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Aims and Scope

Health Sciences Quarterly (Health Sci. Q.) is an open-access journal that publishes original research papers, case reports, and reviews, clinical studies covering a wide range of subjects in life sciences and medicine as well as clinical and experimental investigations only in English.

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

HSQ aims to supply scientists of health with resources in order to provide the scientific knowledge through the publication of peer-reviewed, high quality, scientific papers and other material on all topics related to Medicine, Pharmacy and pharmaceutical sciences, Dentistry, Nursing, Bioethics, History of medicine, Health economics, Pharmacoeconomics, Medical education, Public health, and Epidemiology.

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LETTER TO THE EDITOR

Methotrexate intoxication as a diagnostic challenge: Do patients always tell the truth?

Ece Erbağcı

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Dear editor,

Methotrexate is an effective and safe drug that has been used for many years in the treatment of psoriasis [1]. Clinical and laboratory monitoring is important for toxicity monitoring in patients. Herein, a case of methotrexate intoxication that developed after long-term uncontrolled and irregular use of methotrexate, but had diagnostic difficulties because the patient concealed this condition in her anamnesis, will be presented.

A 47-year-old female patient applied to our outpatient clinic due to psoriatic lesions. The patient, who was previously followed up at another hospital, was previously diagnosed with psoriasis and had previously used cyclosporine and methotrexate treatments alternately for 8-9 years, and was unable to tolerate the adverse effects of acitretin treatment. After the last use of cyclosporine, renal function tests showed abnormalities and acute renal failure. She stated that she was concerned about the adverse effects of biological agent treatments. The patient was informed about the adverse effects and her tests were requested to start biological treatment. In laboratory tests, serum creatinine: 4.16 mg/dl, BUN: 57 mg/dl, glomerular filtration rate: 11.93 mg/min/1.73m^2. The patient was consulted to nephrology. Her drug history was questioned in detail and she was strictly informed not to use any nephrotoxic drugs. However, the patient re-admitted a few days later with painful sores in the mouth. Antiviral treatment was started considering herpes virus infection. After the worsening of oral lesions and the development

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of new ulcerated skin lesions under antiviral treatment, the patient was questioned again with the suspicion of methotrexate intoxication (Figure 1 and 2). Although not stated in her previous history, the patient reported that she had used subcutaneous methotrexate a week ago to improve her psoriatic lesions before going on vacation and was hesitant to mention it. Laboratory tests showed pancytopenia with WBC: 1480/µl, neutrophil: 800/µl, lymphocyte: 450/µl, hemoglobulin: 8.5 gr/dl, platelet: 76000/µl. The patient was hospitalized, methotrexate was stopped, and hematology, infectious diseases and nephrology consultations were requested. Empirical intravenous antibiotic and intravenous folinic acid treatments were started. Mucocutaneous intoxication findings regressed within a week, and pancytopenia regressed within 3-4 weeks.

Oral mucositis, cutaneous erosions (especially on psoriatic plaques), and pancytopenia are characteristic clinical findings in patients who develop acute methotrexate toxicity [2,3]. Methotrexate inhibits rapidly cycling cells such as mitotically active hematopoietic, gastrointestinal, and cutaneous cells. Renal insufficiency may increase methotrexate toxicity because its elimination depends on glomerular filtration and tubular secretion [4]. In patients with psoriasis, clinicians should be alert to the warning signs of acute methotrexate toxicity, such as mucocutaneous ulcerations, mucositis, and pancytopenia, even if patients do not report methotrexate use in their history. Methotrexate should be used with caution in patients with abnormal renal function tests.

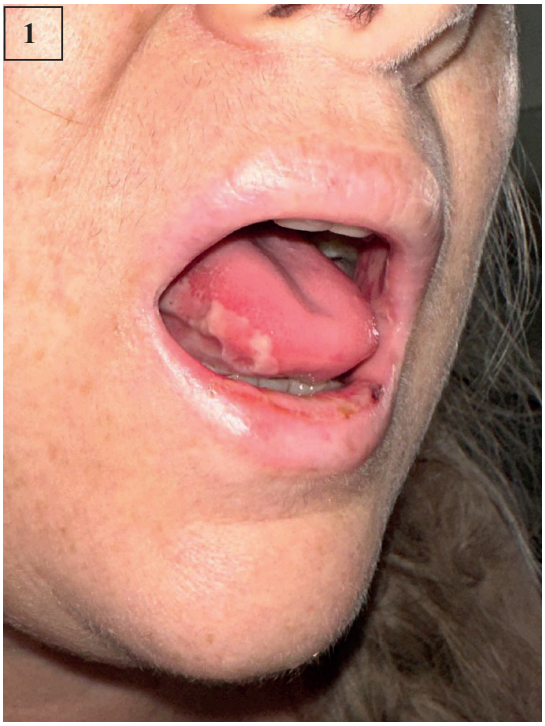

Figure 1. Mucocutaneous findings due to methotrexate intoxication.

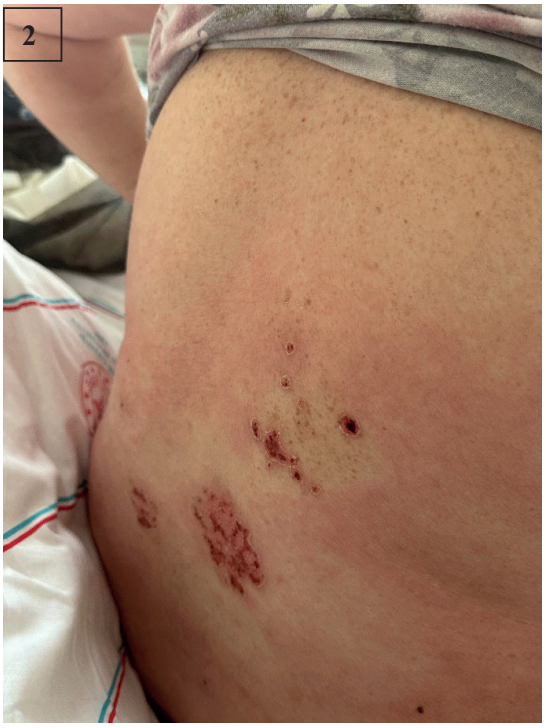

Figure 2. Mucocutaneous findings due to methotrexate intoxication.

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Conflict of interest

There is no conflict of interest.

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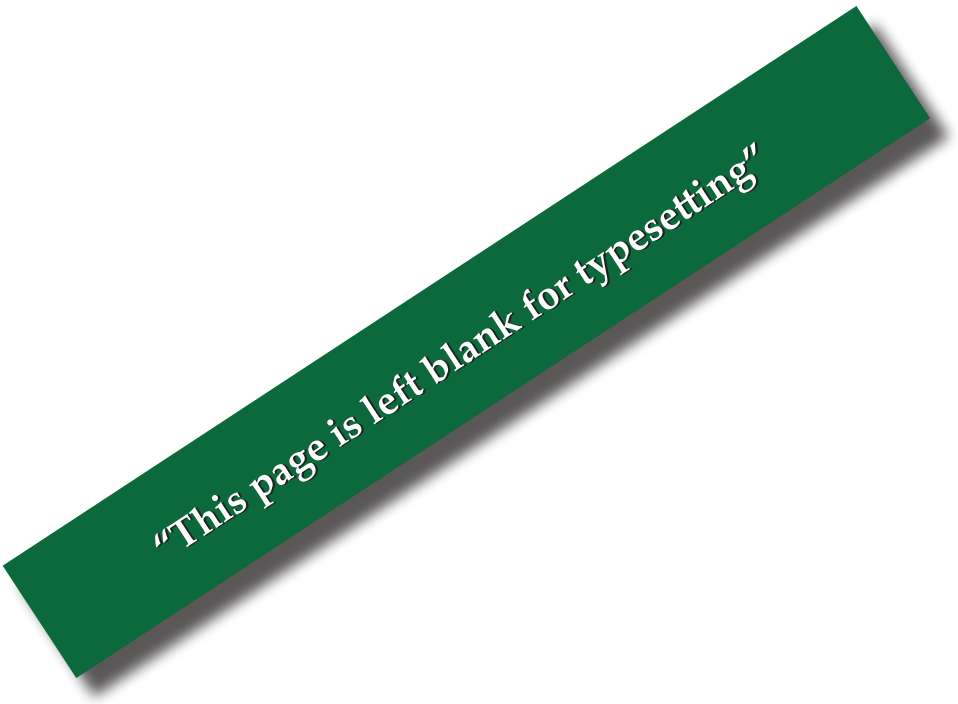
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ORIGINAL ARTICLE

The evaluation of giant-cell arteritis (temporal arteritis) cases with optical coherence tomography angiography (OCT-A)

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Abstract

To make measurements using optical coherence tomography angiography (OCT-A) in inactive giant cell arteritis (GCA) cases who have previously had GCA and have been treated and to compare the obtained data with healthy volunteers. In this observational case-control study, 18 eyes of 18 GCA cases previously diagnosed, treated with anterior arteritic ischemic optic neuropathy (AAION). 22 eyes of 22 ophthalmically healthy volunteers were included in the study. After external ophthalmic examinations of all participants were performed, their measurements were made with serial OCT-A. Superficial capillary plexus (SCP), deep capillary plexus (DCP), foveal avascular zone (FAZ), area covering 300 degrees around the fovea (FD-300), choriocapillaris (CC), retinal nerve fiber layer (RNFL), cup/disc (C/D) ratio and optic disc vessel densities (OD-VD) were evaluated. $p<0.05$ was considered significant. There was no difference between the two groups in terms of age, gender and shooting quality. Whole-SCP, SCP-foveal, SCP-parafoveal and SCP-perifoveal VD values were lower in the patient group. Whole-DCP, DCP-parafoveal and DCP-perifoveal VD values were also low in the patient group. FAZ areas were similar between groups, but the FD-300 VD was different. Whole-OD VD and inside-OD VD were significantly lower in the patient group. Peripapillary-OD VD and RNFL values were similar. The C/D ratio was higher in the patient group. The effect on the microvascular process was significant in OCT-A. This suggested that even if the ischemic process still continues and there is no active inflammation, microvascular structures may continue to be affected.

Keywords: Deep capillary plexus, giant cell arteritis, microvascular structures, optical coherence tomography angiography, superficial capillary plexus

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Introduction

Giant-Cell Arteritis (GCA), also known as Temporal Arteritis or Horton's Disease, is a type of chronic granulomatous vasculitis that typically affects the aortic arch and its primary and distal branch vessels. This disease is usually detected over the age of 50 and peaking at 70 years of age [1,2]. GCA-related vision loss is usually severe and irreversible. Several cases of vision loss caused by Anterior Arteritis Ischemic Optic Neuropathy (AAION), which occur most frequently secondarily to the involvement of the short posterior ciliary arteries, have been reported [3-6]. About twice as many women as men experience this disease. The frequency of ophthalmic manifestations in GCA ranges between 14% and 70% [5, 6]. Ischemia is detected in the laminar and prelaminar segments of the optic nerve. Pallor and edema of the optic disc may develop in classic AAION due to serious irregularity in blood circulation. Common clinical characteristics of GCA include headache, scalp and temporal artery tenderness, and symptoms of Polymyalgia Rheumatica (PMR). Chewing muscle ischemia is responsible for the symptoms of "jaw claudication". Visual symptoms, including monocular or binocular blindness and aortic aneurysm rupture or dissection, are the most severe complications of GCA. The diagnosis is based on a characteristic pattern of symptoms, physical examination outcomes, elevated acute phase reactants (Erythrocyte Sedimentation Rate [ESR] and C-Reactive Protein [CRP]), biopsy findings, and vascular imaging. Optical Coherence Tomographic Angiography (OCT-A) provides high-resolution, non-invasive, 3D imaging of retinal and choroidal vessels. The ability of OCT-A in showing deeply resolved details of the vasculature in the Z-axis provides a distinct advantage over conventional fluorescent angiography [3]. OCT-A is also an important diagnostic tool for a variety of retinopathies, including central serous chorioretinopathy, macular telangiectasia, and polypoidal choroidopathy, among others [4-6]. The distinctive characteristic of GCA that can be detected by Fluorescent Angiography (FA), is a delayed choroidal and retinal perfusion in the peripapillary region [3,4,7,8]. OCT-A with depth identification offers a novel, non-invasive, high-resolution imaging technique for the optic nerve head microvasculature [7,8]. Previous studies found that smoking increases the risk of GCA in women, but not in men. In addition, some researchers reported a possible relationship between GCA and Varicella Zoster Virus (VZV) [9,10]. To date, only a few studies described the use of OCT-A to characterize microvascular optic nerve head changes in acute ischemic optic neuropathy [11,12]. Given that ischemic is the most common recognized cause of vision loss in GCA, the investigation of ocular blood flow has actracted a great interest on the researchers about this topic. Studies such as fluorescein angiography have long been used to detect ocular ischemia, but OCT-A is also among the alternatives described. On OCT-A, patients with GCA-induced anterior ischemic optic neuropathy may show peripapillary microvascular dilation and focal non-perfusion status, which are nonspecific but common outcomes for GCA [13]. Wide-scope scan source OCT-A can confirm choroidal infarction in GCA [14]. Thus, OCT-A, as a recent diagnostic method in GCA, can make a useful contribution to the clinical diagnosis and understanding of this disease.

The aim of this study was to report the OCT-A outcomes in patients with GCA causing AAION and evaluated at the vascular level and to compare the results with those of healthy subjects.

Materials and Methods

OCT-A measurements of 18 eyes in 18 patients with giant-cell arteritis and 27 eyes of 27 systemic and ophthalmically healthy patients were collected between December 2022 and February 2023. The study was carried on the Afyonkarahisar Health Sciences Universtiy, Faculty of Medicine, Department of Ophthalmology unit. All patients underwent clinical examination and ophthalmological evaluation at the first and last visits and the cases with visual acuity measurement, cornea, and fundus examination were included in the study. Cases who had giant-cell arteritis and recovered were included in the study as the patient

group, whereas systemic and ophthalmically healthy patients were included in the study as the control group. All subjects affected by other diseases (active giant-cell arteritis, non-ischemic arteritis optic neuropathy, non-giant-cell arteritis vascular pathology, glaucoma, cataract, retinopathy, keratopathy, congenital ocular anomaly, systemic vascular disease including diabetes or systemic hypertension, pupil dilation, or hypersensitivity or intolerance to topical anesthetics or mydriatics), pregnant or breastfeeding women and patients who had undergone ocular surgery within 6 months, were excluded from the study. All participants underwent a complete ophthalmic examinations including best-corrected visual acuity, measurement of Intraocular Pressure (IOP) with Goldmann Applanation Tonometry, slit lamp examination, and fundus examination. B-scan ultrasonography was performed to evaluate the ocular and orbital structure. Central Corneal Thickness (CCT) and Axial Length (AL) were recorded by using Lenstar LS900 (Haag-Streit AG, Switzerland).

All interventional procedures in this study were performed in accordance with both ethical and Helsinki Declaration standards. Ethics Committee approval of this study was obtained from Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University (Decision date: 02.09.2022, decision no: 2022/437).

Optical Coherence Tomography Angiography (OCT-A) Measurement

OCT provides detailed noninvasive visualization of the retina's structure. OCT-A can simultaneously visualize inner and outer retinal blood flow, allowing the visualization of 3D microcirculation vascular maps of the retina and choroid without using exogenous stains [15]. It is already known that the density of the vessels in the macula and the size of the Foveal Avascular Zone (FAZ) are very important in visual acuity. Recently, OCT-A has been used to diagnose and monitor retinal microvascular pathology by measuring the density of vessels in the macula in patients with diabetic retinopathy, central serous chorioretinopathy, and glaucoma, as well as in evaluating macular edema, age-related macular degeneration, and other disorders [16,17]. In this study, OCTA images were acquired from an optic nerve-centered 6×6 mm2 field by using Optovue AngioVue™ (RTVue XR Avanti, Optovue Inc., Fremont, CA., USA) and AngioAnalytics 2.0 quantization that used the Split-Spectrum Amplitude Decorrelation Angiography Algorithm. The wavelength was 840 nm, the scanning frequency was 70.000 Hz, and the lateral and axial direction discrimination was 15 μm and 5 μm, respectively. The scanning depth was 2-3 mm, the A-scan number was 304×304, and the B-scan was repeated twice in the same spot. Motion Correction Technique and DualTrac were applied throughout the entire process and HD Angio Disc 6 mm mode was used to scan a 6×6 mm area surrounding the optic nerve. The images of four layers were recorded for each patient (Superficial Capillary Plexus Density (SCPD), Deep Capillary Plexus Density (DCPD), Outer Retina (OR), and Choriocapillaris (CC). OCTA images of the macula were acquired with AngioPlex (Carl Zeiss Meditec, Dublin, CA, USA) by using a Cirrus High-Resolution OCT prototype. The macula was imaged by using a 3×3 mm scanning model. The tracking technology was used to reduce the effect of motion artifacts. Only high-quality images with a signal strength >8 were included for analysis. Parameters to evaluate the superficial and deep retinal vessels (from the inner boundary membrane layer to the inner plexus layer), including the Foveal Avascular Zone (FAZ), and vascular density, were calculated by using the manufacturer's angiometric software. Vascular Density (VD) was defined as the linear length of vessels divided into the selected area. Perfusion density represents the area of vessel distribution divided by the selected area. Although both eyes were suitable for the study, only the right eyes were selected in the final data analysis. Each position was measured twice and the peripapillary RNFL and VD were recorded. Optical disc 200×200 mode was made to obtain the RNFL results. Choroidal thickness measurements were made in the upper, lower, nasal, and temporal regions with selected locations including 500 μm, 1000 μm, 1500 μm, and 2000 μm from the fovea. All measurements were performed by an ophthalmologist.

Statistical Analysis

Data were examined by the IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA) software. Average, standard deviation, median and Interquartile Range (IQR) were evaluated as basic descriptive statistical methods. Differences between the groups in term of age, gender distribution and shot quality were evaluated by X^2. The *Kolmogorov-Smirnov* test was used to test whether the data showed normal distribution. The Independent Sample t-test and *Mann-Whitney U*-test were used to test the difference between variables. The relationships of the variables were found by using the *Pearson* Correlation test. The results were evaluated at a 95% Confidence Interval and 5% significance level.

Results

18 eyes of 18 GCA patients (13 women, 5 men) and 27 eyes of 27 completely healthy participants (16 women, 11 men) were examined. There was no difference between the groups in terms of age, gender distribution and shot quality (p>0.05, respectively). The average age of the patient group was 55±16 years, while that of the control group was 56±20 years.

Patients with temporal arteritis met the remission criteria of the "2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis" [18]. The medications currently used by GCA patients in remission is reported in Table 1.

Comparing the superficial and deep vessel densities measured with OCT-A between the groups, all superficial, foveal, parafoveal, and perifoveal vessel densities resulted to be statistically different between the groups (p<0.05) (Table 2).

Deep vessel density measurements were also evaluated and all deep, parafoveal, and perifoveal deep vessel density values were found to be different (p<0.05). Although deep foveal vessel density was found to be relatively decreased in the patient group, the differences were not statistically significant (33.25±6.19, 36.75±7.97, and p>0.05, respectively). In general, superficial and deep vessel density values were found to be significantly decreased in GCA cases when compared to the healthy group. The mean FAZ in GCA cases was 0.33±0.07 mm^2 and was

Table 1. Drugs used by patients in remission.

Drug used	n	%
Metotreksat	12	%66.66
Tosilizumab	3	%16.66
Azatioprin	2	%11.11
Leflunomid	1	%5.55

Table 2. OCTA-VD: Optic Coherens Tomography Angiography-Vessel Density, SCP Whole: Whole Superficial Capillary Plexus, SCP FV: Foveal Superficial Capillary Plexus, SCP PARAFV: Parafoveal Superficial Capillary Plexus, SCP PERIFV: Perifoveal Superficial Capillary Plexus, DCP WHOLE: Whole Deep Capillary Plexus, DCP FV: Foveal Deep Capillary Plexus, DCP PARAFV: Parafoveal Deep Capillary Plexus, DCP PERIFV: Perifoveal Deep Capillary Plexus.

	Variables	Patient (18)	Control (22)	*p*-value
OCTA-VD	*SCP WHOLE*	48.95±4.6	52.9±4.1	0.016
	SCP FV	13.05±7.1	19.9±7	0.043
	SCP PARAFV	52.8±7	55±4.0	0.045
	SCP PERIFV	50.63±2.78	52.81±3.1	0.012*
	DCP WHOLE	54.45±7.5	57±6.7	0.005
	DCP FV	33.25±6.19	36.75±7.97	0.123*
	DCP PARAFV	57±5.1	60±5.2	0.001
	DCP PERIFV	55.6±6.4	59.1±6.7	0.002

larger than in the control group (0.30±0.09), but the differences were not statistically significant (p>0.05) (Table 3). However, a significant difference was found between the patient group and the healthy group in terms of vascular density in areas that covered 300 degrees of the fovea (p<0.05) (Table 3).

Comparison between the patient and control groups in terms of Flow Area (FA) values showed that vessel densities in the areas selected for the outer retina and choriocapillaris were not statistically different between the two groups (p>0.05 for all) (Table 4).

OCT analysis and OCT-A results are given in Table 5. The patient and control groups were similar in terms of mean RNFL (114.83±14.53, 114.44±11.41, and p>0.05, respectively), but the C/D ratio was different between the groups (0.11±0.07, 0.05±0.02, p<0.05, respectively). The values of the patient group were higher than the healthy controls in terms of C/D values. Significant differences were found between the groups in terms of vessel densities in the measurements made with OCT-A. Whole vessel density was 48.53±1.84 in the patient group and 49.94±2.18 in the control group (p<0.05). In terms of whole vessel density, the values of the patient group were lower than the healthy group. Also, inside vascular density was found to be lower in the patient group compared to the control group (49.23±6.32, 52.74±4.31, and p<0.05, for

Table 3. FAZ PARAMETERS: Foveal Avascular Zone Parameters, FAZ Area: Foveal Avascular Zone Area, PERIM: Perimeter, FD-300 (%): Vessel Density within a 300 μm wide region of the Foveal Avascular Zone (FAZ).

	Variables	Patient (18)	Control (22)	*p*-value
FAZ PARAMETERS	*FAZ AREA*	0.33±0.07	0.30±0.09	0.321*
	PERIM	2.23±0.27	2.16±0.42	0.504*
	FD-300 (%)	55.58±3.43	57.44±4.62	0.033

Table 4. FA: Flow Area, OR FA: Other Retina Flow Area, CC FA: Choriocapillaris Flow Area.

	Variables	Patient (18)	Control (22)	*p*-value
FLOW AREA (FA) PARAMETERS	OR FA	7.92±3.9	8.46±2.4	0.711
	CC FA	20.36±1.19	19.84±1.15	0.149*

Table 5. RNFL GLOBAL: Global Retina Nerve Layer Thickness, WHOLE VD: Whole Vessel Density, INSIDE VD: Inside Vessel Density, PERIPAPİLLARY VD: Peripapillary Vessel Density, CUP-DISC RATIO: Optic Disc Cup-Disc Ratio.

	Variables	Patient (18)	Control (22)	*p*-value
OPTIC DISC	*RNFL GLOBAL*	114.83±14.53	114.44±11.41	0.921*
	WHOLE VD	48.53±1.84	49.94±2.18	0.029*
	INSIDE VD	49.23±6.32	52.74±4.31	0.032*
	PERIPAPILLARY VD	52.26±2.14	52.20±2.69	0.992*
	CUP-DISC RATIO	0.11±0.07	0.05±0.02	0.002*

all). Peripapillary vessel density was similar between the groups (52.26±2.14, 52.20±2.69, and p>0.05, respectively). When the patient group correlations were investigated, it was determined that there was a positive, strong, and moderate linear relationship between all variables.

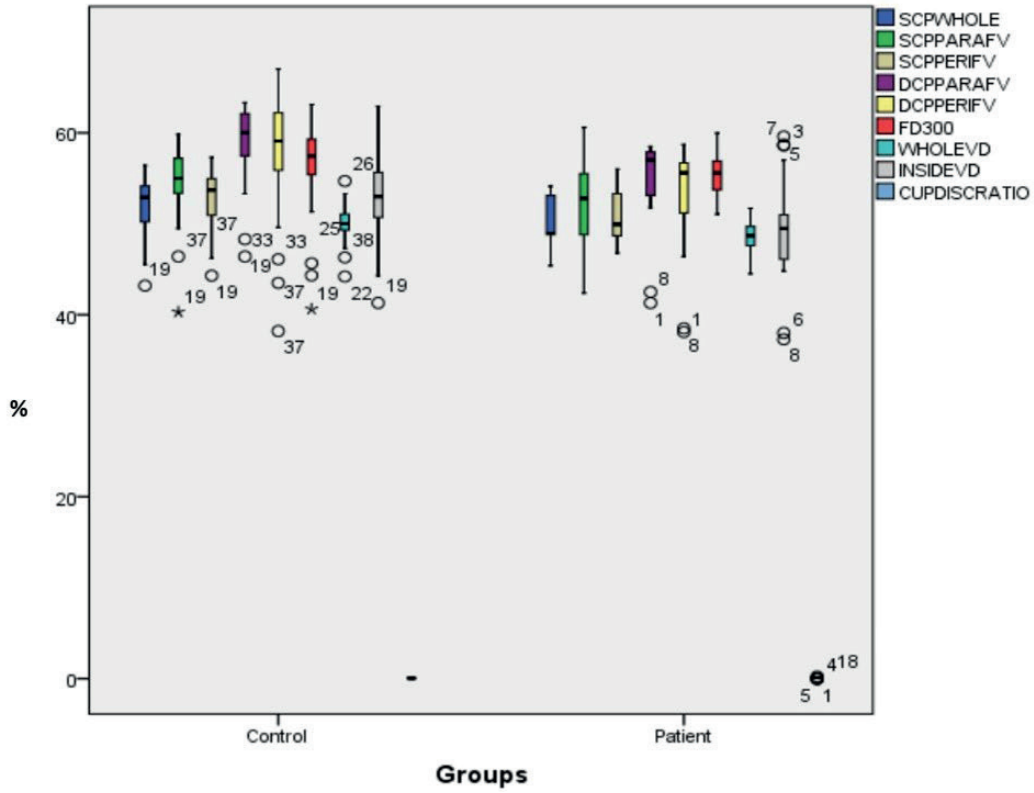

Figure 1. Distribution of SCP, DCP, VD and FD-300 in patient and control groups (SCP: Superficial capillary plexus, DCP: Deep capillary plexus, FD: Flow Density, VD: Optic disc intravascular density).

