietary vitamins (vitamin E and C) and Se diminished osteoarthritic lesions, and it is accompanied by an increase in antioxidative enzyme activity and expression in rats. However, total antioxidant capacity in plasma and synoviocytes of osteoarthritic patients has been observed unchanged (21). Similar results have been reported by Sarban et al. (22) concerning total antioxidative capacity in plasma of OA patients. They found that GPx and CAT levels in erythrocytes were much lower, whereas SOD levels were unaffected (22).

Various therapies known to have long-lasting beneficial effects for osteoarthritis. Three weeks of spa therapy, including rest, balneotherapy with spring water, and medical care (7), two weeks of mud pack and mineral therapy (6), two weeks of balneotherapy at the Dead Sea area (8), and three weeks sulfur bath (9) are some feasible treatment options for osteoarthritis. Their mechanism of action was identified with in vitro studies. According to their results, spa therapy has been proven to have beneficial effects on the oxidant/antioxidant system. Fioravanti et al. (23) have reported that sulfated thermal waters suppress NO generation and apoptosis produced by IL-1 in OA chondrocytes. H2S has been suggested to inhibit the production of inflammatory cytokines (IL-8, IL-1, TNF-α, IL-6, and IL-10) and counteract the formation of ROS and reactive nitrogen species (RNS) by human monocytes (24). There are also in vivo studies to investigate the effects of spa therapy on the oxidation and inflammation markers and antioxidant enzymes. Jokic et al. (25) have observed reductions in serum MDA and carbonyls, as well as SOD and catalase activity (25) and also GPx activity (9) after balneotherapy with sulfurous water. This reduction in oxidative stress during sulfur therapy may be due to lower expression of antioxidant enzymes or increased production of superoxide radicals exhausting the superoxide-scavenging enzymes. Benedetti et al. (26) reported an increase in plasma thiol levels decrease in plasma MDA and carbonyl levels after balneotherapy using sulfurous water and mud in OA (26). Therapeutic baths in mineral water lowered the levels of MDA and activities of catalase, SOD, and GPx, according to Bender et al. (27).

Table 3 shows a statistically nonsignificant decrease in plasma MDA levels and TAC of osteoarthritic patients after the spa therapy. When the patients were evaluated as male and female, a statistically significant decrease in TAC value was found in females and an increase in males. All of the female patients out of two were in the postmenopausal period. Some studies have shown that the effect of estrogens, which are known as strong antioxidants, and TAC levels decrease in postmenopausal women (28). TAC decrease in women at the end of spa cure may be due to estrogens deficiency, sedentary lifestyle, and small muscle mass (28). According to this result, women may need an antioxidant supply in a spa treatment. In our study, plasma T-SH was not changed. While GPx activity was found to be elevated, SOD activity remained unchanged. This discrepancy in antioxidant enzyme activities might be due to the diversity of gene expressions. Although statistically insignificant, the decrease in MDA levels may be related with increased GPx activity.

Despite these conflicting results from the published studies, our findings are similar at some points. For instance, Bellometti and colleagues observed a significant decrease in MDA levels and a nonsignificant increase in GPx activity, transferrin, and ceruloplasmin levels after treatment with peloid packs (11, 12). Ekmekçioğlu and colleagues have found an insignificant increase in peroxide concentrations and a significant improvement in lipid levels in the patients with osteoarthritis at the end of three weeks of spa therapy (9). When the studies searching the effect of balneotherapy on oxidant and antioxidant systems were evaluated, the decrease in oxidant stress was more prominent, and the increase in antioxidant defense was less manifest. This finding may be due to the oxidant effect of hyperthermic treatment and antioxidant consumption when an organism defense against oxidative stress. Spa therapy may decrease oxidant stress by eliminating environmental oxidative factors like air pollution, mental stress and dietary regulation, regular exercise, balneotherapeutic applications like hyperthermic baths, and the chemical effects of thermomineral waters.

We also evaluated plasma lipid levels in osteoarthritics. There was a slight change in plasma lipids other than triglycerides which could be a tendency towards diminution. However, our findings did not reach statistical significance. On the other hand, the decline observed in HDL cholesterol was significant. These results differ from some published studies. For instance, a study on knee OA has shown that balneotherapy with sulfur water decreased patients' cholesterol, triglyceride, and LDL levels and unchanged their plasma total antioxidant capacity (29). However, it has been reported that decreased levels of cholesterol and triglyceride and increased HDL cholesterol levels after balneotherapy treatment (30). Our results share several similarities with Kasperczak et al. (31) findings, who found HDL cholesterol was significantly lower in male osteoarthritic patients after spa therapy. They also found a slight drop in LDL cholesterol levels and an insignificant increase in triglyceride levels after treatment (31).

We are aware that our research may have some limitations. First, we evaluated only the short-term efficacy of spa therapy in a small number of patients. Another disadvantage was the lack of a control group of OA patients who had not received treatment. However, we thought it would have been unethical to leave a patient group without any treatment. Finally, we conducted a single treatment approach. Future studies should include comparisons with other treatment techniques and long-term outcomes with participants.

CONCLUSION

Although spa therapy causes an increase in GPx activity, different mechanisms may play a role in the beneficial effects of spa therapy in OA besides stimulating of antioxidant system. However, because of the divergent results, assessing the impact of spa therapy on oxidant/antioxidant status and lipid metabolism changes will require more research in large groups of patients, preferably using different treatment protocols.

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Factors affecting urticaria control in patients with chronic urticaria

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ABSTRACT

Objective: Urticaria is a condition characterized by the development of blisters (hives), angioedema, or both. Acute urticaria is the appearance of rashes lasting 6 weeks or less, angioedema, or both. It is recommended to use the urticaria control test to evaluate disease control in patients with CSU. This study aimed to evaluate the factors affecting urticaria control in patients followed up with the diagnosis of chronic spontaneous urticaria.

Material and Methods: Urticaria control results of children diagnosed with chronic urticaria were evaluated retrospectively and factors that could affect urticaria control were investigated.

Results: Relationships between the urticaria control test and age, gender, onset time of the complaint, family history of atopy, and laboratory values such as anti-nuclear antibody (ANA) and c4 were examined.

Conclusion: Although chronic urticaria has a mild course in children, parameters such as gender, age, and ANA positivity may affect the control of the disease.

Keywords: Pediatrics, chronic urticaria, urticaria control test

INTRODUCTION

Urticaria is a condition characterized by the development of wheals, angioedema, or both. The wheals are sharply circumscribed, of varying size and shape, often surrounded by erythema, accompanied by itching or sometimes a burning sensation, and the skin returns to its normal appearance, usually within 30 min to 24 h. Angioedema may accompany urticaria in some patients. Urticaria is classified as acute or chronic according to its duration and as inducible or spontaneous according to the role of the triggers.Acute urticaria is defined as the appearance of rashes lasting 6 weeks or less, angioedema, or both. Chronic urticaria (CU) is defined as the appearance of swelling, angioedema, or both, lasting more than 6 weeks. CU may present with signs and symptoms daily or nearly every day or with an intermittent/recurrent course. CU may recur a month or year after complete remission. Urticaria can occur in all age groups, including infants and children. It is recommended to use the urticaria control test to evaluate disease control in patients with CU. Our study evaluated the factors affecting urticaria control in patients followed up with the diagnosis of CU.

MATERIAL AND METHODS

In our study, urticaria control tests of children diagnosed with CU who cured in the Dokuz Eylul Medical Faculty Pediatric Allergy and Immunology Clinic (2018-2021) were evaluated retrospectively and factors that could affect urticaria control were investigated. Although no underlying cause could be found in chronic urticaria disease, we investigated whether there is an underlying cause in chronic urticaria that is recurrent and resistant to treatment. Liver and kidney function tests, complete urinalysis, viral serology, sedimentation and CRP, total IgE, complete blood count, total eosinophilia values, skin prick tests, thyroid autoantibodies, ANA (anti-nuclear antibody), C3-C4 complement levels obtained from each patient diagnosed with chronic urticaria results were evaluated. In the skin prick test, 3 mm or more was considered positive. Additional allergic diseases of the patients and the atopy status of the families were recorded. The angioedema was not observed in any of our patients. Urticaria control test (UCT) scores of the patients were recorded in the outpatient clinic controls. UCT is a questionnaire consisting of 4 questions. The patients are questioned about the physical symptoms of urticaria, their quality of life, the need for antihistamines, and the level of subjective control with the disease.

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Each question contains 5 answer options ranging from 0 to 4, with 0 meaning "too much" and 4 points "not at all". Accordingly, if the score was 12 and above, the disease was considered under control, and if it was 11 and below, it was considered as uncontrolled. The families of patients answered the urticaria control test under the age of 5.

Ethics committee approval (IRB)

Approval was obtained from the ethics committee of Dokuz Eylül University Faculty of Medicine (7193-GOA)

Statistical Analysis

The relationships between the UCT and the factors that may affect this scoring were examined with the multiple linear regression model. The regression model was estimated using the ordinary least squares error method in Stata 13.0. The statistical significance of the explanatory variables included in the model can be analyzed according to their p values. The confidence interval was determined as 95%. Based on the adjusted R2 value, all explanatory variables in the model explain approximately 90% of the changes in the patient's urticaria control.

RESULTS

In our study; In the 2-21 age range (median 10 years), 88 (3.52%) of the 2500 patients who applied to our outpatient clinic with the complaints of urticaria were evaluated as chronic urticaria. 59.1% of patients were girls, and 41.9% were boys. The median time of onset of the patients' complaints of urticaria was 8 years (1-18 years). Liver and kidney function tests, complete urinalysis, viral serology, sedimentation, and CRP results were normal. Total IgE level was 112.5 mg/dl (2-1166 mg/dl), eosinophil level was 200 10^3(100-1700 10^3). Thyroid autoantibody elevation was found in 10.2% of the patients, and anti-nuclear antibody positivity was found in 39.8% of the patients. Anti-DFS 70 positivity was detected in 12.5% of the patients. While the complement levels of 85.2% of the patients were normal, low C3 was found in 5.7% of the patients and low C4 in 9.1% of the patients.

The skin prick test was negative in 81.8% of patients, 6.8% food, 4.5% grass pollen, 5.7% dust, 1.1% animal sensitivity. There was atopy in the families of 37.5% of the patients. No concomitant disease was detected in 76.1%. Asthma was found in 10.2%, Hashimoto hypothyroidism in 5.7%, atopic dermatitis in 3.4%, allergic rhinitis in 3.4%, and epilepsy in 1.1%.

Relationships between the urticaria control test and age, gender, onset time of the complaint, family history of atopy, and laboratory values such as mother and c4 were examined. Accordingly, the effect of gender on the urticaria control test result is as follows: Being male increases the ability to control urticaria by 52.97% compared with women. Up to 5-6 years of age, urticaria control of patients increases by 31%, and the best control is found in this age range, but until the age of 9, the ability to control urticaria decreases by 1.2%. In the 10-15 age group, it decreases by 6.8%. This situation can be evaluated as a factor that makes it difficult to control the disease. Although urticaria control continues to decrease as age progresses after the age of 15, the rate of decrease slows down (graph 1). The presence of individuals with atopy in their family increases the ability to control urticaria by approximately 35.25%. Other factors affecting urticaria control are laboratory values such as ANA and c4. Normal and positive main values increase the controllability of urticaria by approximately 97.27% and 48.96%, respectively. Low C4 increases the controllability of urticaria by 71.44%. Finally, a one-unit increase in the total IgE value reduces the controllability of urticaria by 0.056 (table 1).

As a result, the first three variables most effective in urticaria control are Ana positivity, low C4 and male gender, respectively. Other variables (eosinophil level, thyroid autoantibodies, other comorbidities, DPT) included in the dataset and not included in the model did not significantly affect urticaria control.

Table 1: Factors Affecting Urticaria Control

Dependent Variable	Coefficient	95% Conf. Interval		p
Age	31%	0.211	0.406	0.000
Age^2	-1.1%	-0.015	-0.007	0.000
Gender	52.97%	0.156	0.694	0.006
Time_common_complaint	-7.2%	-0.130	-0.014	0.024
Familial Atopy	35.25%	0.043	0.561	0.061
ANA_Normal	97.27%	0.337	1.021	0.00
ANA_Positive	48.96%	-0.007	0.805	0.038
C4_low	71.44%	-0.035	1.114	0.092
Total IgE	-5.6%	-0.001	0.00004	0.067

Adjusted R2: 0.9024, F (8,80) =102.70, p=0,000, Observation 88

The statistical significance of the explanatory variables included in the model can be analyzed according to their p values. The confidence interval was determined as 95%. Based on the adjusted R2 value, all explanatory variables in the model explain approximately 90% of the changes in the patient's urticaria control.

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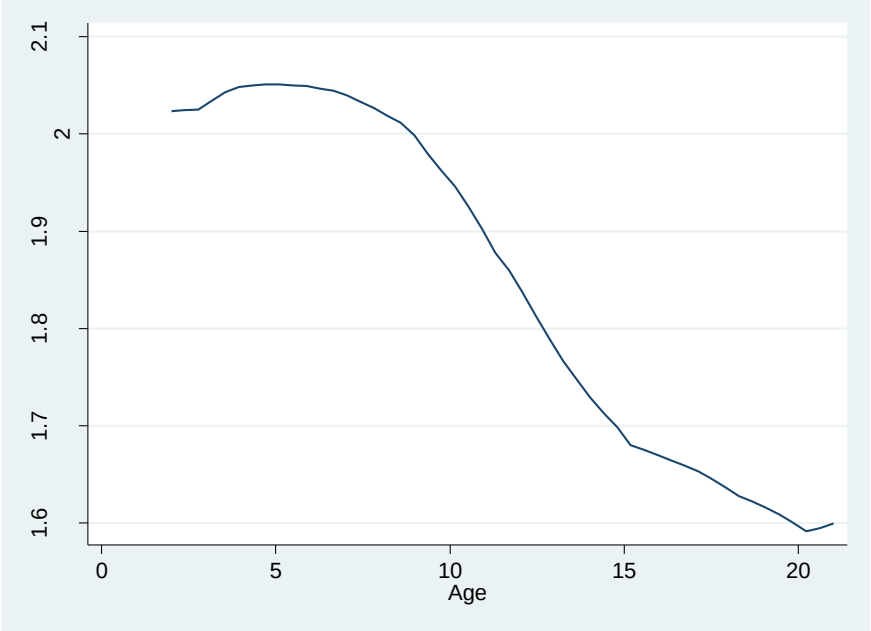

Graph 1: Graph Of The Relationship Between Urticaria Control Test And Age:

DISCUSSION

Urticaria is a skin disease characterized by plaques that are accompanied by severe itching and develop in less than 24 h, significantly affecting the quality of life and tending to turn into a chronic disease.

Chronic urticaria lasts longer than 6 weeks and although it has been shown to be associated with some other chronic infections, such as Helicobacter pylori infection, rheumatological diseases, and parasitic infections, an underlying cause could not be identified in most of patients. CU treatment aims to avoid triggering factors, control urticaria symptoms and minimize treatment-related side effects (1). The urticaria control test (UCT) has 4-item questionnaire about physical symptoms, quality of life, treatment effects, and urticaria control over the previous 4 weeks (2) . In this study, it was evaluated the factors affecting the 4-question urticaria control test (UCT). In our study; among 2500 patients aged 2-21 years (median 10 years) who applied to our outpatient clinic with complaints of urticaria, 88 (3.52%) patients were evaluated as having chronic spontaneous urticaria, 59.1% were female and 41.9% were male. The median time of onset of the patients' complaints was 8 years (1-18 years). Similarly, previous studies have found that CU is more common in schoolchildren (3,4). In our study, CU was observed slightly more frequently in girls than in boys, and its incidence in other studies with children varied between 44% and 54% (5). This finding suggests that the incidence of CU in childhood is similar in both genders. The age range of 5-6 is the age range where urticaria control can be the best. After the age of 9, as the child gets older, urticaria control begins to decrease rapidly until the age of 15. Although urticaria control continues to decrease as age progresses after the age of 15, the rate of decrease slows down. C-reactive protein, sedimentation and helicobacter pylori infection, parasitic infection results were evaluated as normal in all patients. Our patients did not have angioedema complaints.

Angioedema may be less common in children with CU. Physicians reported that 5% to 14% of their pediatric patients with CU had angioedema (6) . The fact that it was not found in our patients may be due to the low number of patients. A one-unit increase in the total IgE value reduced the controllability of urticaria by 0.056, and the effect of eosinophil level on disease control was not detected. A relationship has been shown between pediatric CU and atopic diseases, including asthma, allergic rhinitis (AR), atopic dermatitis (AD), and food allergy (7,8,9). In our study, although the skin prick test was negative in 81.8% of the patients, other observed factors were 6.8% food, 4.5% grass pollen, 5.7% dust, 1.1% animal sensitivity. However, no significant relationship was found between the skin prick test and disease control. It has been shown that the coexistence of atopic diseases has no effect on the probability of recurrence or the duration of CU (10). In our study, 10.2% of the patients with CU had asthma, 5.7% had Hashimoto hypothyroidism, 3.4% had atopic dermatitis, 3.4% had allergic rhinitis, and 1.1% had epilepsy. However, no significant relationship was found between the UCT score and the comorbidities. . In other studies, the frequency of comorbid diseases in patients with CU ranged from 4.3% to 23% (11). There was no data on the causal relationship between patients' comorbidities and CU. It was observed that 35.25% more disease was under control compared with UCT in those with atopy in their family. Autoimmune disorders such as hypothyroidism, hyperthyroidism, celiac disease, Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes mellitus are more common in patients with CU (12). In some patients, an autoimmune mechanism may be present. This concept is supported by the fact that autoimmune diseases that mostly affect the thyroid gland often accompany CU in adults (13). Due to urticaria can be a precursor of rheumatological diseases; The effect of laboratory values such as main and C4, thyroid autoantibodies

related to the rheumatological status of patients on urticaria control was investigated. Normal and positive ANA values increase the urticaria control score by approximately 97.27% and 48.96%, respectively. However, high thyroid autoantibodies were not considered as a factor complicating the control of the disease. Anti DFS 70 positivity was observed in 12.5% of the patients with the main positivity, and it was not found to be significant in terms of the development of rheumatological disease. It has been shown that the presence of autoantibodies in children does not affect the prognosis of the disease, unlike adult patients, where the presence of autoantibodies is associated with a longer duration of the disease, a more severe prognosis, and more intensive treatment methods (14). It is thought that chronic urticaria in children has a more positive outcome than adults (15). Based on demographic data and studies, clear predictors of disease remission could not be determined (16). The most important limitation of our study is that it is a retrospective study based on the examination of patient files.

CONCLUSION

Although chronic urticaria has a mild course in children, parameters such as gender, age, and ANA positivity may affect the control of the disease. Abnormal laboratory values are not common in patients with chronic urticaria, therefore, extensive investigations may not be necessary. However, larger studies are needed to evaluate the factors affecting disease control.

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Author Contributions: OKB, SA, NU, OA, SA and GA: Study design, Literature review, Data collection and processing, Patient therapy, Analysis **OKB:** Data collection, Writing, Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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The effects of whitening mouthrinses on the color stability of CAD/CAM resin matrix ceramics

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ABSTRACT

Objective: This study aimed to evaluate the color change of CAD/CAM resin matrix ceramic, which was exposed to three different whitening mouth rinses and artificial saliva for 12 and 180 hours.

Material and Methods: A total of 60 samples were produced from prefabricated CAD/CAM resin matrix ceramic blocks for experimental study. The samples were randomly divided into four subgroups according to the whitening mouthrinses: Listerine Advanced White, Colgate Optic White, Oral B 3D White Luxe, and artificial saliva. Spectrophotometric measurements were made from each sample at 3 different times, before (initial) exposure to mouthrinses, 12 hours and 180 hours after exposure (ΔE001, ΔE002 and ΔE003). While using the generalized linear models method for the comparison of ΔE00, ΔL, Δa, and Δb color changes according to the mouthrinse and exposure time; multiple comparisons were made with the Tukey HSD Test. The significance level was taken as $p<0.050$.

Results: The results of the two-way analysis of variance showed that the used mouthrinse and the exposure time had a statistically significant effect on the ΔE00 values representing the color change ($p<0.001$), while the interaction between the mouthrinse and the time of use did not play an important role ($p=0.165$).

Conclusion: After exposure time of 180 hours, all whitening mouthrinses induce color change of resin matrix ceramics above clinically noticeable level.

Keywords: Color, CAD/CAM, Hydrogen Peroxide

INTRODUCTION

Today, rising living standards have induced significant changes in individuals' lifestyles and habits, and as a result, human lifespan has been extended (1). Scientists have played an important role in the management of the process by shifting the focus of their work to the technological support of this increasing time (2). All this movement has increased the acceleration of development of computer aided design / computer aided manufacturing (CAD/CAM) technologies in the field of dentistry; in this way, it is aimed to meet both the aesthetic and functional expectations of the patients in the long-term (3). Thus, today, CAD/CAM equipment has shrunk in size, decreased in cost, increased in diversity, and made it possible to produce tooth-colored restorations with excellent aesthetics with alternative materials to traditional dental ceramics (4).

In the search for alternatives, dental materials science first applied to the method of strengthening traditional ceramics with particles such as leucite, lithium disilicate and zirconia (5). However, as stated by Jeong et al., there is still a need for a skilled ceramicist and a laboratory environment in the production of these restorations, and the necessity of heat treatments such as firing in the production of the restoration did not provide a significant reduction in production time (6). Thus, the search continued; force-absorbing resin matrix ceramics with excellent polishability without the need for heat treatment and exhibiting both high resistance and high optical properties to clinical routine at the same time were introduced (7, 8). Although the collaboration of this development with simple milling and polishing techniques allows the production of aesthetic restorations in a short time, the researchers have drawn the note that the effects of monomers such as urethane dimethacrylate (UDMA) and N,N-dimethylacrylamide (DMA), which are also included in the composite resin composition, on the color of resin matrix ceramics should be questioned (9).

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There is consensus in the dental literature that solutions affect the color of composite resins (10). While many studies have examined in detail the effects of acidic beverages, such as cola, orange juice, and wine, on the color of composite resins (11, 12), some researchers have drawn attention to the effects of mouth rinse, which is an indispensable element in the prevention of oral diseases and in the control of oral health, due to its blue and green color (13). Gasparri et al. took these studies one step further and examined the question of how mouthrinses with a whitening effect affect the dental restoration color, while it has an effect on the natural tooth (14).

Whitening mouthrinses were introduced to the market a few years ago with active ingredients such as hydrogen or carbamide peroxide to prevent discoloration, fight plaque accumulation, and prevent discoloration accumulation, and, most importantly, create a fast whitening effect (15). The lower cost compared to the professional whitening procedure and the ease of transportation has enabled these mouthrinses to gain rapid popularity among patients, and paved the way for their accessible forms to vary in terms of concentration, amount, and active ingredient (16). However, scientific publications have not been able to follow this pace, and conflicting results have been reported on the effects of whitening mouthrinses (17, 18). To the present author's knowledge, studies have evaluated the effects of whitening mouthrinses on restorations only in terms of microhardness, microleakage and surface roughness, and the main active ingredient of mouthrinses included in this assessment was limited to hydrogen peroxide. However, as it is known, whitening mouthrinses can contain many active ingredients other than hydrogen peroxide (19). In addition, as Lee et al. also noted, clarification of the effects on the color of the restoration is critical for the long-term use of these solutions (3). In addition, it should not be ignored that different effects can be observed on each restorative material.