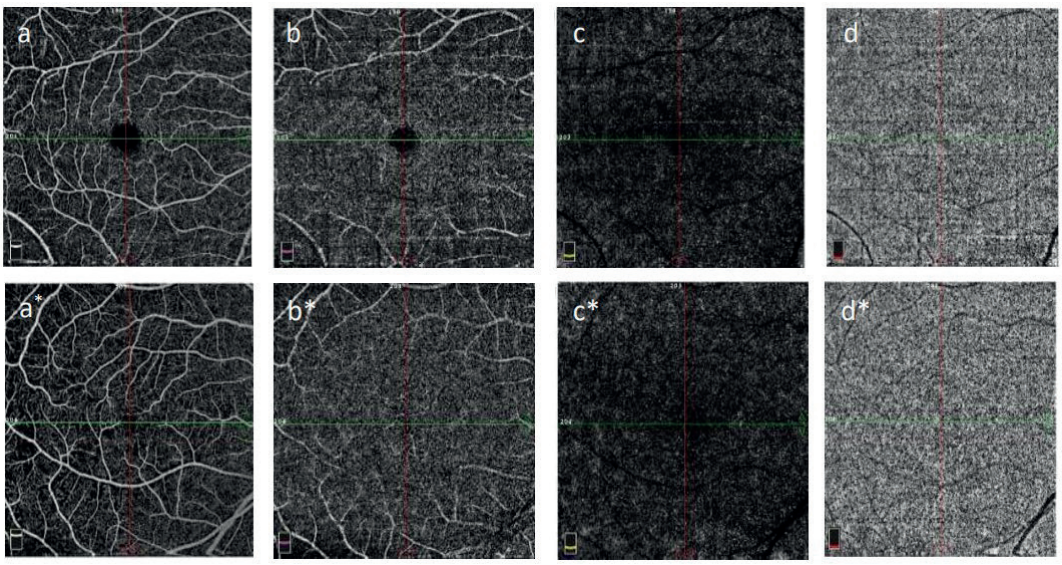

Figure 2. Right eye representation of the Angio Quickview (6.0×6.0 mm scan size with scan quality index = 8/10) segmented at the level of the süperficial capillar plexus (a, a*), deep capillary plexus (b, b*), outer retina (c,c*) and choriocapillaris (d,d*) from GCA patient (letters without asterixis) and healthy subject (letters with asterixis) respectively. Note the lower vessel densities in both superficial and deep capillary plexi in GCA patients (a,b) compared to healthy controls (a*, b*). GCA patients appear to have a similar foveal avascular region compared to healthy subjects. (a, b versus a*, b*).

Figure 1 shows the superficial and deep vessel densities that were measured with OCT-A between the groups. All superficial, foveal, parafoveal, and perifoveal vessel densities, deep, parafoveal, and perifoveal deep vessel densities are indicated. Figure 2 shows the OCTA findings of the patient group and healthy control group.

Discussion

Microvascular structures with OCT-A were investigated in patients previously affected by AAION because of GCA and the results were compared with healthy subjects. Significant reductions in superficial and deep vessel densities were detected in the study. Changes in the superficial microvascular structure, which were not seen in FA, were easily detected because of the superior resolution of OCT-A. The most common ophthalmologic manifestations of GCA are anterior ischemic optic neuropathy and central retinal artery occlusion [19]. It causes profound and irreversible vision loss in the involved eye. Pulse steroid therapy is recommended to preserve the vision of the other eye. SD-OCT shows a diffuse hyper reflection of the inner and middle retina, which represent severe ischemic injury [20]. In a recent study, Kadayifcilar et al., [21] reported that OCT-A showed thickness and reflection of inner retinal layers in the acute stage in patients with central retinal artery occlusion [20]. In the later stages, they showed that the decrease in microvascular vessel density with OCT-A became evident. In this study, decreases were found in SCP and DCP, which supports the study of Kadayifcilar et al [21]. In the present study, although the perfusion of the deep retinal capillary plexus was relatively preserved in focal acute paracentral acute middle maculopathy lesions, a significant decrease was detected in perfusion-related perfusion rate.

GCA is attributed to deep capillary ischemia because the lesion is located in the inner nuclear layer surrounded by the intermediate and deep retinal capillary plexus. Its development after persistent inner nuclear layer thinning explains an ischemic infarction. Reports were presented associating GCA with various retinal vascular diseases, including diabetic retinopathy, [22] retinal artery occlusion, central retinal vein occlusion, sickle cell and purtscher retinopathy. Retinopathy is based on ischemic pathogenesis. OCT-A is a novel method for invasive imaging of retinal vessels and can show individual retinal vessels in different layers. The neural retina is supplied by two independent circulatory systems (*i.e.,* the inner retina is supplied by the retinal artery system, and the outer retina is supplied by the choroidal circulatory system). Because retinal arterial occlusion develops in GCA, decreased vessel densities and thickening of the inner retinal layer may occur in SCP, DCP, and FD-300. Lavin et al., showed that CRAO patients have a higher risk of future cardiovascular and cerebrovascular events [23]. In the study, it was found that vessel density in SCP was reduced compared to normal control eyes. This result suggests that chronic microvascular change persists in GCA patients despite GCA recovery. Previous studies showed changes in FAZ [24] in certain vascular-related diseases such as diabetic retinopathy [25,26] and retinal vein occlusion (RVO) [27]. There are also studies reporting that FAZ is also associated with visual acuity in RVO [28] and diabetic retinopathy without diabetic macular edema [25]. Changes in FAZ can be demonstrated when the probable disease process continues. In this study, no significant changes were found in FAZ in GCA patients. The reason may be that patients whose disease process was terminated were included in the study and the inflammation process may have ended in these patients. In GCA patients, a reduction in vessel density was observed in both SCP and DCP compared to control group. Samara et al. found that both SCP and DCP vessel densities were lower in the RVO-affected eye compared to the unaffected eye in BRVO patients [28]. They also found that the vessel density of DCP was reduced in the unaffected side of the patient's BRVO eye compared to the corresponding side of the other eye [28]. FD-300 represents the vascular density of the whole retina around the 300 μm wide FAZ. FD-300 was found to be significantly reduced in GCA patients when compared to healthy controls and showed a positive correlation with the GCA stage [29]. In this study, FD-300 was found to be reduced in eyes with temporal arteritis compared to that of other eyes. In the present study, retinal vessel densities showed a positive correlation with

BCVA. Visual acuity was lower in cases with GCA and relatively permanent macular edema. More severe macular edema means a higher degree of retinal ischemia, thus considered to lead to worse BCVA. This result is consistent with the significant correlation reported by Ahn et al., regarding initial macular edema with final BCVA in CRAO patients [30].

The Radial Peripapillary Capillaries (RPC) contain straight, long vessels that originate from the peripapillary retinal arterioles located within the RNFL. In a previous study, it was shown that RPC was qualitatively attenuated in OCT-A in RAO patients [31]. In this study, significant reductions in RPCs and vascular densities of parapapillary vasculature were observed in GCA patients. Yu PK et al., reported a relationship between RNFL thickness and RPC volume in normal human donor eyes [32]. These authors argued that a positive correlation between RNFL thickness and RPC volume suggests a supportive role of RPCs for the RNFL. However, in the present study, a thinner RNFL thickness was not detected despite the decrease in RPC vessel density in the patient population. However, a significant increase was detected in the C/D ratio in the patient group. The most important limitation of the study was that the patient group included subjects who had undergone and improved GCA, in other words, none of the subjects had active GCA. Another limitation was the possibility that information outside the captured area could be missed, as OCT-A images can only capture a relatively small area around the macula or optic disc.

These parameters calculated by OCT-A analyses allowed us to acquire more insight into the eyes of GCA patients, so these parameters are promising to establish more significant clinical relevance for GCA patients. OCT-A is a new and valuable tool for evaluating ischemic changes in GCA patients.

Conclusion

In conclusion, the present study is the first in the literature reporting a decrease in capillary perfusion in both superficial and deep layers in GCA patients with OCT-A and involving a large number of participants. Previous studies in the literature are mostly case reports, in which OCT-A findings of active GCA cases were investigated. However, in the present study, the OCT-A findings of inactive and significant numbers of GCA cases were investigated. In OCT-A, the effect on the microvascular process was significant, which suggests that the ischemic process continues and microvascular structures may continue to be affected even if there is no active inflammation. Also, the study can be considered the first in which a large number of cases that would allow statistical analysis participated and the control group was included and compared with the patient group.

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Conflict of interest

The authors declared no conflict of interest.

Data availability statement

Data available on request from the authors.

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ORIGINAL ARTICLE

The effectiveness of education provided to university students on COVID-19 phobia: A quasi-experimental study

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Abstract

This study aimed to determine the effectiveness of education provided to university students on COVID-19 phobia. The study was structured as a pre-test, post-test single-group study, a quasi-experimental research design, conducted on 122 students at a university located in Eastern Anatolia. Pre-test forms (Information Form, COVID-19 Phobia Scale) were sent to the students via email, filled out, and returned to the researcher. Subsequently, online training was provided to the participating students, and post-test (COVID-19 Phobia Scale) data were collected. A statistically significant difference was found between the pre-test and post-test COVID-19 Phobia Scale values (p<.001). This difference was in favor of the pre-test, indicating a reduction in COVID-19 phobia levels after the intervention. The results of this study highlight the importance of pandemic phobia and education. It provides data support for pandemic and COVID-19 phobia for policymakers, healthcare administrators, and the literature.

Keywords: COVID-19 phobia, education, healthcare students, nurse

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Introduction

Coronavirus disease-2019 (COVID-19) has become a new pandemic and a public health problem all around the world. Although it was first reported in Wuhan, China, it was not limited to this country and spread all over the world. The increase in cases and the level of geographic spread led to significant concerns about the situation, which was declared as an "International Health Emergency" on January, 2020 [1]. The epidemic has been reported to have caused millions of deaths worldwide [2]. In Türkiye, as well as all over the world, the pandemic has been influential rapidly and the whole society has been subjected to negative effects of the pandemic [3]. COVID-19 causes many psychological, physical and social health problems and deaths [4-6]. The COVID-19 pandemic has severe effects especially on human psychology. This situation has become a source of fear all around the world. People are anxious and think negatively about the effects of coronavirus for themselves and their families. It is indicated that COVID-19 has created some types of phobia in people all over the world due to its long-term and fatal nature [7]. Pre-existing mental disorders may become much worse with the intense contracting fear of COVID-19 infection (corona-phobia) and may also increase the risk of suicide [8]. Studies on psychological responses to previous epidemics and pandemics suggests that psychological vulnerability factors such as indefiniteness intolerance, perceived distrust towards the disease, and tendency to anxiety may also play a role in corona-phobia [9-12]. Similarly, it is stated that wrong and incomplete information published in the media triggers health-related fears and phobias, which plays a significant role in the emergence of corona-phobia [13]. Health care professionals are the most at risk group in terms of COVID-19 and have psychosomatic problems such as high levels of stress, anxiety, fear and depression due to COVID-19 [4,14-16]. Therefore, phobia may also occur among health care professionals with the influence of negative information and beliefs. Nursing students also go to internships in practice every day, especially during the internship period, and work as the staff of the clinics they are in. They are affected by all problems that apply to health care professionals. Moreover, the risk may be higher since they do not have as much experience and knowledge as the staff of hospitals. The awareness and readiness of health care professionals and students who will perform practices in the management of COVID-19 infection are very important in terms of preventing the further spread of the disease and protecting themselves [17]. The importance of the education to be provided on the issues such as the ways of transmission of COVID-19, the ways of protection, and the measures to be taken during practices is obvious. It is considered that the education to be provided will provide self-confidence and reduce coronavirus phobia by positively affecting the knowledge and attitudes of individuals.

This study was planned to provide nursing students with education on the ways of transmission of COVID-19, the ways of protection, and the measures to be taken and to examine the effectiveness of this education on COVID-19 phobia.

Hypotheses of the Study

H1: Education provided to students will lead to a significant decrease in the total score of COVID-19 phobia.

H2: Education provided to students will lead to a significant decrease in the psychological sub-dimension score of COVID-19 phobia.

H3: Education provided to students will lead to a significant decrease in the somatic sub-dimension score of COVID-19 phobia.

H4: Education provided to students will lead to a significant decrease in the social sub-dimension score of COVID-19 phobia.

H5: Education provided to students will lead to a significant decrease in the economic sub-dimension score of COVID-19 phobia.

Materials and Methods

Population and Sample

This study was conducted as a pre-test, post-test single-group study, one of the quasi-experimental research designs. 150 (interns) students enrolled in the final year of the Fırat University, Faculty

of Health Sciences, Department of Nursing constituted the population of the study. The minimum sample size was calculated as 109 with a confidence interval of 95% and a margin of error of 0.5 with the G Power program. The whole population was reached without sample selection, and the research was finished with 122 people who agreed to attend in the study.

Data Collection Tools

The data of the study were obtained using the Information Form and the Coronavirus-19 Phobia Scale (C19P-S).

Introductory Information Form: This form, which was structured by the researchers, involves 8 questions including personal characteristics and information about coronavirus. (Age, gender, income status, infection with COVID-19, information about COVID-19, etc.).

Coronavirus-19 Phobia Scale (C19P-S): C19P-S, developed by Arpacı et al., was prepared to measure phobia against coronavirus [18]. The Scale is a 5-point Likert type and The Scale items are scored between 1-5 points as "Strongly Disagree" and "Strongly Agree". The sub-dimensions of this scale are; Social (items 3-7-11-15 and 19), Psychological (items 1-5-9-13-17 and 20), Somatic (items 2-6-10-14 and 18) and the Economic (items 4-8-12 and 16).

The total Scale score is obtained between 20 and 100 points. Higher scores mean higher sub-dimensions and total corona-phobia. The total Cronbach's alpha value of the scale is 0.926 [18]. The Cronbach's alpha for this research was determined as 0.904.

Data Collection

The data of the study was collected digitally between January 2021 and May 2021. The pre-test forms ("Introductory Information Form", "C19P-S") sent to the students via e-mail were filled out and sent to the researcher. Then, online education was provided to the students who attend in the study. Education was provided on issues such as information on COVID-19, the ways of transmission, the ways of protection, and the measures to be taken during practices. The duration of the education was 90 minutes. After the education, 3 months of follow-up was performed, and at the end of the 3 months, the post-test data (**C19P-S**) were collected again via mail from the students who participated in education.

Data Analysis

The data obtained in the study were analyzed using the licensed Statistical Package for Social Science 22.00 (SPSS 22) Package Program. While evaluating the data of the research, using statistical methods. (Minimum, Maximum, Mean, Standard deviation, Ratio, Frequency). Since the data whose normality was evaluated with *Kolmogorov-Smirnov* were not normally distributed, the difference between the two dependent groups was evaluated using the *Wilcoxon* test. Significance was considered as $p<0.05$.

Ethical Dimension of the Study

Permission was obtained from Fırat University Social and Human Sciences Scientific Research Ethics Committee (Protocol No: 6267) in order to conduct the study. All participating students were told they were free to participate and could withdraw from the study at any time without prejudice. All of the involved students gave written and oral informed consent before participating in the research. The research was conducted in accordance with the Declaration of Helsinki.

Results

The mean age of the students who attend in the study was 21.79±1.31. 73.8% of the students included in the study were female. The monthly income of 68% of them was equal to their expenses. It was determined that 35.2% of the mothers and 43% of the fathers of the students included in the study were primary school graduates. It was determined that 8.2% of the students, the families of 14.8% of them, the relatives of 47.5% of them, and the friends and neighbors of 45.1% of them were infected with COVID-19. It was determined that 51.6% of the students who attend in the study received education on COVID-19 and that 32% of them received this education from social media. The distribution of students' mean scores of socio-demographic characteristics is presented in Table 1.

Table 1. Distribution of students' socio-demographic characteristics.

Descriptive Variables		n	%
Sex	*Female*	90	73.8
	Male	32	26.2
Mother Education Level	*Literate*	65	53.3
	Primary education	43	35.2
	High school and above	14	11.5
Father Education Level	*Literate*	30	24.6
	Primary education	53	43.4
	High school and above	39	32
Family Income	*Lower*	28	23
	Equal	83	68
	Higher	11	9
***Status of Infection with Corona**	*Own*	10	8.2
	Family	18	14.8
	Relatives	58	47.5
	Friend/Neighbor	55	45.1
Getting Education About Corona	*Yes*	63	51.6
	No	59	48.4
***Knowledge perceived from reference**	*Social media*	39	32
	Seminars and meetings	3	2.5
	Books and articles	17	13.9
	Radio, television	28	23
	Health worker	11	9
	Friend/Neighbor	11	9

* Multiple options are marked.

Table 2. Significance of the difference between pre-test and post-test scores of the Coronavirus-19 Phobia Scale.

C19P-S Scale and Sub-Dimensions	Scores	Ranks	N	M.R.	Testing and significance
Psychological Sub-Dimension	Post-Test Score Pre-Test Score	Negative Ranks	66	66.08	**Z=-2.867 p=0.004**
		Positive Ranks	49	47.12	
		Equal	7		
		Total	122		
Somatic Sub-dimension	Post-Test Score Pre-Test Score	Negative Ranks	66	59.45	**Z=-2.603 p=0.009**
		Positive Ranks	44	49.58	
		Equal	12		
		Total	122		
Social Sub-dimension	Post-Test Score Pre-Test Score	Negative Ranks	75	60.57	**Z=-3.792 p=0.000**
		Positive Ranks	38	49.96	
		Equal	9		
		Total	122		
Economic Sub-dimension	Post-Test Score Pre-Test Score	Negative Ranks	79	60.02	**Z=-4.367 p=0.000**
		Positive Ranks	34	49.99	
		Equal	9		
		Total	122		
Total	Post-Test Score Pre-Test Score	Negative Ranks	81	63.38	**Z=-3.938 p=0.000**
		Positive Ranks	39	54.53	
		Equal	2		
		Total	122		

M.R: Mean Rank.

As a result of the *Wilcoxon* test performed to test whether there was a significant difference between the pre-test and post-test values of the nursing students in the experimental group from the Total Dimension of the **C19P-S**, the difference between the values was found to be statistically significant by $p<.001$. This difference was in favor of the pre-test. In other words, the coronavirus-19 Phobia levels of the students who constituted the experimental group at the end of the group education significantly decreased. (The fact that the **C19P-S** post-test values were lower than the **C19P-S** pre-test values) (Table 2).

Discussion

The world is witnessing epidemiological and psychological problems due to the spread of the COVID-19 pandemic. The number of people infected with COVID-19, the poor prognosis of the disease, and the increasing number of deaths significantly affect human psychology [7]. These new psychological problems may cause people to develop phobia by thinking negatively about themselves and their families [7,18]. As a result of the literature review, no study investigating the relationship between coronavirus-19 phobia and education, and its effects was found. This study, which was conducted to examine the effectiveness of the education provided to students on Coronavirus-19 Phobia, was discussed in accordance with the literature in this section.

It is very important for health workers and health students to have accurate and up-to-date information about COVID-19. When the students who attend in the study were asked whether they had previously received a planned education, 51.6% of the students stated that they had previously received information about COVID-19. When students' sources of information were examined, it was determined that social media ranked first, followed by radio/television. In a study conducted by Alzoubi et al., with university students in Medicine and other fields in Jordan, it was determined that students' main sources of information on COVID-19 were social media, internet and television [19]. In their study conducted with dentists in Türkiye, Duruk et al., reported that 96.27% of doctors obtained information about COVID-19 from personal websites and the internet [20].

The study conducted by Mahmud et al., on COVID-19 phobia and career anxiety in Bangladesh revealed that the participants used social media as the dominant platform for information gathering, followed by local television channels and newspapers [7]. The studies similar to this study indicate that mass media such as social media are preferred to obtain information about COVID-19. In this study, when coronavirus phobia values of students before and after the education were examined, it was determined that coronavirus-19 phobia significantly decreased after the education and that the education negatively affected the total and all sub-dimensions of Coronavirus Phobia, and hypotheses H1, H2, H3, H4 and H5 were accepted. No study examining the effectiveness of education on Coronavirus-19 Phobia was found in the literature. This study was discussed in comparison with other studies on phobia. In the study conducted by Baloğlu et al., on the psychological effects of coronavirus in the general population in Türkiye, the coronavirus-19 phobia level of the society decreased as the level of education increased [21]. Although this study result did not directly reveal the effectiveness of education on coronavirus phobia, it partially supported it. This result indicates that the high level of education was effective in reducing coronavirus phobia by making individuals more conscious about protection from COVID-19 [21].

In a randomized controlled clinical study in which Choi et al. examined the effectiveness of education in reducing topical steroid phobia, it was determined that the phobia level decreased significantly in the experimental group [22]. In their study on whether education could reduce fever anxiety, O'Neill-Murphy et al., emphasized the importance of education in phobias by stating that appropriate education may reduce fever phobia in caregivers [23]. These studies conducted with different phobias reveal that education has a positive effect on reducing phobias. It was determined that nearly half of the nursing students who participated in this study had not received planned education on COVID-19 before and used social media as a source of information. Social media offers

important opportunities to improve health and increase people's knowledge of health, however, since the information spreads rapidly and it is difficult to control, it does not always provide the correct health information and may pose a risk in terms of health protection [24]. Inaccurate and exaggerated information originating from social media may lead to phobia related to coronavirus-19, which has already become a source of fear all around the world. From this point of view, it is considered that education which is correct and up-to-date and includes the measures to be taken for COVID-19 reduce nursing students' level of COVID-19 phobia.

This research emphasizes on safeguarding the, nursing students during pandemics. We believe that the proposed methods will facilitate nurses to better manage crises during the pandemic. The programs prepared using this study as a guide are beneficial in terms of reducing epidemic phobias of nurses, nursing students and health workers working in every field. The lack of a control group in the study is a limitation.

Conclusion

As a result of this study, it was determined that the coronavirus-19 phobia levels of the students provided with education on coronavirus decreased. In accordance with this result, it is recommended to provide students who actively participate in health practices in internship programs with the relevant planned education programs periodically in order to reduce COVID-19 phobia. Education planning is recommended for the populations in need of public health education by determining the level of COVID-19 phobia in different populations. Furthermore, it is also recommended to repeat similar interventional studies in different groups. The result of this study, it will give an opportunity to compare the subject and contribute to the literature.

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Conflict of interest

The authors report no actual or potential conflicts of interest.

Data availability statement

Data sets generated and/or analyzed during the study will be made available by the corresponding author upon request.

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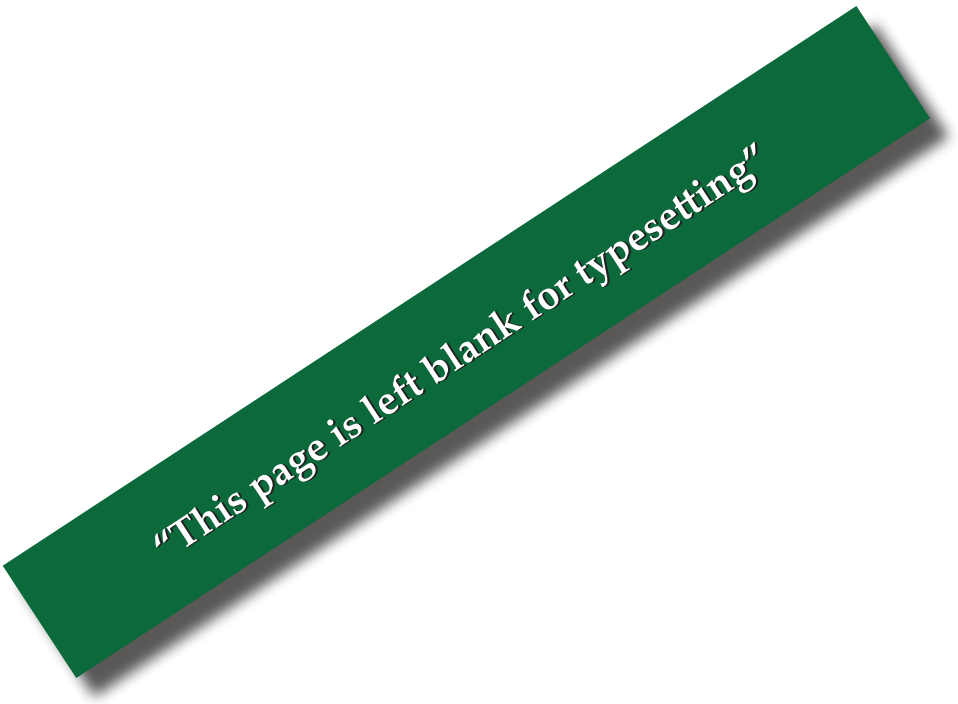
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ORIGINAL ARTICLE

Analysis of the implementation of activities of adolescent girls drinking iron supplement tablets to prevent anemia in West Sumatra Province

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Abstract

The World Health Organization (WHO) has set six global nutrition targets, one of which is to reduce the prevalence of anemia among women of childbearing age by 50%, aiming for a global rate of 18%. According to Indonesia's 2018 Basic Health Research data, the prevalence of anemia in West Sumatra exceeded the national average, reaching 27.6%. This study aims to analyze the implementation of anemia prevention activities among adolescent girls in West Sumatra Province in 2023, focusing on both successful and unsuccessful districts/cities based on the coverage of iron supplement tablet consumption among adolescent girls. This research employed semi-structured interviews and purposive sampling, utilizing appropriate research instruments. Findings indicate that both successful and unsuccessful districts/cities lacked policies formally supporting anemia prevention activities in the form of local regulations. Additionally, differences in health workforce availability between these districts/cities were observed. The presence of Adolescent Health Cadres in schools fulfilled only 7.4% of the required demand. Furthermore, the availability of facilities and infrastructure for hemoglobin testing was hindered by challenges in procuring consumables needed for the tests.