Based on this deficiency in the literature, in the current study, it was aimed to evaluate the color change of CAD/CAM resin matrix ceramic exposed to three different whitening mouthrinses for 12 and 180 hours and to compare it with the determined artificial saliva group, as the control. The first null hypothesis of the study is that no significant color change will occur depending on the exposed solution. The second null hypothesis is that the color change values calculated depending on the exposure times will not show a significant difference.

MATERIAL AND METHODS

Preparation of Specimens and Exposure to Mouthrinses

In the current study, a CAD/CAM resin matrix ceramic and three different whitening mouthrinses were used as the restorative material, and artificial saliva was used as the control group. The details of the restorative materials and solutions like manufacturer, composition etc. are summarized in **Table 1**.

A2 color prefabricated CAD/CAM resin matrix ceramic blocks were used in the production of the samples. A total of 60 plates in the form of 12X14X1.2 mm were produced from the relevant blocks by cutting under water cooling with the help of a diamond precision cutting disc. (n=15). The surface of each sample to be measured was abraded by a single operator for 1 minute under finger pressure with 600-800-1000-1200 grid silicon carbide sandpapers, respectively. Care was taken to keep each sample in an ultrasonic cleaner containing isopropyl alcohol for 10 minutes in order to prevent contamination on the sample surface. In accordance with the manufacturer's instructions, a transparent colored varnish specific to the material was applied to the sample surface, which was dried with a clean towel, with the help of an applicator and left for 10 seconds.

Table 1. Details of the restorative materials and solutions that used in study

Material/Solution	Brand Name	Manufacturer	Composition
CAD/CAM Resin Matrix Ceramic	**Cerasmart**	GC Europe, Leuven, Belgium	Bis-MEPP, UDMA, DMA) and 71% silica and barium glass nanoparticles
Whitening Mouthrinse	**Listerine Advanced White**	Johnson&Johnson, Skillman, NJ, USA	Water, Alcohol, Hydrogen Peroxide, Tetrapotassium Pyrophosphate, Pentasodium Triphosphate, Citric Acid, Poloxamer 407, Sweeteners, Sodium Saccharin, Sucralose.
Whitening Mouthrinse	**Colgate Optic White**	GABA International AG, Therwil, Switzerland	Water, Glycerin, Sorbitol, Pyropylene Glycol, PVM/MA Copolymer, Tetrapotassium Pyrophosphate, Polysorbate 20, Sodium Fluoride, Sodium Saccharin, CI 42051.
Whitening Mouthrinse	**Oral B 3D White Luxe**	Procter&Gamble, GmbH, GrossGerau, Germany	Water, Glycerin, Alcohol, Aroma, Methylparaben, Poloxamer 407, Sodium Fluoride, Cetipyridinium Chloride, Sodium Saccharin Pyropylparaben, CI42051, CI47005
Artifical Saliva	-	-	Sodium chloride (0.4 g/L), potassium chloride (0.4 g/L), calcium chloride-H2O (0.795 g/L), sodium dihydrogen phosphate-H2O (0.69 g/L), sodium sulfur-9H2O (0.005 g/L), and 1000 mL distilled water

The polymerization of the varnish was achieved with an LED light device (3M ESPE Elipar S10, 3M ESPE, St. Paul, USA) with a light intensity of 1200 mW/cm2 throughout. The thickness of the samples after surface treatment was measured from three different points with a digital caliper with 0.01 mm precision and care were taken to ensure that the surfaces were uniform. Those with a final thickness of 1.2±0.2 mm were included in the study. The samples were then randomly divided into four subgroups according to the whitening mouthrinses: Listerine Advanced White, Colgate Optic White, Oral B 3D White Luxe, and artificial saliva as a control. Before the exposure procedure, the mouthrinses were left at room temperature for a minimum of 6 hours, pH values were measured with a digital pH meter, and pH values were adjusted using pH4 and pH7 buffer solutions (Sigma-Aldrich Chemical Company, Merck KGaA, Darmstadt, Germany) when necessary. The same procedure was repeated 4 times for each solution in order to calculate the average pH value. Since a previous study reported that continuous exposure of dental materials to a mouthrinse for 12 hours had clinically the same effect as mouthrinse usage for 1 year (2 times a day, for 1 minute)(20); in the present study, samples were subjected to a 12- and 180-hour mouthrinse exposure procedure. In this way, it was aimed to simulate the effect of whitening mouthrinse use on the color of CAD/CAM resin matrix ceramics for 1 and 15 years.

Spectrophotometric Analysis

Color measurements of the samples were made under standard D65 lamp illumination on a neutral gray background using The International Commission on Illumination (CIE) L*, a*, b* color system. A spectrophotometer with previously reported with high reproducibility (Spectroshade Micro, MHT Optic Research, Verona, Italy) was used for measurements (21). SpectroShade Downloader Version 1.1.1.0 (MHT Optic Research, Verona, Italy) software was used for data processing. Before each measurement, the spectrophotometer was calibrated according to the manufacturer's instructions using white and green calibration units. In order to standardize the data, the measurements were repeated 3 times, and the average was taken and entered into the Microsoft Excel® program.

In the evaluation of the color change due to exposure to mouthrinse, ΔE00, which represents the distance of two colors to the 3-dimensional space, was used. The following formulation was used for the calculation of ΔE00:

$$\Delta E00 = [(\Delta L/KLSL)2+ (\Delta C/KCSC)2+(\Delta H'/KHSH)2 + RT (\Delta C'/KCSC)2+ (\Delta H'/KHSH)2] 1/2$$

As previously defined by Paravina et al. when ΔE00>1.77, discoloration is clinically unacceptable, and when ΔE00=0.81, the color difference was considered to be at a visually detectable level (22).

Measurements were made from each sample at 3 different times, before (initial) exposure to mouthrinses, 12 hours and 180 hours after exposure. While the color change occurring at the inital and after 12 hours of exposure was accepted as ΔE001, the color change occurring between 12 and 180 hours of exposure was calculated as ΔE002 and the color change occurring after the initial and 180 hours exposure was calculated as ΔE003. In addition, ΔL, Δa and Δb calculations were made at the same time intervals in order to interpret the spatial position change of the color change.

Statistical analysis

Data were analyzed with Minitab V14. Conformity to the normal distribution was examined using the Shapiro-Wilk Test. While using the generalized linear models method for the comparison of ΔE00, ΔL, Δa and Δb color changes according to the mouthrinse and exposure time; multiple comparisons were made with the Tukey HSD Test. Analysis results were presented as mean±standard deviation. Significance level was taken as $p<0.050$.

RESULTS

The results of the two-way analysis of variance showed that the used mouthrinse and the exposure time had a statistically significant effect on the ΔE00 values representing the color change ($p<0.001$), while the interaction between the mouthrinse and the time of use did not play an important role ($p=0.165$). However, Listerine Advanced White was found to induce the highest color change (3±1.33) regardless of exposure time. As predicted, the lowest ΔE00 value was calculated in the artificial saliva group (0.86±0.42). Tukey HSD test showed that statistically similar ΔE00 values were detected in Colgate Optic White and Oral B 3D White Luxe groups (Table 2). In addition, it is remarkable that ΔE001 values in all mouthrinse groups are lower than ΔE002 and ΔE003 values, and it can be interpreted that whitening mouthrinses induce the main color change after at least 1 year or more than 1 year of use. ΔE003 values calculated in all whitening mouthrinses except the control group are above the threshold value determined as 1.77; this shows that as a result of long-term use of the related mouthrinses, a clinically unacceptable color change is produced in the CAD/CAM resin matrix ceramic.

According to the current findings, the interaction between the used mouthrinse, the exposure time, and the duration of use affect the ΔL values statistically significantly ($p<0.001$). Based on that, the lowest ΔL value was detected in the artificial saliva group with -0.42 and in the ΔL1 time period, while the highest change was found in the Listerine Advanced White group with 3.61 in the ΔL3 time period (Table 3). When the mouthrinses were evaluated independently of the duration of use, the highest ΔL value belonged to the Listerine Advanced White group with 2.41 and was followed by the Oral B 3D White Luxe (2.23) and Colgate Optic White (2.03) groups, respectively. While available data reveal that whitening mouthrinses have a statistically similar effect on ΔL ($p>0.05$); pointed out that the artificial saliva group showed a quite different effect from the mouthrinse groups. In addition, while ΔL data showed a positive increase in all time periods in the whitening mouthrinse groups; ΔL values in the artificial saliva group have a negative course. This means that the color of the samples in the artificial saliva group darkened; and the whitening mouthrinse groups caused a whitening effect on the color of the samples.

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Statistical results revealed that Δa values showed a significant change like ΔL depending on the interaction between used mouthrinse and exposure time, duration of use and mouthrinses ($p<0.001$). According to the Tukey HSD test findings, the effects of artificial saliva and Listerine Advanced White groups on Δa values were statistically similar, and the highest Δa value was found in the Oral B 3D White Luxe group with 0.96 in the Δa1 time period (Table 4). In addition, regardless of the duration of use, while the color of CAD/CAM resin matrix ceramic shifts to red in the artificial saliva and Listerine Advanced White groups; the fact that the sample color shifts to green in the Oral B 3D White Luxe and Colgate Optic White groups is a very significant finding.

It was determined that the Δb values of CAD/CAM resin matrix ceramics differed statistically depending on the mouthrinse to which they were exposed ($p<0.001$). Accordingly, while the mean value of Δb obtained in the artificial saliva group was 0.27, the value obtained in the Listerine Advanced White group was -0.31, -0.19 in the Colgate Optic White group and -0.31 in the Oral B 3D White Luxe group (Table 5). These findings also mean that the samples exposed to clinical artificial saliva change to yellow color, while all other whitening mouthrinses show a blue color change. In addition, a statistically significant effect was found on the Δb values of the samples ($p=0.018$). The main reason for this effect is that the value calculated in the time period Δb1 is different from the other time periods.

Table 2. Descriptive statistics of ΔE00 color change values by mouthrinse and time

Mouthrinses	Duration Time of Use			Total
	$\Delta E_{00}1$	$\Delta E_{00}2$	ΔE_{003}	
Artifical Saliva	0.84 ± 0.45	0.52 ± 0.15	1.22 ± 0.27	0.86 ± 0.42^{c}
Listerine Advanced White	2.51 ± 1.4	3.24 ± 1.58	3.23 ± 0.93	3 ± 1.33^{a}
Colgate Optic White	1.24 ± 0.81	1.68 ± 0.66	2.59 ± 0.94	1.84 ± 0.97^{b}
Oral B 3D White Luxe	1.67 ± 0.86	2.73 ± 0.82	2.68 ± 0.85	2.36 ± 0.95^{b}
Total	1.56 ± 1.1^{b}	2.04 ± 1.4^{a}	2.43 ± 1.07^{a}	2.01 ± 1.24

Mean ± standard deviation; a-c: There is no difference between the averages of main effects with the same letter.

Table 3. Descriptive statistics of ΔL color change values with mouthrinse and time

Mouthrinses	Duration Time of Use			Total
	ΔL1	ΔL2	ΔL3	
Artifical Saliva	-0.42 ± 0.28^{F}	0.02 ± 0.17^{EF}	-0.4 ± 0.4^{F}	-0.27 ± 0.36^{b}
Listerine Advanced White	0.81 ± 0.77^{DEF}	2.8 ± 1.35^{ABC}	3.61 ± 1.02^{A}	2.41 ± 1.58^{a}
Colgate Optic White	1.37 ± 1.1^{CDE}	1.68 ± 1.15^{BCD}	3.05 ± 1.32^{AB}	2.03 ± 1.37^{a}
Oral B 3D White Luxe	0.62 ± 1.03^{DEF}	2.72 ± 0.91^{ABC}	3.34 ± 1.11^{A}	2.23 ± 1.54^{a}
Total	0.6 ± 1.05^{c}	1.8 ± 1.49^{b}	2.4 ± 1.92^{a}	1.6 ± 1.69

Mean ± standard deviation; a-c: There is no difference between the averages of main effects with the same letter. A-F: There is no difference between interactions with the same letter.

Table 4. Descriptive statistics of Δa color change values with mouthrinse and time

Mouthrinses	Duration Time of Use			Total
	Δa1	Δa2	Δa3	
Artifical Saliva	0.52 ± 0.32^{ABCD}	0.27 ± 0.23^{ABCD}	0.79 ± 0.17^{AB}	0.52 ± 0.32^{a}
Listerine Advanced White	1.22 ± 1.52^{A}	-0.45 ± 1.91^{CDE}	0.77 ± 0.82^{ABC}	0.51 ± 1.6^{a}
Colgate Optic White	-0.05 ± 0.33^{BCDE}	-0.45 ± 0.39^{CDE}	-0.51 ± 0.28^{DE}	-0.34 ± 0.38^{b}
Oral B 3D White Luxe	0.96 ± 0.61^{AB}	-1.02 ± 0.75^{E}	-0.07 ± 0.27^{BCDE}	-0.04 ± 0.99^{b}
Total	0.66 ± 0.95^{a}	-0.42 ± 1.11^{b}	0.25 ± 0.72^{a}	0.16 ± 1.03

Mean ± standard deviation; a-c: There is no difference between the averages of main effects with the same letter. A-E: There is no difference between interactions with the same letter.

Table 5. Descriptive statistics of Δb color change values with mouthrinse and time

Mouthrinses	Duration Time of Use			Total
	Δb1	Δb2	Δb3	
Artifical Saliva	0.16 ± 0.08	0.24 ± 0.13	0.4 ± 0.16	0.27 ± 0.16^{a}
Listerine Advanced White	-0.51 ± 0.48	0.04 ± 0.63	-0.47 ± 0.55	-0.31 ± 0.59^{b}
Colgate Optic White	-0.25 ± 0.3	-0.04 ± 0.57	-0.29 ± 0.55	-0.19 ± 0.49^{b}
Oral B 3D White Luxe	-0.3 ± 0.42	-0.17 ± 0.4	-0.46 ± 0.32	-0.31 ± 0.39^{b}
Total	-0.23 ± 0.42^{b}	0.02 ± 0.48^{a}	-0.21 ± 0.55^{b}	-0.14 ± 0.49

Mean ± standard deviation; a-b: There is no difference between the averages of main effects with the same letter

DISCUSSION

Recent in vitro studies detail the harmful effects of peroxide-containing whitening mouthrinses on enamel, dentin and restoration microhardness, and reported that they may also have effects on restoration color (13, 23). As a result of the current research originating from this focus, it was found that ΔE00, ΔL, Δa and Δb values showed a significant change depending on the used mouthrinse and the duration of use ($p<0.001$). Therefore, both the first and second null hypotheses of the study were rejected.

The present study was designed to evaluate the effects of three different mouthrinses containing hydrogen peroxide and alternative bleaching agents on the color of CAD/CAM resin matrix ceramic. And since the whitening efficacy becomes noticeable after using twice a day for a minimum of 2 weeks, as promised in the majority of whitening mouthrinses (15), the exposure time to the mouthrinse is clinically determined as 12 and 180 hours, corresponding to 1 and 15 years. In addition as reported by Zhang, the recommended minimal thickness for a molar crown restoration is 1 mm (24). In the light of this information, the thickness of the CAD/CAM resin matrix ceramic samples used in the research was adjusted to be 1.2 mm. Swain reported that in his in vitro research, a serious change was detected in both optical and surface properties of dental restorative materials exposed to solutions with lower pH values (25). Therefore, the pH of the solutions tested in the methodology of the present experiment was measured at regular intervals; when deemed necessary, the values were regulated with the help of buffer solutions, and changes that may arise from pH changes and differences were tried to be eliminated.

The change in the color of teeth or restorative materials can be evaluated through many different methods: color scale, colorimeter, digital cameras, spectrophotometers, etc. (15). However, current scientific studies have revealed the shortcomings of scale and digital photographs, which offer easier use, and cause these methods to be defined as inaccurate and subjective (26). The advantages of spectrophotometers, such as the ability to convert data into quantitative data, and the ability to interpret measurements by analyzing the basic components of color in many different color systems, have made it an instrument that researchers often prefer (27). However, Sasany et al. pointed out that the biggest limitation in the use of spectrophotometer is the size of the measurement window; reported that if the measurement window of the instrument to be preferred is smaller than the sample size, the edge loss effect can be observed and the measurement consistency will be negatively affected (28). Considering all these data, in order to guarantee the quality in the color measurement methodology in the current study, a spectrophotometer with a measurement window larger than the sample size was preferred.

The most important finding of the current study is that both short-term and long-term use of whitening mouthrinse triggers a significant ΔE00 value change compared to the control group, artificial saliva. This means that whitening mouthrinses have a whitening effect not only on the tooth surface, but also on CAD/CAM resin matrix ceramics. This finding may be due to the fillers structure with the resin matrix embedded in the porcelain mesh of the resin matrix ceramics. As is known, resin matrices are inherently prone to water absorption (29) and this means the development of an internal discoloration just as with composite restorations (30). Reporting that feldspathic porcelain exhibited significantly higher color stability in the results of an in vitro study examining CAD/CAM resin matrix ceramic and CAD/CAM feldspathic porcelain in terms of susceptibility to color change supports the existing data (31). Among the whitening mouthrinses evaluated, Listerine Advanced White exhibited a higher and clinically detectable ΔE00 value at all time periods. This may be due to the fact that the active ingredient in Listerine Advanced White is hydrogen peroxide. Canay et al. stated that they detected a clinically distinguishable color change in composite resins exposed to 10% hydrogen peroxide (32). On the other hand, in Derafashi et al. study that evaluating the effects of different mouthrinses on the color stability of CAD/CAM materials, they associated the significant color change detected in the Listerine group with the softening of the resin matrix by the alcohol in its content (26). On the other hand, Leal et al. stated that the main reason for the effect was due to both the alcohol content above 30% and the hydrogen peroxide content, since alcohol had a higher sorption and solubility effect on the materials and this increased the penetration of hydrogen peroxide (33). Pelino et al. also noted that the calculated color change in composite resins after 3 months of use was 1.28, in which they included Listerine Advanced White as a whitening mouthrinse (13). And all these studies support the present result. However, Anagnostou et al. applied whitening strips containing carbamide peroxide and hydrogen peroxide from two different concentrations to composite resins and reported that they calculated a color change below the clinically noticeable level in all groups (34). This result may be due to the fact that the application method was strip rather than the product content in the related study and the way it came into contact with the composites was quite different from a mouthrinse.

The current study results show that the duration of use has a significant effect on the calculated ΔE00 value for all solutions; it was found that the observed color change increased as the usage time increased. Therefore, the highest calculated value belongs to the time period ΔE003. Alpkılıç et al. reported that the calculated color change increased with time in all solutions, including the artificial saliva group, which was preferred as the control group, in their study where they examined the color stability of CAD/CAM materials exposed to different mouthrinses (5). In an in vitro study investigating the effects of different mouthrinses on human enamel and the color of different restorative materials, it was noted that increasing the exposure time increased the calculated ΔE value (13). In fact, if physicians will support the use of long-term mouthrinse in patients who will undergo restoration of lamina veneers and crowns, material selection is important; because there are also authors who stated that long-term use in CAD/CAM materials with resin matrix content increases discoloration (28). Harorli et al. also investigated the effects of different whitening mouthrinses on the color of composite resins and determined the exposure time of the samples as 1 and 24 hours. Although there is no clinically noticeable color change in the findings, it is possible to see that the increase in the exposure time results in an increase in the ΔE value (35). All researchers associated this observed condition with the cumulative effect of

mouthrinse increasing with time. According to the research of Ntovas et al., the effectiveness of mouthrinse decreases after 3 weeks of use, and there is not always a positive correlation between the increase in time and color change (15). This difference in data may be due to the use of a maximum application time of 180 hours in the current study.

Every in vitro study inherently has limitations in reflecting in vivo. In the present study, the lack of pellicle layer and the deprivation of the washing effect of saliva are an important example of this situation. However, surface morphological changes that will contribute significantly to the elaboration of the results are excluded from the evaluation. In addition, the mouthrinses used were not selected according to the active ingredients or their concentrations, but by considering the commercial sales frequency. And all of these are important limitations of this research.

CONCLUSION

Based on the findings of this in vitro study, the following conclusions were drawn:

1. There is a significant change in the ΔE00, ΔL, Δa and Δb values of CAD/CAM resin matrix ceramics depending on the preferred whitening mouthrinse and usage time.

2. After exposure time of 180 hours, all whitening mouthrinses induce color change of resin matrix ceramics above clinically noticeable level.

3. Listerine Advanced White is a whitening mouthrinse that triggers the highest ΔE00 values in all time periods.

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Author Contributions: ME: Study design, Literature review, Data collection and processing, Experimental studies, **ME:** Data analysis, Writing, Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Prognostic Value of Novel Hematologic Biomarkers in Patients with Pulmonary Arterial Hypertension

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ABSTRACT

Objective: Pulmonary vascular remodeling and inflammation play a major role in pulmonary arterial hypertension (PAH). Novel hematologic biomarkers have recently been recognized as a risk predictor for cardiovascular, oncologic, and inflammatory diseases. We aimed to investigate the association of hematologic biomarkers with mortality in PAH patients.

Materials and Methods: Fourty-five patients diagnosed with PAH and 45 healthy volunteers were evaluated retrospectively. Concurrent data included clinical, echocardiographic, hemodynamic and hematologic variables. The study population was divided into subgroups based on admission neutrophil to lymphocyte ratio (NLR), neutrophil to monocyte ratio (NMR), platelet to lymphocyte ratio (PLR) values.

Results: The median NMR and NLR levels were lower in healthy subjects than in PAH patients (7.7 (7-8.8) vs 9.2 (6.5-11.6); p= 0.03 and 1.9 (1.4-2.9) vs 2.6 (1.9-3.3); p= 0.04) respectively). The estimated mean survival duration was longer in patients with low NMR levels (93 (95% CI, 86-100) vs. 67 (95% CI, 45-88) months (p=0.006) respectively). NMR independently predicted poor outcome and improved the power of the other prognostic markers (OR 1.4 (95% CI, 1-1.8) p= 0.04); (AUC= 0.91; p< 0.0001).

Conclusions: NMR levels alone or combined with other prognostic factors may predict mortality in patients with PAH.

Keywords: Chronic thromboembolic pulmonary hypertension, Neutrophil to lymphocyte ratio, Neutrophil to monocyte ratio, Pulmonary arterial hypertension, PAH, IPAH

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating disease characterized by increased pulmonary vascular resistance due to vasoconstriction, and pulmonary vascular remodeling, often accompanied by a poor outcome due to right heart failure (1,2). Inflammation is important for the development and progression of PAH (1). As a marker of inflammation and tissue remodeling, elevated hematologic biomarkers have been recently found to have association with disease severity and adverse outcomes in several diseases including cardiovascular and neoplastic diseases (3,4).

Predictive prognostic markers of PAH warrant investigation because some reports have indicated that better treatment results can be achieved by starting affirmative therapies before the PAH begins to worsen (2,5). Uric acid, brain natriuretic peptide, heart rate, 6-minute-walk distance (6MWD), and echocardiographic predictors such as pericardial effusion were indicated to correlation with the prognosis of Idiopathic PAH (5-8). But prognosis assessment in PAH is difficult and no guidance was provided on which parameters were the most important or which values to be used as thresholds.

Until now, the value of hematologic parameters in PAH prognosis has not been reported. Thus, the present study aimed to investigate the potential prognostic role of hematologic biomarkers individually and by combining them with different parameters to enable more robust prognostic information in PAH patients.

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MATERIAL AND METHODS

Data from consecutive patients with PAH (IPAH and chronic thromboembolic pulmonary hypertension (CTEPH)) who were referred to the Department of Cardiology, Türkiye Yüksek İhtisas Training and Research Hospital, Ankara, Turkey, have been prospectively collected in a dedicated database since 2006. Data from a contemporary group of healthy volunteers were also consecutively collected. Healthy controls were individuals with no history of pulmonary or cardiac disease or symptoms.