Keywords: Adolescent girl, anemia, evaluation, iron supplement tablets

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Introduction

The World Health Organization (WHO) has six global nutrition targets, one of which is to reduce the prevalence of anemia among women of childbearing age by 50% [1]. In addition, Indonesia is expected to face a demographic bonus era from 2030 to 2040 [2]. Anemia is diagnosed when the hemoglobin (Hb) concentration falls below a set cut-off value, so the blood's capacity to carry oxygen to tissues is impaired [3]. The Ministry of Health in Indonesia provides a standard for adolescent anemia (aged 10-18 years) with Hb levels <12 g/dl [4]. Indonesia Basic Health Research data in 2018 showed that the prevalence of anemia in Indonesia at the age of 15-19 years reached 30.44% [5]. Adolescent girls are at higher risk of anemia compared to young men. According to Indonesia Basic Health Research data in 2018 anemia in West Sumatra reached 27.6% [5]. Prevention of anemia in adolescent girls can be done by increasing food intake of iron sources, fortification of foodstuffs with iron, and giving iron supplement tablets, especially during menstruation [4]. Consumption of food sources containing protein had a severe deficit of 71.2% in coastal areas and 81.9% in non-coastal areas [6]. Likewise, iron intake from 55 people who were teenagers in SMA 9 Mataram 69.1% were still lacking [7]. On the other hand, Indonesia Basic Health Research data in 2018 showed that only 0.97% of adolescent girls consumed ≥52 grains of iron supplement tablets in West Sumatra Province [8]. According to the Health profile data in 2022, the coverage of iron supplement tablets administration in 2022 in Indonesia reached 50%, while in West Sumatra Province this achievement was lower, namely only 45.9% [9]. This anemia prevention program is one of the specific interventions in stunting prevention efforts, this refers to Presidential Regulation number 72 of 2021 and the National Draft of the Circular Letter of the Director General of Public Health of the Ministry of Health Number HK.03.03/V/0595/2016 concerning Providing Blood Addition Tablets to Adolescent Girls and Women of Fertile Age, the provision of iron supplement tablets to adolescent girls is carried out through School Health Unit in educational institutions (junior and senior high school or equivalent) by determining the day to drink iron supplement tablets together. The dose given is one tablet every week for the whole year [4,10].

This study aims to describe the condition of the implementation of the repatriate anemia prevention program seen from the elements of input, process, and output in West Sumatra Province.

Materials and Methods

This descriptive qualitative research was conducted at the West Sumatra Provincial Health Office from January to June 2024. Data were collected using semi-structured interviews through purposive sampling, with research instruments developed by the researchers. Informants were selected based on specific criteria determined by the researchers, targeting individuals deemed capable of providing relevant information for the study. In addition to primary data collection, secondary data were obtained through the review of reports and documents related to the research. This study has received ethical approval from The Research Ethics Commission of the Faculty of Public Health, Universitas Andalas (approval number: B/20/UN16.12.D/PT.01.00/2024), and permission was granted by the Provincial Health Office prior to data collection. All participants were fully informed about the study's objectives.

Results

Informants consisted of officials at the West Sumatra Provincial Health Office, managers, district/city officials or managers, psychologists, and School Health Unit teachers. Evaluation activities include input, output, and process:

1. Input

a. Policy

The policy for preventing adolescent girls anemia refers to Health Law Number 36 of 2009 concerning Health, this is found in article 142 article 1 which states that nutritional improvement efforts are carried out throughout the life cycle from the womb to prioritizing vulnerable groups including infants and toddlers, adolescent girls and pregnant and lactating mothers [11]. In

addition, Presidential Regulation No. 72 of 2021 concerning the acceleration of stunting reduction is carried out in sensitive interventions targeting adolescent age groups, brides-to-be, pregnant women, nursing mothers, and children aged 0-59 months [10]. *"For adolescent girls, we refer to Presidential Regulation No. 72 concerning stunting prevention, namely the specific indicator of Fe tablet administration is the target of each province. Socialization was carried out two years ago. In 2022 the province issued a Governor's Circular Letter in 2022"* (Information from head of division West Sumatra Provincial Health Office). The implementation of adolescent girls' anemia prevention also refers to National Action Plan for Improving the Welfare of School Age Children and Adolescents (RAN PIJAR). This is a policy in accordance with the Joint Ministerial Decree (SKB) of 4 (four) ministers. *"The activities of checking Hb and providing iron supplement tablets are contained in the RAN PIJAR, which is an agreement between three ministers, namely the Minister of Health, the Minister of National Education, and the Minister of Religion"* (Inf. from section chief West Sumatra Provincial Health Office).

b. Human resources

Human resources (HR) can be shown in the following:

"Health human resources are still not fulfilled in several health centers. Actually, the number of health centers compared to the number of nutrition workers is sufficient, but this is due to the uneven distribution of personnel and mutations. " (Inf. head of division West Sumatra Provincial Health Office)

As for the availability of Adolescent Health Cadres, it can be addressed in the following:

"Ideally there should be 10% of the total number of students in Adolescent Health Cadres. While in reality the number of Adolescent Health Cadres is only 5526 students out of 739,260 total students. So only 7.4% of the expected target has been met" (Inf. in charge of nutrition program, West Sumatra Provincial Health Office).

According to the psychologist, *"Teenagers have their own language in communication. Peer counselors at school will make information more easily accepted by teenagers. Teenagers are even more receptive to information than their parents. In addition, adolescents prefer group actions called community psychology with a cognitive approach. I have an experience when we elaborate information with the condition of the circle of adolescents who are trending at that time from an adolescent counselor, making information faster and easier to accept by adolescents who are given consultation. But in counseling activities sometimes we forget these things ... when we just need to increase the capacity of adolescents who become counselors with psychological theories..."* (Psychologist Informant)

Table 1. Availability of health human resources.

Health human resources	Successful districts/cities (%)	Districts/Cities that have not succeeded (%)
Doctor	100	100
Dentist	100	90.2
Nurse	100	100
Midwife	100	100
Health promotion worker	90	97.6
Sanitation worker	100	85.4
Medical Laboratory Technician	100	95.1
Nutritionist	100	97
Pharmacist	100	100

Table 2. Availability of adolescent health cadres.

Adolescent Health Cadres	n	%
Available	5526	7.5
Not available	73926	92.5

c. Budget

The budget for anemia prevention activities in adolescent girls in 2023 comes from the State Budget and the West Sumatra Provincial Budget in 2023. Activities carried out in the form of campaigns with the theme of Nutritious Action, socialization and advocacy.

"The allocation of funds for Hb examination activities is planned and implemented by each district/city. Meanwhile, Nutritious Action activities have been carried out at the Provincial, District / City and public health center levels, but have not touched all existing targets, therefore it is necessary to increase the budget for nutritious action campaigns at all levels. Not all health centers have conducted Hb checks on adolescent girls, due to limited examination facilities." (Informant 1 of West Sumatra Provincial Health Office). Districts/municipalities said that activities to prevent adolescent girls enemia are sourced from Health Operational Assistance (BOK) Funds, *"The adolescent girl Hb check which is a screening activity of the public health center and the provision of iron supplement tablets is a routine activity of the public health center. These activities come from the BOK funds at the public health center, while for the Nutrition Action activities that have been carried out twice in 'our' city come from the provincial budget."* (Informant from districts / cities Health Office succeeded).

As for the amount of the budget, it can be different in each public health center.

"We do not have a budget at the Health Office for Hb testing and iron supplement tablets administration activities, maybe from the BOK funds for public health center officers, it depends on the public health center later to budget it" (Informant districts /cities Health Office not successful).

Especially in the prevention of anemia in adolescents, there are still socialization and campaign activities, while the budget for coaching activities does not yet exist, as well as financing in improving health promotion.

d. Facilities and infrastructure

Regarding facilities and infrastructure for anemia prevention efforts in adolescents, specific examination tools are required, namely the Hb meter and blood test strips. The Hb meter is provided by the Ministry of Health, while the blood test strips are supplied by public health centers, funded by their respective budgets. However, in 2023, not all public health centers conducted these screening activities for new students in grade VII of junior high school and grade X of high school.

"Actually for the provision of Fe we have no problem, but in checking Hb we have problems in purchasing strips so that the means to carry out this activity is a bit problematic" (districts /cities Health Office informant not yet successful).

Procurement of health promotion media has also not yet reached schools, *"Procurement of health promotion media in the context of preventing anemia in adolescents is still very limited. In 2023 we only procured 30 banners and banners for districts/cities in West Sumatra, this is certainly not as expected because promotional media should also be distributed to schools"* (Informant 2 West Sumatra Provincial Health Office).

"For some schools we have provided posters and banners. School Health Unit teachers are very aware of their duties in preventing adolescent anemia" (Informant 2 District/Cities Health Office)

"For promotional media, we provide 200 leaflets, but there are no posters and banners. In the Nutritious Action activity, billboards have been installed." (inf. districts /cities Health Office not yet successful)

2. Process

a. Planning

Unsuccessful districts/cities shared the steps in the planning process for adolescent girl iron supplement tablets, *"We have planned this activity at the beginning of the year, starting from planning for iron supplement tablets by calculating iron supplement tablets needs in the Public health center area"* (Inf. District/Cities Health Office not yet successful).

However, successful districts emphasize the form of cooperation and commitment of the parties in accordance with RAN PIJAR, *"The planning of Hb and iron supplement tablets testing activities is carried out by involving the Education and School offices. There is an MoU between the Ministry of Education, Ministry of Religious Affairs*

and the Health Office regarding the provision of adolescent girl iron supplement tablets. In addition, requests for support from relevant cross-sectors, The Family Welfare Empowerment Movement (PKK) and Regional Apparatus Organization (OPD)'s are planned to be involved later in nutritious action activities." (Successful District/Cities Health Office informant)

However, in planning there are classic obstacles such as, *"In planning, there is usually a mismatch with the availability of the budget also because the availability of data is not optimal so it is difficult to get the basic problems. In the regions, the low quality of human resources for planning has resulted in copy and paste activities."* (Informant 1 West Sumatra Provincial Health Office)

Differences in perceptions about who is responsible for activities have caused officers to come to schools to be rejected, *"Sometimes schools feel that we are interfering with the teaching and learning process..."* (Informant District/Cities not yet successful)

The above will happen if the 'sense' of ownership of this activity is only a health task, *"If the school feels that this activity belongs to the school, the schedule with the implementation of the program can be adjusted to the teaching and learning process so that the officers do not seem to be a nuisance"*. (Informant 5 West Sumatra Provincial Health Office)

The first activity invited relevant cross-sectors and continued by inviting school principals in Padang City. The output of this activity is the agreement of cross-sectors and school principals in the success of anemia prevention in adolescent girls. At the district/city level, there were no socialization activities due to budget constraints, which was a problem for both successful and unsuccessful districts/cities. However, at the public health center level, socialization activities are focused on cross-sector mini workshops that invite the regional technical implementation unit of the Education Office and the Head of the Public health center. This mini-sector workshop is held once every three months. *"The school principal emphasized the schedule for the implementation of anemia prevention in adolescents. The provision of iron supplement tablets* adolescent girls *is carried out every month at school. Meanwhile, the Hb check is carried out in September. The school principal has received socialization about the Hb check and iron supplement tablets administration and was emphasized again at the lokmin so that it has been agreed that the success of anemia prevention is also part of the school."* (inf. Nutrition Officer, West Sumatra Province). *"For communication and coordination we have carried out with the capdin as well, but for the MoU we are just designing."* (Inf. School age and youth managers)

A problem in the preparation process is that not all public health center have scheduled iron supplement tablets administration activities in an effort to prevent anemia. This activity is expected to be the result of strengthening the partnership between public health center and schools.

b. Implementation

The technical implementation of iron supplement tablets in schools is also different in each district/city. Successful districts tend to strengthen partnerships and supervision from schools. *"The implementation of iron supplement tablets in schools is carried out once a week, for some schools it is also added to activities such as the Annisa forum. The implementation is usually simultaneous in each class involving National Standards Guidelines for Health Care Service for Adolescent (PKPR) officers, nutrition officers including peer counselors. This is the same as other districts / cities, maybe only in the past two years we have held meetings with the Principal / school health unit Teacher of Junior / Senior High School equivalent to coordinate related to the adolescent girl iron supplement tablets program"* (inf. Psychologist).

c. Supervision

Districts/cities that have not been successful tend to leave iron supplement tablets administration activities to schools. Not all schools schedule the provision of iron supplement tablets and the lack of supervision is a problem in the provision of iron supplement tablets for adolescent girls, *"For activities we give a target of 26 iron supplement tablets for a year to be consumed by adolescent girls, for technicalities it depends on each school"* (Inf District/Cities Health Office not yet successful)

"In schools, iron supplement tablets should be taken during the first hour of learning and determine the day of iron supplement tablets consumption, but there are still schools that think that iron supplement tablets is only given during the Nutrition Action so that the Nutrition Action, which is actually a campaign, is considered just a ceremony" (Informant 6 West Sumatra Provincial Health Office).

"It is difficult for us to monitor whether these iron supplement tablets are consumed by adolescent girls, because of the large number of female students who need to be monitored" District/Cities Health Office succeeded)

This is supported by the different perceptions of school health unit teachers about the supervision of drinking iron supplement tablets, *The supervision of drinking is of course the parents..."* (Teacher Informant 1). *"As much as possible, eat the tablets at school in front of the teacher... But hmm... there are students who have not had breakfast so they take them home and at school they will be asked if they have eaten them..."* (Teacher Informant 2).

Supervision or monitoring of students taking iron supplement tablets should be done by the school and preferably by the Adolescent Health Cadres, this is related to the unique psychology of adolescents, *"In fact, it's okay that parents don't know... it should be their peers who become counselors to re-evaluate at school. It is feared that children will be mocked by their parents...'have you taken iron supplement tablets this week... etc'. Optimizing and equipping peer counselors is very good in this case ... psychologically adolescents like activities in groups or what is called community psychology. They will be passionate about the success of their group."* (Psychologist Informant)

In this program, parents are expected to provide support in the urgency of iron supplement tablets for adolescent girls, not to become supervisors but to provide support to schools in implementing the iron supplement tablets adolescent girl program, *"In this case, parents are expected to be supporters, allow and support this program, because in some schools, especially favorite private schools, parents prohibit students from getting drugs and the like at school ... of course this approach is from schools to parents ..."* (District/ Cities informant not yet successful)

From districts/municipalities that have reached and not reached the target, there are differences in the implementation of involving peer counsellors, *"We don't have peer counselors yet, so far every problem is consulted with officers..."* (District / Cities informant not yet successful)

"Peer counselors already exist but are not yet optimal, in solving adolescent girls problems, they still go to the health center officers.." (Inf District / Cities succeeded)

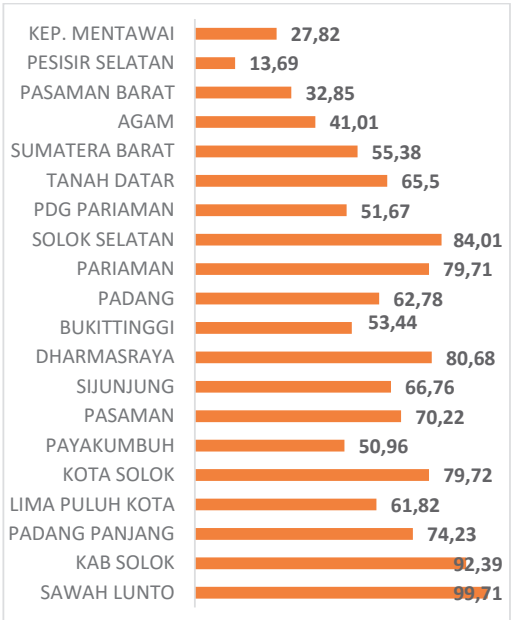

Figure 1. Achievement of adolescent girls who consume iron supplement tablets.

3. Output

Output the coverage of activities is the result of the implementation of the iron supplement tablets program for adolescent girls and is used as a report on the results of activities. The coverage of Fe tablet consumption in West Sumatra has increased as shown in the following:

"Accelerating the reduction of stunting (TPPS) monitors several indicators to accelerate stunting reduction, one of which is the consumption of Fe tablets by adolescent girls. TPPS coordination meetings are held regularly at the provincial level followed by the District/City TPPS. Then the district/city TPPS conducts coordination meetings involving the sub-district TPPS at the sub-district level followed by the health sector, education, Ministry of Religious Affairs, PKK, village government and other related elements, at monthly workshops in order to evaluate the implementation of activities including the provision of iron supplement tablets for adolescent girls. When viewed from the achievements of Fe tablet consumption in West Sumatra, there has been an increase". (Informant 1 Provincial Health Office)

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Efforts to increase the achievements of this program must indeed be made by strengthening partnerships between community institutions and related OPDs.

"Strengthen RAN PIJAR to the Regency / City so that schools schedule so that they have careful planning. So that it does not interfere with the learning process. So that schools know the urgency and purpose of the importance of iron supplement tablets, there is also a feed back to schools. So that schools know the results." (Informant 4 Provincial Health Office, West Sumatra).

Discussion

The policy of providing iron supplement tablets in districts / cities has been successful, we both levels administration adhering to the same regulations, specially Presidential Regulation No. 72 of 2021 and RAN PIJAR No. 1 of 2022 and supported by the Governor's circular of 2022 [10,12]. It is expected that each district/city will enact local regulations. The urgency of local regulations involves stages such as planning, drafting, discussion, enactment, and promulgation. This aligns with research on the importance of local regulation formation programs in improving the performance of the Regional House of Representatives [13]. Budgeting is also a significant issue. The budget for iron supplement tablet distribution has been eliminated, particularly for operational expenses such as distribution, monitoring, and training. This is consistent with research on the financial analysis of maternal and child health programs through the health account method in Jember District. Operational funding is also linked to infrastructure needs, particularly in supporting anemia screening activities among school children. The success of anemia prevention efforts in adolescent girls is closely related to the distribution of iron supplement tablets. This success is strongly supported by effective cross-sectoral cooperation, adequate health personnel, the availability of communication, information, and education media, and the low adherence rate of adolescent girls to iron tablet consumption. These findings are consistent with research on the evaluation of the iron supplement tablet program for adolescent girls in Pekanbaru City in 2019 [14]. Adolescent behavior is inseparable from the psychological uniqueness of this age group. Research on factors influencing iron supplement tablet consumption intentions among adolescent girls in two high schools in Pariaman City in 2019 found a significant relationship between perceived benefits, perceived barriers, family support, and peer support, with consumption intentions showing an odds ratio (OR) of 6.910 [15]. Additionally, peer influence plays a crucial role, as demonstrated by research on

experts' perceptions of motivators and barriers to sustainable healthy eating behavior among adolescents. This study found that peer influence in the social environment is the most decisive factor for intervention targets (N = 13; urgency M = 6.38) [16].

Conclusion

The input component reveals the absence of local regulations addressing the prevention of anemia in adolescent girls. Additionally, health human resources, which should meet the standard of nine healthcare workers, have only reached 80% of the requirement. The availability of adolescent health cadres remains very low, at just 7.5%. The number of socialization and campaign activities remains broad in scope and limited in terms of health promotion media provision. Districts/ municipalities that have met the target have established partnerships with schools, enabling schools to better understand the importance of adolescent girls consuming iron supplement tablets at school. However, inadequate supervision in the prevention of anemia among adolescent girls has resulted in low compliance with iron tablet consumption activities.

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

More data is available in the author. Please contact the corresponding author for more data.

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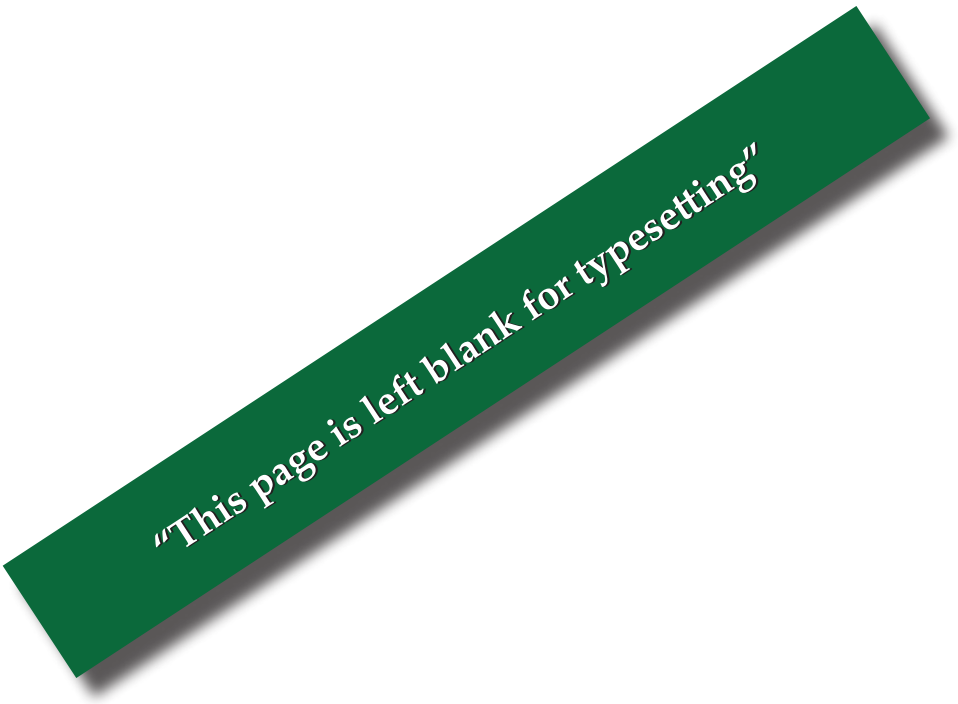
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ORIGINAL ARTICLE

Anatomists' views on cadaver and cadaver procurement in medical education

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Abstract

Despite the importance of cadavers in anatomy education, there are a great difficulties in procuring cadavers in Türkiye due to the low quantity of donations. Anatomists have important roles in matters related to cadaver donation. Some of these roles are to explain to students and the public the value of cadavers in medical education and to inform them about cadaver donation. The aim of this study is to investigate anatomists' thoughts about cadavers and their supply. The study was conducted on anatomists who accepted the survey invitation sent from the digital platform. 100 volunteer anatomists participated in the survey. Ethics committee approval was received for the study. Anatomists argue that education with cadavers is a must (92%). Routine dissection is performed in 64% of the institutions to which the participants are affiliated. 78% of anatomists know the legal regulations regarding cadaver procurement, and 67% care about the method of procurement of the studied cadaver. While the participating anatomists found it appropriate to use unclaimed bodies for educational purposes, there was no common opinion among the anatomists in terms of ethics. Anatomists are more willing to recommend cadaver donation to someone they do not know than to donate a cadaver from their own family member. Only 13% of anatomists feel ready for body donation. The survey results show that anatomists have high knowledge and awareness about cadavers and their supply. High awareness has relatively less impact on anatomists' attitudes and behaviors regarding cadaver donation. It was determined that the majority of anatomists who participated in the research did not feel ready to donate cadavers. We think that bringing donation issues to the agenda more through trainings and events can contribute to the perspectives of anatomists.

Keywords: Cadaver, anatomist, survey, body donation, cadaver procurement

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Introduction

Cadaver dissection is considered a universal symbol in anatomy education. Since the birth of the science of anatomy, education with cadavers has been a basic method of anatomy [1]. It is thought that current technological innovations cannot replace the cadaver and the gold standard for anatomy is still the cadaver [2].

Today, the largest acquisition of cadavers around the world is through body donation programs and unclaimed bodies that have no relatives or friends to request burial. In some countries where available body donations are low, the need for cadavers is met by importing cadavers from other countries [3,4]. Almost all developed countries such as the USA, Japan, Australia and European countries have successful donor programs. The dead bodies used in medical schools in these countries are the bodies of people who voluntarily donated their bodies to science before they died [3,5,6]. In countries that do not have a body donation program due to religious and/or cultural reasons, the most common option for procuring cadavers is unclaimed bodies [3]. However, this situation has given rise to different ethical thoughts and discussions. According to some authors, anatomists attribute the use of unclaimed bodies as cadavers to legal reasons and ignore the ethical aspect [7]. Due to ethical debates in cadaver procurement, the International Federation of Anatomist Associations (IFAA) published recommendations on the use of human organs in 2012. These recommendations also include a call for voluntary body donation. In addition, it was requested to end the use of the bodies of executed criminals and homeless people as a source of cadavers [8,9].

In Türkiye, a legal framework for cadavers to be used for education and research was established with the law no. 2238 enacted in 1979 and the articles added later [10,11]. There are similar cadaver procurement methods in Türkiye as in the world. These are voluntary body donations, imported cadavers and unclaimed bodies [5]. The most common option for cadaver procurement in Türkiye is unclaimed bodies. Although voluntary body donation has been recommended by IFAA as a source of cadavers, the number of donated cadavers in our country is quite insufficient [5]. While there is a positive attitude towards organ donation in Turkish society, the willingness to donate for whole body donation is quite low. The reason for this reluctance can be considered as the lack of information and awareness in the society about body donation [12].

The Turkish Society of Anatomy and Clinical Anatomy (TSACA) has work through studies on the cadaver donation problem in Türkiye. A guide containing solution suggestions on the issue has been published [13]. Anatomists in Türkiye organize events during anatomy week to draw attention to cadaver donation [14]. Celebrities donating cadavers is also an important issue in terms of encouraging donation. On the other hand, raising the issue in the media can attract public attention [15].

When we look at the literature, there are many thoughts and judgments about cadavers and cadaver procurement that vary according to factors such as socio-cultural, economic, education and profession in different societies [16-18]. Anatomists are aware of the value of cadaver donation and have direct access to information regarding donation procurement and procedures. There are few studies investigating the attitudes of anatomists in Türkiye about cadaver donation and procurement. For this reason, it was aimed to investigate the opinions of anatomists in our country regarding cadavers and cadaver procurement.