In this retrospective study, all patients with clinically defined PAH i.e. mean pulmonary arterial pressure (MPAB) ≥25 mmHg at rest and pulmonary artery wedge pressure ≤15 mmHg as measured by right heart catheterization, were included (9). PAH was classified as being associated with chronic thromboembolic pulmonary hypertension and idiopathic as described in recent guidelines (9). PAH patients other than these two etiologic groups including PAH patients associated with congenital heart disease and patients with concomitant left heart disease defined by a left ventricular ejection fraction ≤45% or a pulmonary wedge pressure ≥15 mmHg were excluded from the study. Also, patients with known hematologic diseases and active inflammation were excluded. Date of diagnosis of PAH was established as the date of the first confirmatory right heart catheterization performed in our institution.

Upon referral to our Centre, all patients underwent a complete assessment, including clinical history, physical examination, venous blood samples, echocardiography, lung function test, arterial blood gases, ventilation/perfusion lung scan, 6-minute walking distance (6MWD) under standardized conditions, right heart catheterization and laboratory testing, including serological tests for autoimmune diseases and hematologic parameters (10). Left heart catheterization or computed tomography of the lungs was performed in all patients with suspected left heart or respiratory diseases and when clinically indicated. All tests were performed in our clinic and set as the baseline assessment. These data were collected in a dedicated database along with the time between diagnoses of PAH and subsequent follow-up period. Following referral to our Centre, all of the patients were uniformly treated according to the current guidelines and proposed treatment with algorithms-approved PAH-specific drugs (9). Data from 1 January 2006 to 28 February 2015 were analyzed. The study was conducted in accordance with the Helsinki Declaration after being approved by the ethics committee of our hospital.

Blood Sample Analysis

A complete blood count analysis was performed using the peripheral venous blood samples taken upon admission. The blood samples were collected in a calcium EDTA (Ethylenediaminetetra- acetic acid) tube, and blood counts were evaluated using an auto-analyzer. Some hematologic biomarkers were calculated from the whole blood cell counts. NLR was calculated as the ratio of neutrophils to lymphocytes, PLR was calculated as the ratio of platelets to lymphocytes, and NMR was calculated as the ratio of neutrophils to monocytes. In addition, other routine laboratory findings and serologic tests were examined using the electronic database.

Transthoracic Echocardiography

Comprehensive TTEs were performed to all participants (Philips HD11XE and Envisor HD; Phillips USA, Andover, MA). We acquired images from standard echocardiographic views in accordance with the recommendations of the American Society of Echocardiography (11). Pulmonary artery systolic and mean pressure were derived as the sum of the tricuspid regurgitant gradient and pulmonary regurgitant gradients obtained from continuous wave Doppler and the right atrial pressure as estimated from the inferior vena cava, respectively (11). A great deal of data pertaining to right ventricle tricuspid annular plane systolic excursion measurements was also assessed.

Follow-Up Assessment and Identification of Survival Predictors

During the study period, all participating patients were interviewed at a control visit and quarterly thereafter in our clinic to evaluate symptoms, World Health Organization functional classification, current medication, and any potential worsening cardiopulmonary events that might have occurred since last observation. Pulmonary endarterectomy therapy was planned for none of our chronic thromboembolic pulmonary hypertension (CTEPH) patients. Follow-up was censored at the date of the outcome event and treating physicians or relatives were asked for the cause and circumstances of death. Echocardiographic parameters, laboratory parameters, and 6MWD were analyzed for their predictive value on survival.

Besides, the study population was divided into subgroups based on PLR, NLR, NMR values. Effects of these biomarkers on outcome were studied by constructing a receiver–operating characteristic (ROC) curve. High risk groups were defined as follows according to their cut-off values: For PLR >134, for NLR >2.2, for NMR >9.2. Tricuspid Annular Plane Systolic Excursion (TAPSE), 6-minute walking distance (6MWD), mean pulmonary artery pressure (MPAP) and pericardial effusion were considered as prognostic factors for PAH (5-7). All-cause mortality was the primary outcome. A further stratification model was generated according to NLR, PLR and NMR levels and the presence of pericardial effusion.

Statistical Analyses

We used the Kolmogorov-Smirnov test to assess the normality of numeric variables. We made comparisons between 2 groups by Mann-Whitney U test and we presented descriptive statistics for subgroup comparisons, including median and interquartile range. To analyze categorical data, we used a $\chi 2$ test (or Fisher's exact test if any expected cell count was <5), and we presented descriptive statistics as number and percentages. Although the primary objective of our study was the comparison among PAH subgroups according to their hematologic biomarkers; We also performed descriptive statistical analysis comparing the baseline laboratory and demographic characteristics of PAH patients, with that of the healthy population. A P-value ≤0.05 was considered statistically significant. Statistical tests were two-sided.

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To evaluate the correlations between hematologic biomarkers and the currently known PAH associated prognostic indicators (TAPSE, 6MWD and MPAP), we used the Spearman's ρ correlation analysis. Furthermore, we used the ROC curve to determine the cut-off point and the area under the curve (AUC) of significant biomarkers. For clinical convenience, we displayed the cut-off values of those; neutrophil to monocyte ratio (NMR), neutrophil to lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR); as a pre-specified dichotomous variables in order to determine the prognostic significance (that was done to facilitate a meaningful clinical interpretation of the results). In addition, the study tested the statistical significance of the difference between the areas under the ROC curves using the method proposed by Hanley and McNeil (12). When indicated, we also reported analyses performed using those variables as a continuous variable.

For the survival analysis, all causes of mortality were included in the Kaplan–Meier analysis. No patient died of non-cardiopulmonary causes, and no patients were lost to follow-up till the end of our study. Kaplan–Meier survival curves were assessed and compared with the log-rank test according to the clinical subgroups. The date of the first confirmatory right heart catheterization establishing the presence of idiopathic PAH or CTEPH was considered to be the baseline from which survival was measured. Cox proportional-hazards models, both univariate and adjusted for adopted prognostic factors including patient age at first confirmatory right heart catheterization, were performed as additional analyses. Also, we looked for the collinearities among covariates to analyze appropriate Cox models and all variables in cox-regression analysis were normally distributed as shown by Kolmogorov–Smirnov tests.

Model and score derivation

To develop a mortality risk score, we assigned points to predictor variables proportional to the size of their regression coefficients in the model. For the variables above the categorized levels, we constructed two risk score models derived from hematologic biomarkers according to the presence of pericardial effusion. We appointed 2 points for pericardial effusion, 2 points for NMR, 1 point for NLR, and 1 point for PLR, and data was analyzed according to the cumulative risk scores (SCORE and PE-SCORE). Also we preselected TAPSE, 6MWD and MPAP as currently known indicators of PAH related adverse events (6-8). ROC curve was used to determine the optimized cut-off points and to compare the AUC of our risk models. High risk groups were defined according to following cut-off values: For SCORE ≥3 points and for PE-SCORE ≥5 points.

Comparison of the predictive performance of models for mortality

Logistic Regression with a forward stepwise variable selection was used to predict the probability of death in PAH. By using the currently known prognostic factors and our proposed hematologic scoring variables, we created different models for the probability of mortality. The c-statistic, a measure of the area under the ROC curve (which tests the hypothesis that these models performed significantly better than chance (indicated by a c-statistic ≥0.5)) was used to quantify the predictive validity and discriminatory capacity of our proposed models (13). In addition to model discriminatory ability (the ROC curve analysis), model calibration of each adjusted model was tested by the Hosmer-Lemeshow goodness-of-fit test. Explanatory power was tested using the pseudo- R^2 statistic according to the ‘‘Nagelkerke R^2’’ to assess the degree to which the model explained the variance of the binary outcome.

Internal validation group

We used a split-sample approach to develop and internally validate our mortality risk score. As a subsidiary analysis, we also ran the same analyses in a validation group that had the two thirds of our study group (IPAH patients). All analyses were performed with IBM SPSS 14 (SPSS Statistics version 14, IBM Corp).

RESULTS

Demographic, clinical, hematologic and echocardiographic characteristics of PAH patients on admission.

A total of 45 patients with PAH were included. Median age was 49 (32-58) years, 29 patients (64%) were females, 30 had IPAH (67%), and 15 (33%) had CTEPH. CTEPH patients were older, more likely to have pericardial effusion, higher CRP and RDW levels, and shorter 6MWD. Functional class was similar in PAH subgroups and didn’t alter the effect of our hematologic biomarkers or derived models on mortality.

Of the 45 PAH patients, 18 (40%) had PLR >134, 27 (60%) had NLR >2.2 and 21 (47%) had NMR >9.2. Seventy-eight (n=14) and eighty-one (n=17) percent of PAH patients who had PLR and NMR values above the categorized points in sequence; also had NLR values above the cut-off point of 2.2 (p=0.04 and p=0.007). While PAH patients with PLR >134 levels had median NLR values higher than the ones with PLR ≤134 levels; no difference observed in terms of median NMR values between PLR subgroups (3.3(2.3-5.2) vs 2.1(1.8-2.9) p=0.009 and 9.3(7.2-11.6) vs 8.6(6.3-9.9) p=0.55 respectively). In patients with high NLR levels, 6MWD was shorter, NMR, PLR values were higher, and pericardial effusion was more common.

The median age of controls was 49 (30-59) years and 30 subjects (67%) were females. Although no difference was observed between the median WBC and platelet counts; the groups were not similar in terms of median MCV, RDW, and MPV levels. Median values of NMR and NLR were lower in controls than that of the overall PAH patients (7.7 (7-8.8) vs 9.2 (6.5-11.6) p=0.03 and 1.9 (1.4-2.9) vs 2.6 (1.9-3.3) p=0.04 respectively). Demographic, clinical, echocardiographic, functional, and hematologic characteristics of the study patients are shown in Table 1 and 2.

All of our patients were treated with approved PAH-specific medications. Treatment of patients at the end of the follow-up according to the PAH subgroups is shown in supplementary table 1. A larger number of patients with PAH after diagnosis were treated with endothelin receptor antagonists. In the overall population, 20 (44%) patients were treated with combination therapy. Treatment modality had no significant effect on mortality regardless of being whether mono-therapy or combination treatment.

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Table 1: Demographic, clinical and echocardiographic characteristics of the study patients.

	Control N=45	Overall PAH n=45	*p-value	IPAH n=30	CTEPH n=15	**p-value
Age, (years)	49 (30-59)	49 (32-58)	0.94	40 (28-50)	58 (53-68)	**0.001**
Sex n, (%)						
Female	30 (67)	29 (64)	0,8	19 (63)	10 (67)	0.8
Follow-up duration (months)		26 (14-56)		27 (14-56)	26 (20-63)	0.57
Hemoglobin (mg/dL)	13.8 (13.2-15.9)	13.6 (12.3-15.3)	0.82	14.1 (12.4-15.7)	12.6 (11.9-13.7)	0.06
Platelet (10^3/mm^3)	222 (204-251)	204 (175-276)	0.35	203 (161-269)	248 (190-298)	0.06
White blood cells (x10^9/L)	7 (6.5-8.3)	7.6 (6.6-8.9)	0.28	7.8 (6.1-9.2)	7.4 (6.7-7.9)	0.92
MCV (fl)	90 (83-92)	85 (78-91)	**0.04**	86 (81-92)	83 (74-88)	0.14
MPV (fl)	8.8 (8.2-9.6)	9.2 (8.7-10.2)	**0.02**	9.2 (8.6-10.4)	9.2 (8.7-9.6)	0.77
RDW (%)	13.6 (13-15)	16.5 (14.1-17.4)	**0.001**	15 (13.9-17.3)	17.2 (15.9-18.7)	**0.03**
NLR	1.9 (1.4-2.9)	2.6 (1.9- 3.3)	**0.04**	2.7 (1.9-3.9)	2.3 (1.9-3.1)	0.59
PLR	97 (86-123)	106 (83-157)	0.12	104 (71-164)	141 (89-153)	0.39
NMR	7.7 (7-8.8)	9.2 (6.5-11.6)	**0.03**	9.4 (6.9-11.9)	8.4 (5.6-9.5)	0.09
Creatinine (mg/dL)		0.9 (0.7-1)		0.8 (0.7-0.9)	1 (0.8-1.1)	0.05
CRP (mg/L)		5.7 (3.4-11.4)		4 (2.9-7.3)	8.6 (5.9-14.9)	**0.02**
Iron (µg/dL)		61 (40-68)		62 (39-68)	60 (43-69)	0.82
Ferritin (ng/mL)		25.3 (13.3-38.4)		26.6 (13.3-46.1)	21.4 (14.0-28.8)	0.16
mPAP (mmHg)		55 (45-65)		52 (45-66)	55 (45-65)	0.9
TAPSE (mm)		13 (12-15)		13 (12-15)	12 (11-13)	0.4
6MWD (meters)		290 (220-340)		335 (240-380)	280 (130-310)	**0.03**
Functional Class n, (%)						
Class II		21 (47)		17 (57)	4 (27)	**0.03**
Class III		18 (40)		8 (27)	10 (67)	
Class IV		6 (13)		5 (16)	1 (6)	
Pericardial effusion n, (%)		22 (49)		11 (37)	11 (73)	**0.02**
PLR ≤134 n, (%)		27 (60)		20 (67)	7 (47)	0.19
PLR >134 n, (%)		18 (40)		10 (33)	8 (53)	
NLR ≤2.2 n, (%)		18 (40)		12 (40)	6 (40)	1.00
NLR >2.2 n, (%)		27 (60)		18 (60)	9 (60)	
NMR ≤9.2 n, (%)		24 (53)		14 (47)	10 (67)	0.2
NMR >9.2 n, (%)		21 (47)		16 (53)	5 (33)	
Medication n, (%)						
Mono-therapy		25 (56)		16 (53)	9 (60)	0.67
Combination treatment		20 (44)		14 (47)	6 (40)	
Death n, (%)		9 (20)		4 (13)	5 (33)	0.13

MPV, mean platelet volume; MCV, mean corpuscular volume; RDW, red blood cell distribution width; NLR, neutrophil to lymphocyte ratio; NMR, neutrophil to monocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein; mPAP, mean pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; 6MWD, six-minute walk distance; IPAH, idiopathic pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension. * Comparisons between controls and PAH **Comparisons between IPAH and CTEPH subgroups.

Correlations between hematologic biomarkers and PAH associated prognostic indicators

After we investigated the correlations of hematological parameters with each other, we did the same analysis with PAH associated prognostic indicators in our study group. In addition to the identified correlation between RDW and PLR, MPV showed mild correlation with NMR (rs =0.36, p=0.01and rs =0.30, p= 0.04 respectively). Both CRP and age showed no correlation with prognostic factors. Similar to the relationships, found between TAPSE, 6MWD and our risk score (PE-SCORE) (rs =0.44, p=0.003) and (rs = -0.60, p<0.0001), TAPSE and 6MWD were negatively associated with increased NLR (rs = -0.37, p=0.01 and rs = -0.40, p= 0.007 respectively). There was a lack of association between NMR, PLR and the PAH associated prognostic indicators.

Follow-Up, survival analyses, and prognostic factors

In the overall observation period of 26 (14-56) months, 9 cardio-pulmonary deaths occurred in patients with PAH and estimated mean survival time was 85 (95% CI, 72-99) months. In the overall population, Five-, 9-, 11-, 12- and 40-month survival rates were 98%, 95%, 93%, 86%, 80% and 74% respectively (Figure 1A).

Estimated mean survival times according to categorized biomarker levels were: for NMR, 93 (95% CI, 86-100) vs. 67 (95% CI, 45-88) months (p=0.006); for NLR 103 (95% CI, 92-113) vs. 67 (95% CI, 50-84) months (p=0.047); for PLR 100 (95% CI, 90-110) vs. 62 (95% CI, 42-82) months (p=0.024) respectively.

In patients with IPAH, estimated mean survival time was 82 (95% CI, 69-96) months and five-, 9-,11-,12- , 24- and 40-month survival rates were 96% (95% CI, 89–100%), 93% (95% CI, 83– 97%), 93% (95% CI, 83– 97%), 89% (95% CI, 79–96%), and 80% (95% CI, 70–90%) respectively. Also in patients with CTEPH, 5-, 9-, 11-, 12- , 24- and 40-month survival rates were 100%, 100%, 93% (95% CI, 91– 100%), 80% (95% CI, 70– 91%), 65% (95% CI, 40– 89%) and 65% (95% CI, 40– 89%) respectively (p= 0.22) (Figure 1C).

As significant associations of hematologic biomarkers with unfavorable outcome observed, we analyzed predictive ability of each biomarker and pairwise comparisons of their predictive abilities were investigated. NMR, NLR and PLR had significantly better predictive ability compared with TAPSE, 6MWD and MPAP (all p<0.05), whilst there were no significant differences among the first three biomarkers (Table 3). While NMR had the highest sensitivity (89%), PLR was the most specific (72%) for prediction of mortality, with appropriate cut-off values.

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Table 2. Baseline characteristics of the patient subgroups based on neutrophil to monocyte ratio levels.

	Overall N=45	NMR ≤9.2 n=24	NMR >9.2 n=21	p-value
Age, (years)	49 (32-58)	50 (36-64)	41 (31-52)	0.12
Sex n, (%)				
Female	29 (64)	15 (62)	14 (67)	0.77
Type n, (%)				
CTEPH	15 (33)	10 (42)	5 (24)	0.20
IPAH	30 (67)	14 (58)	16 (76)	
Follow-up duration (months)	26 (14-56)	31 (15-70)	24 (12-51)	0.39
Hemoglobin (mg/dL)	13.6 (12.3-15.3)	12.6 (11.8-15.3)	13.6 (12.6-15.2)	0.41
Platelet (10^3/mm^3)	204 (175-276)	207 (182-286)	204 (173-269)	0.60
White blood cells (x10^9/L)	7.6 (6.6-8.9)	6.9 (6.3-8.5)	7.8 (7.2-10.1)	0.19
RDW (%)	16.5 (14.1-17.4)	15.9 (14-18)	16.7 (14.6-17.3)	0.99
MCV (fl)	85 (78-91)	86 (72-91)	85 (82-91)	0.41
MPV (fl)	9.2 (8.7-10.2)	9.2 (8.7-9.8)	9.5 (8.7-10.4)	0.41
NLR	2.6 (1.9- 3.3)	1.9 (1.5-2.8)	2.9 (2.4-4.5)	**0.001**
PLR	106 (83-157)	102 (81-155)	128 (92-157)	0.5
NMR	9.2 (6.5-11.6)	6.6 (5.5-8.3)	11.6 (9.6-12.4)	**<0.001**
Creatinine (mg/dL)	0.9 (0.7-1)	0.9 (0.7-1.1)	0.9 (0.7-1)	0.50
CRP (mg/L)	6 (3-11)	6 (3-13)	5 (4-9)	0.72
Iron (µg/dL)	61 (40-68)	62 (37-94)	52 (42-67)	0.59
Ferritin (ng/mL)	25 (13-38)	23 (13-29)	32 (15-43)	0.19
mPAP (mmHg)	55 (45-65)	60 (45-65)	55 (45-65)	0.61
TAPSE (mm)	13 (12-15)	13 (12-15)	12 (11-14)	0.62
6MWD (meters)	290 (220-340)	295 (200-380)	290 (220-340)	0.29
Functional Class n, (%)				
Class II	21 (47)	12 (50)	9 (43)	
Class III	18 (40)	11 (46)	7 (33)	0,15
Class IV	6 (13)	1 (4)	5 (24)	
Pericardial effusion n, (%)	22 (49)	10 (41)	12 (57)	0.30
PLR ≤134 n, (%)	27 (60)	15 (62)	12 (57)	0.71
PLR >134 n, (%)	18 (40)	9 (37)	9 (43)	
NLR ≤2.2 n, (%)	18 (40)	14 (58)	4 (19)	**0.007**
NLR >2.2 n, (%)	27 (60)	10 (42)	17 (81)	
SCORE	2 (1-3)	1 (0-1.5)	3 (3-4)	**<0.001**
PE-SCORE	3 (1-4)	1.5 (0-3)	5 (3-6)	**<0.001**
Medication n, (%)				
Mono-therapy	25 (56)	12 (50)	13 (62)	0.42
Combination treatment	20 (44)	12 (50)	8 (38)	
Death n, (%)	9 (20)	1 (4)	8 (38)	**0.007**

CTEPH, chronic thromboembolic pulmonary hypertension; IPAH, idiopathic pulmonary arterial hypertension; RDW, red blood cell distribution width; MCV, mean corpuscular volume; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; NMR, neutrophil to monocyte ratio; PLR, platelet to lymphocyte ratio; CRP, C-reactive protein; mPAP, mean pulmonary arterial pressure; TAPSE, tricuspid annular plane systolic excursion; 6MWD, six-minute walk distance; PE-SCORE, pulmonary emboli SCORE.

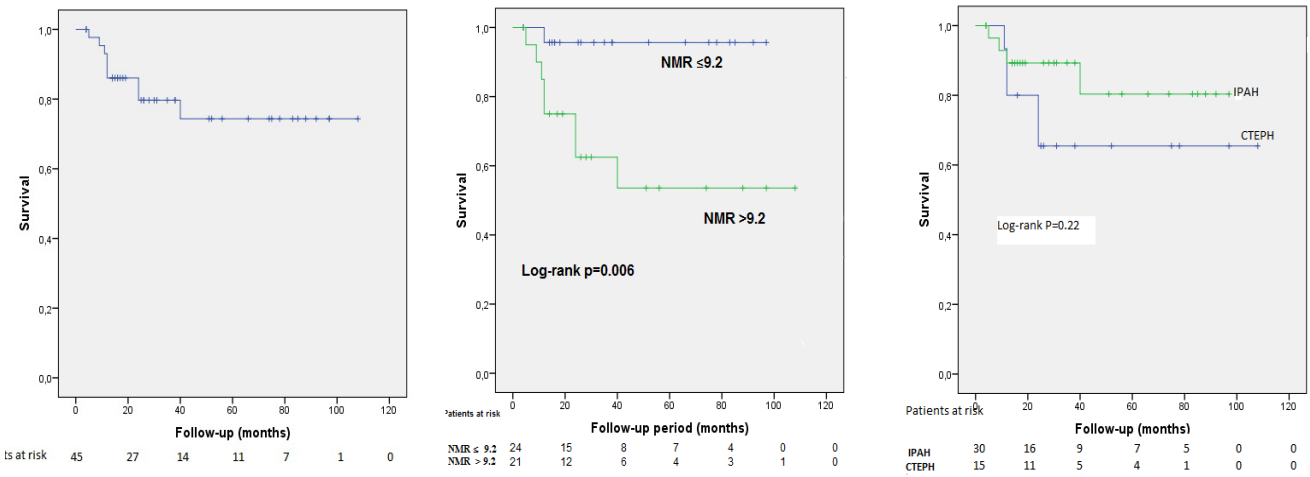

Figure-1. Kaplan-Meier cumulative survival curves of the patients with pulmonary arterial hypertension A) in all patients B and C) in subgroups. IPAH indicates idiopathic pulmonary arterial hypertension and CTEPH indicates chronic thromboembolic pulmonary hypertension. NMR, neutrophil to monocyte ratio.

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Table-3. Comparison of the predictive ability of prognostic factors and models in patients with PAH.

	AUC (95% CI)	p-value
NMR	0.77 (0.63-0.91)	0.01
NLR	0.72 (0.53-0.92)	0.04
PLR	0.76 (0.59-0.94)	0.02
TAPSE	0.30 (0.14-0.46)	0.07
6MWD	0.32 (0.14-0.49)	0.09
mPAP	0.56 (0.37-0.76)	0.56
PE-SCORE+RF	0.91 (0.81-1.00)	<0.0001
PE-SCORE	0.90 (0.79-1.00)	<0.0001

NMR, neutrophil to monocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; TAPSE, tricuspid annular plane systolic excursion; 6MWD, six-minute walk distance; mPAP, mean pulmonary arterial pressure. PE-SCORE, Pulmonary emboli SCORE. RF, model derived from TAPSE, 6MWD and MPAP; SCORE, model derived from NMR, NLR and PLR; PE-SCORE, model derived from pericardial effusion, NMR, NLR and PLR; AUC, area under curve; CI, confidence interval.

In PAH patients with NMR above the categorized level, 5-, 9-,11-,12- , 24- and 40-month survival rates were 95% (95% CI, 95–100%), 90% (95% CI, 78–96%), 85% (95% CI, 69–92%), 75% (95% CI, 55–86%), 62% (95% CI, 40–78%), 54% (95% CI, 32–63%) respectively (p= 0.006) (Figure 1B). While In IPAH patients with NMR above the categorized level 5-, 9-,12-, and 40-month survival rates were 93% (95% CI, 86–100%), 87% (95% CI, 78–95%), 80% (95% CI, 70–93%), 67% (95% CI, 50–82%), CTEPH group with NMR above the categorized level had 80%(95% CI, 65–100%), 60% (95% CI, 38–82%), and 20% (95% CI, 5–39%) 11-,12- and 24-month survival rates respectively. In IPAH patients with lower NMR, all patients survived and only one death was observed in CTEPH patients with similar categorized levels.

Cox regression analyses confirmed the difference across our clinical subgroups of PAH in terms of categorized hematologic biomarkers. In the univariate analysis NLR, PLR, NMR, MPAP and pericardial effusion were found as the significant predictive variables (Supplementary table 2). Of the available individual clinical characteristics, NMR was the only significant prognostic factor after adjusting for appropriate confounding factors (6MWD, MPAP) by cox regression analysis (OR 1.4 (95% CI, 1-1.8) P=0.04). Than we performed the analysis considering only two (NMR and pericardial effusion) variables and found an independent association between NMR and mortality (OR 1.1 (95% CI, 1-1.2) p=0.04). Also pericardial effusion tended to be an independent significant factor for prognosis (OR 6.3 (95%CI 0.76-53) p=0.08). When the multivariate analysis performed considering pericardial effusion and optimized cut-off levels of NMR and PLR, only categorized NMR level was independently associated with mortality (OR 7.9, 95%CI (1.1-65) p= 0.04).(PLR: OR 3.2 (95%CI 0.6-17) p=0.18; pericardial effusion: OR 3.9 (95%CI 0.4-38) p=0.24). The percentage of death in our patients according to the categorized NMR level and the presence of pericardial effusion is shown in figure 2.

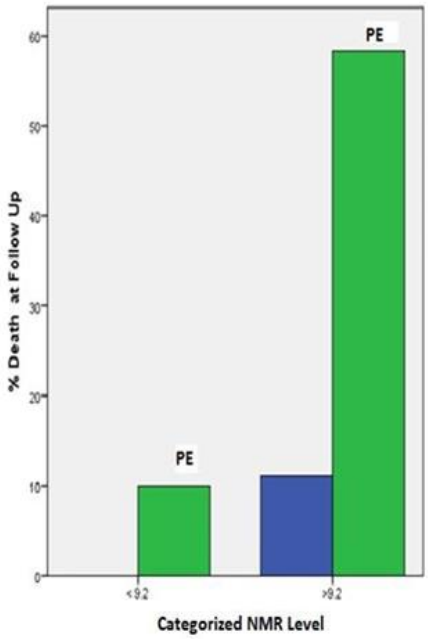

Figure 2: The mortality rates during follow-up period according to categorized neutrophil to monocyte ratio (NMR) level in PAH patients with and without pericardial effusion (PE).

Risk stratification models and risk score performance to predict events

In our group, we developed mortality risk scores by using the regression coefficients of the predictive variables (NMR, NLR, PLR and pericardial effusion), which were detected as 2.6, 1.4, 1.5, 2.5 respectively. The predictive ability and the explained degree of mortality for the two risk score models derived from our variables; with and without pericardial effusion, were 91%, 0.54 and 89%, 0.46 respectively. Patients who died had higher risk scores than those who survived (supplemantary table 2), and the two risk scores had the significantly better predictive ability for cardio-pulmonary death than the score derived from known prognostic indicators. Both scores were significantly associated with mortality on the univariate analyses (SCORE: OR 3.2, 95% CI 1.4-6.9 p=0.005; PE-SCORE: OR 2.3, 95% CI 1.4–4 p=0.002). When multivariable analysis was performed, including both scores with the model (RF) derived from known prognostic indicators separately, associations with unfavorable outcomes continued to be significant (SCORE: OR 4.8, 95%CI 1.4-15 p=0.008; PE-SCORE: OR 3.2, 95%CI 1.4–7.1 p=0.004). The crude associations of our risk scores with unfavorable outcomes are shown in Figure 3. Within the PE-SCORE, the percentage of hematologic biomarkers above the categorized levels are shown in figure 4.

Estimated mean survival times according to categorized risk levels for our models were (for PE-SCORE) 102 (95% CI, 94-110) months vs. 37 (95% CI, 17-58) months and (for SCORE) 104 (95% CI, 97-111) vs. 55 (95% CI, 34-75) months (Figure 5A and 5B).

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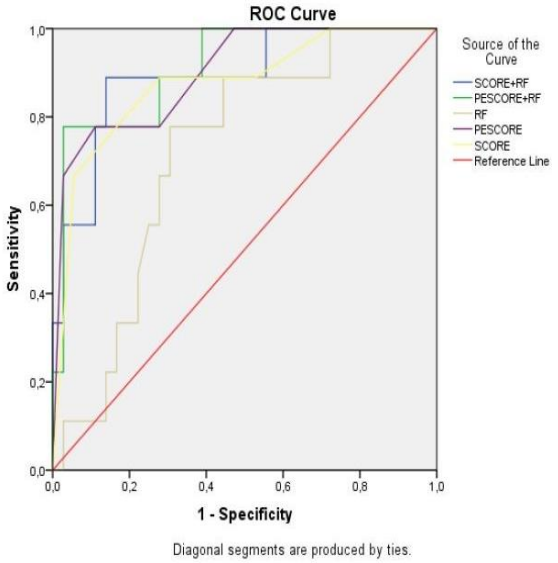

	AUC (95% CI)	P-value	Nagelkerke R Square*	Predictive probability %
PESCORE+RF	0.91 (0.81-1.00)	<0.0001	0.58	91
PESCORE	0.90 (0.79-1.00)	<0.0001	0.54	91
SCORE + RF	0.89 (0.77-1.00)	<0.0001	0.53	89
SCORE	0.87 (0.74-1.00)	0.001	0.46	89
RF	0.72 (0.55-0.88)	0.04	0.14	78

Figure-3. Comparison of ROC curves of our proposed risk stratification models individually and in combination with other models in predicting mortality in patients with PAH. RF, model derived from TAPSE, 6MWD and MPAP; SCORE, model derived from neutrophil to monocyte ratio (NMR), neutrophil to lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR); PE-SCORE, model derived from pericardial effusion, NMR, NLR and PLR; AUC, area under curve; CI, confidence interval. *By using the pseudo- R^2 statistic according to the ‘‘Nagelkerke R^2’’, explanatory power of our models was tested to assess the degree to which the model explained the variance of the mortality.

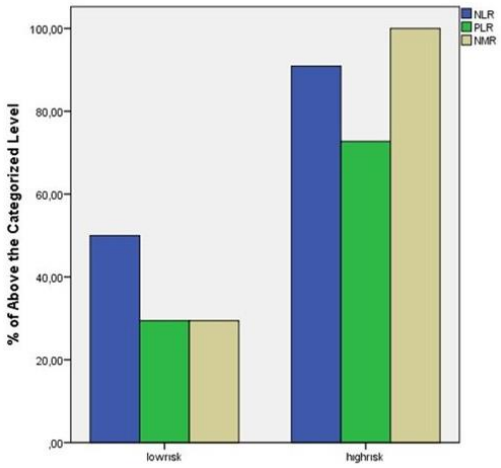

Figure 4: The percentage of hematologic biomarkers above the categorized level according to combined risk stratification score with presence of pericardial effusion (PE-SCORE). NMR, neutrophil to monocyte ratio; NLR, neutrophil to lymphocyte ratio and PLR, platelet to lymphocyte ratio.

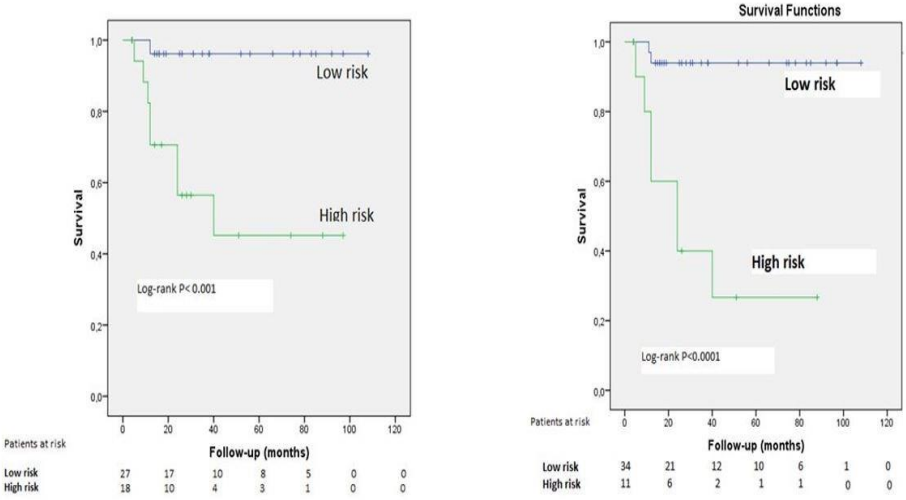

Figure 5: Kaplan-Meier cumulative survival curves of patients with pulmonary arterial hypertension A) according to combined risk stratification score without the presence of pericardial effusion (SCORE) B) according to combined risk stratification score with presence of pericardial effusion (PE-SCORE)

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Internal validation group

Analyses of the IPAH patients (n= 30) yielded essentially identical results. Patients with unfavorable outcomes had higher values of risk scores, compared with patients who survived (median SCORE of 2 (1-3) vs. 4 (4-4) and median PE-SCORE of 2 (0-3) vs. 6 (6-6) respectively, all p=0.002). The predictive ability for the two risk score models derived from our variables; with and without pericardial effusion, were 97% and 93% respectively. The model derived from known prognostic indicators, both risk scores and combined scores were compared for cardio-pulmonary death by ROC curve analysis. For combined scores AUC was 0.98 (95%CI 0.94-1) p=0.002, for PE-SCORE 0.98 (95%CI 0.93-1) p=0.002, for SCORE 0.96 (95%CI 0.89-1) p=0.003 and for known prognostic indicator score 0.77 (95%CI 0.59-0.96) p=0.08 respectively. Other analyses with the biomarkers and combined scores also yielded essentially identical results as shown for our group (data not shown).

DISCUSSION

The present study is the first to investigate the potential prognostic role of hematologic biomarkers in PAH patients. Our results showed that as a marker of inflammation and remodeling, NMR increased in PAH patients compared to healthy controls, independently predicting mortality. Our risk stratification model on admission identified patients with poor outcomes more accurately than other prognostic factors.

A comprehensive assessment of prognosis in PAH patients helps clinicians determine the therapeutic strategy in clinical practice. Although a number of biomarkers (e.g. CRP, uric acid, NT-proBNP) have been reported in association with disease severity and prognosis in PAH, only NT-proBNP is widely used in clinical settings (14). Hematologic biomarkers might provide a promising new marker for estimating the prognosis of patients with PAH as they are readily available worldwide.

Association between inflammatory cell types and immune response to inflammation and vascular remodeling may be relevant to several different aspects of PAH (1). Inflamed tissues due to the deregulated immunity and altered metabolism, are attributable to the recruitment of monocytes and neutrophils, in addition to locally proliferating lymphocyte populations (1). Elevated levels of several cytokines and chemokines correlate with a worse clinical outcome in PAH patients and may serve as biomarkers of disease progression. The fact that inflammation precedes vascular remodeling in experimental PAH suggests that altered immunity is a cause rather than a consequence of vascular disease. Although little attention has been given to the neutrophils in the pathogenesis of PAH, it is evident both in experimental and clinical studies that neutrophil elastase can influence pathogenesis. Enhanced neutrophil elastase has recently been revealed in smooth muscle cells from patients with IPAH (1,15). Neutrophil elastase can trigger immune inflammatory response, and by repressing it both clinical and experimentally, induced disease progression regresses (16). During inflammatory conditions, neutrophil count increases, and the amount of circulating blood monocytes decrease by migration to tissues and differentiation to macrophages. Experimental and certain PAH related diseases are characterized with macrophage infiltration. Even in patients with IPAH, recruitment of lung macrophages is evident (1,17). Activation of macrophages is also closely linked to epigenetic changes that stimulate and induce pro-inflammatory cytokines, proliferation of vascular fibroblasts and altered host metabolism in experimental models of PAH. Changes in metabolic phenotype involving a switch to glycolysis, fatty acid oxidation, and production of reactive oxygen species underlie the abnormal interaction of fibroblasts and macrophages. Also, there is recent evidence for macrophage granulocyte-macrophage colony-stimulating factor (GM-CSF) and leukotriene B4 (LTB4) signaling pathways in PAH development. Reversing the metabolic phenotype by blocking macrophage-derived LTB4 biosynthesis or signal transduction reverses experimental PAH and the pathological features of PAH in terms of macrophage recruitment and activation (18). Besides, higher levels of RDW were shown to be associated with inflammation and systolic pulmonary arterial pressure (19, 20). Recently, Can et all, found that although no difference observed in platelet count, MPV was significantly high in adult patients with IPAH than in healthy control patients (21). They suggested that platelet activation may directly impact the pathogenesis of PAH. In addition to the parallel findings with this study, MPV, RDW, NMR and NLR were also significantly higher in our patients according to normal subjects. CRP level failed to be found as a prognostic marker in our analysis, and also it was not different in our subgroups, possibly due to the exclusion of patients with increased CRP assuming a subclinical infection. Observed significant correlations of our hematologic biomarkers with MPV and RDW suggest them as a marker of underlying inflammation and confirm the interactions of inflammatory cells with each other in PAH. Zheng et all, supported our idea by defining significant associations between elevated MPV levels and IPAH severity though they observed no difference in terms of prognosis (2). By determining individual prognostic values of NMR, NLR, and PLR and independent prognostic values of NMR, our data revealed the reported findings regarding inflammation above.

Consistent with previous findings, the prognostic value of pericardial effusion, a known surrogate marker of survival in PAH patients, was significant with unadjusted analyses but showed a clear trend to be significant after adjustment (8). Also patients with higher NMR levels had higher mortality rates if they had pericardial effusion. Increased functional class, treatment modality, and uric acid level did not predicted poor prognosis for PAH patients. Some established risk factors like 6MWD, and TAPSE failed to reach statistical significance. This discrepancy might be explained by the small study population and few patients who were severely diseased in functional class IV in our study. In ROC analyses, hematologic biomarkers outperformed TAPSE, mPAP, and 6MWD in predicting prognosis. Even after adjusting for these established markers, only NMR independently predicted mortality in multivariate analysis. This finding suggested NMR as a prognostic non-invasive, in-expensive and easily accessible marker complementary to currently used markers irrespective of treatment modality and functional class. Also, by excluding patients with known hematologic diseases and active inflammation, the idea of higher NMR levels being an element of the PAH disease process rather than a result of other comorbid conditions is favored.

In PAH patients, Humbert et all, reported 1-year and 3-year survival rates of 83% and 58%, with a baseline NYHA functional class III and IV rate of 67% and 14% (22). In our study, 12-month and 40 month survival rates were 93% and 74% respectively. Baseline NYHA functional classes and treatment modalities might explain why the survival in our study was relatively better. Although survival rates were not different between CTEPH and IPAH patients, when the outcome had analyzed according to optimized NMR levels, lower survival rates were observed in CTEPH group. Distinct inflammatory profiles and alterations in metabolic function of PAH vascular cells can be the cause of different phenotypic characteristics of different PAH subtypes.

It is likely that identifying new biomarkers with different origins or making combined use of them can provide additional prognostic information for an individual patient; therefore risk stratification models are needed. NMR and pericardial effusion were the dominant risk factors in our models. Our risk scores appeared to provide an improved clinical risk stratification model on which to add such biomarkers with the goal of optimal risk prediction. Testing in additional data sets will assess the broader generalizability of our findings, and in this manner, treatment goals can be identified to reduce functional impairment and prolong life.

This study represented a retrospective single-center experience conducted in a small patient group due to the rarity of the disease. The limited outcome did not allow including many variables in multivariable analyses of mortality. Nonetheless, NMR remained predictive of mortality after individually adjusting for important clinical variables, supporting its robust prognostic value. To minimize referral bias, we started our survival analysis from the first diagnosis of PAH by right heart catheterization. Finally, we did not validate our score performance in an external cohort. Future large studies with long follow-up and diverse population are needed to confirm the clinical relevance of our findings.

CONCLUSION

The present study demonstrates NMR as an independent prognostic factor in patients with PAH. A combination of hematologic biomarkers enabled us to develop a novel risk stratification model for survival.

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Author Contributions: BŞ, NÖŞ, MS, OT: Study design, Literature review, Data collection and processing, Patient therapy, Analysis **BŞ:** Data collection, Writing, Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Supplemantary Table 1: Medication of our study patients.

Medical treatment n, (%)	Overall PAH n=45	IPAH n=30	CTEPH n=15	Deaths n=9	Survivors n=36
Prostanoids	4 (9)	1 (3)	3 (20)	1 (11)	3 (8)
ERA	18 (40)	15 (50)	3 (20)	1 (11)	17 (47)
PDE	3 (7)	0 (0)	3 (20)	2 (22)	1 (3)
Prostanoids+ ERA	4 (9)	3 (10)	1 (7)	2 (22)	2 (5)
Prostanoids + PDE	1 (2)	0 (0)	1 (7)	0 (0)	1 (3)
ERA + PDE	8 (18)	4 (13)	4 (26)	1 (11)	7 (20)
Prostanoids + Era + PDE	7 (15)	7 (24)	0 (0)	2 (23)	5 (14)
Mono-therapy	25 (56)	16 (53)	9 (60)	4 (44)	21 (58)
Combination treatment	20 (44)	14 (47)	6 (40)	5 (56)	15 (42)

ERA, Endothelin receptor antagonists; PDE, Phosphodiesterase type-5 inhibitors.

Supplemantary Table 2: Comparison of the baseline characteristics of the fatal cases and survivors.

	Overall n=45	**Deaths N=9**	**Survivors N=36**	**p-value**	**Univariate OR (95% CI)**	**p-value**
Age, (years)	49 (32-58)	50 (32-57)	47 (33-59)	0.9	0.9 (0.9-1)	0.86
Sex n, (%)						
Female	29(64)	7(78)	22(61)	0.45	2.2 (0.4-12.3)	0.35
Follow-up duration (months)	26 (14-56)	12 (11-24)	31 (16-74)	**0.003**	1.0 (0.99-1.15)	0.05
Hemoglobin (mg/dL)	13.6 (12.3-15.3)	12.6 (12.2-13.6)	14 (12.3-15.5)	0.15	1.4 (0.9-2)	0.14
Platelet (10^3/mm^3)	204 (175-276)	256 (204-306)	197 (163-271)	0.06	1.1 (0.9-1.2)	0.08
RDW (%)	16.5 (14.1-17.4)	17.1 (15.1-18.2)	15.9 (14-17.3)	0.33	0.96 (0.75-1.2)	0.75
White blood cells (x10^9/L)	7.6 (6.6-8.9)	7.4 (7.2-8)	7.7 (6.4-9)	0.74	0.9 (0.6-1.2)	0.57
MCV (fl)	85 (78-91)	83 (82-91)	85 (77-91)	0.91	0.98 (0.9-1.1)	0.72
MPV (fl)	9.2 (8.7-10.2)	9.2 (8.6-9.7)	9.2 (8.7-10.2)	0.84	1.2 (0.6- 1.25)	0.51
NLR	2.6 (1.9- 3.3)	3.3 (2.3-6.3)	2.4 (1.8-3.2)	**0.04**	1.3 (1.04-1.58)	**0.02**
PLR	106 (83-157)	157 (135-300)	103 (78-146)	**0.01**	1.0 (1.00-1.01)	**0.02**
NMR	9.2 (6.5-11.6)	10.1 (9.4-11.8)	8.3 (6.1-9.8)	**0.01**	1.1 (1-1.2)	**0.01**
Creatinine (mg/dL)	0.9 (0.7-1)	0.8 (0.7-0.99)	0.9 (0.7-1)	0.5	2.7 (0.7-102)	0.6
CRP (mg/L)	5.7 (3.4-11.4)	5.7 (3.6-6.8)	5.6 (3.3-14)	0.4	0.36 (0.93-1.2)	0.36
Iron (µg/dL)	61 (40-68)	47 (42-65)	61 (39-76)	0.5	1.01 (0.98-1.0)	0.25
Ferritin (ng/mL)	25.3 (13.3-38.4)	38 (22.3-61.6)	24 (13-34)	0.1	0.98 (0.96-1)	0.15
mPAP (mmHg)	55 (45-65)	55 (50-55)	55 (45-65)	0.56	1.02 (1.01-1.03)	**0.01**
TAPSE (mm)	13 (12-15)	12 (11-12)	13 (12-15)	0.06	1.4 (0.9-2.1)	0.08
6MWD (meters)	290 (220-340)	240 (160-320)	300 (240-375)	0.09	1 (0.99-1)	0.10
Functional Class n, (%)						
Class II	21 (47)	2 (22)	19 (53)	0.24	3.6 (0.6-22)	0.28
Class III	18 (40)	5 (56)	13 (36)			
Class IV	6 (13)	2 (22)	4 (11)			
Pericardial effusion n, (%)	22 (49)	8 (89)	14 (39)	**0.01**	12.6 (1.4-111.7)	**0.02**
Type n, (%)						
KTEPH	15 (33)	5 (56)	10 (28)	0.13	0.3 (0.07-1.4)	0.12
IPAH	30 (67)	4 (44)	26 (72)			
PLR ≤134 n, (%)	27 (60)	2 (22)	25 (69)	**0.01**	7.9 (1.4-44.6)	**0.02**
PLR >134 n, (%)	18 (40)	7 (78)	11 (31)			
NLR ≤2.2 n, (%)	18 (40)	1 (11)	17 (47)	0.06	7.1 (0.8-63)	0.08
NLR >2.2 n, (%)	27 (60)	8 (89)	19 (53)			
NMR ≤9.2 n, (%)	24 (53)	1 (11)	23 (64)	**0.007**	10.1 (1.3-80.6)	**0.03**
NMR >9.2 n, (%)	21 (47)	8 (89)	13 (36)			
SCORE	2 (1-3)	4 (3-4)	2 (0-3)	**<0.0001**	3.2 (1.4-6.9)	**0.005**
PE-SCORE	3 (1-4)	6 (5-6)	2 (1-4)	**<0.0001**	2.3 (1.4-4)	**0.002**
Medication						
Mono-therapy	25 (56)	4 (44)	21 (58)	0.48	1.5 (0.4-5.7)	0.52
Combination treatment	20 (44)	5 (56)	15 (42)			

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Alcohol use in Macau Secondary School Students and relating family factors

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ABSTRACT

Objective: To understand the current status of alcohol use in Macau secondary students and to explore the relationship between alcohol use behaviour in the students and various family factors. At the same time, the study also aimed to analyze the predictive power of various family factors on alcohol use, to provide a reference for the formulation of strategies for prevention and control of alcohol use in Macau adolescents.