Materials and Methods

Our research is a cross-sectional study conducted on anatomists in Türkiye and was conducted by 100 anatomists who accepted the survey invitation sent from the digital groups for communication. The study was approved by the İzmir Katip Celebi Non-Interventional Clinical Studies Institutional Review Board with the decision numbered 0248. Participants were informed about the purpose of the survey and their consent was obtained. In addition, the participants were assured by the researchers about the confidentiality of their identity information before participating in the survey. The data were obtained between June 2023. Survey data was obtained digitally using

the "Google Forms" application (Google Inc., Mountain View, CA, USA).

The survey was divided into two sections: demographic characteristics of the participants and their opinions about cadavers and cadaver procurement. Demographic data in the first part of the survey included gender, level of expertise, and years of service. To investigate the possible effect of the participants' level of expertise, six groups were formed: Professors (16), associate professors (15), assistant professor (20), medical specialist (8), research assistants (33) and MSc-PhD students (8). Additionally, five groups were created to investigate the possible impact of years of service. Groups were classified according to five years of experience (0-5, 5-10, 15-20, 20 and above). The second part included questions about cadavers and their supply. The attitudes and behaviors of anatomists were investigated with questions about the place of cadavers in education, ways to procure cadavers-legal processes, the use of unclaimed bodies as cadavers, the emotional impact of cadavers, and cadaver donation. They were also asked about anatomists' willingness to donate themselves. A survey with three answer options: Yes/No and Undecided was used.

The data were evaluated in IBM SPSS Statistics 25.0 (IBM Corp, Armonik, New York, USA). The number of units and percentage values were given as descriptive statistics. For categorical variables, the exact method of the Chi-Square test was used for comparisons between groups. A value of $p<0.05$ was considered statistically significant.

Results

The survey was answered by 100 anatomists. 61 of the anatomists were women (61%) and 39 were men (39%). Other demographic information about the participants is included in Table 1.

The results of the opinions regarding cadavers and cadaver procurement in the second part of the survey are given in Table 2. Almost all of the participants (92%) think that cadavers should definitely be included in anatomy education. Most participants stated that they knew the ways to obtain cadavers (78%), that it was important to know the source of the cadavers they worked with (67%), and that working with donor cadavers had a positive impact on them (61%). While 62% of the participants find it correct in terms of education to use unclaimed bodies as cadavers, 46% find it ethically correct. 67% of participants think that knowing the cadaver donor while they are alive may affect them emotionally, and 57% do not want their families to become cadaver donors. While 71% of the participants felt responsible for informing the society about cadaver donation, 51% stated that they would encourage people around them to donate. Only 13% of participants feel ready to donate.

Table 1. Demographic characteristics of participants.

Demographic parameters	*n* (%)
Gender	
Female	61 (61)
Male	39 (39)
Academic title	
Prof. Dr.	16 (16)
Assoc. Prof	15 (15)
Asst. Prof	20 (20)
Medical specialist	8 (8)
Research assistant	33 (33)
MSc-PhD students	8 (8)
Years of Teaching Experience	
0-5	42 (42)
5-10	17 (17)
10-15	15 (15)
15-20	9 (9)
20+	17 (17)

Comparison of the answers to the survey questions between genders is given in Table 3. There is no statistically significant difference between genders in the answers given (p>0.05).

A comparison of the anatomists' answers to the survey questions according to their level of expertise and years of service is given in Table 4. In the seventh question (Q7), faculty members with Associate Professor degrees find the use of abandoned cadavers in medical education ethically correct when compared to other groups (p<0.05) (Figure 1). The fifteenth question was answered negatively by anatomists with less than five years of service (Figure 2).

Table 2. Distribution of answers to survey questions.

Questions	Yes *n* (%)	No *n* (%)	I'm not sure *n* (%)	Total *n* (%)
Q1. Is it necessary to have education with cadavers?	92 (92)	3 (3)	5 (5)	100 (100)
Q2. Does your institution perform regular dissection studies with cadavers for educational purposes?	64 (64)	28 (28)	8 (8)	100 (100)
Q3. Do you know the necessary legal arrangements regarding cadaver procurement?	78 (78)	11 (11)	11 (11)	100 (100)
Q4. Is it important for you to know how the cadaver you are working with was supplied?	67 (67)	30 (30)	3 (3)	100 (100)
Q5. Does working with a cadaver that you know is a donor affect you positively?	61 (61)	21 (21)	18 (18)	100 (100)
Q6. Do you think the use of unclaimed/ unidentified bodies in medical education is correct in terms of education?	62 (62)	21 (21)	17 (17)	100 (100)
Q7. Do you think it is ethically correct to use unclaimed/ unidentified bodies in medical education?	46 (46)	31 (31)	23 (23)	100 (100)
Q8. Does knowing the body donor while he/she is alive affect you emotionally?	67 (67)	21 (21)	12 (12)	100 (100)
Q9. Would you like your family to be a body donor?	16 (16)	57 (57)	27 (27)	100 (100)
Q10. Would your family approve of you becoming a cadaver donor?	7 (7)	74 (74)	19 (19)	100 (100)
Q11. Do you feel the responsibility to raise awareness/inform the public about cadaver donation?	71 (71)	13 (13)	16 (16)	100 (100)
Q12. Would you encourage people you know or don't know to become cadaver donors?	51 (51)	24 (24)	25 (25)	100 (100)
Q13. Do you feel ready for a cadaver donation?	13 (13)	57 (57)	30 (30)	100 (100)
Q14. Do you think it is right for the family to prevent body donation after death, even if the deceased person has made a written declaration of donation?	37 (37)	50 (50)	13 (13)	100 (100)
Q15. Do you think it is right that even if the deceased person does not have a written declaration of donation, they can be donated by their relatives if they have the consent of their first-degree relatives?	28 (28)	54 (54)	18 (18)	100 (100)

Discussion

Cadaver dissection is one of the most important building blocks of anatomy education. Due to the insufficient number of cadavers in Türkiye, dissection opportunities are limited for both anatomists and students [5]. Body donation is an important factor in increasing the number of cadavers. There are studies on the attitudes and behaviors of doctors, health professionals, and people in different professional groups towards cadavers and body donation [17,19,20]. In this study, anatomists' thoughts about cadavers and their supply were investigated. The majority of participants think that cadavers should be included in education. In addition, they care about how the cadavers they work with are obtained, and working with donor cadavers has a positive impact on them. Despite the necessity of cadaver anatomy education and the positive effect of donor cadavers, participants do not feel ready for cadaver donation.

Table 3. Comparison of the answers given to the survey questions according to gender.

Questions	*p**
Q1	0.527
Q2	0.727
Q3	0.960
Q4	0.673
Q5	0.116
Q6	0.225
Q7	0.092
Q8	0.978
Q9	0.737
Q10	0.522
Q11	0.580
Q12	0.896
Q13	0.991
Q14	0.790
Q15	0.811

*: comparison by gender, Pearson's chi-squared test

Table 4. Comparison of the answers given to the survey questions according to academic title and years of teaching experience.

Questions	*p**	*p***
Q1	0.272	0.371
Q2	0.341	0.746
Q3	0.414	0.199
Q4	0.359	0.307
Q5	0.293	0.870
Q6	0.069	0.417
Q7	0.028***	0.466
Q8	0.458	0.076
Q9	0.435	0.303
Q10	0.289	0.569
Q11	0.096	0.468
Q12	0.760	0.052
Q13	0.469	0.448
Q14	0.121	0.375
Q15	0.077	0.038***

*comparison by akademic title, Pearson's chi-squared test . **comparison by years of teaching experience, Pearson's chi-squared test. *** significant result (p<0,05).

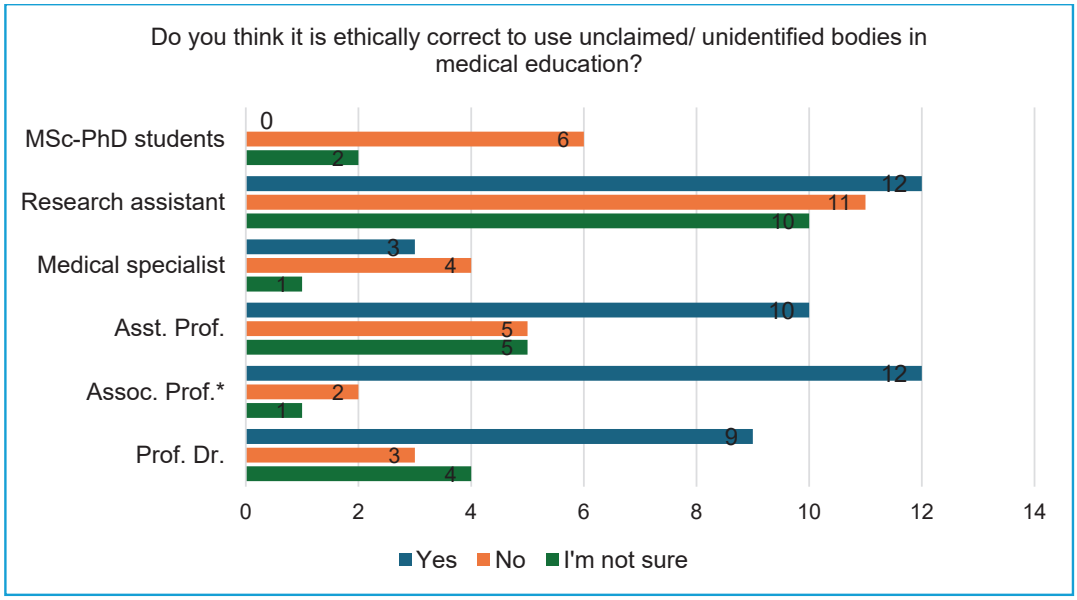

Figure 1. Distribution of the answers to the seventh question in the questionnaire according to the academic title.

The anatomists participating in the study are aware of the legal regulations regarding cadaver procurement. There is no consensus among participants about whether the deceased's family can prevent it, even though the deceased has a donation declaration. Complex situations such as the donor's desire to have a say in donor's body and donor family's wishes to hold a funeral can be considered among the reasons for indecision among anatomists. On the other hand, it is important for anatomists to communicate effectively with the family before the donor dies. This can reduce the likelihood of the family preventing donation after the donor's death [13]. 54% of participants do not find it correct that the deceased's family can donate even though donor does not have a written declaration of donation. The reason for this opinion of the participants may be that when a person dies, his/her personal rights are legally transferred to his/her family [13]. However, participants may think that the person's consent before death is more important. There are studies in the literature that reach similar conclusions regarding the legal processes of cadaver procurement and donation. Ballala et al. stated that medical doctors in India have heard of body donation and have information about ways to obtain cadavers. They also stated that they knew the legal regulations regarding cadaver donation [21].

Regular dissection studies are mostly carried out at the universities where the anatomists participating in the survey work. Participants believe that the use of unclaimed bodies as cadavers is correct in terms of education. However, ethical consensus has not been reached and there is a significant difference between the groups compared according to the level of expertise. The reason for this disagreement may be due to senior anatomists' consideration of the inadequacy of cadaver resources. Although it is right to use unclaimed bodies for good purposes in medical education, there are ethical debates about this issue. The biggest ethical problem is the lack of information and consent of the unclaimed cadaver. One of the ways to solve this problem is to work with donated cadavers instead of unclaimed cadavers. Anatomists have great responsibilities in this transition process [13].

According to the results of this study, the majority of anatomists who participated in the survey show that knowing the cadaver donor will affect them emotionally. Getting to know the cadaver donor may cause emotional fluctuations in the individual during dissection, and this may make the job of anatomists difficult. One study reported that anatomists felt uncomfortable at the thought of dissecting their own companions [22]. Similarly, the respondents do not want

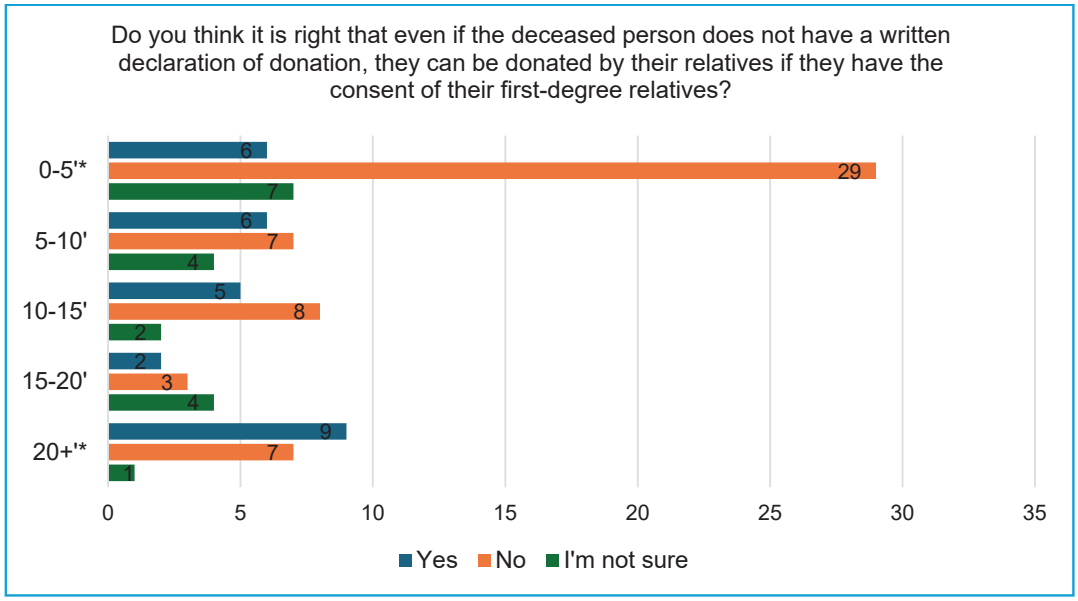

Figure 2. Distribution of answers to the fifteenth question in the questionnaire according to years of teaching experience.

their family members to be cadaver donors. In a study, medical doctors tend to recommend body donation to someone from the community rather than their family [23]. While participants do not want family members to be cadaver donors, they are willing to encourage someone they do not know. In addition, participants feel responsible for raising awareness in society about cadaver donation. With this sense of responsibility, various donation campaigns and events are currently organized in Türkiye [14]. On the other hand, there are also findings on body donation encouragement in our study that contradict the literature. Reported participant views (71% felt responsible and 51% said they would encourage people) do not correlate with the studies that evaluate Turkish anatomy departments' official websites [5,24]. In the literature reported that the anatomy departments of all the institutions in Türkiye had informative official web pages. However, only twelve (12%) departments provided information and/or documents on body donation [24]. It shows that anatomists are willing to promote body donation on an individual level, although not on an institutional level.

There is also a general reluctance among anatomists to donate their own bodies [22,25]. In our study, results similar to other studies were obtained. Only 13% of participants feel ready for cadaver donation. In another study, only 15% of anatomists were willing to donate bodies [12]. The fact that anatomists' attitudes towards body donation have not changed over the years should be evaluated carefully. Cadaver and donation issues should be covered more during anatomy specialty training and these issues should be kept on the agenda in anatomy meetings to be held across the country. In addition, anatomists stated that his/her family would not accept him/her being a donor. In a study conducted with Nigerian anatomists, the most common reason for reluctance in body donation was that the person's wish to be a cadaver donor was not accepted by his/her family [26]. The fact that most families of anatomists are reluctant to donate body compared to society may be due to the fact that they have more knowledge about dissection. Having deeper knowledge may create psychological factors such as anxiety and tension in families. In addition, many reasons such as religious, traditional, social issues and the person's psychological unpreparedness may play a role in the reluctance to donate body [25].

Conclusion

Our study reveals the opinions of anatomists in Türkiye about cadavers and their supply. The supply of cadavers, which are of invaluable value in anatomy, and the attitude of anatomists in relation to this make it important to address this issue. Because anatomists have an important role in raising public awareness about cadaver donation.

The majority of anatomists surveyed were familiar with the legal framework. In addition, although most anatomists feel responsible for informing the society, they are not willing to donate themselves as cadavers. Increasing anatomists' willingness to donate may enable the public to positively support donation campaigns in the near future.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Data availability statement

The data are available for review upon request.

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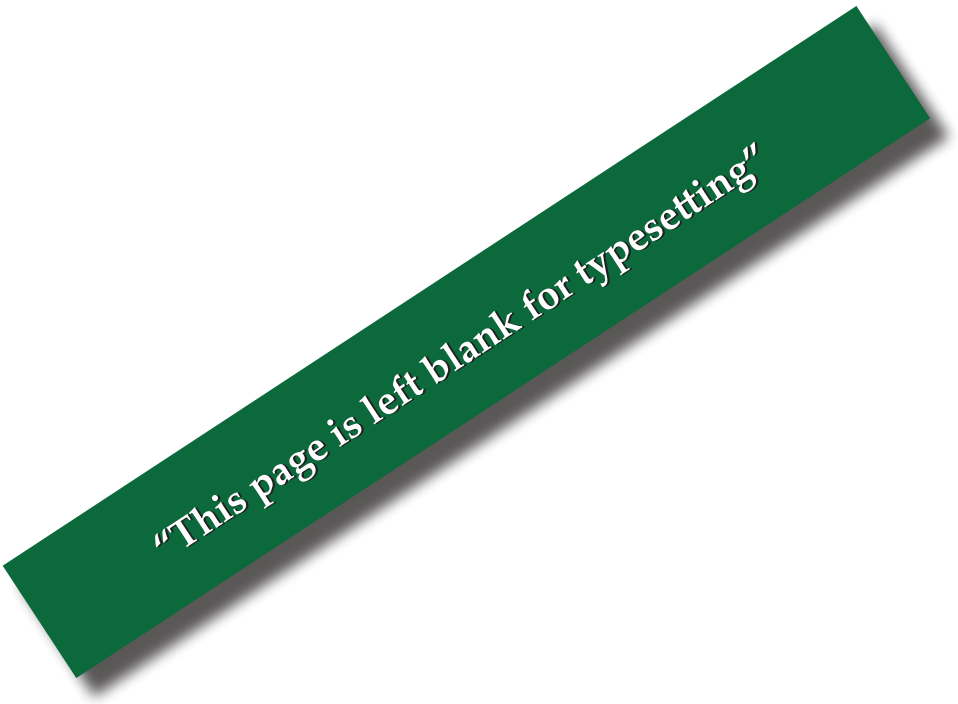
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ORIGINAL ARTICLE

Effect of Metformin usage on Vitamin B12 deficiency in patients with Type 2 Diabetes Mellitus

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Abstract

Metformin is the most commonly used drug in antihyperglycemic treatment in patients with type 2 diabetes mellitus (T2DM). In recent years, there have been many studies reporting B12 deficiency in diabetic individuals using metformin drug. This study evaluates B12 deficiency in individuals with T2 DM diagnosis using metformin in our hospital. This study is a cross-sectional and descriptive research. In this study, the data of 786 patients who applied to the Muğla Education and Research Hospital Internal Medicine outpatient clinic with T2DM diagnosis and used metformin between January 01, 2018 and March 01, 2019 were evaluated. Demographic data, vitamin B12, HbA1c levels of the patients were obtained retrospectively from the hospital information system records. Patients with missing data were excluded from the study. 347 (44.1%) male and 439 (55.9%) female patients were included in the study. Metformin dose of 248 (31.6%) of the patients was 1000 mg or less, 123 (15.6%) was 1700 mg, 414 (52.8%) was 2000 mg or more. According to the distribution of medication use, 161 (20.5%) patients were receiving metformin only, 322 (41%) patients were receiving metformin + other oral antidiabetic agents (OAD), and 303 (38.5%) patients were receiving metformin + insulin treatment. Vitamin B12 deficiency (57.8%) was higher in patients aged 60 years old and was over who used metformin (p<0.001). 347 (44.1%) of the patients included in the study received vitamin B12 replacement. We detected serious B12 deficiency in patients with T2DM who used metformin, especially in patients aged over 60 years old. Therefore, we emphasize the importance to monitor vitamin B12 levels in patients who are started on metformin and to perform B12 replacement in patients who are found to be deficient.

Keywords: Vitamin B12 deficiency, metformin, type 2 diabetes mellitus

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Introduction

Diabetes mellitus (DM) is a significant chronic metabolic disease with increasing frequency in developed and developing countries [1]. The prevalence of diabetes was estimated as 10.5% worldwide in 2021 by The International Diabetes Federation. It is estimated that it will increase to 11.3% in 2030 [2]. Metformin, a biguanide, has been used in the treatment of type 2 diabetes mellitus (T2DM) in Europe since 1957. According to the results of clinical researches, metformin improves cardiovascular outcomes in individuals with T2DM. Its proven efficacy, safety, and the fact that it can be used with other antidiabetic drugs have made metformin the most frequently used drug in the treatment of diabetes in the world [3]. The most common side effects of metformin are gastrointestinal origin such as loss of appetite, nausea, gas and metallic taste in the mouth. Another known important side effect of metformin is B12 malabsorption. In recent years, there have been many studies taking attention to vitamin B12 deficiency in diabetic individuals using metformin [4]. In 1969, Berchtold and colleagues reported evidence that vitamin B12 malabsorption developed in patients treated with metformin in a short period of 3 months [5]. In 1971, Tomkin and colleagues recommended annual B12 testing in patients using metformin for a long time [6]. Vitamin B12 deficiency itself causes neuropathy and should not be confused with diabetic neuropathy. On the other hand, B12 deficiency can become more pronounced and impair cognitive functions, especially in elderly individuals using metformin, due to the decrease in gastric parietal cells that produce intrinsic factor with aging [4]. Diagnosis and treatment of vitamin B12 deficiency are important, especially in elderly individuals using metformin. The Turkish Endocrine and Metabolism Association 2024 Diabetes Guideline recommends that B12 should be checked periodically in patients using metformin [7]. Although the relationship between metformin usage and vitamin B12 deficiency is known, the prevalence and onset of B12 deficiency among T2DM patients using metformin have not yet been fully elucidated [8]. Vitamin B12 which is also known as cobalamin, is a water-soluble cobalt-containing vitamin and is an important cofactor in many metabolic reactions. Vitamin B12 is found in many different forms such as 5-deoxyadenosyl cobalamin (adenosyl-Cbl), methycobalamin, hydroxocobalamin and cyanocobalamin. All forms of vitamin B12 are converted into methylcobalamin and adenosyl-Cbl within the cell. As a cofactor, it plays critical role in intracellular enzymatic reactions related to fatty acid and amino acid metabolism and DNA synthesis, and these enzymatic reactions are necessary for central nervous system functions and erythropoiesis [4]. In high-income countries, the most common cause of B12 deficiency is pernicious anemia, while in low-income countries, it is more likely due to inadequate B12 intake. Pernicious anemia can affect all ages, but its incidence increases with age. It is seen in 2-3% of individuals over the age of 65. Clinical B12 deficiency with classic hematological and neurological findings is rare. Low or borderline B12 deficiency without hematological and neurological findings is more common [9]. Diagnostic criteria for vitamin B12 deficiency are controversial; there is no full agreement on which biomarkers to use and which cut-off values to use [4]. In research and in the field, the cut-off value for vitamin B12 deficiency is used as < 148 pmol/L (200 pg/mL) and 200 pmol/L. While the 148 pmol/L value cannot find individuals with a deficiency of 3-5%, the 200 pmol/L value can find all individuals with deficiency. The most commonly used low-normal definition for serum vitamin B12 levels varies between 150 and 220 pmol/L [4].

This research was conducted to evaluate B12 deficiency in T2DM patients using metformin and followed up at the Muğla Education and Research Hospital Internal Medicine Polyclinic.

Materials and Methods

Ethics committee approval was accepted by the Muğla Sıtkı Koçman University Presidency Clinical Research Ethics Committee with the decision numbered 05/II dated 28/03/2019. This study is a retrospective cross-sectional and descriptive study. 786 patients who were followed up with a diagnosis of diabetes in the Muğla Education and Research Hospital Internal Medicine outpatient clinic between January 01, 2018 and March 01, 2019. Data required for the

study criteria were registered in the system and who were using metformin were included in the study. The patients' B12 levels and HbA1c levels were obtained by scanning through the Hospital Information Management System (HIMS). According to records, patients with T2 diabetes duration and a duration of metformin use of at least one year were included in the study. Diabetic patients were divided into 3 groups as those using only metformin, those using metformin and oral antidiabetic drugs (OAD) and those using metformin and insulin. According to metformin usage doses, 3 groups was taken as metformin doses of 1000 mg and below, 1700 mg, 2000 mg and above. HIMS records were also examined to see if they had taken vitamin B12 in the last year. According to age, they were divided into two groups as under 60 and over 60. As exclusion criteria, patients under 18 years of age, those with known diseases such as malabsorption that may cause vitamin B12 deficiency were not included in the study. The level for vitamin B12 deficiency was taken as <200 pg/mL (148 pmol/L). Vitamin B12 levels of all patients were studied with the electrochemiluminescence method on cobas e immunological test analyzers. HbA1c levels were also studied with the turbidimetric inhibition immunological test (TINIA) for hemolyzed whole blood on cobas c and COBAS INTEGRA systems.

Statistical Analysis

Data were tested with SPSS 25 package program. Descriptive statistics of the evaluation results will be given as number and percentage for categorical variables, mean and standard deviation for numerical variables. The conformity of the data to normal distribution was checked with *Kolmogorov-Smirnov* Test. Comparisons of numerical variables between two independent groups were made with Student T test when the normal distribution condition was met, and *Mann Whitney U* test when it was not met. Differences between the ratios of categorical variables in independent groups were tested with Chi-Square analysis. Spearman correlation analysis was used to determine the relationship between numerical data. Statistical significance level was accepted as $p<0.05$.

Results

In the study, data of individuals with T2DM who applied to Muğla Education and Research Hospital Internal Medicine outpatient clinics between January 01, 2018 and March 01, 2019, who had been using metformin for at least 1 year and whose B12 and HbA1c levels were examined were obtained retrospectively from the hospital information system. The data of 786 individuals with T2DM were examined within the study. The data of 786 individuals with T2DM were grouped according to the metformin dose they

Table 1. Characteristics of individuals with T2DM in terms of gender, medication use, and B12 replacement.