Material and Methods: The study was a cross-sectional study with data collection using a self-constructed questionnaire. The study samples were students in formal or vocational education in Macau in the school year 2020/2021, with randomization using randomized multistage stratified cluster sampling. A total of 939 valid samples were collected for data analysis. The distributions of the background variables and the behavior of alcohol use were analyzed using descriptive analysis, while Chi-square test (Chi-square), one-way analysis of variance (One-Way ANOVA), Kruskal-Wallis one-way analysis of variance, and logistic regression analysis were used for inferential statistical analysis.

Conclusion: There is an increased risk of current alcohol use in the students whose siblings also have a drinking habit, who have helped family members buy alcohol, and whose parents are more positive about drinking and who think their parents do not care about them. Intervention measures should be formulated targeting these factors.

Keywords: adolescent alcohol use, family relationship, Macau

INTRODUCTION

According to the World Health Organization (WHO) data, harmful alcohol use is an important factor leading to disease burden in the world. In 2016, over three million people in the world died due to harmful alcohol use, summing up to 5.3% of the world's mortality rate. If we estimate the harmful effect of disability disability-adjusted life years, alcohol accounted for 5.1% of the world's disease and injury burden in the same year (1). Harmful alcohol use has severe effects to the users and the society as a whole.

In fact, alcohol is one of the most commonly abused substances among adolescents (2). The report by WHO in 2019 mentioned that 1.6 billion adolescents of age 15-19 years old were current alcohol users, which accounted for over 1/4 of all adolescents in that age group (1). During adolescence, young people go through a period of rapid change physically, psychologically, and socially. In this period, young people are curious about anything new, and they like excitement and are ready for adventures. This is the period when they start to try substances of abuse, including alcohol, cigarette, and illicit drugs.

In addition, developing brains can be easily affected by substances of abuse, this would have long term effect on the neurological development of the adolescents (3) The younger the age of first alcohol use, the more likely it is to develop alcohol dependence, illicit drug use and other high risk behaviors in adult lives (4). Thus, alcohol use in adolescents is an important public health problem that needs special attention.

Research data suggested that parents' attitude towards drinking, drinking behavior and parenting style is significantly correlated with adolescent alcohol use (5). According to the study, lower parents' educational level and lower parental monthly income would lead to higher rate of alcohol use in adolescents (6). On the other hand, family structure such as single parent family, parental comment of the children, and drinking in parents and siblings are also correlated with alcohol use in adolescents (7).

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According to Macau Centre of Disease Control and Prevention, there has been a rising trend on alcohol use in Macau secondary students from 2012-2013 to the school year 2017-2018. These included the data on "ever drank alcohol", "recent alcohol use of at least once in the past 30 days" and "ever binge drank in the past 30 days", there were 2.7%, 0.5% and 2.5% increases respectively from 2012 to 2018 (8) (9).

This study sought to assess for the current condition of the behavior alcohol use in Macau secondary students and to examine the association of current alcohol use with different family factors among the students. We hypothesize that early alcohol use in the secondary students are related to family background and the students' relationship with their parents. To our knowledge, this is the first study done in Macau on the association between family factors and alcohol use in secondary students. With the study, we aim to provide data that would be of use in the future for local Public Health strategy in managing adolescent alcohol use.

MATERIAL AND METHODS

General Study Information: The Study is one part of a cross-sectional study named "Alcohol Use in Macau Secondary Students---a Study on Knowledge, Belief and Behavior of Alcohol Use and their Correlating Factors". In the survey, students aged 11-20 were asked to fill in a questionnaire containing a total of 73 questions on 7 different parts. This included background information, knowledge about alcohol use, beliefs towards alcohol use, behaviors of alcohol use, family factors, peer factors and mental health condition. Parental consents were obtained for the participation of the students under the age of 18.

Measures of Behavior of Alcohol Use

There were 10 questions in the questionnaire about alcohol use. The questions were:

1. Have you ever had any alcohol?
2. How old were you when you drank alcohol for the first time?
3. What was the reason for drinking alcohol for the first time?
4. In the past 1 month, how many days on average you have had alcohol?
5. In the past 1 month, have you ever had more than 5 glasses of alcohol in several hours?
6. In the past 1 month, what was the average amount of consumption (in alcohol unit) each time for the type of alcohol that you consumed most often?
7. Have you ever got drunk?
8. Have you ever had bad consequences due to drinking?
9. Where do you usually obtain alcohol?
10. Where do you usually drink?

For question number 6, we showed different types of glasses to demonstrate the alcohol unit, so that it is easier for the students to report the drinking amount by alcohol unit. For questions number 8-10, students could select more than one answer.

Measures of Family Factors

Family factors included family structure, family interaction and parental factors.

The 9 questions on this part included "family members who live together", "father and mother's education level", "father and mother's work", "drinking habit of the family members who live together", "ever helped family members buying alcohol", "perceived parental attitudes towards drinking", "perceived parental care", "relationship with parents" and "family financial situation".

Sampling, Sample Size and Recruitment Process: In the survey, a total of 24789 secondary students from formal education and vocational education in Macau were eligible for randomization. It was calculated that at least 648 samples have to be included to achieve a confidence level of 99%, with a sampling error of <5%. Randomization was done by randomized multistage stratified cluster sampling on school and class bases. 974 students from 6 schools and 30 classes were invited to fill-in the questionnaires and 939 valid questionnaires were collected for data analysis.

Data Analysis: After questionnaire collection, valid questionnaires were coded, and data analysed using SPSS 26. Data analysis included:

1. Descriptive analyses such as average, median, percentage and standard deviation for the distributions of the variables
2. Using Chi-square test to analyse the difference between various family factors and the alcohol use behaviour in the samples
3. Using One-way ANOVA to check if there were significant differences in alcohol use behaviour with changes in different family factors. If there was significant difference, for variables with group number of <30, Kruskal-Wallis one way analysis of variance was used
4. Using logistic regression analysis to check if the changes in different family factors can predict current alcohol use (alcohol use of at least once within the past 30 days).

RESULTS

Demographic Data

Among the 939 adolescents who filled in the questionnaires and provided data for this study, 491 (52%) were males and 448 (48%) were females; the age range was 11-20 years old. Details are shown in table 1.

Table 1. Demographic data

Variable	Group	Number	%
Sex	M	491	52.3
	F	448	47.7
Class	Secondary 1	161	17.1
	Secondary 2	165	17.6
	Secondary 3	168	17.9
	Secondary 4	153	16.3
	Secondary 5	146	15.5
	Secondary 6	146	15.5
Age	11-12	100	10.7
	13-14	292	31.2
	15-16	315	33.7
	17-18	214	22.9
	19-20	15	1.6

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Behavior of Alcohol use

The results are as followed (see table 2):

1. About 70% of all students have used alcohol before.
2. The most common age of first drink of alcohol was "7-12 years old" (37.1%), followed by "≤ 6 years old" (27%) and "13-15 years old" (26.4%). Only 9.5% had their first alcoholic drink at 16 years old or after.
3. The most common reason for the first drink was "curiosity" (65%), followed by "family request" (19.1%), "friends' encouragement" (4.7%) and "others" (7.5%). "Being in a bad mood" (3.8%) was the least common reason for first drink.
4. Within the previous 1 month before the survey, about 17% of the students had engaged in binge drinking.
5. The most common place for obtaining alcohol was "home" (53.8%), followed by "shop" (45.5%), "restaurant" (32.6%), "pub or Karaoke" (23.1%) and "others" (5.4%).
6. Most students drank at home (66.5%). 41.9% drank in restaurant, 20.9% of them drank in friends' homes, 17.6% drank in pub or Karaoke, 7.5% drank outdoors such as on the street or in the park, and 5.4% drank in other places.
7. Beer was the most frequently consumed alcohol (64.2%), followed by red or white wine (17.7%), spirits 7.4), and sake (5.8%). Rice liquor was the least frequently consumed alcohol (4.8%).
8. 33% of the students were current alcohol users (use of alcohol of at least once within the past 30 days).
9. Within the past 1 year before the survey, 35.5% of the students had never taken any alcohol. The most common frequency of drinking was once or less than once per month (44.5%), followed by 2-4 times per month (15.5%). 2.7% of the students drank 2-3 times per week and 1.8% drank 4 times or more per week
10. In the study, an accident such as falling down (2.9%) was the most commonly reported bad consequence of drinking, followed by "absence from school" (2%), "led to a fight with others" (1.2%) and "led to a quarrel" (1.1%).

Table 2. Alcohol use behavior in the study samples

Behavior	Group	No	%
Ever drank alcohol	Yes	663	70.6
	No	276	29.4
Age when first drank	≤ 6 years old	177	27.0
	7-12 years old	243	37.1
	13-15 years old	173	26.4
	≥16 years old	62	9.5
Reason of first drink	Curiosity	432	65.0
	Family request	127	19.1
	Encouraged by friends	31	4.7
	Bad mood	25	3.8
	Others	50	7.5
Ever had 5 drinks or more in several hours in the past 1 month	Yes	114	17.1
	No	551	82.9
Ever binge drunk	Never	500	75.2
	Rarely	113	17.0
	Sometimes	42	6.3
	Always	2	0.3
	All the time	8	1.2
Usual place of obtaining alcohol (more than one answer allowed)	Shop (supermarket etc.)	303	45.5
	Pub or Karaoke	154	23.1
	Restaurant	217	32.6
	Home	358	53.8
	Others	36	5.4
Usual place of obtaining alcohol (more than one answer allowed)	Home	433	66.5
	Restaurant	279	41.9
	Pub or Karaoke	117	17.6
	Outdoors (park or street)	50	7.5
	Friend's home	139	20.9
	Others	36	5.4

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Table 2. Alcohol use behavior in the study samples (cont.)

Behavior	Group	No	%
The alcohol most frequently consumed in the past 1 month	Beer	199	64.2
	Red wine or white wine	55	17.7
	Spirits	23	7.4
	Rice liquor	15	4.8
	Chinese liquor	0	0
	Sake	18	5.8
Current drinker	Yes	310	33.0
	No	629	67.0
Frequency of drinking in the past 1 month	No drinking	236	35.5
	≤1 time per month	295	44.5
	2-4 times per month	103	15.5
	2-3 times per week	18	2.7
	≥ 4 times per month	12	1.8
Bad consequences due to drinking (more than one answer allowed)	Accident (fall down etc.)	19	2.9
	Absence from school	13	2.0
	Fight with others	8	1.2
	Quarrel with others	7	1.1
	Others	9	1.4

In addition, we also calculated the average alcohol unit consumed each time the students drank in the previous 1 month before the study. In our study, the average alcohol unit consumed each time was 3.09 (S. D. 3) for all students. Male consumed more unit than female which was 3.47 alcohol unit (S.D. 3.43) each time. For female, the average alcohol unit consumed was 2.65 (S.D. 2.36). According to the US National Health Institute, heavy drinking is defined as > 4 alcohol unit per day in males of age ⩽65 years old and >3 alcohol unit per day in female of any age (10). Considering the above-suggested alcohol limit, about 31% of male students in our study has had heavy drinking the corresponding figure for female students was 26.8% (see table 3).

Table 3. Heavy drinking in the past 1 month

Alcohol use	Group	Male No. (%)	Female No. (%)	Total
Drinking exceeding suggested limit for heavy drinking in past 1 month	Yes	51(31.3)	38(26.8)	89(29.2)
	No	112(68.7)	104(73.2)	216(70.8)

Table 4. Chi-square test for family factors and alcohol use behavior in the study samples

Variables	Group	No.	Current drinker No N (%)	Current drinker Yes N (%)	χ^2
Parents divorced	Yes	102	66(64.7)	36(35.3)	0.34
	No	799	540(67.6)	259(32.4)	
Father's education level	Primary or below	97	63(64.9)	34(35.1)	0.08
	Secondary	297	197(66.3)	100(33.7)	
	Diploma	79	47(59.5)	32(40.5)	
	University or above	334	224(67.1)	110(32.9)	
Mother's education level	Primary or below	96	67(69.8)	29(30.2)	
	Secondary	329	209(63.5)	120(36.5)	0.64
	Diploma	90	49(54.4)	41(45.6)	
	University or above	311	217(69.8)	94(30.2)	
Parents' work condition	Both not on shift	464	301(64.9)	163(35.1)	1.31
	Either one on shift	197	131(66.5)	66(33.5)	
	Both on shift	119	84(70.6)	35(29.4)	
Father drinks	Yes	452	272(60.2)	180(39.8)	13.89***
	No	362	263(72.7)	99(27.3)	
Mother drinks	Yes	253	137(54.2)	116(45.8)	20.47***
	No	571	402(70.4)	169(29.6)	
Siblings drink	Yes	111	48(43.2)	63(56.8)	35.06***
	No	507	367(72.4)	140(27.6)	
Ever helped family members to buy alcohol	Yes	207	100(48.3)	107(51.7)	42.10***
	No	730	528(72.3)	202(27.7)	

Note: *** $p < .001$

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Family Factors and Alcohol Use in Secondary Students

We used Chi-square test to assess the relationship between different family factors and the behaviour of alcohol use in the students. As is shown in table 4, several factors are significantly correlated with current alcohol use in the students. These included "father with the habit of drinking" ($\chi 2=13.89$, $p < .001$), "mother with the habit of drinking" ($\chi 2=20.47$, $p < .001$), "drinking habit in siblings" ($\chi 2=35.06$, $p < .001$), "ever helped family members buying alcohol" ($\chi 2=42.10$, $p < .001$), "parents' attitude towards drinking alcohol" ($\chi 2=106.56$, $p < .001$), "perceived parental care" ($\chi 2=7.53$, $p < .01$) and "relationship with parents" ($\chi 2=8.24$, $p< .01$)

Table 4. Chi-square test for family factors and current alcohol use in the study samples (cont.)

Variables	Group	No.	Current drinker		χ^2
			No N (%)	Yes N (%)	
Parents' attitude towards drinking	Very much disagree	98	93(94.9)	5(5.1)	106.56***
	Disagree	187	150(80.2)	37(19.8)	
	Neutral	513	332(64.7)	181(35.3)	
	Agree	119	51(42.9)	68(57.1)	
	Very much agree	22	3(13.6)	19(86.4)	
Perceived parental care	Never care	9	7(77.8)	2(22.2)	7.53**
	Not care	35	17(48.6)	18(51.4)	
	In between	217	135(62.2)	82(37.8)	
	Care	445	301(67.6)	144(32.4)	
	Care very much	233	169(72.5)	64(27.5)	
Relationship with parents	Very bad	17	8(47.1)	9(52.9)	8.24**
	Bad	41	30(73.2)	11(26.8)	
	Average	285	170(59.6)	115(40.4)	
	Good	444	310(69.8)	134(30.2)	
	Very good	152	111(73.0)	41(27.0)	
Quarrel between parents	Never	211	144(68.2)	67(31.8)	1.18
	Rarely	327	227(69.4)	100(30.6)	
	Sometimes	292	184(63.0)	108(37.0)	
	Always	81	56(69.1)	25(30.9)	
	All the time	25	15(60.0)	10(40.0)	
Quarrel with parents	Never	134	95(70.9)	39(29.1)	3.02
	Rarely	326	221(67.8)	105(32.2)	
	Sometimes	357	241(67.5)	116(32.5)	
	Always	90	51(56.7)	39(43.3)	
	All the time	31	20(64.5)	11(35.5)	
Family financial condition	Poor	25	13(52.0)	12(44.0)	0.67
	Below average	105	71(67.6)	34(32.4)	
	Average	515	355(68.9)	160(31.1)	
	Above average	232	138(59.5)	94(40.5)	
	Good	61	51(83.6)	10(16.4)	

Note：**P< .01,***P< .001

Family Factors to Predict Current Alcohol Use in Secondary Students

With the results in table 4, all factors that were with significantly correlated with current alcohol use in the students were put in logistic regression analysis (LRA) to assess if the factors can predict current alcohol use in the students. The factors include"father with the habit of drinking", "mother with the habit of drinking", "drinking habit in siblings", "ever helped family members buying alcohol", "parents' attitude towards drinking ","perceived parental care" and"relationship with parents". Student's reported status of current alcohol use (use of alcohol within the past 30 days) was the dependent variable and all other above-mentioned factors were independent variable.

As is shown in table 5, it is found that 4 factors are significantly associated with increasing risk of current alcohol use, these included"drinking habit in siblings", "ever helped family members buying alcohol", "parents' attitude towards drinking alcohol and "perceived parental care". The factor that is most predictive of the students' current drinking behavior is "parents' attitude towards drinking", the more positive the parents are towards drinking, the more likely it is for the students to be current alcohol user, the risk is increased by 2 times. For students whose siblings also had drinking habits and those who had helped family members buy alcohol, the risk of being current alcohol drinkers was increased by 1.98 and 1.87 times, respectively. Finally, the risk of current alcohol drinking was decreased by 54% for the students who believed that their parents cared about them.

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Table 5. LRA of current drinking behavior in the students relative to different family factors

Variables	B	S.E.	Wald	*P*	Exp(B)	95% Confidence Interval	
						Lower Limit	Upper Limit
Male	0.37	0.21	3.28	NS	1.45	0.97	2.17
Senior Secondary Classes (Secondary 4-6)	0.90	0.38	5.62	*	2.46	1.17	5.19
Age Group							
13-14Y	0.72	0.43	2.77	NS	2.04	0.88	4.74
15-16Y	0.10	0.51	0.04	NS	1.11	0.41	3.03
17-18Y	0.22	0.58	0.14	NS	1.24	0.40	3.87
19-20Y	-0.50	0.93	0.28	NS	0.61	0.10	3.77
Father with drinking habit	-0.03	0.23	0.02	NS	0.97	0.62	1.52
Mother with drinking habit	0.40	0.24	2.70	NS	1.49	0.93	2.39
Siblings with drinking habit	0.68	0.28	6.07	*	1.98	1.15	3.40
Ever helped family buying alcohol	0.62	0.24	6.92	**	1.87	1.17	2.97
Parents positive about drinking	0.71	0.15	24.00	***	2.04	1.53	2.70
Think parents care about them	-0.61	0.30	4.24	*	0.54	0.30	0.97
Good relationship with parents	-0.26	0.27	0.90	NS	0.77	0.45	1.32

Note：*P < .05, **P < .01, ***P< .001, NS not significant

DISCUSSION

In our study, about one-third of the secondary students reported being alcohol users. This is a 5% increase compared to previous Macau data in 2013 and 2018 (8-9) and also 10% higher than that of similar study in China (11). For binge drinking, our results of 17% in the students also suggested an increasing trend compared to previous data (8-9). Alcohol use in adolescents, especially harmful alcohol use including frequent alcohol use and binge drinking can lead to severe harmful effects (12). Aside from the well-known physical harmful effects such as acute intoxication, cancer, damage to the liver, gastrointestinal and cardiovascular system etc. (13), it is also related to traffic accidents (14). Study has shown that the rate of traumatic brain injury leading to hospitalization is 50% more in child and adolescents who are current drinker compared to non-drinker (15). In this case, our results of rising trend in the rate of current drinker and binge drinker in the adolescents should be given serious attention.

In fact, early alcohol use in adolescents is especially harmful due to its effect on neurological development. During this period of rapid growth, the human brain, especially the hippocampus, is particularly vulnerable to alcohol damage (16). Long term heavy drinking in adolescents can be fatal to the neurons, inhibiting tissue growth in neurological system and may lead to cognitive and emotional dysfunction (17). Alcohol has also been shown to affect memory more severely in adolescents than adults (18). In our study, over 70% of the secondary students have tried alcohol before, this is 20% higher than that suggested by similar studies in China (11, 20). Among the students have tried alcohol, 60% of them started using alcohol before 13 years old, this is also 2 times higher than 2018 statistics (9). It is well known that early alcohol use would lead to the more severe problem of alcohol and other drug abuses in the long term (20-23), thus strategies should be implemented on the promotion of alcohol harmful effects to prevent and decrease alcohol use in the students, the earlier the better.

In order to tackle the problem of alcohol use in students, it is important to understand their reasons for first use. In our study, most secondary students reported first use of alcohol due to “curiosity”, however “family request” was also the reason for nearly one-fifth of the students. These results suggested that health promotion to increase awareness of alcohol harmful effects is essential, not only education provided directly to the students but also health promotion through advertisements on mass media, on the internet, and popular social networking system. Other ways to deal with the problem of early alcohol use is through rules and regulations that prevent easy access to alcohol. In our study, the common places of obtaining alcohol and alcohol consumption are in the restaurants, pubs and karaoke, so it is important to have rules and regulations which forbid selling alcohol to all underage citizens.

Considering family influence being an important risk factor for adolescent alcohol use, our study looked into the correlation between various family factors and alcohol use in the secondary students. In our study, 4 family factors were predictive of current alcohol use in the secondary students, namely “drinking habit in siblings”, “ever helped family members buying alcohol”, “parents’ attitude towards drinking” and “perceived parental care”. These results were similar to previous studies done in Taiwan (5, 7). However, the factors that were shown to be related to alcohol use in previous studies including family structure, parental education level, family financial condition were not related to current alcohol use (6-7). We believe that the current low alcohol tax in Macau maybe one explanation for the reason why family financial condition was not significantly related to alcohol use in Macau secondary students. This suggested that increasing alcohol tax can be one way of decreasing alcohol use in the adolescents since this should decrease the availability of alcohol to the students who have less money to spend.

In our study, parents' attitude towards alcohol drinking is most predictive of the students' current alcohol use. Current alcohol use was reported more in the students whose parents were positive attitude toward drinking. This result does correlate with our other finding that "family request" was the second most common reason for the students' first use of alcohol. It is likely that those parents who think that alcohol can be enjoyable, who enjoy drinking themselves or who believe that alcohol is for celebration in the family would ask the students to drink with them or try alcohol at earlier age, leading to the development of long-term drinking habit. Possibly related to parental attitude towards alcohol drinking is the factor of "ever helped family members buying alcohol". Parents who are more positive about drinking would more likely to ask their children to help them to buy alcohol. The increased risk can be explained by increased exposure to alcohol, so there were more temptations to try alcohol in the first place, leading to an increased likelihood of being current alcohol user.

Even though drinking habit in all family members was significantly related to current alcohol use in the students, there was an increased risk in current alcohol use only for the students whose siblings also had drinking habit. This suggested that the students are more easily influenced by their similar age siblings than their parents. This is understandable because adolescents likely want to be independent from their parents while siblings' behaviour probably has a similar effect as that of the well-known peer effect on alcohol use (24). Finally, though "perceived relationship with parents" was not predictive of current alcohol use in the students, the students who believed that their parents care about them were less likely to be current alcohol users. We think this may suggest less emotional problem in the students with more care from parents and thus less use of alcohol as an escape from the emotional issues. As is previously shown in different studies, alcohol use in adolescents is associated with various different psychiatric and emotional problem (25-27)

Summing up the study findings, there are several suggestions in terms of decreasing alcohol use in the secondary students:

1. Health education and health promotion target younger students to prevent early alcohol use.
2. Health promotion campaign to increase public knowledge about harmful alcohol effects, especially to parents, building correct attitude towards alcohol drinking, aiming to decrease the students' exposure to alcohol in the family.
3. Implementation of rules and regulation to forbid selling and provision of alcohol to underage students.
4. Increase alcohol tax, making alcohol less avoidable by the students.
5. Social service and support to help parents to build better relationships with the students

There are several limitations from our study. Firstly, this is a cross-sectional study which only showed correlations, it cannot explain the cause and effect relationship of the family factors with current alcohol use in the students. Secondly, the methodology of a survey by self-reported questionnaire has the potential of recall bias, leading to deviation from real-life situations.

Future studies should consider the methodology of longitudinal studies and qualitative studies to have an in-depth understanding of the issue. Finally, due to the limitation of the scope of the study, we didn't go into deeper analyses of each of the individual family factors. Future studies should consider to include parents' report instead of relying only on that of the students. More detailed assessment of student's alcohol use should also be conducted using validated assessment tools such as those used for alcohol use disorder.

CONCLUSION

The study is conducted on secondary students in formal education in Macau. The results can help in understanding the current situation of alcohol use in the students and the relationship with various family factors. The study design specifically targeted previous research results in Macau and various neighboring regions for the purpose of observing changes in the trend of alcohol use and for comparison of correlation between different family factors and current alcohol use.

Our findings have shown that "drinking habit in siblings", "ever helped family members buying alcohol", "parents' positive attitude towards drinking alcohol" and "thinking that their parents do not care about them" are associated with significant risk for current alcohol use in the secondary students, with about 2 times increased risk compared to students without the condition. There is an increasing trend of alcohol use in all secondary students as well as early alcohol use in younger students in Macau. Thus, strategies to decrease alcohol use in the secondary students, some of which target specific family factors, should be implemented.

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Analysis of factors predicting the efficacy of Imatinib in patients with Chronic Myeloid Leukemia: A retrospective analysis

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ABSTRACT

Objective: Imatinib is a commonly used first generation tyrosine kinase inhibitor for patients with chronic myeloid leukemia (CML). The efficacy has been reported as very high even in recent studies.

Material and methods: A retrospective analysis was made of newly diagnosed CML patients treated with Imatinib as a first-line agent from January 2010 to January 2020. The patients were classified as those who obtained an adequate response and those for whom treatment was discontinued due to inadequate efficacy. The two groups were compared to analyze factors predicting the efficacy of the agent.

Results: Evaluation was made of a total of 47 CML patients, comprising 20 females (42.6%) and 27 males (57.4%) with a median age of 55 years. Imatinib was discontinued in 19 patients because of inadequate response, and 28 patients were still continuing the treatment at the end of median 33.3 months follow-up duration. At the end of follow-up, there were 44 survivors (93.6%), and 3 non-survivors (6.4%). Median Bcr-Abl (IS, %) at the time of diagnosis in patients with response was higher than patients in discontinued group (67.6 [0.0-291.4] vs 41.9 [0.0-208.5], p=0.022). All other disease and demographic characteristics were similar in both groups (p>0.05).

Conclusion: Almost 10 years of follow-up demonstrated that there is still an unmet need to determine factors predicting the response to Imatinib in CML patients. Larger population-based studies are required to specify patients with high risk at the time of diagnosis to monitor closely.

Keywords: chronic myeloid leukemia, CML, Imatinib, efficacy, response

INTRODUCTION

Chronic myeloid leukemia (CML) is defined as a chronic myeloproliferative disease. CML is characterized by clonal proliferation in myeloid cells due to abnormal tyrosine kinase activity (TKA), which is also a fatal disease after its transformation from chronic phase (CP) to accelerated phase (AP) and blastic phase (BP) if untreated. The permanently active TKA is caused by the Bcr-Abl (breakpoint cluster region- Ableson leukemia virus) fusion gene, resulting from an abnormal genetic translocation between chromosomes 9 and 22 (1).

Tyrosine kinase inhibitors (TKIs) inhibit the protein's enzyme activity by strongly blocking the interaction between Bcr-Abl 1 onco-protein and adenosine triphosphate (ATP), thereby controlling immortal TKA and malignant clonal proliferation. When the disease course of patients diagnosed with CML with a tyrosine kinase inhibitor, which is defined as targeted therapy, was examined, the survival rate reached 90% and almost approached the normal population (2-4). Imatinib mesylate is a selective inhibitor of Bcr-Abl tyrosine kinase, which plays a key role of the pathogenetic mechanism of CML. It also prevents ATP's interaction with ABL protein and protein phosphorylation. The IRIS [International Randomized Study of Interferon and STI571] demonstrated the superior cytogenetic and hematological responses of Imatinib than interferon alfa and cytarabine, Imatinib became the first TKI agent to be used in CML patients (5).

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This study aimed to determine whether there is a possible early predictor of response to Imatinib treatment by evaluating the response analysis after Imatinib treatment in CML patients, including demographic and disease characteristics.

MATERIAL AND METHODS

A retrospective analysis was made with newly diagnosed CML patients who were treated with Imatinib as a first-line agent from January 2010 to January 2020 in the Hematology Department of Diskapi Yildirim Beyazit Training and Research Hospital. We classified the patients as those who achieved adequate response and those who were discontinued due to inadequate efficacy (6).

Patients in whom Imatinib was cessated due to adverse events or other causes were excluded. Two groups were compared to analyze factors predicting the efficacy of the agent. While the "Independent Sample-t" test (t-table value) is used to compare the measurement values of two independent groups in the data with normal distribution; "Mann-Whitney U" test (Z-table value) statistics were used to compare the measurement values of two independent groups in the data that do not have a normal distribution X2-cross tables were used to examine two qualitative variables.

RESULTS

Totally 47 CML patients with a median age of 55 years were included. There were 20 female (%42,6) and 27 male (%57,4) subjects. Among them, Imatinib was discontinuated in 19 patients because of inadequate response whereas 28 patients were still going on at the end of the median 33,3 months follow-up duration. At the end of follow-up, there were 44 survivors (%93,6), and 3 nonsurvivors (%6,4). There was no mortality in patients who achieved optimal response. Demographic characteristics of the patients were given in **Table1**. Mean Imatinib treatment duration in patients for whom Imatinib was discontinued due to inadequate response was 18,79±20,34 months (median 13,7 months). Evaluation of differences or relationships in hematological and biochemical parameters in Imatinib-responsive and unresponsive patients is given in **Table2**. There is no significant difference among all parameters according to the groups (p>0,05). The comparison of disease characteristics and treatment responses of Imatinib-responsive and unresponsive patients is given in **Table 3**. A statistically significant difference was found between the groups in terms of initial BCR-ABL value. Patients who responded optimally to Imatinib treatment had a statistically significantly higher BCR-ABL value at the time of diagnosis than those discontinued due to insufficient efficacy. (p=0,022). As a result of the Logistic regression model (Backward: LR) revealed no parameter had an impact on response to Imatinib treatment (p> 0.05).

Table 1. The demographic characteristics of the patients

	All patients (N=47)	Optimal Response (n=28)	Inadequate response (n=19)
Gender			
Female	20 (42,5%)	12 (%42,9)	8 (%42,1)
Male	27 (57,5%)	16 (%57,1)	11 (%57,9)
Age, median, range [years]	55 [25-89]	53,32±13,95	55,42±14,52
Follow-up duration			
median,range(month)	33,9[0,23-171,9]	24,9[0,23-138]	44[5,7-171,9]
Final status			
Survivor	44 (93,6%)	28 (100%)	16 (84,2%)
Nonsurvivor	3 (6,6%)	0	3 (15,8)

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Table 2. Evaluation of hematological and biochemical parameters in Imatinib-responsive and unresponsive patients

N=47	İmatinib treatment		*P*
	Inadequate response (n=19)	Optimal Response (n=28)	
Gender			
Female	8 (%42,1)	12 (%42,9)	0,959
Male	11 (%57,9)	16 (%57,1)	
Age (year)	55,42±14,52	53,32±13,95	0,621
Hemoglobin(g/dL) Median [Min-Max]	11,16±3,21	11,60±2,41	0,594
WBC($\times10^3/mm^3$) Median [Min-Max]	155000,0 [8000,0-576500,0]	62400,0 [5100,0-252430,0]	0,260
Neutrophil ($\times10^3/mm^3$) Median [Min-Max]	60103,5 [3970,0-393000,0]	51200,0 [3200,0-214600,0]	0,500
Platelet($\times10^3/mm^3$) Median [Min-Max]	315000,0 [206000,0-1190000,0]	266500,0 [64000,0-3803000,0]	0,335
Basophil ($\times10^3/mm^3$) Median [Min-Max]	220,0 [0,0-25310,0]	330,0 [0,0-21400,0]	0,879
Monocyte ($\times10^3/mm^3$) Median [Min-Max]	2150,0 [400,0-28440,0]	1710,0 [200,0-8600,0]	0,480
LDH(/l) Median [Min-Max]	792,0 [184,0-2287,0]	532,0 [165,0-2253,0]	0,569
Ferritin (ng/mL) Median [Min-Max]	60,0 [4,0-1119,0]	58,0 [2,2-543,0]	0,831
Vitamin B12 (pmol/L) Median [Min-Max]	803,26±578,96	1044,16±540,26	0,163
Platelet/ lymphocyte	57,0 [7,4-172,1]	56,7 [9,1-845,1]	0,982
Lymphocyte/monocyte	3,3 [0,4-10,7]	2,8 [0,7-20,0]	0,889
Neutrophil/lymphocyte	11,0 [1,2-53,0]	8,4 [1,8-33,3]	0,787

Table 3. The comparison of disease characteristics and treatment responses of Imatinib-responsive and unresponsive patients

N=47	Imatinib treatment		*P*
	Inadequate response (n=19)	Optimal Response (n=28)	
Splenomegaly			
No	10 (%52,6)	9 (%32,1)	0,217
Yes	9 (%47,4)	19 (%67,9)	
Bone marrow blast at diagnosis			
<%5	8 (%72,7)	9 (%64,3)	0,889
%5-10	2 (%18,2)	3 (%21,4)	
>%10	1 (%9,1)	2 (%14,3)	
Eutos score Median [Min-Max]	9,5 [0,0-82,0]	13,0 [0,0-131,0]	0,364
Sokal score Median [Min-Max]	0,9 [0,6-2,7]	1,0 [0,6-2,0]	0,963
ELTSeutos score Median [Min-Max]	1,88±0,56	1,68±0,46	0,248
BCR-ABL IS at diagnosis (%) Median [Min-Max]	41,9 [0,0-208,5]	67,6 [0,0-291,4]	**0,022**
Bcr-Abl IS at 3rd month			
≤10	8 (%57,1)	15 (%71,4)	
>10	6 (%42,9)	6 (%28,6)	0,611
Bcr-Abl IS at 6th month			
≤1	7 (%50,0)	17 (%85,0)	
>1	7 (%50,0)	3 (%15,0)	0,054
Bcr-Abl IS at 12th month			
≤0,1	2 (%18,2)	13 (%76,5)	
>0,1	9 (%81,1)	4 (%23,5)	**0,006**
Final status MMR			
Yes	8 (%42,1)	7 (%25,0)	0,339
No	11 (%57,9)	21 (%75,0)	

DISCUSSION

Imatinib is the first and still commonly used TKI for patients with CML. The higher efficacy was reported in many studies even in recent real-life experiences. In a recent study, after approximately 11 years of long-term follow-up, the overall survival rate in patients receiving Imatinib was reported as 83.3%, while the complete cytogenetic remission rate (CCyR) was 83%, and the 10-year major molecular response (MMR) rate was 93% (7). However, long-term results of the IRIS study showed that 33% of the patients who received first-line Imatinib treatment did not have a complete hematological response while 39% of the patients did not achieve major cytogenetic response at the end of 5-year follow up (8). In the current study, 40% of patients could not continue the drug due to efficacy after the first-line Imatinib treatment, and similar results were observed with the studies. Although there are second and advanced-generation TKIs for Imatinib-unresponsive patients, the whole world had no chance to obtain those agents due to financial or other medical reasons. Therefore, it would have been better to know factors that have an impact on Imatinib efficacy, especially those easily obtainable and modifiable risk factors. Sokal, Euro, and European Treatment of Outcome Study (EUTOS) and Hasford scores are used to determine the most appropriate treatment and follow-up program before the treatment (9). According to risk stratification, high and low risk patients not only change their initial TKI agents but also the likelihood of reaching CCyR and MMR values early, which is lower in high risk patients. Furthermore, unfortunately, high-risk patients have a higher chance of the disease transforming into CML-AP or CML-BP. As we know that initial risk stratification of the patients is very important, there is still no consensus about the effect of those scores on long term Imatinib response. It has been shown that the early molecular response (BCR-ABL1 transcripts [IS] <10% at 3 months) has a strong prognostic value and can also be achieved with Imatinib or other TKIs. Studies also state that patients on CCyR under Imatinib treatment have similar survival without reaching MMR. Patients with negative and/or BCR-ABL1 transcripts [IS] <1% by FISH analysis from peripheral blood at 6 or 12 months are likely to be in CCyR (6).

Although ABL seems to be a minimal residual disease marker in CML patients, the Bcr-Abl ratio may give false low transcript rates. The prognostic impact of the 3-month BCR-ABL transcript response may be related to the harshness of treatment response or the tumor burden. Therefore, there are studies suggesting that the half-log reduction rate at the BCR-ABL transcript level in 3 months is more accurate in terms of prediction (10). On the contrary, some studies have determined that patients with high Bcr-Abl transcript levels are less likely to benefit from imatinib treatment (11). Both studies were based on Bcr/Abl/gus IS values, and achieving different results showed that there is still a need for studies on the prognostic prediction of Imatinib treatment. In the current study, a statistically significant difference was found between the groups in terms of initial Bcr-Abl value. Patients who responded optimally to Imatinib treatment had a statistically significantly higher Bcr-Abl value at the time of diagnosis than those discontinued due to insufficient efficacy. However, as a result of the Logistic regression model revealed no parameter had impact on response to Imatinib treatment.

There are also some limitations in our study. Patients diagnosed with CML whose survival rates are close to the normal population with current treatments should have a longer total follow-up period. We obtained patient data from a single center, which may limit the generalizability of the results. Other limitations are that the study is a retrospective design and the need for larger prospective studies to be analyzed.

CONCLUSION

In conclusion, with Imatinib, a commonly used TKI in CML patients, survival rates approached the healthy population statistics and similar results were obtained when the response rates and side effects of the study were compared with the results of real-world studies. Response after Imatinib treatment in CML patients was evaluated, including demographic and disease characteristics and it revealed no impact of any parameter on response to Imatinib treatment. Larger population-based studies are needed to determine significant factors.

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The importance of biomarkers in determining the prognosis of patients requiring intensive care hospitalization due to COVID-19 infection

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ABSTRACT

Objective: This study aims to investigate the effect of biomarkers such as CRP, ferritin, troponin, lymphopenia, and D-dimer in predicting disease severity and clinical outcome. Identifying an effective and predictive biomarker will help to evaluate patients' risk and improve overall clinical management of patients with COVID-19

Material and Methods: In this retrospective cohort study, 1458 patients who were taken to intensive care follow-up due to COVID-19 across the province of Bursa were evaluated. Age, gender, and laboratory data such as ferritin, D-dimer, White Blood Cell (WBC), C-reactive protein, troponin values, chronic diseases, length of stay in the intensive care unit, and mortality were recorded. The relation of these variables with mortality was analyzed.

Results: There was no significant difference between the groups regarding age and length of stay in the intensive care unit (p=379, p=0.094). There was a statistically significant difference between the groups for ferritin, CRP, D-dimer, troponin, and WBC variables (p<0.001). In the ROC analysis, it was seen that the sensitivity value for ferritin was 86.08%, the specificity value was 85.23%, and the AUC: 0.902 had a high level of diagnostic value.

Conclusion: An increase in acute phase reactants was associated with mortality in patients followed up for COVID-19. This may be related to the increased cytokine response triggered by the disease.

Keywords: COVID-19, mortality, acute phase reactants, disease severity

INTRODUCTION

Coronavirus spreading from China to the world, rapidly gained a global magnitude (1). Around the world, approximately 582,928,015 cases and 6,415,652 deaths were reported (2). Since the first COVID-19 case in Turkey was seen on 10th March 2020, the cumulative number of cases was 16,295,817, and the number of deaths was 99,678 (3).

Although COVID-19 infection progresses with a good prognosis in many patients, also, it can progress to acute respiratory distress syndrome (ARDS), and end-stage organ failure in individuals with advanced age and comorbidities. For this reason, the need for intensive care and mechanical ventilator follow-up may arise in individuals with severe infection (4, 5). This requirement has forced to test researchers in many health services such as intensive care and ventilators in many countries during the pandemic. As COVID-19 cases increased, the number of patients followed in intensive care compelled many countries, especially China, Italy, France and Spain (6, 7). In 2020, while Spain, France and especially Italy were affected by the pandemic, southern Mediterranean countries experienced a relatively more comfortable pandemic process with a limited number of patients admitted to intensive care units compared to these European countries (8,9). The necessity of developing strategies and making choices for the effective use of the capacity of increasing intensive care needs has emerged. Accurate identification of critically ill COVID-19 patients has gained importance for the need for intensive care. Studies have reflected different findings and experiences on the follow-up and treatment processes of COVID-19 patients in intensive care, mechanical ventilator management, and intensive care indications (5).

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In the light of studies investigating that COVID-19 disease is associated with mortality, cardiovascular disease, diabetes mellitus, chronic lung diseases, hypertension, chronic renal failure, and diseases that require immunosuppressive therapy were considered as important comorbidities (10-13). In a meta-analysis of 1558 patients and six studies conducted in China, chronic obstructive pulmonary disease, cardiovascular disease, diabetes, and hypertension were found to be the most important independent risk factors for mortality, respectively (14). In a retrospective study of COVID-19-related mortality in Italy, the mean number of pre-existing comorbidities was 2.7, and no comorbid disease was found in only three (0.3%) patients. Older age and male gender were considered independent risk factors in studies conducted in China, Italy, and USA, due to a disproportionately high number of deaths (13, 15-16). The increased mortality prevalence, especially in males, may be due to males' predisposition to cardiovascular disease. In a comment by the Center for Disease Control and Prevention, it was emphasized that men and women interpret COVID-19 differently, increased incidence of smoking in men with other comorbidities seen in men are independent risk factors for COVID-19, and treatment initiation and adherence to treatment are more unsuccessful for men than women (16-18).

In the literature, factors associated with estimating the severity of COVID-19 infection are age, comorbidities, and high inflammatory markers (19,20). Literature research indicates that one of the predictive acute phase reactants associated with predicting the severity of coronavirus disease is ferritin (21). In cases with a high pathogenic load, the increase in ferritin will reduce the iron supply to the microorganism, thus playing a protective role in the body's defense. Ferritin not only reduces the iron supply for the pathogen, but also regulates the release of cytokines and prevents them from entering the cytokine storm. Ferritin is a component of iron metabolism that protects the host in pathogen infections (22-24). Iron is an essential micronutrient for both energy production at the mitochondrial level and nucleic acid replication at the nuclear level (25). For these processes to take place, microorganisms compete with the body's cells for iron binding (26). When the innate immunity is activated, and cytokine cascades begin, interlokines stimulate hepcidin expression in the liver and reduce intestinal absorption, thus storing ferritin accumulated in macrophages and limiting iron bioavailability (27, 28).

C-reactive protein (CRP) is an acute phase reactant synthesized in the liver secondary to inflammation or an infectious process. Unlike profound changes in plasma levels during the catabolism of most acute phase proteins, CRP remains almost constant in plasma. During acute infection, serum concentrations increase, making CRP a striking marker for inflammatory processes such as sepsis. CRP contributes to the pro-inflammatory process by activating inflammatory cytokines in the body (29,30). CRP levels increase in patients with COVID-19, and the median CRP value of survivors is 40mg/dl, and the median CRP value of those who died due to COVID-19 is 125mg/dl, demonstrating that CRP has a strong relationship with disease severity and prognosis (31).

CRP and serum ferritin play an important role in the initiation of inflammatory processes. The main finding of immune pathology in COVID-19 is cytokine storm. The virus multiplies rapidly in the endothelial and epithelial cells of the body, which causes the synthesis of cytokines and chemokines. Studies have shown that high levels of cytokines and chemokines released during infections are associated with poor outcomes of respiratory viral infections (32,33). Overproduction of inflammatory cytokines increases the severity of COVID-19 infection by contributing to the picture leading to ARDS and multi-organ failure (34,35).

Among the hematological markers, lymphopenia was clearly associated with disease severity (36). The lymphocyte counts of patients who died from COVID-19 were found to be significantly lower than those who survived. Lymphopenia and involvement of specific T-cells have been associated with both its characteristic and poor prognosis for COVID-19 (37-40). In the previous pandemic of SARS, the peak of viral load occurred 7 days later, followed by elevation in IL-6 and IL-8, regression to the lowest lymphocyte count, and subsequent pulmonary leakage, suggesting that lymphopenia may mediate the immune system dysregulation rather than direct damage to clinical symptoms (41).

During sepsis, a decrease in antithrombin is observed followed by upregulation of the tissue factor resulting in an increase in plasma thrombin, while at the same time, decreased production of Prothrombin-C and upregulation of type 1 plasminogen activator inhibitor further inhibit fibrinolysis. All these changes lead to a high level of coagulation tendency. With the addition of increased coagulation and hypotension with sepsis, it brings with it life-threatening multi-organ failure. The D-dimer is a measure of the coagulation process and assesses the severity of the host response, making it an important role in the classification of patients with sepsis. One study showed that the higher the D-dimer levels, the higher the risk for the patient for septic shock and the greater the likelihood of sepsis (42–44). Studies are showing that D-dimer elevation > 1 ug/L among coagulation parameters is the strongest independent predictor of mortality (13,45).

Although the clinical manifestations of COVID-19 are mainly related to the respiratory tract, with the increase in the number of infected patients, major cardiac complications have been reported in a significant number of COVID-19 patients (14, 46, 47). Acute cardiac injury, defined as the marked elevation of cardiac troponins, is a frequent complication reported in 8-12% of COVID-19 patients (48). In the explanations made so far regarding the cardiovascular impact of COVID-19, it has been suggested that chronic cardiovascular diseases may occur as a result of the imbalance between the increased metabolic demand caused by the infection and the decreased cardiac reserve in the case of a viral infection (49). Studies evaluating COVID-19 patients with signs of cardiac injury show that it is associated with poor prognosis and that arrhythmic events are not uncommon (50, 51). High cardiac troponin levels in COVID-19 patients indicating cardiac injury, were associated with mortality in critically ill patients (52, 53).

This study aims to investigate the effect of biomarkers such as CRP, ferritin, troponin, lymphopenia, and D-dimer in predicting disease severity and clinical outcome. Identifying an effective and predictive biomarker will help to evaluate patients' risk and improve overall clinical management of patients with COVID-19, particularly in the local region.

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MATERIAL AND METHODS

The study was assessed retrospectively in PCR-positive patients who were evaluated in the emergency services of public hospitals and COVID-19 outpatient clinics and admitted to the intensive care unit due to COVID-19 in Bursa between January 1 and June 1, 2021. During the study planning process, approval was obtained from the Bursa City Hospital ethics committee, and the principles of Research and Publication Ethics were followed. Age, gender, and laboratory data of the patients included in the study such as ferritin, D-dimer, White Blood Cell (WBC), C-reactive protein, troponin values, chronic diseases, length of stay in the intensive care unit, and mortality were recorded. Patients under the age of 18, patients with positive thorax imaging for COVID-19 but negative PCR test results and treated as possible COVID-19 cases, and patients whose file data could not be accessed were excluded from the study.