Gender	***n***	***%***
Male	354	45
Female	432	55
Metformin doses		
1000 mg ≤	248	31.6
1700 mg	123	15.6
≥2000 mg	415	52.8
Drug usage		
Metformin	161	20.5
Metformin + OAD (oral antidiabetic agents)	322	41
Metformin + insülin	303	38.5
B12 replacement		
Administered	347	44.1
Non-administered	439	55.9

used, medication usage and B12 replacement status in the last year. pg/mL was used as the unit for vitamin B12 level. 55.9% (n=439) of the individuals included in the study were female, 44.1% (n=347) were male. The characteristics of individuals with T2DM in terms of gender, medication usage and B12 replacement are given in Table 1.

The median age, B12 and HbA1c levels, and diabetes duration of individuals with T2DM were found to be 59 years, 181.35 pg/mL, 6.5, and 5 years, respectively.

In our study, it was observed that B12 levels increased as metformin dose increased. It was determined that B12 levels were higher in those using only metformin.

There was a positive correlation between HbA1c level and B12 replacement (p=0.001). HbA1c level was found to be lower in those who underwent B12 replacement. There was a positive correlation between B12 level and B12 replacement (p=0.000). B12 level was found to be

Table 2. B12 levels according to metformin dosage and type of usage.

		B12 level (median)	***Min-max***
Metformin dose	**1000 mg and below**	124	76-928
	1700 mg	134	67-634.8
	2000 mg and above	261	73-986
Metformin usage form	**Only metformin**	207.2	70-928.70
	Metformin + other OAD	181.8	73-934.70
	Metformin + Insulin	167	67-986

Table 3. Relationship between B12 level and age in the last year.

	B12 level (200 pg/mL below)		***B12 level (200 pg/mL and above)***			***p***
Age	**n**	**%**	**n**	**%**	**Total**	
Under 60 years old	207	50	207	50	414	**0.029**
Above 60 years old	215	57.8	157	42.2	372	

B12 levels were lower in patients aged 60 years and older (p=0.029).

Table 4. Relationship between B12 replacement status in the last year and gender, age, DM duration, B12 and HbA1c levels.

		B12 replacement done (n=347)	***No B12 replacement done (n=439)***	***p***
Age	Mean	59.82	57.60	0.032
	Median	60	58	
DM time	Mean	5.68	5.95	0.210
	Median	5	5	
B12 level	Mean	168.25	276.34	**0.000**
	Median	135	249	
HbA1c level	Mean	6.68	7.13	**<0.001**
	Median	6.4	6.6	
Gender		**n**	**%**	0.471
	Male	151	42.7	
	Female	203	57.3	

lower in those who underwent B12 replacement. There was a positive correlation between age and B12 replacement (p=0.032). The mean age of those who underwent B12 replacement was found to be higher. No significant relationship was found between B12 replacement status in the last year and gender and DM duration. The relationship between B12 replacement status in the last year and gender, age, DM duration, B12 and HbA1c levels is shown in Table 4.

The correlation between B12 replacement and metformin dose was found to be statistically significant (p=0.001). While 28.9% of those who received B12 replacement used 2000 mg and above metformin, 71.1% of those who did not receive replacement were using high dose metformin. No significant relationship was found between the type of metformin use and B12 replacement status. The relationship between B12 replacement status in the last year and metformin dose and usage status is shown in Table 5.

When the mean age was examined according to the method of metformin use, the mean age of the group using only metformin was found to be significantly lower than the other groups (p=0.046). No significant relationship was found between B12 levels and the method of metformin use. When the duration of DM was examined according to the method of metformin use, the duration of DM in the group using only metformin was found to be significantly lower than the other groups (p=0.001). When the HbA1c level was examined according to the method of metformin use, the HbA1c level in the group using only metformin was found to be significantly lower than the other groups (p=0.001). The relationship between the method of metformin use and age, duration of DM, B12 and HbA1c levels is given in Table 6.

Table 5. Relationship between B12 replacement status in the last year and metformin dose and method of use.

		B12 replacement done (n)		***No B12 replacement done (n)***			***p***
		n	**%**	**n**	**%**	**Total**	
Metformin dose	**1000 mg and below**	156	62.9	92	37.1	248	**0.001**
	1700 mg	71	57.7	52	42.3	123	
	2000 mg ve üzeri	120	28.9	295	71.1	415	
Metformin usage form	**Only metformin**	61	37.9	100	62.1	161	0.119
	Metformin + other OAD	141	43.8	181	56.2	322	
	Metformin + Insulin	145	47.9	158	52.1	303	

Table 6. Relationship between metformin use and age, DM duration, B12 and HbA1c levels.

		Only metformin	***Metformin + other OAD***	***Metformin + Insulin***	***p***
Age	Mean	56.73	59.57	58.51	**0.046**
	Median	57	60	59	
DM time	Mean	4.78	5.53	6.70	**0.001**
	Median	5	5	6	
B12 level	Mean	243.12	221.29	228.67	0,187
	Median	207.20	181.80	167.00	
HbA1c level	Mean	6.28	6.85	7.37	**0.001**
	Median	6.1	6.5	7	

Discussion

In our study of 786 patients with T2DM using metformin, the B12 level of 422 (53.69%) patients was found to be below 200 pg/mL (148 pmol/L). 347 (44.1%) of the patients were replaced because they had vitamin B12 deficiency. B12 levels were lower in patients who received replacement. Studies in the literature have shown that there are different rates of B12 deficiency in people using metformin. Our study found a high rate. It varies between 5.8% and 52% in the literature [4,10]. Randomized clinical studies have shown that metformin significantly reduces vitamin B12 levels after several months of use [3]. In cross-sectional studies, the decrease in vitamin B12 levels due to metformin use was found to be between 17.8% and 26.8%, while this decrease was found to be 6.3% and 18.7% in clinical researches lasting 6-16 weeks [11]. A randomized controlled study conducted by De Jager et al. showed that the decrease in vitamin B12 due to 4.3 years of metformin use was 19%. This study is the first to show a progressive decrease in vitamin B12 over the years in patients using metformin [12]. In the study conducted by Raizada et al., B12 deficiency was found to be 35.5% [13].

Many studies have shown that long-term and/or high-dose metformin use affects serum vitamin B12 levels [12,14,15]. In our study, B12 levels were found to be higher in patients using high-dose metformin than in those who did not use it. This situation, which is different from the literature, is thought to be due to the long duration of diabetes in patients using high-dose metformin and since our study did not examine replacement levels before 1 year, the patients may have previously received B12 replacement. In our study, when the groups using only metformin and those using metformin and other antidiabetic drugs were compared, the B12 level was found to be higher in the group using only metformin. The mean age of this group was lower than in the other group. 'Reinstatler et al.' In their study on patients with T2DM, B12 levels were found to be higher in patients with T2DM who used metformin than in those who did not use it [16].

In our study, B12 deficiency was more common in patients aged 60 and over who used metformin. There is limited research on the prevalence and determinants of vitamin B12 monitoring in elderly patients using metformin. In a study conducted in the United States, it was estimated that 6% of individuals under the age of 60 and 20% of individuals over the age of 60 had B12 deficiency (serum B12<148 pmol/L) [17].

B12 intake is low in individuals over the age of 60, and B12 malabsorption may occur due to atrophic gastritis [18]. In addition, drugs such as proton pump inhibitors, H2 receptor antagonists, and metformin also inhibit B12 absorption [19,20]. It is estimated that nearly 92 million metformin prescriptions were written in 2021 alone, a more than 2-fold increase since 2004 [21]. Despite the increase in metformin prescriptions, a single-center chart review study from the Veterans Affairs Medical Center (VAMC) found that only 40% of patients on high-dose metformin (≥2000 mg/day) had their serum vitamin B12 levels checked, and 50% of those treated with metformin for more than 10 years had never had their vitamin B12 levels checked [22]. Elderly diabetic patients with B12 deficiency are at higher risk for peripheral neuropathy, neuropathic pain, and related mobility limitations than younger patients and those without diabetes [19]. These patients have a variety of risk factors for peripheral neuropathy. Since these patients have a history of T2DM, their complaints may be directly attributed to diabetic neuropathy, and a simple treatable cause such as B12 deficiency may be overlooked. This may lead to polypharmacy and inappropriate medication prescribing [14]. Therefore, screening and treatment for B12 deficiency should be recommended for all patients, especially elderly patients, due to possible effects. The limitations of our study include not looking at the patients' B12 replacement before 1 year and the duration of Metformin use, and not including comorbidities in the study.

Conclusion

T2DM is increasing day by day in the world and in our country. Metformin is the most commonly used drug in treatment. Side effects such as B12 deficiency are emphasized in the literature. As

a result of our 1-year retrospective follow-up in the Muğla Education and Research Hospital Internal Medicine outpatient clinic, we detected serious B12 deficiency in T2DM patients using metformin, especially in patients over the age of 60. Therefore, we emphasize the importance to monitor vitamin B12 levels in patients who are started on metformin and to perform replacement in patients with deficiency.

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Conflict of interest

There is no conflict between the authors.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ORIGINAL ARTICLE

Synthesis, characterization and cytotoxicity analyzes of novel AB-Type Amphiphilic Block Copolymers

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Abstract

AB-type novel amphiphilic poly(L-lactide)-*block*-(*N*-isopropylacrylamide) (PLLA-*b*-PNIPAM) and poly(L-lactide)-*block*-(*N*-vinyl-pyrrolidone) (PLLA-*b*-PNVP), diblock copolymers were synthesized through the combined use of ring-opening polymerization (ROP) and controlled/living radical polymerization (CRP) techniques. (PLLA-*b*-PNIPAM) block copolymer was prepared via combination of ROP and atom transfer radical polymerization (ATRP) using the novel PLLA-based ATRP macroinitiator. (PLLA-*b*-PNVP) block copolymer was synthesized via combination of ROP and reversible addition-fragmentation chain transfer (RAFT) polymerization using the PLLA-based RAFT macro chain transfer agent (CTA). For this purpose, at first 2,4-difluorobenzyl alcohol **(1)** was used to initiate the ROP of (L-LA) using tin(II) 2-ethylhexanoate Sn(Oct)2 as a catalyst at 120 °C for synthesis of PLLA-OH **(2)**. Secondly, bromoester end-functionalized PLLA-based ATRP macroinitiator **(3)** was synthesized by esterification of hydroxyl end group of **(2)**. The first block copolymer, (PLLA-*b*-PNIPAM) **(5)**, was synthesized by ATRP of NIPAM using **(3)** in presence of copper(I) chloride/tris[2-(dimethylamino)ethyl]amine (CuCl/Me6TREN) as catalyst system in DMF/water at 25 °C. For the synthesis step of second block copolymer, at first PLLA macro chain transfer agent (CTA) **(4)** was then synthesized via substitution reaction of **(3)** with potassium ethyl xanthogenate (KEX) and finally PLLA-*b*-PNVP **(6)** diblock copolymer was prepared via RAFT polymerization of NVP using **(4)**. The molecular structures of novel polymers (**2-6**) were elucidated by spectroscopic (FTIR and 1H NMR) methods. In the application phase of this study, the effectiveness of copolymers was examined on cervical cancer cells. Cytotoxicity effects were evaluated in vitro on HeLa cell lines.

Keywords: AB-type amphiphilic block copolymer, ROP, RAFT polymerization, cytotoxicity

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Introduction

The preparation of block copolymers with amphiphilic character consisting of a biodegradable hydrophobic portion and a hydrophilic portion by combination of ROP controlled/living radical polymerization (CRP) techniques has made a great contribution to the studies in biomaterial and nanomedicine. ROP is one of the polymerization methods that can be performed depending on the variations of catalyst/initiator system and the monomer in the syntheses of several aliphatic polyesters [1]. Polyesters such as poly(lactide) (PLA) and poly(ε-caprolactone) (PCL) used for controlled drug delivery studies were generally prepared via ROP as the most chosen technique [2,3]. Among biodegradable polyesters, PLA is a bio-based and bio-compatible polymer used in many applications such as biomedicine, agriculture, packaging etc. not only because of its renewability, biocompatibility, and excellent process ability, but also because it decomposes to H2O and CO2 when degraded, forming non-toxic and non-carcinogenic products. [4,5]. Atom transfer radical polymerization (ATRP), the one of most used of CRP methods, is extensively used in macromolecular through the combination of suitable catalyst-ligand systems with halogen-containing initiators [6]. This technique has also been proven for the controlled polymerization of various monomers, including those with a range of functional groups [1,7]. Reversible addition-fragmentation chain transfer (RAFT) polymerization replicates the characteristics of living polymerization and enables the polymerization of a wide variety of functional monomers that are generally not compatible with other CRP methods [8].

Poly(*N*-isopropylacrylamide) (PNIPAM) is a hydrophilic character polymer widely employed to form the temperature-responsive copolymers with other polymers [9]. Advancements in synthetic methods have made it possible to prepare various block copolymers consisting of a hydrophobic part containing PLA and a hydrophilic part containing PNIPAM. Most of the studies have focused on preparation of AB-type [9,10] diblock or ABA-type [11] or ABC-type [12] triblock copolymers consisting of PLA and PNIPAM through various polymerization methods have been studied extensively by numerous researchers. The amphiphilic block copolymers consisting of polyester and PNIPAM with advanced macromolecular architectures have also been investigated as carriers for drug delivery systems. The copolymerization of PNIPAM with PLA combines the thermosensitivity of PNIPAM and degradability of PLA, enabling its use as a carrier in drug delivery systems [11]. Poly(*N*-vinyl pyrrolidone) (PNVP) is a hydrophilic polymer that can be used in the pharmaceutical and biomedical fields due to its properties such as water solubility and low toxicity [13,14]. PNVP has been used extensively in pharmaceutical tablets and hydrogels [15,16]. The studies focusing on synthesis of block copolymers including PNVP and PLA or PCL using the combination ROP and RAFT polymerization have been investigated extensively by many researchers in recent years. Polymeric micelles formed from biocompatible PNVP-based block copolymers, such as PNVP-*b*-PCL [17,18] and PNVP-*b*-PDLLA [19] have been synthesized using via combination ROP and RAFT and their properties in terms of micelle formation have been evaluated for drug delivery applications. In addition to these literatures, Shin et al. prepared PVP-*b*-PLLA using a dual initiator via combination ROP and RAFT in one-step procedure [20]. In this work novel AB-type block copolymers were prepared in five stages via combination of ROP and ATRP or RAFT polymerizations of L-lactide, NIPAM or NVP, respectively. Firstly, PLLA **(2)** was prepared by ring opening polymerization (ROP) of (L-LA) at 120 °C using **(1)** as initiator. Secondly, bromoester end-functionalized PLLA macroinitiator **(3)** was synthesized by esterifying hydroxyl groups of **(2)**. Thirdly, PLLA macro chain transfer agent (CTA) **(4)** was then synthesized via substitution reaction of **(3)** with potassium ethyl xanthogenate (KEX). The first diblock copolymer, (PLLA-*b*-PNIPAM) **(4),** was prepared by ATRP of NIPAM as monomer using **(3)** in presence of copper(I) chloride/tris[2-(dimethylamino)ethyl]amine (CuCl/Me6TREN) as catalyst system in DMF/water at 25 °C. Finally, the second block copolymer, PLLA-*b*-PNVP **(6)**, was synthesized RAFT polymerization of NVP

using **(5)**. Characterization of the molecular structures for the novel polymers were elucidated by spectroscopic (FTIR and 1H NMR) methods. In the application phase of this study, the effectiveness of copolymers was examined on cervical cancer cells. The cytotoxicity of polymers was evaluated in vitro on HeLa cell lines.

Experimental Section

Materials

Reactions were carried out under an atmosphere of argon using standard Schlenk techniques. *N*-isopropylacrylamide (NIPAM, Sigma-Aldrich, 97%), was purified by re-crystallization from *n*-hexane/toluene mixture and dried in vacuum. *N*-Vinyl pyrrolidone (NVP) was dried over anhydrous magnesium sulfate and distilled under reduced pressure. L-lactide (L-LA, TCI, 98%) was purified by recrystallization from ethyl acetate/*n*-hexane twice and dried in vacuum at room temperature and kept in freezer. Copper(I) chloride (CuCl) (98%; Aldrich) was purified by stirring it overnight in glacial acetic acid to eliminate Cu^{2+} ions, followed by filtration, washing with ethanol, and drying under vacuum at 70 °C for two days. 2,2′-Azobis(isobutyronitrile) (AIBN) was received from TCI (>98%). After recrystallisation from methanol it was stored at 4 °C. Tris[2-(dimethylamino)ethyl] amine (Me_6TREN) was prepared according to published procedure [21]. Dichloromethane (DCM ≥99.5%) was dried over calcium hydride (CaH_2) and stored over molecular sieves (4 Å). 2-Bromopropionyl bromide (Sigma-Aldrich, 97%), 2,4-difluorobenzaldehyde (Sigma-Aldrich, 98%), potassium ethylxanthate (TCI, >95%), triethylamine (TEA, Sigma-Aldrich, ≥99%), sodium borohydride $NaBH_4$ (Sigma-Aldrich, 98%), pyridine (Sigma-Aldrich, ≥99%) and tin(II) 2-ethylhexanoate ($Sn(Oct)_2$, Sigma-Aldrich, >92.5%) were used as received. Conventional methods were employed for purification of all solvents [22].

Measurement

Transmission IR spectra was recorded on a FTIR-ATR spectrophotometer (Perkin-Elmer 1600) in the spectral range 4000–400 cm^{-1} with samples. ^{1}H NMR spectra were recorded on the Bruker AVANCE III 400 MHz NMR instrument was used for the characterization Varian Mercury 400 MHz spectrometer with CDCl3 as solvent at ambient temperature. Tetramethylsilane (TMS) is used as the internal standard and the chemical shifts were given in parts per million (ppm) relative to this standard.

Synthesis of 2,4-difluorobenzyl alcohol (1)

2,4-Difluorobenzyl alcohol was synthesized the reduction of 2,4-difluoro benzaldehyde in presence of $NaBH_4$ in methanol according to published literature [23]. To a stirred solution of 2,4-difluorobenzaldehyde (1.67 mL, 2.18 g, 15 mmol) in methanol (10 mL) was added $NaBH_4$ (752 mg, 19.5 mmol) portion wise at 0 °C overnight. After completion of the reaction, methanol was removed under reduced pressure, diluted ice-cold water (50 mL) and extracted with ethyl acetate (2x25 mL). The combined organic layers were washed with H_2O (2x25 mL) and brine (2x25 mL) and dried over $MgSO_4$ and concentrated to obtain the light-yellow liquid. Yield was 90%.

^{1}H NMR (400 MHz, $CDCl_3$, **δ**): 7.46-7.34 (Ar**H**, 1H), 6.89-6.78 (Ar**H**, 2H), 4.72 (Ar–C**H**$_2$–,2H), 1.78 (CH_2–O**H**, O*H*).

Synthesis of (2) in the presence of initiator (1) via ROP

PLLA-OH **(2)** was prepared as follows: Into a Schlenk tube equipped with a magnetic stirrer, ROP initiator **(1)** (0.06 g, 0.4 mmol), L-LA (1.47 g, 10 mmol) and $Sn(Oct)_2$ ($3.41x10^{-3}$ mL, 0.01 mmol) in dry toluene (3 mL) were introduced. The flask with reaction mixture was degassed and then immersed into an oil bath at 120 °C for 24 h. The reaction mixture was poured into methanol with stirring and the polymer was precipitated. The white powder polymer **(2)** was re-precipitated using dissolve/precipitate process (DCM/methanol), collected, and then dried in the vacuum at 30 °C.

Yield: 1.29 g, Conversion: 84%. M_n (theo.); 3160 g/mol; M_n (NMR); 3320 g/mol; FTIR (ATR, cm^{-1}): 2994, 2946, 1756, 1453, 1358, 1185, 1083, 868, 753; ^{1}H NMR ($CDCl_3$, δ) = 7.34 (Ar***H***, H^b), 6.85 (Ar***H***, H^{a+c}), 5.16 (main chain, –C***H***(CH_3)OCO) H^e), 4.34 (terminal, –C***H***(CH_3)OH, H$^{e'}$), 1.57 (main chain, –CH(C***H***$_3$)OCO-, H^f), 1.49 (terminal, –CH(C***H***$_3$) OH, H$^{f'}$).

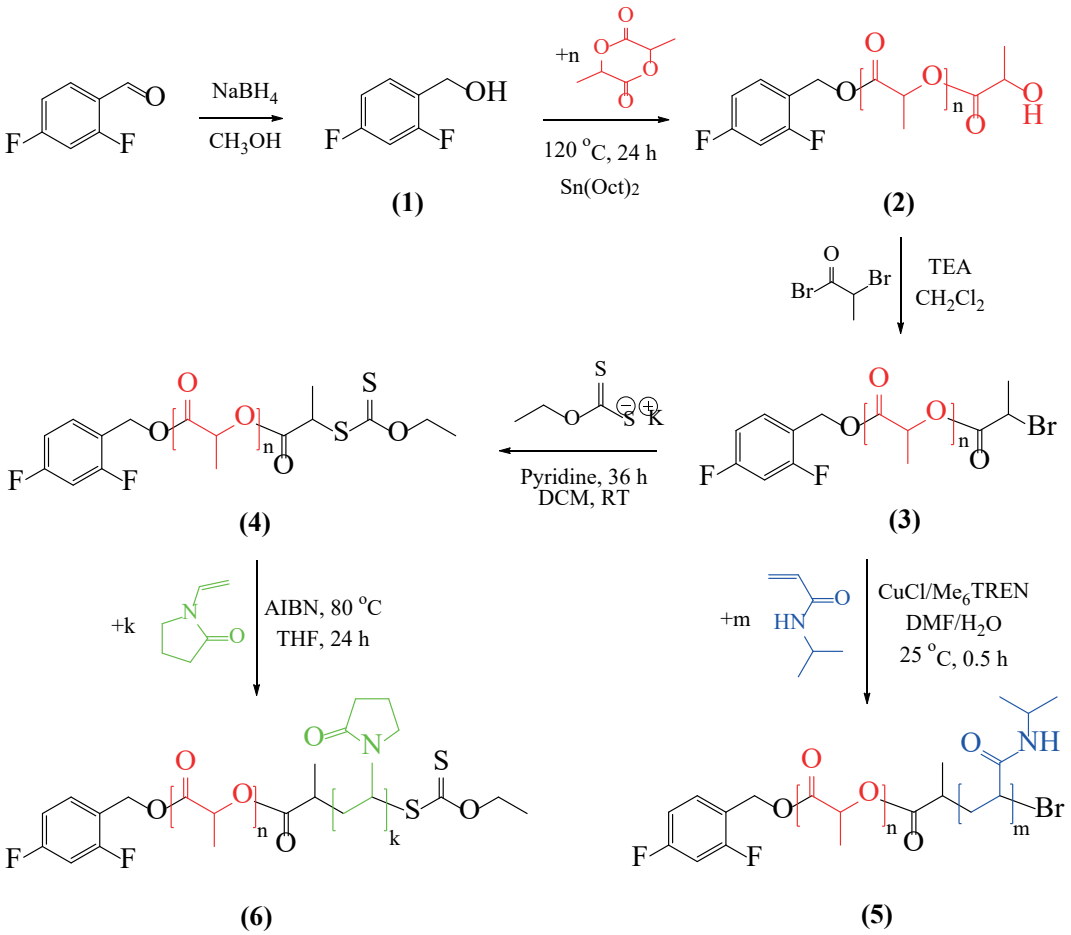
Synthesis of bromoester-ended PLLA (3)

PLLA-OH **(2)** was converted to bromoester functionalized (PLLA-Br) by using 2-bromopropionyl bromide. **(2)** (1.0 g, 0.301 mmol, M_n (NMR) =3320 g/mol) was charged a round-bottom two-necked flask and dissolved in dry DCM (15 mL). TEA (0.123 mL, 0.903 mmol) was added to the mixture. The reaction was cooled down to 0 °C and 2-bromopropionyl bromide (0.066 mL, 0.588 mmol) in dry DCM (5 mL) was added dropwise for 30 min. The reaction continued at room temperature for 36 h with stirring. After the removal of precipitated salt, the filtrate was diluted with 30 ml of DCM and washed with 5% aqueous $NaHCO_3$ (3x20 mL), then water (3x20 mL), dried over $MgSO_4$, and filtered. The concentrated solution was precipitated into cold methanol and the bromoester ended PLLA **(3)** was dried overnight in vacuum at 40 °C.

M_n (NMR): 3460 g/mol; ^{1}H NMR ($CDCl_3$, δ) = 7.34 (Ar***H***, H^b), 6.85 (Ar***H***, H^{a+c}), 5.16 (main chain, –C***H***(CH_3)OCO) H^e), 4.43 (–C***H***(CH_3)Br, H^g), 1.85 (–CH(C***H***$_3$)Br, H^h), 1.57 (main chain, –CH(C***H***$_3$)OCO-, H^f), 1.49 (–CH(C***H***$_3$)O, $H^{f'}$)

Synthesis of xanthate terminated PLLA (4)

The functional polyester **(3)** was converted into a PLLA-based RAFT-CTA **(4)** via substitution reaction of **(3)** with potassium ethyl xanthogenate (KEX) using molar ratio of reagents; [**(3)**: KEX: pyridine]: 1:3:55. In a typical synthesis process, **(3)** (0.15 g, 0.043 mmol, Mn, (NMR) =3460 g/mol) and potassium ethylxanthate (KEX) (0.021 g, 0.129 mmol) were taken in a dried and argon purged round-bottom flask and the flask was immersed in a cold ice bath. In another dried flask, pyridine (0.19 mL, 2.37 mmol) dissolved in 20 mL DCM and this solution was added dropwise to first reaction mixture during stirring for 30 min. The reaction mixture continued at room temperature for 48 h with stirring. The reaction mixture diluted with 60 mL of DCM was washed successively with saturated NH_4Cl solution (3x30 mL), saturated $NaHCO_3$, solution



(1) **(2)** **(3)** **(4)** **(5)** **(6)**

Scheme 1. Synthesis of PLLA-based macroinitiators and block copolymers.

(3x30 mL), and water (3x 50 mL), dried over $MgSO_4$ and filtered. After the filtrate was brought to dryness, the residue was dissolved in THF and precipitated into hexane. The PLLA macro-CTA **(4)** was dried overnight under vacuum.

M_n (NMR); 3620 g/mol; ^{1}H NMR ($CDCl_3$, δ) = 7.33 (Ar***H***, H^b), 6.86 (Ar***H***, H^{a+c}), 5.17 (main chain, –C***H***(CH_3)OCO) H^e), 4.64 (O–C***H***2CH_3, H^i), 4.45 (–C***H***(CH_3)Br, H^g), 1.57 (–CH(C***H***$_3$)OCO-, H^f), 1.52 (–CH(C***H***$_3$)O, H^h), 1.41 (O–CH_2C***H***$_3$, H^j).

Synthesis of PLLA-*b*-PNIPAM (5)

PLLA-*b*-PNIPAM **(5)** was prepared using **(3)** as macroinitiator via ATRP. In a dried Schlenk flask, **(3)** 0.09 g (0.026 mmol, M_n (NMR)= 3460 g/mol), NIPAM 304 mg (2.6 mmol) and 2.6 mg (0.065 mmol) CuCl were dissolved in 1.5 mL DMF, then 0.3 mL of distilled water were added to the reaction mixture. After three freeze-pump-thaw cycles, 13.7 µL (0.065 mmol) Me_6TREN were added under argon atmosphere. The reaction was then allowed to proceed under stirring at 25 °C for 0.5 h. The viscous solution was precipitated by adding diethyl ether. The crude product dissolved in DCM was passed through a neutral alumina column. The resulting filtrate was concentrated, precipitated in cold diethyl ether and the obtained polymer **(5)** was dried under vacuum for 48 h.

Conversion: 19%. M_n (theo.):5610 g/mol; M_n (NMR): 5460 g/mol; FTIR (ATR, cm^{-1}): 3293, 3070, 2972, 2924, 1756, 1638, 1536, 1455, 1365, 1183, 1088, 1043, 872, 837; ^{1}H NMR ($CDCl_3$, δ): 6.61 (–N***H***CH(CH_3)$_2$, H^3**,** in PNIPAM), 5.13 (–C***H***(CH_3) OCO) H^e), in PLLA], 3.98 (–C***H***(CH_3)$_2$, H^4, in PNIPAM), 2.12 (–CH_2–C***H***– , H^2), 1.79 (–C***H***$_2$–CH– , H^1, in PNIPAM),1.55 (–CH(C***H***$_3$)OCO-, H^e, in PLLA), 1.12 (–CH(C***H***$_3$)$_2$, H^5, in PNIPAM).

Synthesis of PLLA-*b*-PNVP (6)

In a dried Schlenk flask, **(4)** (54 mg, 0.015 mmol, M_n (NMR)= 3620 g/mol) was dissolved in 1 mL THF and then NVP (0.16 mL, 1.50 mmol) and AIBN (1.23 mg, 0.0064 mmol) were added. The homogeneous solution was degassed with argon and continued for 0.5 h with stirring. The flask was immersed in an oil bath at 80 °C and the reaction was allowed to proceed for 24 h. The reaction mixture was diluted with THF (4 mL), precipitated with 250 mL of hexane and the precipitated polymer was separated by centrifugation. The obtained polymer **(6)** was purified by dissolution/precipitation procedure two more times and dried under vacuum at 30 °C.

Conversion: 23%. M_n (theo.): 6175 g/mol; M_n (NMR); 5890 g/mol; FTIR (ATR, cm^{-1}): 3435, 2974, 2946, 2925, 2886, 1755, 1650, 1421, 1289, 1182, 1084, 842, 735; ^{1}H NMR ($CDCl_3$, δ) = 5.14 (H^e, in PLLA), 4.62 (O–C***H***$_2$$CH_3$, H^i), 4,04–3.51 (CH_2C***H***, H^7 in PNVP backbone), 3.51–3.02 (–NC***H***$_2$$CH_2$$CH_2$, H^{10}, in PNVP ring), 2.55–1.81 (–NCH_2CH_2C***H***$_2$, H^8 and –NCH_2C***H***$_2$$CH_2$, H^9**,** in PNVP ring)), 1.67–1.12 (H^{f+6+i}).

Cell Culture

For this study, human cervical cancer (HeLa) cell lines obtained from Kırşehir Ahi Evran University, Department Medical Pharmacology, were used. The cells were cultured at 37 °C with 5% CO_2 in RPMI medium supported with 10% Fetal Bovine Serum and 1% penicillin-streptomycin.

Cytotoxicity Analyses

The cytotoxic impact of polymers HeLa cells was evaluated using the XTT assay kit (Biological Industries, USA). 800 cells were seeded per well in a 96-well plate. Following a 24-hour incubation period, the cells were exposed to copolymer. After 72 h of incubation, the solutions from the XTT kit were introduced to the cells. Cell viability was then measured using a microplate reader (BIOTEK ELX808, USA) at a wavelength of 450 nm. The IC50 value was determined. As a result of the readings the obtained values, the inhibition rates of cells were calculated using the following formula: % inhibition: (A450 nm test – A450 nm control/A450 nm control) ×100.

Results and Discussion

The synthetic route is depicted in Scheme 1. The main route used in the preparation of block copolymers, according to monomers or methods, is as follows:

The PLLA block was first synthesized by the ROP of L-LA using $Sn(Oct)_2$ as catalyst, followed by the ATRP of NIPAM or RAFT polymerization

of NVP. In this study the novel synthesized PLLA-based block copolymers were prepared in five stages; the synthesis of PLLA via ROP (i), esterification of PLLA hydroxyl group with 2-bromopropionyl bromide (ii), substitution reaction of bromine end group with potassium ethyl xanthogenate (KEX), synthesis of PLLA-*b*-PNIPAM **(5)** via ATRP of NIPAM initiated by **(3)** (iv), synthesis of PLLA-*b*-PNVP **(5)** via RAFT polymerization of NVP using macroCTA **(4)** (v). For this purpose, at first PLLA was synthesized ROP of L-LA with molar ratio of ([monomer]:[initiator]=25:1) using **(1)** as the initiator and $Sn(Oct)_2$ as catalyst. The structure of **(2)** was elucidated by FTIR and ^1H NMR.

FTIR spectra of PLLA **(2)**, PLLA-*b*-PNIPAM **(5)** and PLLA-*b*-PNVP **(6)** are depicted in Figure 1. In the spectrum of **(2)** (in Figure 1A), the absorption band of the carbonyl group of PLLA block was observed at 1756 cm^{-1}. The bands at 1185 and 1083 cm^{-1} were attributed to carbon-oxygen stretching.

Figure 2A showed ^1H NMR spectrum of PLLA **(2)**. In the ^1H NMR spectrum of **(2)** the signal ($H^{e'}$) of terminal methine group of PLLA was observed at 4.34 ppm. The peaks of methine (H^e) and methyl (H^f) protons, corresponding to PLLA repeating units, were detected at 5.15 and 1.57 ppm, respectively. The peaks at δ =7.34 (H**b)** and 6.85 (H^{a+c}**)** are also assigned to the aromatic protons of **(1)**. M_n (NMR) of polymer **(2)** was determined by using the integral ratio of the methyl proton peaks of PLLA (δ = 1.57 ppm) to the methine proton peak of terminal unit of PLLA (peak **e'** in Figure 2A). The calculated value of molecular weight by NMR spectra is close to M_n (theo.). M_n (NMR) of PLLA was calculated by integral area of related peaks displacements according to equation (1)

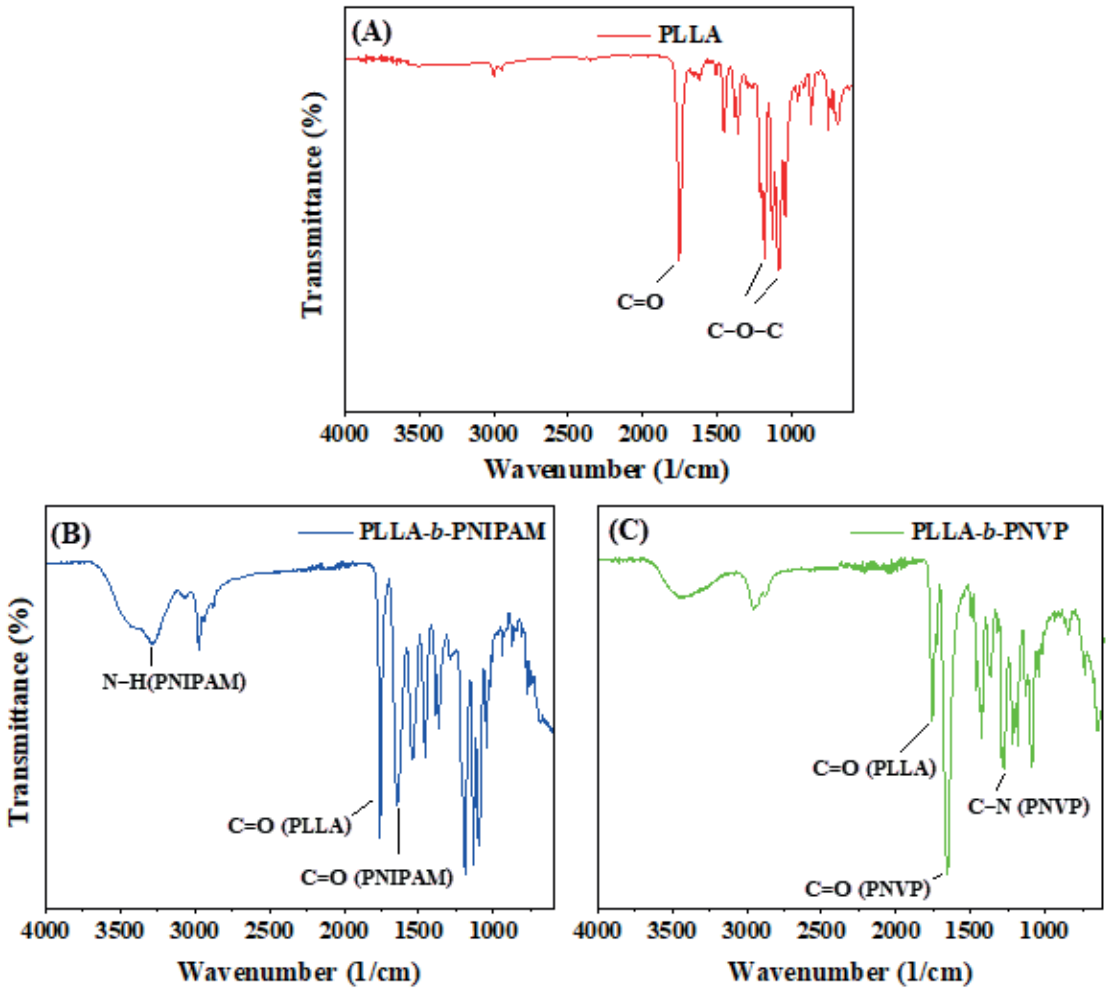


Figure 1. FTIR spectra of PLLA (A), PLLA-*b*-PNIPAM (B) and PLLA-*b*-PNVP (C).

$$M_n\,(NMR) = \left(\frac{I_f}{I_{e'}} \times M_{monomer}\right) + M_{initiator} \quad (1)$$

Here, $M_{monomer}$ and $M_{initiator}$ are molecular weights of the L-lactide and initiator, respectively.

M_n (theo.) was calculated according to equation

$$M_n(theo.) = \left(\frac{[M]}{[I]} \times M_{monomer} \times Conversion\%\right) + M_{ini} \quad (2)$$

In the second step, ATRP macroinitiator **(3)** was synthesized by esterifying of end group of **(2)** with 2-bromopropionyl bromide. ^{1}H NMR spectrum of **(3)** is displayed in Figure 2B. After esterification of hydroxyl end groups of PLLA, two novel signals appeared at 4.43 and 1.85 ppm. These signals were attributed to methine (H^g) and methyl (H^h) protons of bromo propionate end, respectively. The disappearance of peak at 4.34 ppm, which corresponds to the methine protons adjacent to terminal hydroxyl end groups of PLLA end, indicates that the esterification was successful. The peaks of methine and methyl

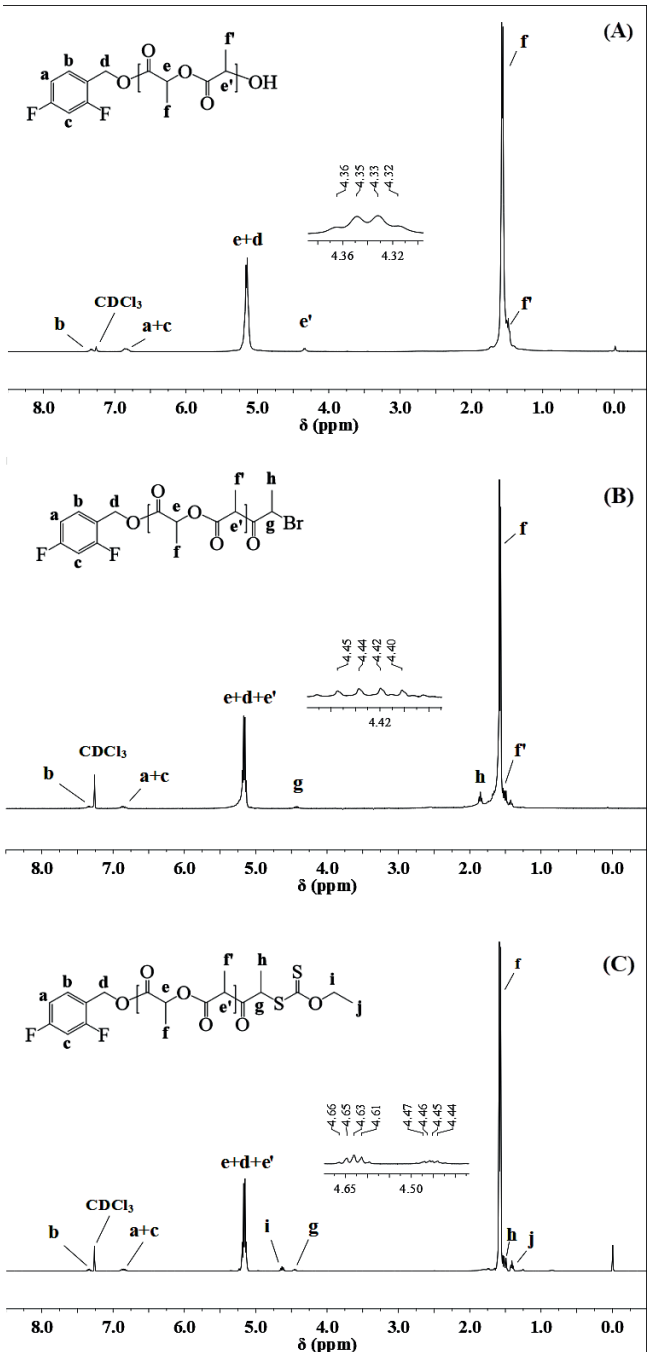


Figure 2. ^{1}H NMR spectra of (A) PLLAOH, (B) PLLA-Br macroinitiator, (C) PLLA macro CTA.

protons of the repeating units of PLLA main chain at 5.16 (H^e) and 1.57 (H^f) ppm were detected, respectively. The aromatic protons of **(1)** gave multiple signals at 7.35 and 6.86 ppm. M_n (NMR) of **(3)** calculated by comparing the peak integrals derived from the methyl protons' peaks of PLLA (δ = 1.57 ppm) and the methine proton peak of end group (peak g in Figure 2B).

In the third step, PLLA macro CTA **(4)** was synthesized via substitution reaction of **(3)** with KEX. ^{1}H NMR spectrum of **(4)** is displayed in Figure 2C. After the substitution reaction two novel signals appeared at 4.64 and 1.41 ppm, which correspond to methyl (H^i) and methyl (H^j) protons of xanthate end group, respectively. The peaks of methine and methyl protons of the PLLA at 5.17 (H^e) and 1.57 (H^f) ppm were detected, respectively. The signals for the aromatic protons of initiator fragment **(1)** in macro-CTA agree with the values recorded the previous spectrum (Figure 2B).

In the fourth step, PLLA-*b*-PNIPAM **(5)** was synthesized by ATRP of NIPAM as monomer using **(3)** as macroinitiator with molar ratio of monomer to initiator, i.e. [M]:[I] =100:1. FTIR spectrum of block copolymer is depicted in Figure 1B. As seen in FTIR spectrum of **(5)**, the appearance of bands at 3285 cm^{-1} (N-H stretching), 1640 cm^{-1} (C=O stretching) and 1538 cm^{-1} (N-H bending) belonging to PNIPAM indicated polymerization of NIPAM was successful [24]. In addition to these data, C=O

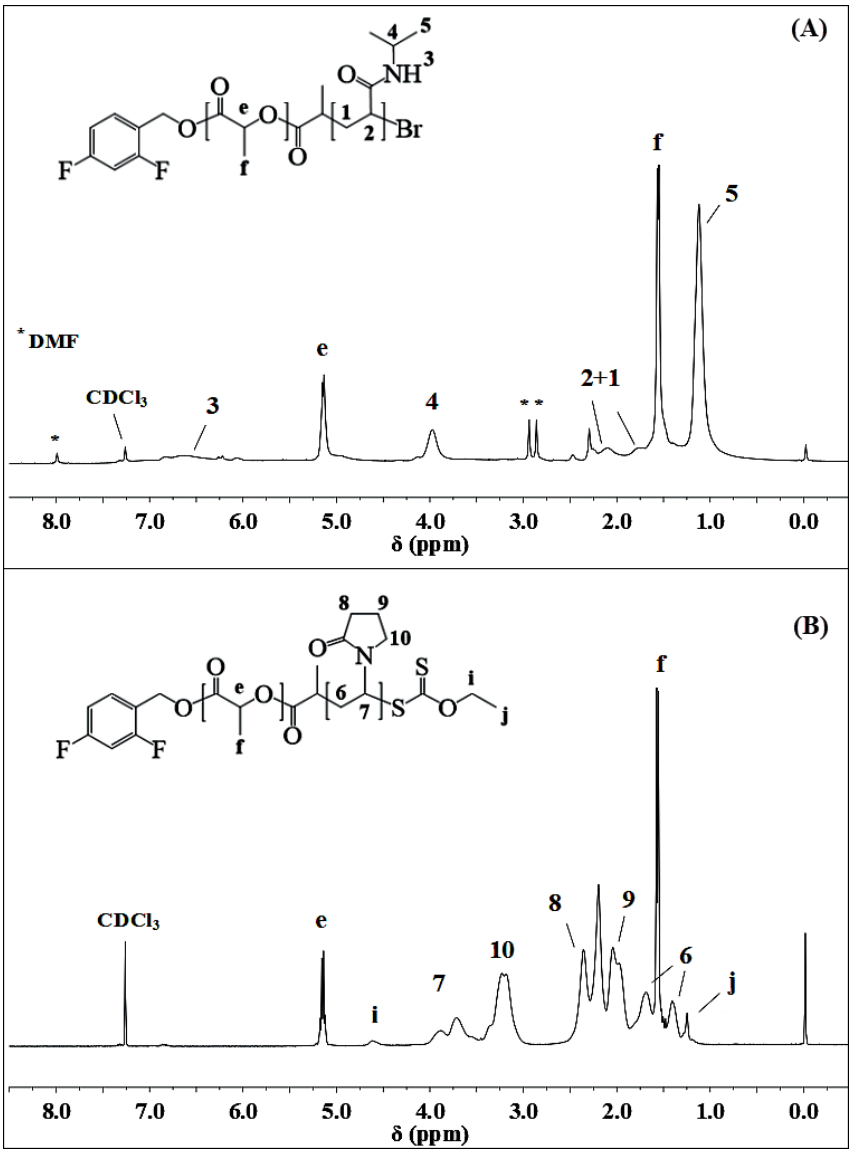


Figure 3. ^{1}H NMR spectra of (A) PLLA-*b*-PNIPAM, and (B) PLLA-*b*-PNVP.

band at 1755 cm^{-1}, attributable to the PLLA block, supports the formation of block copolymer.

^{1}H NMR spectrum of **(5)** (in Figure 3A) displayed characteristic signals at 3.98 and 1.12 ppm assigned to the methine (H^4) and methyl (H^5) protons of PNIPAM, respectively. The signals at 5.13 and 1.55 ppm were ascribed to methine and methyl protons of PLLA, respectively. A broad signal appeared at 6.61 ppm (H^3), which show the presence of proton of –NH group. The signals at 2.12 (H^2) and 1.79 (H^1) ppm are also attributed to the methine and methylene group of PNIPAM backbone, respectively. M_n (NMR) of **(5)** was determined by comparing the peak integrals derived from the methine proton peaks of PNIPAM (δ = 3.98 ppm, peak '**4**') and the methine proton signal of PLLA (δ = 5.13 ppm, peak '**e**' in Figure 3A) according to equation (3 and 4)

$$M_n\,(NMR) = (\,DP_{NIPAM} \times M_{monomer}\,) + M_{n,PLLA} \quad (3)$$

$$DP_{NIPAM} = \left(\frac{I_4}{I_e} \times DP_{PLLA}\right) \quad (4)$$

Here, DP_{PNIPAM} and DP_{PLLA} are degree of polymerization for PNIPAM and PLLA segments, respectively. $M_{monomer}$ is also molecular weight of the NIPAM.

Finally, PLLA-*b*-PNVP **(6)** was synthesized RAFT polymerization of NVP using **(4)**. FTIR spectrum of **(6)** is shown in Figure 1C. As seen in the FTIR spectrum of **(6)**, peaks corresponding to PVP can be detected by the appearance of C=O and C–N peaks at 1656 and 1289 cm^{-1}, respectively.

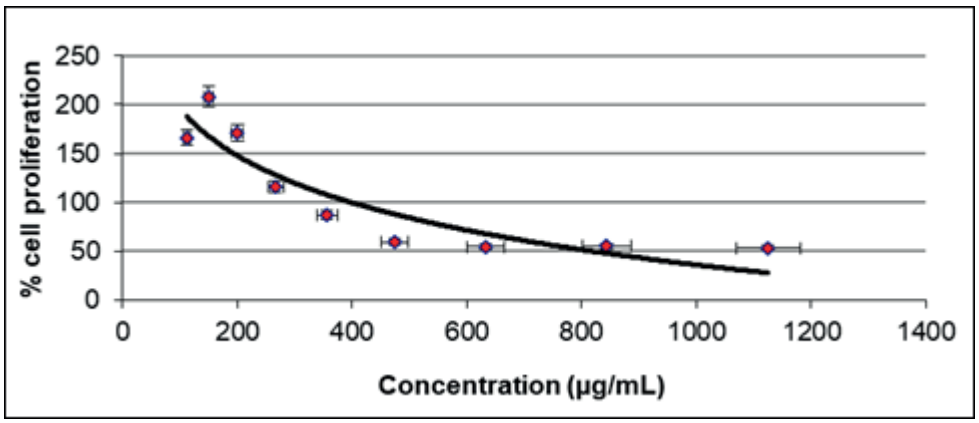


Figure 4. Cytotoxicity assay of PLLA-*b*-PNIPAM block copolymer.

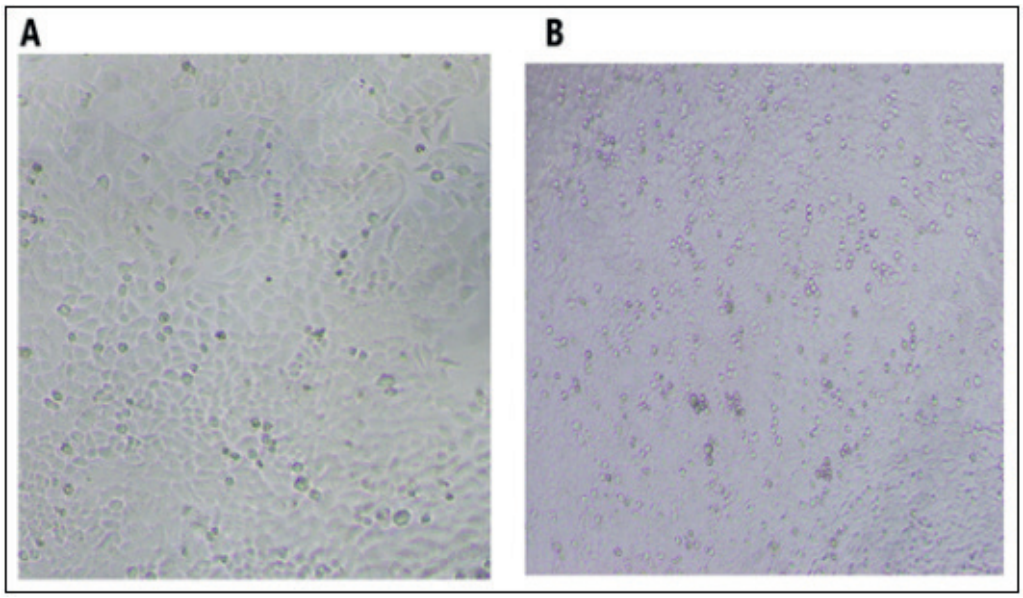


Figure 5. A; Control group (Non copolymer treated) Hela cell line B; PLLA-*b*-PNIPAM block copolymer treated cells (1000 ug/ml) (X40).

In addition to these values, the peak belongs to PLLA the appearance of C=O at 1755 cm^{-1} supports the formation of block copolymer.