Statistical analysis: The data of the study were analyzed using the 'The jamovi project (2021). jamovi (Version 2.0.0) (Computer Software). Descriptive statistics were expressed as mean ± standard deviation or median values and an interquartile range (IQR) of 25–75 %, while categorical variables were expressed as numbers and percentages (%). Kolmogorov–Smirnov test and Shapiro-Wilk test were used for the normality distribution of the data. While the significance of the difference between the groups in terms of continuous numerical variables in which parametric test statistics assumptions were provided was examined with Student's t test, the significance of the difference in terms of continuous numerical variables where parametric test statistics assumptions were not met was evaluated with the Mann-Whitney U and Kruskal-Wallis tests. Chi-square and Fisher's exact test were used to analyze whether there was a relationship between categorical variables. The variables that may be effective for mortality were evaluated using the "enter" method in logistic regression analysis. The ROC curve was drawn to investigate the diagnostic value of the ferritin, lymphocyte, CRP, D-dimer, and troponin. $p < 0.05$ was considered statistically significant. Results were given at 95 % confidence interval.

RESULTS

In our study, the data of a total of 1576 patients were analyzed retrospectively. 9 patients were excluded from the study because they were under the age of 18, and the data of 109 patients could not be accessed.

A total of 1458 patients were included in the study. 57.9% (n:844) of the 1458 patients included in the study were male, with a median age of 71(IQR:25-75)(62-79), median ferritin value 493.5 (IQR:25-75)(187.15-987), CRP median value 74 (IQR:25-75)(24.625-132), D-dimer median value 1.97 (IQR:25-75)(0.87-5.48), troponin median value 31.44 (IQR:25-75)(12-83.95) , WBC median value was 5.92 (IQR:25-75)(3.4-11.39), median length of stay in the intensive care unit was 6 (IQR:25-75) (3-12) days (**Table-1**).

When we look at the comorbidity distribution of the patients, it was seen that 35.4% (n:516) did not have any additional disease, 21.2% (n:309) of the patients with comorbidities had HT, 10% (n:146) DM, 7.2% (n:105) COPD (**Figure-1**). Mortality developed in 42.9% (n:625) of the patients during their follow-up, and we found that 64.3% (n:402) of the patients were male (**Figure-2**). Mortality was grouped into developing and non-developing patients, and statistical analyses were performed. Continuous variables did not fit the normal distribution with the Kolmogorov-Smirnov test, and statistically significant differences between the groups were calculated with the Mann-Whitney U test (**Table-2**). There was no significant difference between the groups in terms of age and length of stay in the intensive care unit (p=379, p=0.094). There was a statistically significant difference between the groups for ferritin, CRP, D-dimer, troponin and WBC variables (p<0.001).

In the Chi-Square test performed for gender and comorbidity variables, a statistically significant difference was observed in both variables (p<0.001, p<0.001). The distribution of gender and comorbidity variables by binomial logistic regression analysis is given in **Table-3**. Male gender, malignancy, HT and DM were found to have significant effects on mortality (p<0.001, OR:1.598, p=0.01, OR:5.819, p<0.001, OR:3.708, p<0.001, OR:2.657).

Regarding the diagnostic values for mortality in patients admitted to the intensive care unit due to COVID-19 in the ROC analysis, it was seen that the sensitivity value for ferritin was 86.08%, the specificity value was 85.23%, and the AUC: 0.902 had a high level of diagnostic value. ROC curve is given in **Figure-3** and ROC analysis results are shown in **Table-4**. In addition, graphical distributions of ferritin, CRP, D-dimer, troponin and WBC variables according to mortality are demonstrated in **Figure-4**.

Tablo 1: Descriptive statistics of the study population

						Percentiles	
	Mortality	**N**	**Median**	**Minimum**	**Maximum**	**25th**	**75th**
Ferritin	Yes	625	999.00	23.000	2000.0	719.450	1560.00
	No	833	232.80	21.000	2000.0	116.890	437.60
CRP	Yes	625	100.30	1.300	439.0	51.000	161.40
	No	833	52.90	0.700	339.9	13.900	114.70
D-Dimer	Yes	625	3.29	0.100	89.0	1.180	8.60
	No	833	1.42	0.190	45.0	0.760	3.54
Troponin	Yes	625	56.00	0.100	9893.9	16.270	152.80
	No	833	24.00	0.200	6092.0	9.550	55.72
WBC	Yes	625	4.90	0.190	70.6	3.150	9.62
	No	833	6.90	0.260	87.6	3.730	12.12
	SEX	**N**	**Median**	**Minimum**	**Maximum**	**25th**	**75th**
Age	Male	844	70.00	20.0	97.0	61.00	78.0
	Female	614	74.00	22.0	100.0	64.00	81.0
ICU Time	Male	844	6.00	0.0	88.0	3.00	12.0
	Female	614	6.00	0.0	126.0	3.00	13.0

CRP: C-reactive protein, WBC: White blood cell, ICU: Intensive care unit

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Table 2: Association of variables with mortality

Independent Samples T-Test			
		Statistic	p
Age	Mann-Whitney U	253320	0.379
ICU Time	Mann-Whitney U	247010	0.094
Ferritin	Mann-Whitney U	51173	< .001
CRP	Mann-Whitney U	175977	< .001
D-Dimer	Mann-Whitney U	178795	< .001
Troponin	Mann-Whitney U	180814	< .001
WBC	Mann-Whitney U	226065	< .001

Table 3: Results of Binomial Logistic Regression Analysis

Model Coefficients - Mortality							
						95% Confidence Interval	
Predictor	**Estimate**	**SE**	**Z**	**p**	**Odds ratio**	**Lower**	**Upper**
Intercept	-1.024	0.116	-8.816	< .001	0.359	0.286	0.451
Comorbities:							
KOAH – No Comorbities	0.146	0.225	0.646	0.518	1.157	0.744	1.799
HT – No Comorbities	0.977	0.149	6.541	< .001	2.657	1.983	3.561
Renal Failure – No Comorbities	-0.371	0.306	-1.213	0.225	0.690	0.379	1.257
SVO – No Comorbities	0.593	0.268	2.214	0.027	1.810	1.071	3.059
DM – No Comorbities	1.310	0.198	6.634	< .001	3.708	2.517	5.460
Asthma – No Comorbities	0.457	0.333	1.372	0.170	1.579	0.822	3.035
Neurological – No Comorbities	0.180	0.456	0.394	0.694	1.197	0.490	2.924
Malignancy – No Comorbities	1.761	0.687	2.562	0.010	5.819	1.513	22.385
Cardiac Failure – No Comorbities	0.481	0.179	2.689	0.007	1.618	1.139	2.298
SEX:							
Male – Female	0.469	0.112	4.172	< .001	1.598	1.282	1.991

Model Fit Measures			
Model	**Deviance**	**AIC**	**R^2_{McF}**
1	1886	1908	0.0529

Table 4: ROC analysis results

Cutpoint	Sensitivity (%)	Specificity (%)	Youden's index	AUC
Scale: Ferritin				
445	92.48%	75.87%	0.684	0.902
503	89.76%	80.91%	0.707	0.902
576	86.08%	85.23%	0.713	0.902
616.7	84%	86.79%	0.708	0.902
Scale: CRP				
18.27	90.4%	30.49%	0.209	0.662
31.13	85.12%	38.66%	0.238	0.662
62.2	68.16%	54.14%	0.223	0.662
72.2	63.84%	58.7%	0.225	0.662
Scale: D-Dimer				
1.44	71.36%	50.06%	0.214	0.657
1.9	63.84%	58.34%	0.222	0.657
2.12	60.32%	64.23%	0.245	0.657
2.74	55.2%	69.99%	0.252	0.657
Scale: Troponin				
28.52	64.96%	55.94%	0.209	0.653
36.2	59.52%	64.23%	0.237	0.653
36.32	59.52%	64.35%	0.239	0.653
47.69	52.96%	71.67%	0.246	0.653
Scale: WBC				
0.5	99.04%	1.2%	0.00240	0.434
2	89.76%	12.61%	0.02365	0.434
16.83	10.24%	87.76%	-0.02005	0.434
19.15	8.32%	91.12%	-0.00564	0.434

CRP: C-reaktif protein, WBC: White blood cell, AUC: Area under curve,

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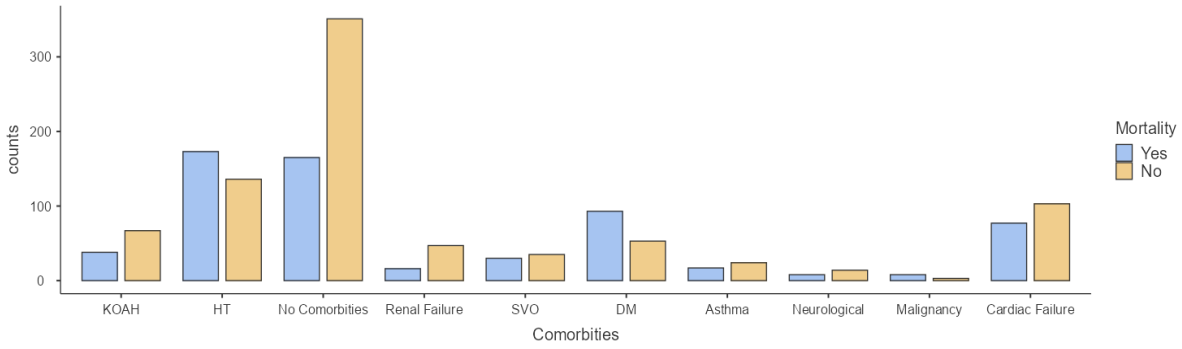

Figure 1: Distribution of comorbidities in patients with mortality

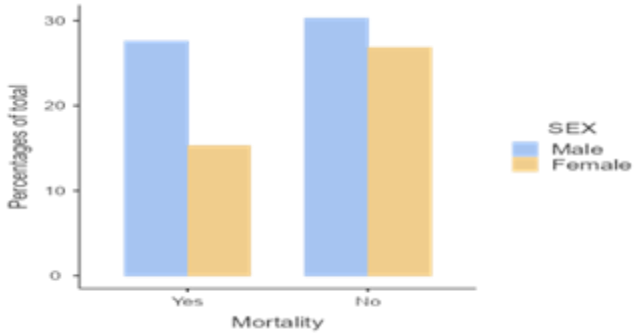

Figure 2: Mortality and sex distribution

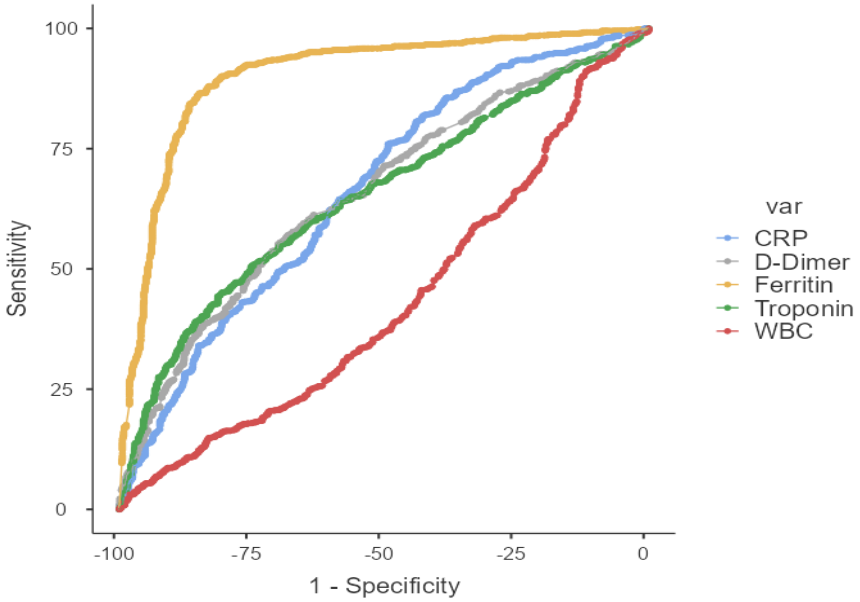

Figure 3: ROC Curve: Combined

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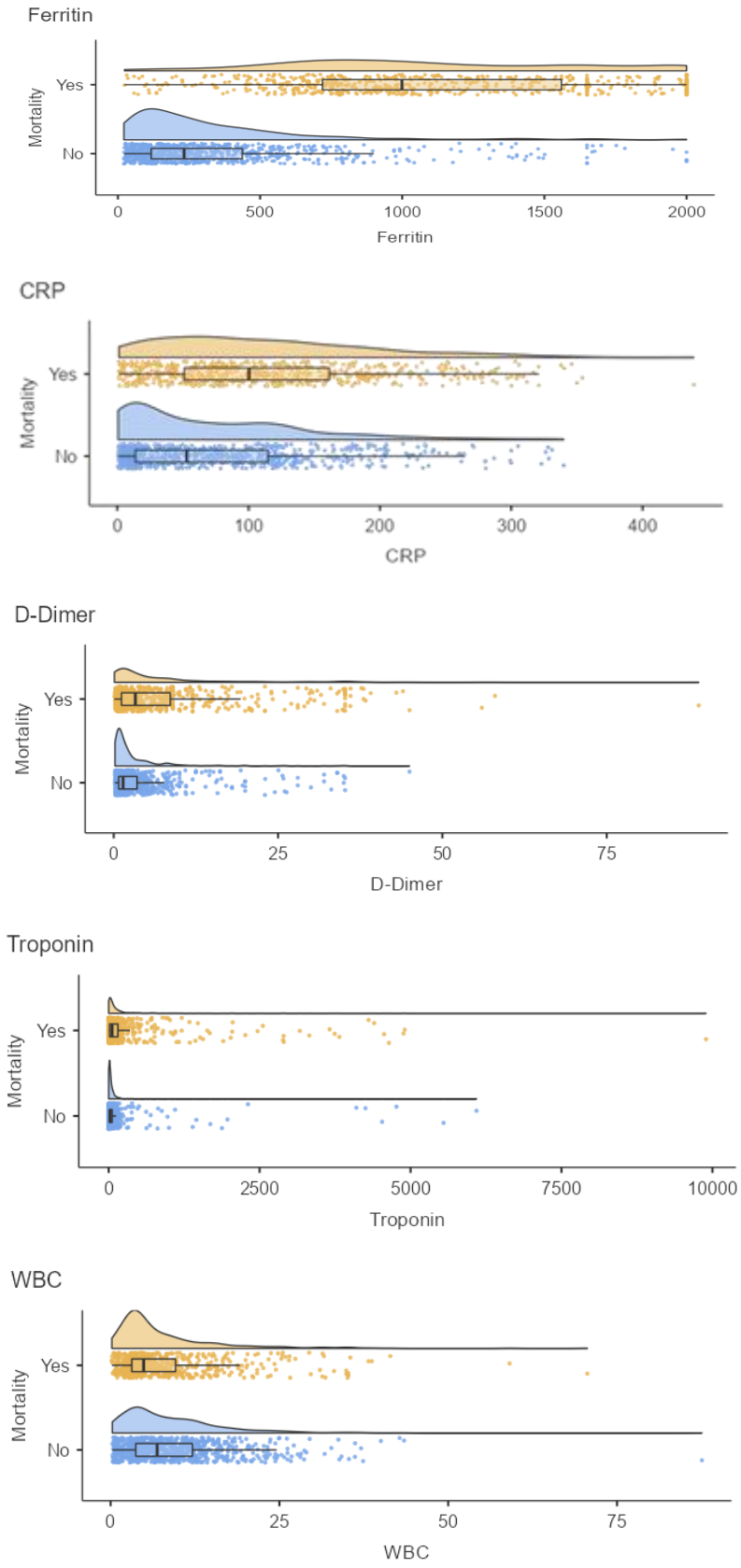

Figure 4: Mortality Distributions of Laboratory Variables

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DISCUSSION

In our study, we defined the sociodemographic characteristics, laboratory findings, length of hospital stay, and mortality in critically ill patients with COVID-19. In our study, risk factors associated with death in patients with COVID-19 in intensive care were also identified.

It was previously reported that advanced age is an important determinant of mortality. Overall, the data analyzed also suggest that serious illness can be expected in the elderly (54-57). The age range in severe patients is 52 to 66 years in most of the Chinese studies (53, 58). Similarly, in the study conducted in Italy, the mortality rate increases with age; 12% in patients older than 70 years and 20% in patients older than 80 years (8). In addition, in our study the increasing age of the patients was an independent predictor of COVID-19 mortality, and a significant correlation was found with the severity of the disease. The relationship between advanced age and the mortality of COVID-19 has been found in many studies in the literature (34,59,60). This may be because older people are more vulnerable to Coronavirus and are more likely to have chronic illnesses (34, 58, 61).

Our study was comparable to the previous ones and revealed the male predominance of 69% in the previous study on 336 COVID-19 patients in Pakistan, 71% in the retrospective study on 239 cases in Italy and Lombardy, and 75% in the study conducted in Wuhan, China with 28 cases (62-64). In our study, as stated previously by Zheng et al, we found that the group with the most severe course of COVID-19 was higher in men, in terms of gender distribution (65)

Most of the patients in our study had one or more comorbidities. Hypertension, diabetes mellitus, and coronary artery disease were the most common chronic diseases in the patients. In a multicenter study conducted in China, it was observed that approximately half of the patients had comorbid diseases, the most common comorbidity was hypertension, followed by diabetes mellitus and coronary artery disease, respectively (66).

In our study, the ferritin elevation was seen in mortal COVID 19 patients; Previously, ferritin's predictive power of death was similar in Algeria with a series of 157 patients, in New York in a cohort of 330 cases, and in a retrospective review of 942 patients (62,67,68). In a study on ferritin by Pastora et al. in 2020, it has been shown that the ferritin level of COVID 19 patients is below 400 in those who do not have severe involvement, and that it can increase 1.5-5.3 times the normal limit of 400 in severe involvement (69).

Although our data on C-reactive protein is significantly higher in the mortality threshold group, it is compatible with the literature that high CRP indicates a longer hospitalization period, poor prognosis in terms of the course of the disease, the need for intensive care follow-up, and predicts mortality (70, 71). The increase in CRP reflects the magnitude of the systemic inflammatory syndrome present in severe forms of the disease. The increase in CRP reflects the severity of the systemic inflammatory syndrome present in severe forms of the disease. It is believed that, in addition to multi-organ failure, the onset of ARDS results in the release of inflammatory cytokines that create a "cytokine storm" responsible for acute tissue damage, and in the research conducted in 2020, the high CRP was proved to be a predictor of both the need for invasive mechanical ventilators and to detect the patients who would need intensive care unit follow-up in the ward (72,73).

Although the cut-off value of the normal level differed in relation to the significantly low lymphocyte count in the COVID-19 patient group who died in our analysis, it showed similar results with studies using a cut-off point of <1100 µL (12, 66, 74-76). Interestingly, it was seen that the relationship between lymphopenia and COVID 19 was stronger in young patients than in elderly patients. The possible hypothesis to explain the low lymphocyte count in the young was that the immune system is affected by a wider range of active lymphocyte kinetics at the young than in the elderly (20, 32).

These results are also consistent with data reported by Rodriguez et al., which revealed the presence of common biological abnormalities such as elevated inflammatory marker levels (elevated CRP and lymphopenia) in a meta-analysis (77). The frequency of lymphopenia observed by us suggests that COVID-19 may act on lymphocytes, particularly T lymphocytes, perhaps leading to the depletion of CD4 and CD8 cells. This idea has been demonstrated in severe acute respiratory syndrome (SARS) (78). Given its cost-effectiveness and easy-to-perform, such as complete blood count, lymphopenia can serve as a prognostic tool to predict the severity and poor prognosis of COVID-19 in a primary clinic. Therefore, it may be a useful biomarker to consider for risk-adjusted medical resource allocation during this pandemic period.

In retrospective cohorts, baseline d-dimer levels were increased in 33% of COVID 19 patients admitted to the hospital earlier (11, 12, 34, 53). In a pooled analysis of these 4 studies involving 553 patients, baseline D-Dimer levels were associated with COVID-19 severity. Another analysis showed that D-dimer levels could be a useful marker for predicting mortality in hospitalized COVID-19 cases (79,80). Tang et al. reported that D-dimer level was associated with 28-day mortality in a series of 449 patients with COVID-19 (81). In an analysis of 343 patients, one study reported that D-dimer level was associated with death above a D-dimer cut-off value of >2 µg/mL (82). The mechanisms underlying the D-dimer increase in COVID-19 patients are not fully understood. In retrospective cohorts, Tang et al. found that 71.6% of non-survivors met the criteria for coagulopathies from sepsis, compared to 0.6% of survivors (45). Accordingly, there are some evidence that COVID-19 is associated with a prothrombotic condition leading to an increased risk of venous thromboembolism (83, 84). The increase in D-dimer levels can simply explain this prothrombic state. Several case reports have shown an association between COVID-19 and thrombosis formation at the microvascular level (85, 86). In a study of 81 severe COVID-19 patients admitted to the intensive care unit in China, 25% of the 81 people who were not under prophylaxis had venous thromboembolism (87). In a more recent prospective study, the incidence of venous thromboembolism was reported as 27% in 184 patients admitted to the intensive care unit (88). Therefore, thromboprophylaxis is required in all hospitalized COVID-19 patients. An awareness call on the need for adapted thromboprophylaxis in COVID-19 patients was recently published (89). In our study, the troponin level

was found to be significantly higher in the group, that resulted in mortality in the population with COVID-19 compared to the other group. In a study similar to our result, with 55% sensitivity and 80% specificity, troponin elevation was associated with an almost five-fold increase in mortality (90). A meta-regression showed that the relationship between high troponin level and mortality rate did not change according to age, male gender, hypertension, diabetes or coronary artery disease, which showed that some of the factors we mentioned were associated with mortality rate and myocardial damage (91-95). In addition to heart damage, COVID-19 can lead to arrhythmia, myocardial ischemia and thromboembolism (96,97). Natriuretic cardiac biomarkers are elevated in COVID 19 patients, indicating a poor prognosis (98).

Limitations

Various limitations should be considered when interpreting the results of our study. A causal relationship could not be established due to the retrospective and non-randomized nature of the study. This study included patients from 14 different public hospitals in Bursa, and there were unmeasurable differences in approach to patient care between the hospitals. The effect of changes in ICU admission criteria, differences in ICU staff specialties, the threshold for initiating invasive mechanical ventilation, and initiating several additional treatments at the discretion of the treating physician could not be determined. Since the mean duration of any treatment for COVID-19 is less than 10 days, we chose the laboratory values at day-1 of admission to the ICU, day-10 of ICU stay, and the highest values during ICU stay. Given the variable frequency of laboratory sample collection, we are unable to determine whether these values accurately represent pre- and post-treatment values in all study groups. We believe that our population represents a real-world cohort and what we have found regarding current COVID-19 is generalizable.

CONCLUSION

To our knowledge, this is the largest cohort study of critically ill patients with COVID-19 admitted to the intensive care unit in Turkey. COVID-19 has high mortality rates, and patients with advanced age and comorbidities may require care in the intensive care unit. We found that ferritin, hs-troponin, d-dimer and C-reactive protein levels were significantly higher in patients who died at the time of admission. In addition, hospitalization lymphocyte was significantly lower in patients who died compared to patients who were discharged.

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Author Contributions: SM, SE, HA, CD: Study design, Literature review, Patient therapies, **SE:** Data collection, Analysis, Writing, Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Evaluation of factors affecting smoking cessation in people treated with Varenicline

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ABSTRACT

Objective: Aim of the study is to evaluate factors affecting treatment success among individuals receiving varenicline therapy for smoking cessation.