^{1}H NMR spectrum of PLLA-*b*-PNVP **(6)** is displayed in Figure 3B. In the spectrum, methylene protons of pyrrolidone ring, corresponding to the characteristic peaks of PVP backbone, were detected at 3.51–3.02 (H^{10}) and 2.55–1.81 (H^{8+9}) ppm. The other peaks of methine proton (H^{7}) of PNVP chain appeared at 4,04–3.51 ppm. The observation of the peak at 5.14 of the methine (H^{e}) protons of PLLA block and the overlapped peaks at 1.67–1.12 ppm methylene (H^{6}) of PNVP block with methyl (H^{f}) protons of PLLA indicates the formation of block copolymer. M_n (NMR) of **(6)** was calculated by comparing the peak integrals derived from the methylene protons' peaks of PNVP (δ =3.24 ppm, peak '**10**') and the methine proton peaks of PLLA (δ = 5.19 ppm, peak '**e**' in Fig. 3B) according to equation (5 and 6)

$$M_n\,(NMR) = (\,DP_{NVP} \times M_{monomer}\,) + M_{n,PLLA} \quad (5)$$

$$DP_{PNVP} = \left(\frac{I_{10}}{I_e} \times DP_{PLLA}\right) \quad (6)$$

Here, DP_{PNVP} and DP_{PLLA} are degree of polymerization for PNVP and PLLA segments, respectively. $M_{monomer}$ is also molecular weight of the NVP.

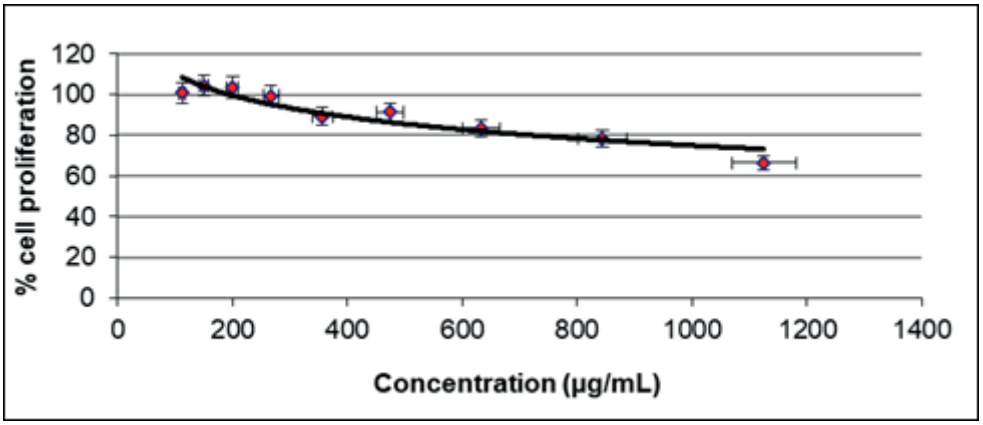


Figure 6. Cytotoxicity assay of PLLA-*b*-PNVP.

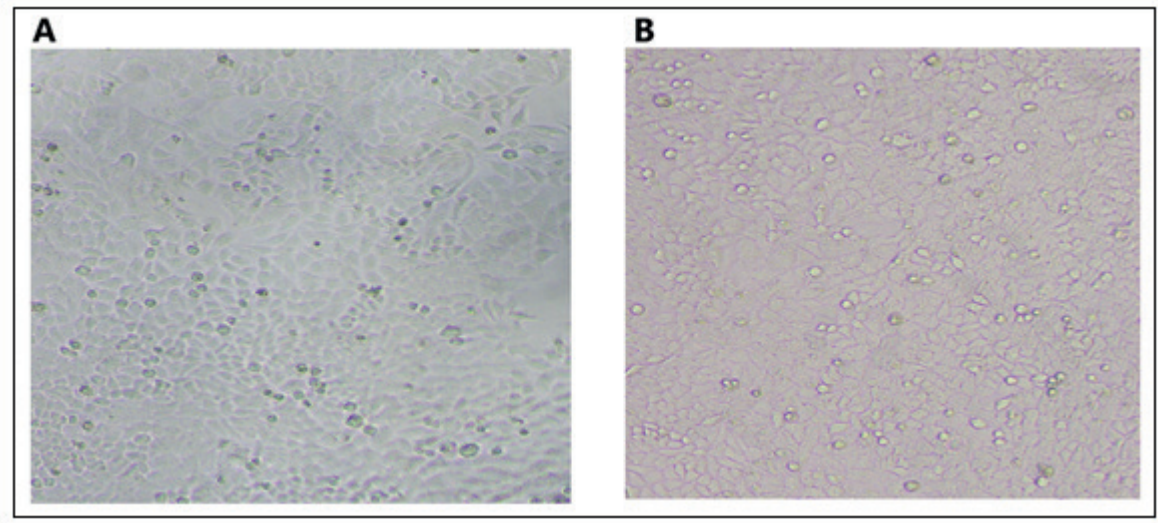


Figure 7. A; Control group (Non copolymer treated) Hela cell line B; (PLLA-*b*-PNVP) block copolymer treated cells (1000 ug/ml) (X40).

In Vitro Investigation

In vitro cytotoxicity studies in cancer cell lines are an important assay to evaluate the potential activity and toxicity of new drug carriers [25]. XTT analysis was performed to investigate the cytotoxic effect of synthesized block copolymers on cervical cancer (HeLa) cells. Considering vitro analyses, the cytotoxicity of synthesized block copolymers was investigated in cervical cancer cell lines at dose ranges of 100-1125 ug/mL. According to the obtained analyses results, it was observed that the first synthesized block copolymer PLLA-*b*-PNIPAM had no toxic properties on cells at doses below 350 ug/ml and the doses above 350 ug/mL killed approximately 50% of the cells. The results obtained are shown in Figure 4 and Figure 5. This result may be attributed to the trace amounts of copper that could remain in the block copolymer during the polymer purification process.

For PLLA-*b*-PNVP block copolymer, the cytotoxic effect of (6) on HeLa cell lines was also evaluated at dose ranges of 100-1125 ug/mL. According to the results obtained, (6) had no significant toxic effect on cells (Figure 6 and Figure 7).

Conclusion

In this work novel AB-type block copolymers, (PLLA-*b*-PNIPAM) and (PLLA-*b*-PNVP), were prepared by combining of ROP and controlled/living radical polymerization (CRP) techniques, ATRP or RAFT polymerization of NIPAM or NVP as monomers. The synthesis utilized a novel PLLA-based macroinitiators, created using a novel initiator, 2,4-difluorobenzyl alcohol, not previously used in polymerization of L-LA. The molecular structures of the compounds were confirmed using FTIR and ^{1}H NMR methods. The M_n of the obtained polymers was calculated by comparing the peak integrals of related NMR spectra and agreed with theoretical values. Considering vitro analyses, the cytotoxicity of synthesized block copolymers was investigated in cervical cancer cell lines at dose ranges of 100-1125 ug/ml. According to the obtained analyses results, it was observed that the first synthesized block copolymer PLLA-*b*-PNIPAM **(5)** had no toxic properties on cells at doses below 350 ug/ml and the doses above 350 ug/mL killed approximately 50% of the cells. This effect may be due to the fact that trace amounts of copper in the block copolymer are not completely removed during the purification process. The cytotoxic effect of (PLLA-*b*-PNVP) on HeLa cell lines was also evaluated at dose range of 100-1125 ug/ml. PLLA-*b*-PNVP **(6)** had no a significant toxic effects according to the results obtained. Furthermore, it was observed that if the (PLLA-*b*-PNIPAM) is further purified, both block copolymers could be used in future cancer treatments and drug delivery applications.

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Conflict of interest statement

The author declared no conflict of interest.

Ethics approval and consent to participate

Not applicable

Data availability statement

Raw data that support the findings of this study are available from the corresponding author, upon reasonable request.

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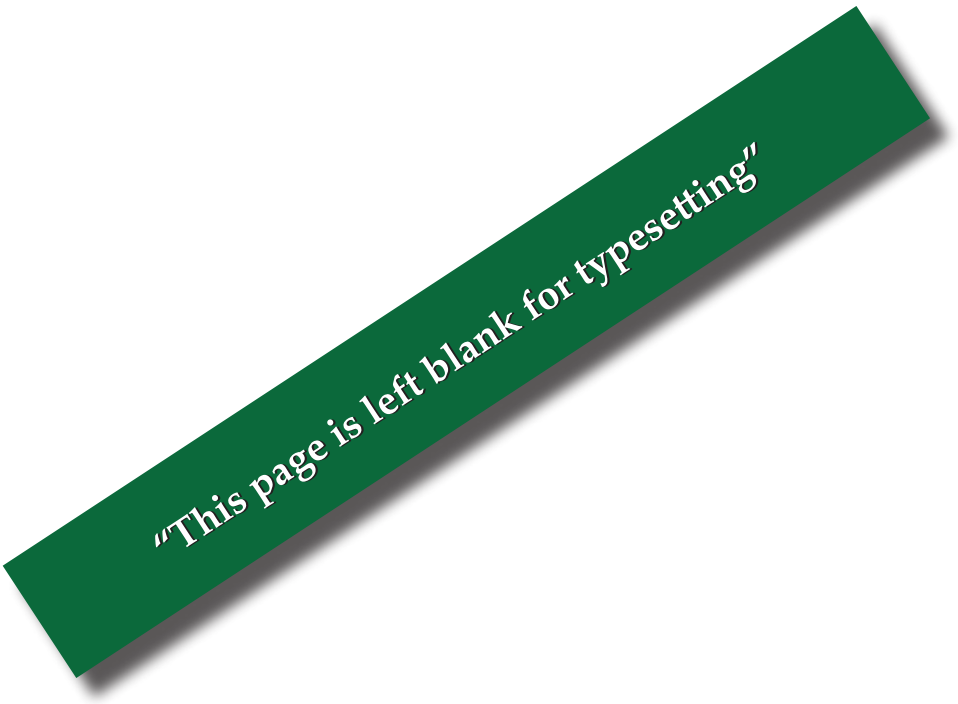
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ORIGINAL ARTICLE

Evaluation of current survival and prognostic factors in multiple myeloma: Staging ISS or R-ISS?

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Abstract

Multiple myeloma (MM) is a complex hematological malignancy, and understanding the factors influencing prognosis and survival is crucial for improving patient outcomes. This study aims to evaluate the factors influencing the prognosis and survival of MM patients by comparing the International Staging System (ISS) with the Revised ISS (R-ISS). MM patients treated and followed up between 2015 and 2023 were retrospectively analyzed. According to ISS staging, 21.4% of patients were categorized as Stage 1, 30% as Stage 2, and 48.6% as Stage 3. Similarly, the R-ISS system revealed 14.3% as Stage 1, while 42.9% were Stage 2, and 42.9% were Stage 3. These findings indicate that the two systems provide differing stage distributions, which could impact prognosis evaluation. Mortality occurred in 58.6% of patients during the follow-up period, highlighting the severity of the disease in later stages. Further analysis revealed that higher levels of red cell distribution width (RDW), phosphorus content, lactate dehydrogenase (LDH), and beta-2 microglobulin levels were significantly associated with mortality, emphasizing their potential as markers of poor prognosis. In particular, ISS Stage II and III, R-ISS Stage III, along with elevated RDW, total protein, phosphorus, and LDH, were identified as independent prognostic factors. These results suggest that while both staging systems offer valuable insights, specific biomarkers play a crucial role in refining prognostic accuracy. In conclusion, while the ISS system appears to provide more meaningful staging information in this cohort compared to R-ISS, integrating additional biomarkers like RDW and LDH could enhance the prediction of patient outcomes.

Keywords: Multiple myeloma, ISS, R-ISS, LDH, RDW

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Introduction

Multiple myeloma (MM) is a complex hematological malignancy characterized by the clonal proliferation of abnormal plasma cells within the bone marrow, leading to a variety of clinical manifestations. It is marked by distinct genetic features, including chromosomal translocations involving oncogenes and mutations in key tumor suppressor genes. These genetic alterations contribute to the pathogenesis of MM by promoting uncontrolled cellular proliferation and survival, which in turn can lead to significant complications such as osteolytic bone lesions, renal impairment, anemia, and hypercalcemia [1]. Globally, MM is diagnosed in approximately 2% of all cancer cases, accounting for 13% of all hematological malignancies [2,3]especially in the US, Australia, and Western Europe. In the US, MM accounts for almost 2% of cancer diagnoses and over 2% of cancer deaths (more than double the global proportion. In Türkiye, the burden of this disease is substantial, with an estimated annual incidence of 7,500 new cases and around 3,000 fatalities attributable to MM each year [4]. The increasing prevalence underscores the need for enhanced awareness, early diagnosis, and the development of effective therapeutic strategies to improve patient outcomes.

The incidence and mortality rates of MM remain high, despite the promising results of the markers presently employed for the diagnosis and follow-up of the disease. Results from randomized clinical trials indicate that the median survival in MM is approximately 6 years [5]. However, predicting survival is challenging and requires consideration of multiple factors. Commonly used biomarkers for assessing survival include evaluations of tumor burden and disease risk classification in patients diagnosed with MM. The development of effective, sensitive, and specific prognostic biomarkers is crucial for detecting the disease in its early stages and combating malignancy more effectively [6].

Studies on prognostic factors in the diagnosis and follow-up of MM have increased in recent years. The *Durie-Salmon* Staging System (DSS), first introduced in 1975, is still used today due to its applicability in diagnosing MM [7]. However, advancements in genetic research have highlighted the role of genetics in the etiology of MM, creating a need for new classifications. It has also been observed that a standardized international system is required for MM staging. Currently, patients are classified into high-risk and low-risk genetic groups based on simple cytogenetic and fluorescence *in situ* hybridization analyses. To address this, the International Staging System (ISS) was developed in 2005 [8]. Although the ISS was widely used at first, it required revision as it did not consistently predict clinical outcomes. This led to the development of the Revised-International Staging System (R-ISS) in 2015, followed by the Second Revision of the International Staging System (R2-ISS) in 2022 [9,10]. Despite these updates, the biomarkers used to determine prognosis in MM follow-up remain unclear and are not always helpful in guiding treatment decisions. As a result, these staging systems are continually updated, while studies investigating the impact of other biomarkers, such as immunological markers, socioeconomic status, and genetic factors, on MM prognosis are ongoing [11-13].

A review of the literature highlights the need for further research to better understand the prognosis of MM, assess the effectiveness of the ISS and R-ISS staging systems, and identify biomarkers that can predict outcomes using routine laboratory tests. In response to these gaps, this study aimed to evaluate the relationship between key factors including demographic characteristics (age and gender), diagnostic groups (immunoglobulin types), and ISS/R-ISS stages and survival in patients diagnosed with MM. By exploring these relationships, we hope to contribute valuable insights that can improve prognostic accuracy and guide more personalized treatment approaches in MM management.

Materials and Methods

Study Population and the Data Collection

This descriptive, cross-sectional study analyzed data from 70 patients aged 18 and older, diagnosed with MM and treated at the Division of Hematology between 2015 and 2023. Patients

who were pregnant or lactating, were excluded from the study. Age, gender, ISS and R-ISS stages, diagnostic group, date of diagnosis, survival time, laboratory findings (complete blood count and biochemistry), and prognosis (with or without mortality) data were recorded and analyzed. In accordance with regulations on processing and protecting personal health data, and the principles set out in the Declaration of Helsinki, all patient identities were anonymized. Myeloma-defining events include the presence of clonal plasma cells exceeding 60% in the bone marrow, a free light chain ratio above 100, and the presence of more than one focal lesion measuring 5 mm or larger on whole-body magnetic resonance imaging. In addition, hypercalcemia, renal failure, anemia, and bone disease serve as key indicators of malignancy. This study included the data from patients diagnosed with MM within the specified date range. Declaration of Helsinki, all identity information of the patients was anonymized, and approval was received for the study from the Medical Ethics Committee of Aydın Adnan Menderes University (2023/230).

IgG, IgA, IgM, ISS and R-ISS System

The patients' immunoglobulin (Ig) levels, including IgG, IgA, and IgM, as well as beta-2 microglobulin (B2M) levels, were measured using a nephelometric system. For quantitative and qualitative assessments, serum immunofixation electrophoresis and protein electrophoresis were employed as standard procedures in the follow-up of all patients. Kappa and lambda light chain levels were determined using electrophoresis. Serum lactate dehydrogenase (LDH) activity and albumin levels were analyzed using the chemiluminescence method and measured spectrophotometrically. The response criteria established by the International Myeloma Working Group served as the basis for evaluating patient responses [14].

Statistical Analysis

Descriptive statistics were presented as numbers (n), percentages (%), medians (interquartile ranges, IQR), means (± standard deviation), and minimum-maximum values. The suitability of the data for normal distribution was assessed using the *Shapiro-Wilk* test. The Chi-square test was applied to identify factors affecting prognosis. Variables found to be significant in binary analyses, as well as those identified in the literature, were included in the model for Cox regression analysis. Additionally, age and variables significant in binary analyses (phosphorus, RDW, and LDH) were categorized into two groups based on the median. Beta-2 microglobulin levels were divided into three groups according to the values used in the ISS and R-ISS systems (3.5-5.5 mg/L). Survival analyses were conducted using *Kaplan-Meier* analysis. The Statistical Package for the Social Sciences (SPSS) version 22 (SPSS Inc., Chicago, IL, USA) was utilized for the analysis, and a *p*-value of less than 0.05 was considered statistically significant.

Results

Data from a total of 70 patients were evaluated, with a mean age of 70.69 ± 10.6 years (minimum: 42, maximum: 87). Among the patients, 52.9% (n=37) were aged 73 or younger, and 41.4% (n=29) were women. The mean follow-up period was 1149.74 ± 781.01 days (minimum: 11, maximum: 2571). According to the ISS staging, 21.4% (n=15) of patients were classified as Stage 1, 30% (n=21) as Stage 2, and 48.6% (n=34) as Stage 3. In terms of the R-ISS staging, 14.3% (n=10) were Stage 1, 42.9% (n=30) were Stage 2, and 42.9% (n=30) were Stage 3. Mortality occurred in 58.6% (n=41) of the patients during the follow-up period (Table 1).

When evaluating factors affecting prognosis, the mortality rate was found to be higher in patients over 73 years of age, in males, and in those with high R-ISS stages; however, these findings were not statistically significant. Similarly, mortality increased significantly with higher ISS stages (Linear trend, Table 2).

In examining laboratory values, RDW, phosphate, LDH, and B2M levels were significantly higher in patients who experienced mortality ($p<0.005$) (Table 3).

According to the results of the *Kaplan-Meier* survival analysis, the median survival time was 1104 days for patients aged ≤ 73 years and 709 days for those aged > 73 years; 1482 days for females and 708 days for males; 961 days for ISS Stage 2 and 600 days for Stage 3; 1449 days

for R-ISS Stage 2 and 583 days for Stage 3; 737 days for IGA diagnosis; and 925 days for IGG diagnosis (Figure 1).

Regarding laboratory results, median survival times were calculated as 634 days for RDW (>15.55), 665 days for phosphate levels (>3.6 mg/dL), 586 days for LDH (>187.5 U/L), and 605 days for B2M (≥5.5 mg/L) (Figure 1). In the Cox regression analysis, ISS Stage II and III, R-ISS Stage III, RDW, total protein, phosphate, and LDH were identified as independent variables influencing prognosis. Specifically, ISS Stage II was associated with a 4.02-fold increase in mortality, Stage III was linked to a 4.6-fold increase, and R-ISS Stage III was associated with a 3.02-fold increase in mortality risk (Table 4).

Discussion

The current study examined the effects of age and gender on mortality, as well as the staging systems used for the prognosis in patients diagnosed with MM. In MM, as age increases, the ISS stage also rises, leading to decreased survival times. A large multicenter study (n=10,549) found that advanced age is a significant risk factor for early mortality [15]. The mean age of mortality in MM was 75 years, with approximately 80% of deaths occurring in individuals over the age of 65 [16]. Similarly, a retrospective study identified a significant relationship between age and mortality rates [17]. In a recently published retrospective cohort study, survival times were reported to decrease significantly with increasing age [18]. In our study, although the mortality rate increased with age, the result was not statistically significant. This may be due to the smaller sample size of our study compared to others.

The literature indicates that MM is more commonly diagnosed in men than in women [19]. However, a single-center retrospective study found no significant difference in survival time between male and female patients diagnosed with MM [20]. Similarly, a retrospective cohort study focused on patients with extramedullary MM, a rare subtype, also reported no significant association between gender and survival outcomes [21]. In our study, while the mortality rate was higher among men, we did not observe a statistically significant difference, aligning with these previous findings.

The ISS, an international staging system that is easy to apply in clinical practice, is cost-effective and has been used for nearly 20 years to predict the course of the disease. Serum albumin and B2M were identified as independent prognostic markers, leading to the creation of three subgroups, with Stage 3 being associated with the worst survival outcomes [22]. A retrospective study also found that early mortality was linked to advanced disease stage [23]. Similarly, a single-center study reported that survival rates

Table 1. The demographic and clinical features of the study group.

Age	**Median (IQR)**	**73 (63-79)**
Gender, n (%)	Female	29 (41.4)
	Male	41 (58.6)
ISS, n (%)	Stage 1	15 (21.4)
	Stage 2	21 (30)
	Stage 3	34 (48.6)
R-ISS, n (%)	Stage 1	10 (14.3)
	Stage 2	30 (42.9)
	Stage 3	30 (42.9)
Ig content, n (%)	IGA kappa	13 (18.6)
	IGA lambda	5 (7.1)
	IGG kappa	23 (32.9)
	IGG lambda	28 (40)
	Kappa light chain	1 (1.4)
Follow-up period (day)	Median (IQR)	943 (468-1870)
Prognosis, n (%)	Alive	29 (41.4)
	Mortality	41 (58.6)

decreased as the ISS stage increased [24]. In our study, ISS stage was found to be an independent risk factor for mortality. Compared to Stage 1, mortality was 4 times higher in Stage 2 and 4.6 times higher in Stage 3. The relatively high proportion of patients at ISS Stage 3 in our cohort

Table 2. Evaluation of factors affecting prognosis in patients diagnosed with MM.

	Factors	***Mortality (-) n (%)***	***Mortality (+) n (%)***	***p****
Age	*≤ 73 years*	17 (45.9)	20 (54.1)	**0.417**
	>73 years	12 (36.4)	21 (63.6)	
Gender	*Female*	14 (48.3)	15 (51.7)	0.328
	Male	15 (36.6)	26 (63.4)	
ISS, n (%)	*Stage 1*	11 (73.3)	4 (26.7)	**0.017****
	Stage 2	7 (33.3)	14 (66.7)	
	Stage 3	11 (32.4)	23 (67.6)	
R-ISS, n (%)	*Stage 1*	6 (60)	4 (40)	0.185
	Stage 2	14 (46.7)	16 (53.3)	
	Stage 3	9 (30)	21 (70)	
IG content	*IGA*	8 (44.4)	10 (55.6)	0.698
	IGG	20 (39.2)	31 (60.8)	

*: Chi-square test.

**: Linear trend

Table 3. Comparison of laboratory findings and prognosis.

Laboratory Parameters	***Mortality (-) (n=29) Mean (SD)***	***Mortality (+) (n=41) Mean (SD)***	****P values Mortality (-) vs Mortality (+)***
Hemoglobin (g/dL)	10.57 (2.21)	9.71 (2.08)	0.074
RBC (x10^6/µL)	3.6 (0.83)	3.33 (0.89)	0.068
WBC (µL)	6436.2 (2157.32)	5497.07 (2126.83)	0.055
MNS (µL)	3831.37 (1776.37)	3157.8 (1585.6)	0.156
MLS (µL)	1694.19 (840.37)	1585.12 (758.16)	0.482
RDW-CV (%)	**14.70 (1.46)**	**16.92 (2.54)**	**<0.001**
Total Protein (g/L)	87.79 (20.96)	79.82 (18.82)	0.109
Albumin (g/L)	35.96 (6.55)	35.85 (7.08)	0.680
Calcium (mg/dL)	9.34 (1.01)	9.82 (1.85)	0.579
Phosphate (mg/dL)	3.44 (0.71)	3.96 (1.04)	0.030
ALP (U/L)	78.17 (34.24)	76.02 (24.92)	0.981
Creatinine (mg/dL)	1.66 (1.86)	1.41 (1.05)	0.531
Uric acid (mg/dL)	6.23 (1.87)	6.7 (2.86)	0.919
Urea (mg/dL)	56.72 (46.8)	52.15 (27.93)	0.612
LDH (U/L)	**184 (56.54)**	**273.9 (170.94)**	**0.002**
B2M (mg/L)	**6 (5.75)**	**10.06 (11.63)**	**0.025**
Sedimentation (mm/h)	87.1 (36.49)	79.85 (44.85)	0.515
CRP (mg/L)	22.64 (46.67)	19.86 (36.75)	0.314
Ferritin (ng/mL)	211.53 (198.73)	382.95 (468.09)	0.109

*: *Mann Whitney U* test. SD: standard deviation.

may explain the significantly higher mortality rate.