Material and Methods: This research was carried out at Istanbul Medeniyet University Göztepe Training and Research Hospital between January 2018 and January 2019. A total of 209 patients in the smoking cessation outpatient clinic who were treated with varenicline Varenicline were constituted into the study group. The Fagerstrom Nicotine Dependence Level Test (FTND) was used to determine individuals' nicotine addiction levels, and the Hospital Anxiety and Depression Scale (HADS) was used to evaluate anxiety and depression levels.

Results: There were 90 (43.1%) women and 119 (56.9%) men in the study group and mean age was 41.34 ± 10.93 (21-64) years. Overall, 63.2% (n=132) of varenicline recipients quit smoking. The frequency of quitting smoking due to physician advice was higher in those who quit than those who did not (p=0.011). Multiple logistic regression revealed that the independent factors associated with the lower likelihood of smoking cessation were higher number of cigarettes per day (p=0.008), higher HADS-Total score (p<0.001), post-treatment nervousness (p=0.046), and post-treatment depressive mood (p=0.007), whereas being able to remain smoke-free for longer periods in previous quitting attempts was associated with higher likelihood of success (p=0.005).

Conclusion: The success of smoking cessation with varenicline therapy is lower in the presence of the following factors: having high risk for anxiety and depression, smoking a greater number of cigarettes per day, shorter periods of remaining smoke-free in previous quitting attempts, and experiencing nervousness during withdrawal. Receiving physician advice to quit also appears to increase the chance of quitting smoking.

Keywords: Smoking; Smoking Cessation; Smoking Cessation Agents; Varenicline; Anxiety; Depression

INTRODUCTION

Smoking causes oxidative stress and leads to a wide variety of chronic diseases and cancers that place a significant burden on health systems (1). It is reported that life expectancy in smokers is shortened by more than 10 years compared to those who have never smoked. On the other hand, quitting smoking before age 40 reduces the risk of smoking-related death by approximately 90% (2). With smoking cessation, risks for cardiovascular events and mortality decrease remarkably (3).

Professional support while quitting makes it easier to quit smoking (4). Varenicline is an FDA-approved cost-effective smoking cessation therapeutic that works by countering the effects of nicotine on nAChRs (5, 6). Although possible neuropsychiatric events with varenicline treatment were reported in earlier years, current evidence shows that such a relationship does not exist (7).

Most smokers state that they smoke in response to stress or other negative mood disorders, which makes it challenging to quit smoking (8). Smoking remains the most important modifiable risk factor for health disparities; therefore, identifying factors associated with the success of smoking cessation therapy in different regions and populations are critical to ensure that smokers can reliably quit this extremely dangerous addiction (9). As such, we aimed to determine factors affecting smoking cessation among individuals who received varenicline treatment.

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MATERIAL AND METHODS

This retrospective study was carried out in Istanbul Medeniyet University Göztepe Training and Research Hospital Family Medicine Clinic, Smoking Cessation Outpatient Clinic between January 2018 and January 2019. Ethics committee approval was obtained for the study, and the research was carried out in accordance with the Declaration of Helsinki (Approval date: June, 2018, no:2018\0255).

Within the scope of the study, the files of patients who applied to the smoking cessation outpatient clinic between January 2017 and January 2018 to quit smoking were analyzed retrospectively. Among the 970 files examined, patients who were started on varenicline treatment for smoking cessation and continued the treatment for at least 1 month were selected for evaluation. In order to be able to assess smoking cessation accurately, we only included patients in which at least 6 months of post-treatment data (after varenicline treatment) were available. This inclusion/exclusion assessment resulted in the identification of 327 patients; 209 of these patients who could be reached by phone and agreed to participate in the study constituted the study group. Sociodemographic variables, comorbidities, alcohol consumption, smoking-related characteristics (starting age, pack-years, previous quitting attempts etc.) and other relevant parameters were questioned and analyzed.

The smoking cessation polyclinic is operated by a family medicine specialist with a "Tobacco Addiction Treatment Training" certificate. Patients can apply to the clinic as walk-in patients by making an appointment with the 171 smoking cessation hotline or being referred with a smoking cessation recommendation from other clinics. At the first admission to the clinic, electrocardiogram (ECG), pulmonary function tests (PFTs), postero-anterior chest X-ray, brief biochemistry and hemogram examinations are performed. Patients are called for routine control once a month, but if they need earlier support or want to get feedback on any side effects, they can also apply to the center at their discretion. Patients are informed about the health hazards of smoking and the economic burden it brings, and brochures about these issues are distributed.

Sociodemographic characteristics, medical history, smoking behaviors and attitudes, reasons for quitting smoking, nicotine addiction levels, and anxiety and depression status were recorded from the patients' medical records. In order to obtain the most up-to-date information about the smoking cessation status of the patients in the study group, each patient was contacted by phone to record data. Among the patients, those who quit smoking within 3 or 6 months and stated that they started smoking again at the 6th or 12th month, respectively, were defined to have experienced relapse.

The Fagerström test for nicotine dependence (FTND): The FTND was applied to determine the nicotine addiction levels of individuals. This test was developed in 1978 by Fagerström and colleagues. The score that can be obtained from the test consisted of six questions ranging from 1 to 10. If the total score is 0-2, it is evaluated as very low addiction, 3-4 low-level addiction, 5 medium-level addiction, 6-7 high-level addiction, and 8-10 very high-level nicotine addiction (10, 11).

The Hospital Anxiety and Depression Scale (HADS): The HADS, developed by Zigmond and Snaith, was used to evaluate anxiety and depression levels. Anxiety (items 1, 3, 5, 7, 9, 11 and 13) and depression (items 2, 4, 6, 8, 10, 12 and 14) were evaluated. In the Turkish version of the HADS, the cut-off value was reported as 10 for the anxiety sub-domain and 7 for the depression sub-domain. In addition, by summing both subfield scores, the patients' mood can be classified as euthymic, minor depressive, or major depressive (12, 13).

Statistical Analysis: All analyses were subject to the classical significance testing threshold ($p \leq 0.05$) and were performed on version 25.0 of the SPSS software (IBM, Armonk, NY, USA). For the normality check, histograms and Q-Q plots were used and continuous variables were described with mean ± standard deviation or median (1st quartile - 3rd quartile) according to the presence or absence of normal distribution (respectively). Nominal data were reported with counts and relative frequency. Normally distributed variable comparisons were performed with the independent samples t-test. Non-normally distributed variable comparisons were performed with the Mann-Whitney U test. Categorical variable distributions were compared with appropriate chi-square tests or the Fisher's exact test. Multivariable (multiple) logistic regression analysis was performed with the forward conditional method to determine factors independently associated with unsuccessful treatment.

RESULTS

There were 90 (43.1%) women, and 119 (56.9%) men in the study group and the mean age of the group was 41.34 ± 10.93 (21-64) years. The frequency of smoking cessation was determined to be 63.2% (n=132) among varenicline recipients. The groups were similar in terms of age (p=0.188), sex (p=0.737), marital status (p=0.569), occupation (p=0.966), education status (p=0.197), comorbidities (p=0.308) and alcohol use (0.923). The median HADS-anxiety (p<0.001), HADS-depression (p<0.001) and HADS-total (p<0.001) scores were higher in quitters. The frequency of anxiety (p<0.001), depression (p<0.001), and major depression (p<0.001) was significantly higher in those who could not quit smoking (**Table 1**).

Age at onset of smoking (p=0.238) and number of pack-years (p=0.620) were similar between the groups. The median number of cigarettes smoked per day was significantly lower in those who stopped smoking (p=0.011). The frequency of patients who had previously attempted to quit smoking was similar in the two groups (p=0.816). Patients who quit smoking after varenicline treatment reported longer periods of remaining smoke-free (months) during their prior attempts to quit (p<0.001). The groups were similar in terms of seeking professional support (p=0.421). The three most common reasons for quitting smoking were fear of contracting a disease (71.8%), economic reasons (48.8%), and being bothered by bad odor (37.8%). There was no difference between the groups in terms of existing diseases (p=0.582), anxiety to contract a disease (p=0.174), harm to the environment (p=0.373), economic reasons (p=0.059), beliefs (p=0.330), aspiring to be a model individual (p=0.128), social pressure (p=0.196), embarrassment (p=0.366), and being bothered by bad odor (p=0.694).

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Table 1. Summary of patient characteristics with regard to smoking status after treatment.

	Total (n=209)	Smoking (n=77)	Quit (n=132)	p
	Mean ± SD.	**Mean ± SD.**	**Mean ± SD.**	
Age	41.34 ± 10.93	40.04 ± 10.38	42.11 ± 11.2	0.188
	n (%)	**n (%)**	**n (%)**	
Sex				
Female	90 (43.1)	32 (41.6)	58 (43.9)	0.737
Male	119 (56.9)	45 (58.4)	74 (56.1)	
Marital status				
Married	125 (59.8)	48 (62.3)	77 (58.3)	0.569
Single	84 (40.2)	29 (37.7)	55 (41.7)	
Occupation				
Working	151 (72.2)	55 (71.4)	96 (72.7)	0.966
Not-working	58 (27.8)	22 (28.6)	36 (27.3)	
Education status				
Illiterate	1 (0.5)	0 (0.0)	1 (0.8)	0.197
Primary school	48 (23.0)	21 (27.3)	27 (20.5)	
Secondary school	31 (14.8)	12 (15.6)	19 (14.4)	
High school	72 (34.4)	30 (39.0)	42 (31.8)	
University	57 (27.3)	14 (18.2)	43 (32.6)	
Comorbidities	91 (43.5)	30 (39.0)	61 (46.2)	0.308
Chronic obstructive pulmonary disease	12 (5.7)	6 (7.8)	6 (4.5)	0.365
Diabetes mellitus	33 (15.8)	14 (18.2)	19 (14.4)	0.598
Hypertension	27 (12.9)	10 (13.0)	17 (12.9)	1
IM	9 (4.3)	3 (3.9)	6 (4.5)	1
Coronary artery disease	20 (9.6)	6 (7.8)	14 (10.6)	0.672
Other	32 (15.3)	9 (11.7)	23 (17.4)	0.362
Alcohol use	51 (24.4)	18 (23.4)	33 (25.0)	0.923
HADS-anxiety score (Mean ± SD.)	7.83 ± 3.95	9.69 ± 3.91	6.75 ± 3.57	**<0.001**
<10	141 (67.5)	41 (53.2)	100 (75.8)	**0.001**
≥10	68 (32.5)	36 (46.8)	32 (24.2)	
HADS-depression score (Mean ± SD.)	6.74 ± 3.56	8.17 ± 3.54	5.90 ± 3.31	**<0.001**
<7	114 (54.5)	29 (37.7)	85 (64.4)	**<0.001**
≥7	95 (45.5)	48 (62.3)	47 (35.6)	
HADS-total score (Mean ± SD.)	14.55 ± 6.66	17.86 ± 6.37	12.61 ± 6.06	**<0.001**
Euthymic (≤12)	92 (44.0)	16 (20.8)	76 (57.6)	**<0.001**
Minor depressive (13-18)	56 (26.8)	26 (33.8)	30 (22.7)	
Major depressive (≥19)	61 (29.2)	35 (45.5)	26 (19.7)	

HADS: Hospital Anxiety and Depression Scale, SD.: Standard deviation, n: number, %: percent, Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

The frequency of quitting smoking after receiving physician advice was higher in those who could quit (p=0.011), and the frequency of quitting due to workplace pressure was higher in those who could not quit (p=0.006).

The median FTND score was significantly higher among non-quitters compared to those who had quit (p<0.001). According to the FTND score, the frequency of being 'highly dependent' was higher in those who could not quit smoking (p=0.024). The frequency of people who taked nicotine replacement therapy in addition to varenicline treatment was similar between the two groups (p=1.000).

There was no difference between the groups in terms of treatment duration (p=0.115). The three most common symptoms found after treatment was uneasiness (20.6%), insomnia (16.7%), and nervousness (15.8%). The frequency of nervousness (p=0.004), uneasiness (p=0.018), and depressive mood (p=0.011) were significantly higher among non-quitters. There was no difference between the groups in terms of other symptoms. The frequency of side effects after treatment was 23.4%, and there was no difference between the two groups (p=0.182). The groups were similar in terms of treatment follow-up time (p=0.182). The median time spent without smoking was higher in those who quit smoking (p<0.001, **Table 2**).

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Table 2. Summary of patients' smoking and quitting characteristics with regard to smoking status after treatment.

	Total (n=209)	Smoking (n=77)	Quit (n=132)	p
	Median (IQR)	Median (IQR)	Median (IQR)	
Age at onset of smoking	18 (15 - 19)	17 (15 - 19)	18 (16 - 19)	0.238
Number of cigarettes, in a day	20 (20 - 30)	30 (20 - 40)	20 (20 - 30)	**0.011**
Number of pack-years	24 (16 - 36)	24 (16 - 38)	24.5 (16 - 36)	0.62
Tried to quit before	174 (83.3%)	63 (81.8%)	111 (84.1%)	0.816
Longest period without smoking, month, before treatment	1 (0.1 - 3)	0.25 (0.1 - 1)	1.42 (0.25 - 6)	**<0.001**
	n (%)	n (%)	n (%)	
Professional help for quitting	57 (27.3)	18 (23.4)	39 (29.5)	0.421
Pharmacological	46 (22.0)	16 (20.8)	30 (22.7)	
Acupuncture	4 (1.9)	0 (0.0)	4 (3.0)	0.411
Psychiatric	7 (3.3)	2 (2.6)	5 (3.8)	
Reason to quit				
Existing diseases	52 (24.9)	17 (22.1)	35 (26.5)	0.582
Anxiety to catch a disease	150 (71.8)	51 (66.2)	99 (75.0)	0.174
Harm to environment	69 (33.0)	22 (28.6)	47 (35.6)	0.373
Economic reasons	102 (48.8)	31 (40.3)	71 (53.8)	0.059
Beliefs	10 (4.8)	2 (2.6)	8 (6.1)	0.33
To be a model individual	39 (18.7)	19 (24.7)	20 (15.2)	0.128
Social pressure	6 (2.9)	4 (5.2)	2 (1.5)	0.196
Embarrassment	23 (11.0)	6 (7.8)	17 (12.9)	0.366
Bothered by the smell	96 (45.9)	34 (44.2)	62 (47.0)	0.694
Doctor advice	79 (37.8)	20 (26.0)	59 (44.7)	**0.011**
Workplace pressure	15 (7.2)	11 (14.3)	4 (3.0)	**0.006**
	n (%)	n (%)	n (%)	
Factors increasing smoking				
Tea/Coffee	112 (53.6)	43 (55.8)	69 (52.3)	0.617
Alcohol	17 (8.1)	5 (6.5)	12 (9.1)	0.689
Postprandial	148 (70.8)	55 (71.4)	93 (70.5)	1
Stress	153 (73.2)	58 (75.3)	95 (72)	0.714
Other	18 (8.6)	8 (10.4)	10 (7.6)	0.657
Another smoker at home	132 (63.2)	50 (64.9)	82 (62.1)	0.684
Anybody non-smoker at home	143 (68.4)	51 (66.2)	92 (69.7)	0.603
FTND score (Mean ± SD.)	6.88 ± 1.98	7.48 ± 1.57	6.53 ± 2.12	**<0.001**
Minimally dependent (0-3)	8 (3.8)	0 (0.0)	8 (6.1)	
Moderately dependent (4-6)	74 (35.4)	23 (29.9)	51 (38.6)	**0.024**
Highly dependent (7-10)	127 (60.8)	54 (70.1)	73 (55.3)	
Treatment				
Varenicline	176 (84.2)	65 (84.4)	111 (84.1)	1
Varenicline + NRT	33 (15.8)	12 (15.6)	21 (15.9)	
Duration of treatment				
One month	11 (5.3)	1 (1.3)	10 (7.6)	
Two months	79 (37.8)	28 (36.4)	51 (38.6)	0.115
Three months	119 (56.9)	48 (62.3)	71 (53.8)	
Symptoms after treatment				
Nervousness	33 (15.8)	20 (26.0)	13 (9.8)	**0.004**
Uneasiness	43 (20.6)	23 (29.9)	20 (15.2)	**0.018**
Concentration problems	26 (12.4)	14 (18.2)	12 (9.1)	0.088
Insomnia	35 (16.7)	10 (13.0)	25 (18.9)	0.358
Anxiety	6 (2.9)	2 (2.6)	4 (3.0)	1
Fatigue	23 (11.0)	13 (16.9)	10 (7.6)	0.065
Abnormal dreams	18 (8.6)	3 (3.9)	15 (11.4)	0.109
Tremor/Shivering	4 (1.9)	2 (2.6)	2 (1.5)	0.626
Drowsiness	12 (5.7)	7 (9.1)	5 (3.8)	0.13
Oral aphthae	17 (8.1)	7 (9.1)	10 (7.6)	0.901
Constipation	30 (14.4)	10 (13.0)	20 (15.2)	0.821
Palpitation	2 (1.0)	1 (1.3)	1 (0.8)	1
Depressive mood	7 (3.3)	6 (7.8)	1 (0.8)	**0.011**
Other	49 (23.4)	17 (22.1)	32 (24.2)	0.852
Side effect	49 (23.4)	17 (22.1)	32 (24.2)	0.852
Follow-up time, month (range 6-21)	10 (8 - 16)	10 (9 - 18)	9 (8 - 14)	0.182
Quit smoking and restart	69 (33.0)	69 (89.6)	-	N/A
Duration without smoking, month	8 (4 - 9)	3 (3 - 5)	9 (8 - 11)	**<0.001**
Re-apply	14 (6.7)	14 (18.2)	-	N/A

FTND: Fagerström Test for Nicotine Dependence, n: number, %: percent, SD.: Standard deviation, N/A: Not-Applicable, IQR: Interquartile range. Data are given as mean ± standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

We performed multiple logistic regression analyses to determine significant factors independently associated with relapse after treatment. We found that higher daily cigarette count (p=0.008), higher HADS-Total score (p<0.001), nervousness (p=0.046) and depressive mood (p=0.007) were independently associated with unsuccessful treatment. In addition, we found that individuals who were able to remain smoke-free for longer periods before treatment (p=0.005) were more likely to quit smoking. Other variables included in the model, trying to quit due to doctor advice (p=0.160), trying to quit due to workplace pressure (p=0.309), HADS-Anxiety score (p=0.908), HADS-Depression score (p=0.770), FTND score (p=0.450) and uneasiness after treatment (p=0.105) were found to be non-significant (**Table 3**).

Table 3. Significant factors of the unsuccessful Varenicline treatment, multiple logistic regression analysis.

	β coefficient	Standard Error	p	Exp(β)	95.0% CI for Exp(β)	
Number of cigarette, in a day	0.048	0.018	**0.008**	1.049	1.013	1.086
Longest period without smoking, month	-0.194	0.07	**0.005**	0.823	0.718	0.944
HADS Total score	0.145	0.03	**<0.001**	1.156	1.089	1.227
Nervousness after treatment	0.882	0.443	**0.046**	2.416	1.014	5.756
Depressive mood after treatment	3.673	1.368	**0.007**	39.353	2.693	575.129
Constant	-3.73	0.716	<0.001	0.024		

Dependent variable: Continue/restart smoking; Nagelkerke R2=0.422, CI: Confidence Interval, %: percent

DISCUSSION

Varenicline, which relieves withdrawal and craving symptoms that occur when not smoking, has been demonstrated to increase smoking cessation rates compared to other pharmacotherapeutics (14). In this study, we examined factors affecting the success of smoking cessation with Varenicline.

In the current study, 63.2% of varenicline recipients successfully quit smoking. This is a remarkable result because various studies have reported 12-month cessation rates of 35.3% and 24.5% in varenicline recipients (15,16). The high success found in our study may be explained by various characteristics of the study group, including sociodemographics, comorbidities, motivation to quit, health literacy and the differences in the interventions and methods applied for smoking cessation.

In this study, the three most common motivations were fear of disease (71.8%), economic reasons (48.8%), and being bothered by bad odor (37.8%). In the study of Buczkowski et al., the three most common motivations to quit smoking were reported as a smoking ban at home or work, high cigarette prices, and influences of peers (17). In the study by Dickens et al., it was reported that health concerns were the primary reason for quitting smoking (18). Concerns regarding physical fitness are also reported in different populations and the cost of tobacco products (19). In a study from Turkey by Yaşar et al., the three most common reasons for quitting smoking were reported as medical advice, current illness and fear of illness, indicating that fear of disease and physician advice appears to be effective on patients in Turkey (20). It was concluded that the motivation to quit smoking ould be increased by providing knowledge regarding the effects of smoking on health, keeping the price of tobacco products high, and ensuring that physicians advise patients whenever possible, especially in Turkey.

In this study, the frequency of quitting smoking due to physician advice was significantly higher in those who successfully quit smoking with Varenicline. This again shows the importance of positive health behavior recommendations about smoking, especially when received from physicians.

Nicotine replacement therapy is based on the controlled administration of nicotine, which facilitates tobacco abstinence by partially replacing the nicotine obtained from previous tobacco use. With nicotine replacement therapy, nicotine receptors are stimulated, reducing the desire to smoke and withdrawal symptoms (4). In the current study, we found that adding nicotine replacement therapy to Varenicline was not independently effective in smoking cessation success. According to a meta-analysis by Guo et al., in which randomized controlled trials of varenicline therapy were assessed, it was reported that combined treatments with Varenicline, bupropion and nicotine replacement therapy produced more positive results than monotherapies (21). According to the results of another study, it was reported that Varenicline in combination with nicotine replacement was more effective than Varenicline alone in the treatment of tobacco withdrawal (22). In the study of Baker et al., there was no significant difference in the prevalence of smoking cessation between those treated with varenicline and nicotine patches and those treated with varenicline monotherapy (23). Therefore, it appears that adding nicotine replacement therapy to varenicline treatment should be decided on

Those with high nicotine addiction have difficulty quitting smoking compared to those with lower addiction levels (24). In some previous studies, it was reported that the median FTND score was higher in those who could not quit smoking, similar to our study (20,25). The main feature of nicotine addiction is the desire to feel the positive pharmacological effects of nicotine, such as psychoactive stimulation, and to avoid possible withdrawal symptoms (4). Withdrawal symptoms such as depressed mood, insomnia, and irritability occur when the target nAChR receptors are no longer occupied by nicotine. These negative feelings are reported to facilitate the urge to continue smoking (26). In this study, the three most common symptoms found after treatment were uneasiness (20.6%), insomnia (16.7%) and nervousness (15.8%). The frequency of these symptoms was higher among those who could not quit smoking. In another study, the most common withdrawal symptoms were reported as nervousness, craving for cigarettes, and loss of concentration (20). Smoking cessation rates may be increased by supporting

patients who report these symptoms at greater frequency or severity.

In this study, a lower cigarette count per day was one of the independent predictors of smoking cessation, which was a replication of the findings from the study by Klemperer and colleagues (27).

Of note, a study from Turkey reported conflicting results to the literature and found no relationships between depression or anxiety among those who did and did not quit smoking (20).

CONCLUSION

This study shows that a higher HADS-Total score, higher number of daily cigarettes, suffering from nervousness after treatment initiation, and having depressive mood were independently associated with unsuccessful varenicline therapy; whereas being able to quit smoking for longer periods in prior attempts to quit was associated with higher likelihood of successful cessation. Following up on individuals who will receive Varenicline for smoking cessation in terms of anxiety and depression and treating these diseases in at-risk individuals may increase treatment success. It also appears that receiving physician advice increased the motivation to quit smoking and the success of cessation therapy, which might be important factors to consider in patients from Turkey. We conclude that prospective and more comprehensive studies evaluating factors affecting smoking cessation success with Varenicline are required, especially in Turkey.

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