The R-ISS was developed by adding two additional prognostic factors to the original ISS staging system for MM. These include genetic risk that is assessed by fluorescence in situ hybridization, and LDH levels [9]. In an international clinical study (n=3,060), five-year survival rates were reported as 82% for R-ISS Stage 1, 62% for Stage 2, and 40% for Stage 3 [25]. Another study found three-year survival rates of 88% for R-ISS Stage 1, 75% for Stage 2, and

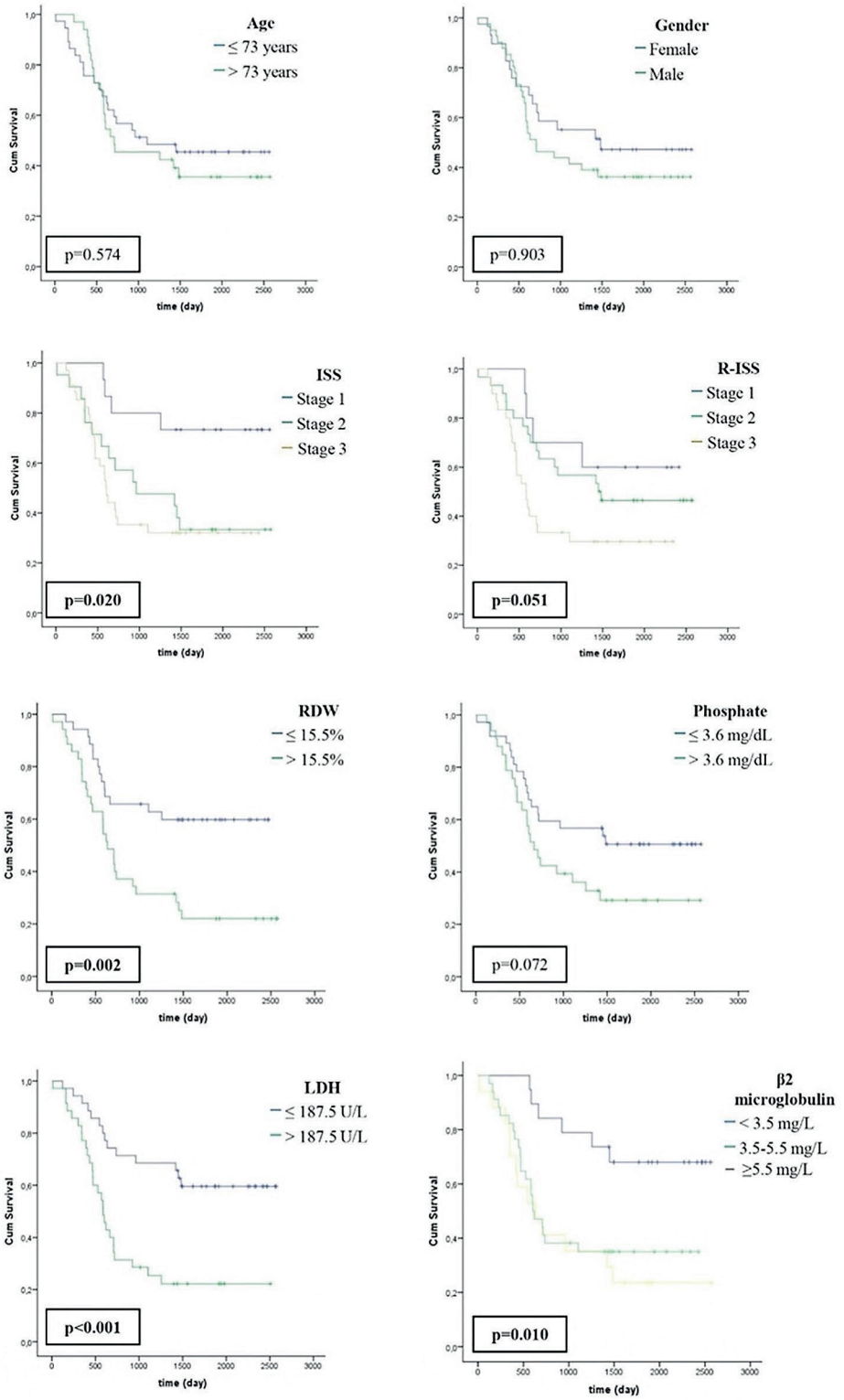

Figure 1. *Kaplan-Meier* survival graphics for different prognostic factors.

56% for Stage 3 [26]. In the present study, these rates were lower, with survival rates of 60%, 47%, and 30%, respectively. In a retrospective cohort study, R-ISS Stage 3 was identified as one of the strongest predictors of early mortality in patients aged 70 and older [27]. Similarly, in a smaller-scale study (n=102), R-ISS was found to be a more useful prognostic tool than ISS for risk stratification in MM patients who were not suitable for transplantation [28]. However, in a study using data from three clinical trials, no significant difference in prognosis was found between the ISS and R-ISS systems for newly diagnosed MM patients [29]. In the current study, while R-ISS did not show a significant difference in prognosis in binary analysis, it became significant in regression analysis, with Stage 3 increasing mortality threefold compared to Stage 1.

It has recently been reported that RDW may serve as an inflammatory biomarker in cardiovascular diseases [30]. However, its significance has rarely been explored in MM patients. In a study conducted in Korea, it was found that patients with higher RDW levels had shorter survival times during the follow-up period [31]. Similarly, a retrospective study showed that RDW levels decreased in patients in complete remission and increased as the disease progressed. Furthermore, the study reported that patients with high RDW values before treatment had shorter survival times [32]. In our study, RDW was also identified as an independent risk factor for mortality. Based on these findings, RDW may be a simple and easily accessible biomarker for both monitoring and predicting prognosis in MM patients. An increased RDW not only has a high negative predictive value for diagnosing various disorders but also provides crucial information regarding short- and long-term prognosis. In our study, phosphate levels, like RDW, were also found to be a significant risk factor in predicting mortality and were higher in patients who did not survive. Kidney and parathyroid diseases, which frequently cause phosphate metabolism disorders, have been reported as complications associated with MM [33,34]. However, the low creatinine levels observed in MM patients who developed mortality complicates the association between renal dysfunction and elevated phosphate levels. Additionally, the lack of a significant difference in calcium levels between groups does not support a clear relationship with parathyroid dysfunction. Therefore, it is hypothesized that a different mechanism may exist between MM pathogenesis and phosphate metabolism.

Lactate dehydrogenase has long been recognized as a critical biomarker in various cancers, and its role in MM prognosis is no exception. In our study, LDH levels were significantly higher in patients who did not survive and were identified as an independent risk factor for prognosis. Similarly, a retrospective study found that elevated LDH levels are a marker of poor prognosis in MM patients [35]. Another study reported that high LDH levels were an independent risk factor for shorter survival times, particularly in elderly MM patients [36]. The results of our study align with these findings in the literature, further confirming the importance of LDH as a prognostic indicator in MM.

Beta-2 microglobulin has long been recognized as an important biomarker in the assessment of disease burden and prognosis in MM [37]. While this protein is produced at a constant rate under normal physiological conditions, elevated serum concentrations are observed in various autoimmune, renal, and hematological diseases. In MM, increased B2M levels have been associated with poor prognosis and treatment resistance [38]. B2M is one of the criteria included in the ISS and R-ISS staging systems, where serum levels above 5.5 mg/L classify the disease as Stage 3. A retrospective study found that patients with high B2M levels had lower overall survival rates [39]. Similarly, another study reported that elevated B2M was a negative prognostic factor, reducing remission rates [40]. In our study, while a significant increase in LDH was detected in patients who developed mortality, B2M lost its significance in multiple analyses and was no longer identified as an independent risk factor.

Conclusion

In conclusion, the current study provides valuable insights into the prognostic factors influencing mortality in patients diagnosed with MM, with a particular focus on age, gender, and various staging systems. Key findings indicate

that ISS and R-ISS are commonly used to predict patient prognosis, with the ISS demonstrating greater effectiveness in assessing mortality risk. As patients age, their ISS stage tends to increase, correlating with decreased survival rates. Gender differences in MM prognosis remain ambiguous, as this study, along with previous research, found no significant difference in survival times between male and female patients, despite higher mortality rates observed in men. The ISS, which incorporates serum albumin and B2M as independent prognostic markers, was associated with increased mortality in advanced stages. The R-ISS was developed to enhance the prognostic capabilities of the ISS by including additional factors such as genetic risk and LDH levels. However, this study reported lower survival rates across R-ISS stages compared to previous findings. Additionally, this study examined RDW and phosphate levels as emerging prognostic markers, both of which were associated with an increased risk of mortality. LDH levels were confirmed as significant prognostic indicators, consistent with existing literature, whereas B2M, despite its established relevance, lost statistical significance in multiple analyses in this study.

The limitations of our study include its single-center design, small sample size, and the lack of evaluation of treatment and other factors that could influence prognosis. However, the strengths of this study lie in its eight-year follow-up period, providing up-to-date data from the Mediterranean region, and the assessment of staging systems whose clinical relevance is still under debate. Additionally, the scarcity of similar studies in literature further underscores the importance of this research.

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Conflict of interest

The authors declare no competing interests.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon a reasonable request.

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ORIGINAL ARTICLE

In elderly with cardiovascular disease over 65 years of age the relationship between frequency of frailty and quality of life

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Abstract

This study aim was designed as an analytical cross-sectional study to assess the prevalence of frailty in patients aged 65 years and older with cardiovascular disease and to investigate its relationship with quality of life. The population consisted of a State Hospital Cardiology patients, and the sample consisted of 255 patients, who were calculated according to the incidence of the event (frequency of frailty) (25%) at the 95% confidence interval. Data were collected face to face by interview method between 25.07.2019-01.04.2020. In this study, frailty was observed in 30.9% of cardiovascular patients aged 65 and older. Frailty is mostly seen in illiterate people, women, single people, those who state that their income does not meet their expenses, and those who live alone, and there is a statistically significant difference between them ($p \leq 0.05$). A statistically significant relationship was found between frailty and factors such as the number of comorbidities, fall history in the past year, frequency of hospitalizations, and the number of medications taken within the last year in patients with cardiovascular disease. This study identified a negative correlation between the total score of the quality of life scale, its sub-dimension scores, and frailty (r=-0.414: p=0.000). Additionally, it was observed that patients with cardiovascular frailty experience a lower quality of life. In our study the frequency of frailty due to sociocultural factors is high in elderly individuals living alone with cardiovascular disease.

Keywords: Cardiovascular disease, elderly, frailty, quality of life

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Introduction

With the rise in life expectancy, the global elderly population, particularly in our country, is growing. This demographic shift brings about new age-related health challenges. Frailty, a key issue among older adults, is characterized by a gradual decline in physical, psychological, and social functioning [1]. Geriatric frailty increases with advancing age. Vulnerability affects approximately 6% to 42 percent of the population over 65 years of age [2-5]. Frailty is linked to multiple morbidities. Vulnerability leads to increased burnout associated with illness. Frailty makes the elderly dependent on basic activities of daily living. Cardiovascular diseases associated with frailty are important causes of morbidity in the aging population. Common risk factors and pathophysiological processes in the elderly increase both the risk of cardiovascular disease and the risk of frailty [6-8]. Frailty is about three times more common in those with cardiovascular disease than in those who are not elderly. There is a bidirectional relationship between cardiovascular disease and frailty [9]. Frailty increases the risk of cardiovascular disease. The risk of death is also higher in cardiovascular patients [10]. In a study, it was determined that cardiovascular disease increased the frailty frequency by 2.7 times (95% CI: 1.5-5.1). [11]. In another study, it was found that the risk of frailty increased by 1.26 times (95% CI: 0.79-2.03) in those with congestive heart failure, 1.47 times (95% CI: 1.25-1.73) in coronary heart patients [12]. In their review article, Singh et al. (2014) highlighted the negative impact of frailty on the prognosis of cardiovascular disease and quality of life. They noted that frailty is often underrecognized in clinical settings and stressed the importance of considering it when planning interventions for high-risk individuals [13]. A study exploring the link between frailty and quality of life in patients with atrial fibrillation found that 53.1% of patients were frail, with 25.9% experiencing moderate frailty, 10.1% having moderate frailty, and 17.1% exhibiting severe frailty. Frailty has been stated that the quality of life is low and arrhythmia is more common in fragile patients [14]. In the study investigating the quality of life and frailty in coronary artery patients, it was emphasized that the quality of life was low in patients who underwent percutaneous coronary intervention and that the expected improvement could not be observed due to frailty [15]. In a meta-analysis study examining quality of life and frailty in the elderly, it was stated that interventions aimed at reducing frailty could improve quality of life [16]. Upon reviewing the literature, it becomes evident that there are limited studies addressing the relationship between quality of life and frailty in patients with conditions such as atrial fibrillation, hypertension, venous thromboembolism, coronary artery disease, myocardial infarction, or those who have undergone percutaneous coronary intervention. In their 2020 study, Sławuta et al. highlighted the scarcity of research exploring the link between frailty and quality of life in patients with chronic diseases [14]. Similarly, Wleklik et al. (2022) emphasized the need for further studies to better understand the connection between frailty and cardiovascular diseases, in order to mitigate or prevent their adverse effects [10].

Materials and Methods

Approval for the study was granted by the Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Nursing (approval number 2019/105, date: 08.07.2019). Written informed consent was provided by all participants. The research was carried out in full compliance with the ethical guidelines outlined in the Declaration of Helsinki.

Research Type

The type of research is cross-sectional and analytical.

Sample

A review of the literature reveals a range of reported frequencies for frailty, with estimates between 20 and 30% [17]. The mean fragility frequency was deemed to be 25%. In this study, the sample size was determined based on the event's incidence rate. A total of 255 elderly patients participated, with a standard deviation of ±0.05 and a 95% confidence interval. According to data provided by the Turkish Statistical Institute (TUIK), individuals over the age of 65 comprise

9.8% of women and 7.7% of men in Turkish society. As a result, 143 of the participants were female, and 112 were male. Inclusion criteria were as follows: patients over 65 years of age, hospitalised in cardiology clinics, not in the terminal period, diagnosed with cardiovascular disease. Exclusion criteria: patients diagnosed with Alzheimer's and dementia according to the International Classification of Diseases (ICD-10) system codes F.00 -F.09 in the patients' electronic medical records.

Sample calculation if the number of individuals in the population is known.

N=Nt2*pq / d2 (N-1) + t2pq

N=2183 (1.962*0.252*0.75/0,05*(2183-1)+1.962*0.75*0.25=255

Data Collection Forms

The data for this study were obtained through face-to-face interviews with patients aged 65 and above. A Patient Information Form was completed with the patients. This included socio-demographic data, information on drugs and diseases that affect the frequency of frailty, created as a result of a literature review. Frailty was determined with the Edmonton Frail Scale. Quality of life was determined with the Quality of Life Scale for the Elderly (CASP-19) (Item 3 out of 41 questions in total) [11,18,19].

Edmonton Frail Scale: The scale, created by Rolfson et al. (2006), was designed to assess frailty in older adults [20]. Its Turkish validity and reliability were established by Aygör et al. (2018) [21], with a Cronbach's alpha coefficient of 0.75. The scale includes 11 items that evaluate various aspects of elderly health, such as cognitive function, general health, functional independence, social support, medication use, nutrition, mood, continence, and overall functional performance. The results are evaluated according to the frailty analysis score. 0-4 points is not fragile, 5-6 points are fragile, 7-8 points is slightly fragile, 9-10 points are moderately fragile, a score of 11 and above is severely fragile. The scale score is between 0 and 17 [21]. In our study, those who scored 7 or higher on the Edmonton Vulnerability Scale were considered fragile. In the study, the Cronbach's alpha (α) value of the scale was found to be 0.74.

Elderly Quality of Life Scale (CASP-19): The scale, developed by Hyde et al. (2003), was designed to assess the quality of life in older adults [22]. Türkoğlu et al. (2014) conducted the Turkish adaptation of the scale, establishing its validity and reliability [19]. The scale consists of 4 sub-dimensions. The Cronbach's alpha value of each sub-dimension was found to be between 0.59 and 0.77. Item-total score correlation coefficients were found to be between r=0.35 and r=0.67. The scale consists of 19 items and 4 sub-dimensions (control, autonomy, pleasure, self-actualization). Scale items are scored between 0-3 points. A higher total score on the scale indicates a better quality of life [22]. In the study, the Cronbach's alpha (α) value of the scale was found to be 0.76.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows version 22. The results were assessed with a 95% confidence interval and a significance level of $p<0.05$. Descriptive statistics, *Mann Whitney U-* test were used. Factors affecting vulnerability were analyzed by logistic regression. Correlation analysis was used to assess the relationship between quality of life and frailty. The strength of the correlation coefficient; very weak (0.00-0.25), weak (0.26-0.49), moderate (0.50-0.69), high (0.70-0.89), very high (0, 90-1.00) was evaluated [23].

Results

Participants was the mean age of 72.34±6.08 years, 55.1% were male, more than half (59%) were elementary school graduates and 71.1% were married. It is seen in Table 1 that nearly three quarters of the participants stated that their income sufficient expense, one-third have at least one chronic disease other than cardiovascular disease, approximately one-third have a history of fall in the last year and 54.3% take between five and eight drugs in per day. There was frailty in 79 (30.9%) of 256 participants.

Those who are not frail have a low mean rank according to age, frailty is highest in literate (52.8%), women (55.7%), single (52.7%), those who state that their income sufficient expense (50.8%), it was determined that it was more common in people living alone (55.9%) and the difference was statistically significant (Tablo 2).

Table 3 shows that there is a significant difference between the number of chronic diseases, the history of falls in the last year, the number of hospitalizations in the last year, the number of drugs per day and the development of frailty. In the without chronic disease, frailty is observed in 15.9% of the elderly, when the number of chronic diseases increases (the frailty rate in 1 chronic disease: 24.7; frailty in the presence of two chronic diseases 43.4%). The frequency of the elderly with frailty increases, 3 and the presence of more chronic diseases did not cause an increase in the frailty rate compared to the elderly with 2 chronic diseases. There is a very weak positive correlation between the number of drugs per day by the elderly and the frailty total score.

Upon comparing the total score of the quality of life scale, its sub-dimensions, and frailty among the participants, it was found that the mean rank values of the frail elderly for the CAPS 19 and its sub-dimensions were significantly lower than those of the non-frail elderly (Table 4).

Table 1. Socio-Demographic characteristics, health status and frailty frequency of the participants (n=256).

Socio-Demographic Characteristics		**Mean**	**Standard Deviation**
	Age	72.34 (min 65 max 101)	6.08
	Number of drugs per day	4.8 (min 1 max 15)	2.77
		n	**%**
Gender	Female	115	44.9
	Male	141	55.1
Educational level	Literate	53	20.7
	Elementary	151	59
	Secondary	18	7
	High School	19	7.4
	University	15	5.9
Marital status	Married	182	71.1
	Single	74	28.9
Income status	Income is sufficient for expense	195	76.2
	Income is not sufficient for expense	61	23.8
Living	With wife	178	69.5
	With family	44	17.2
	Alone	34	13.3
Health Status		**Mean**	**Standard Deviation**
	Body Mass Indeks	27.14	4.48
Medical history	No	44	17.2
	1 chronic disease	93	36.3
	2 chronic diseases	76	29.7
	3 and over chronic diseases	43	16.8
Falls in the last year	No	178	69.5
	Yes	78	30.5
Physical therapy history	No	232	90.6
	Yes	24	9.4
Hospitalization in the last year	No	154	60.2
	1-2 times	66	25.8
	3-4 times	20	7.8
	5 and over times	16	6.3
The frequency of frailty	Not frail	177	69.1
	Frail	79	30.9

A moderate negative correlation was observed between the total score of the quality of life scale and the self-actualization sub-dimension, as well as the total frailty score in the elderly. Additionally, weak negative correlations were found between the frailty total score and the control, autonomy, and pleasure dimensions of the quality of life scale (Table 5).

Table 2. Participants' frailty status based on socio-demographic characteristics.

Socio-Demographic Characteristics			Frailty				
			Not Frail (n=177)		Frail (n=79)		
			Mean Rank		Mean Rank		
			108.95		172.3		
Age		*Mann-Whitney U*	3531				
		p value	**0,000**				
			n	**%**	**n**	**%**	**n**
Gender		Female	51	44.3	64	55.7	115
		Male	126	89.3	15	10.7	141
		Pearson Chisquare	17.804 (df:1)				
		p value	**0,000**				
Educational level		Literate	25	47.2	28	52.8	53
		Elementary	104	68.9	47	31.1	151
		Secondary and over*	48	92,3	4	7.7	52
		Pearson Chisquare	25.076 (df:2)				
		p value	**0,000**				
Marital status		Married	142	78	40	22.2	182
		Single	35	47.3	39	52.7	74
		Pearson Chisquare	23.276 (df:1)				
		p value	**0,000**				
Income status		Income is sufficient for expense	147	75.4	48	24.6	195
		Income is not sufficient for expense	30	49.2	31	50.8	61
		Pearson Chisquare	14.954 (df:1)				
		p value	**0,000**				
Living		With wife	142	79.8	36	20.2	178
		With family	20	45.5	24	54.5	44
		Alone	15	44.1	19	55.9	34
		Pearson Chisquare	30.983 (df:2)				
		p value	**0,000**				

*Since frailty was not determined in those with high school and university, the patients in this group were analyzed by including them in the class of those with secondary and over.
df: degrees of freedom

Table 3. Participants' frailty status based on their health conditions (n=256).

Health Status		Frailty				
		Not Frail (n=177)		**Frail (n=79)**		
		Mean Rank		**Mean Rank**		
		127.21		131.39		
Body Mass Indeks	*Mann-Whitney U*	6763				
	p value	0,676				
		n	**%**	**n**	**%**	**n**
Medical history	No	37	84.1	7	15.9	44
	1 chronic disease	70	75.3	23	24.7	93
	2 chronic diseases	43	56.6	33	43.4	76
	3 and over chronic diseases	27	62.8	16	37.2	43
	Pearson Chisquare	12,679 (df:3)				
	p value	**0,005**				
Falls in the last year	No	138	77.5	40	22.5	178
	Yes	39	50	39	50	78
	Pearson Chisquare	19.262 (df:1)				
	p value	**0,000**				
Physical therapy history	No	160	69	72	31	232
	Yes	17	70.8	7	29.2	24
	Pearson Chisquare	0.036 (df:1)				
	p value	>0,005				
Hospitalization in the last year	0	135	87.7	19	12.3	154
	1-2	35	53	31	47	66
	≥3-4	7	19.4	29	80.6	20+16
	Pearson Chisquare	74.46 (df:2)				
	p value	**0.000**				
Number of drugs per day		Frailty Total Score				
	Pearson Correlation	0.144				
	p value	**0.021**				

Table 4. Variation in Quality-of-Life Scores based on frailty status of participants (n=256).

	Frailty		***Mann-Whitney U***	***p* value**
	Not Frail (n=177)	**Frail (n=79)**		
	Mean rank	Mean rank		
CAPS 19	148.16	84.46	3512.5	**0.000**
CAPS 19 Control	137.53	108.26	5392.5	**0.003**
CAPS 19 Autonomy	145.72	89.92	3943.5	**0.000**
CAPS 19 Self Realization	147.86	85.13	3565.5	**0.000**
CAPS 19 Pleasure	142.5	96.8	4487.5	**0.000**

Table 5. Association between frailty and quality of life in the participants (n=256).

	Frailty	
	***Pearson* Correlation**	
	r value	***p* value**
CAPS 19	-0.414**	0.000
CAPS 19 Control	-0.165**	0.008
CAPS 19 Autonomy	-0.429**	0.000
CAPS 19 Self Realization	-0.520**	0.000
CAPS 19 Pleasure	-0.359**	0.000

**Correlation significance level: 0.01

Discussion

In this study, frailty was observed in 30.9% of cardiovascular patients aged 65 and older. Carneiro et al. (2017) utilized the Edmonton Frailty Scale in their research on the prevalence of frailty among the elderly [2]. They found frailty in 54.4% of cardiovascular patients aged 65 and over. The prevalence of frailty in the study by Carneiro et al. (2017) was higher compared to our findings. This difference is likely due to age-related factors. In our study, the average age of participants was 72.34±6.08, while in Carneiro et al.'s study, the average age was 75±7.6. Additionally, 89 (24.7%) of the 360 participants in the Carneiro et al. study were aged 80 or older, whereas only 12.10% of participants in our study were over 80 years old. In Qayyum et al.'s (2020) study on coronary artery disease patients aged 80 and above, the mean age of frail patients was found to be 84.4±3.4 years, while non-frail patients had a mean age of 82.2±1.8 years [15]. Similarly, Liu et al. (2021) studied hypertensive patients over 60 years of age and reported that frail patients had a mean age of 81.15±8.42 years, while non-frail patients had a mean age of 67.92±6.58 years [24]. The frequency of frailty increases with advancing age in cardiovascular patients [13]. In the study of Düzgün et al. (2021), the fragility score of individuals in the older age group was found to be higher [25]. Based on our findings, both cardiovascular disease and age appear to be linked to physical frailty. In the 12-year cohort study of Tazzeo et al. (2021), elderly people with certain diseases were evaluated at six years and 12 years. The relative risk ratio of frailty was found at six years was 2.25; 95% CI:1.13–4.49 and at years 12 was 4.81; 95% CI:1.59–14.60 in those with cardiovascular disease [26].

According to our findings, the frequency of frailty in women (55.7%) is higher than in men (19.9%). In the study by Carneiro et al. (2017) on frailty prevalence in the elderly, frailty was observed in 48.8% of women and 41.8% of men [2]. In the study by Hiriscau et al. (2022), 76% of frail cardiovascular patients aged 65 and older were women [27]. Comparing our findings with those of other studies, it appears that female gender is a risk factor for frailty. In our study, the prevalence of frailty in women was lower than that reported by Hiriscau et al. (2022), but higher than the findings from Carneiro et al. (2017) [2,27]. Since cardiovascular diseases are known to increase the prevalence of frailty, all participants in our study had cardiovascular conditions, unlike in the study by Carneiro et al. (2017), where not all participants had cardiovascular disease. This may explain the higher frequency of frailty in women in our study. Additionally, in Carneiro et al.'s study, the greater prevalence of frailty among male participants compared to our study may be attributed to differences in age [2]. In their study, 65.2% of individuals over 80 years of age were found to be frail. Similarly, Liu et al. (2021) reported a mean age of 81.15±8.42 years for frail patients, with 60.4% of them being male [24].

In this study, frailty according to education level was found mostly in illiterate people (52.8%). In the study of Hiriscau et al. (2022), the frequency of frailty was found to be 82% in cardiovascular patients over 65 years ogf age with primary education [27]. As the level of education rose,

the prevalence of frailty decreased. In the study by Carneiro et al. (2017), elderly patients with lower educational levels were found to have a higher incidence of frailty [2]. In the study of De Oliveira et al. (2020), it was determined that the education level of fragile patients over 60 years ogf age was low [28]. The results of this study are similar to our study finding. In the study of Liu et al. (2021), frailty was found the most (37%) in hypertensive patients over 65 years ogf age and older with secondary education [24]. Wang et al. (2022) reported in their systematic review that high education level is a risk factor for frailty [29]. Education is a social factor. While some studies suggest that frailty prevalence increases with higher educational levels, the differing results in our study may be attributed to factors such as the number of comorbidities, disease duration, and age. In our study, frailty prevalence was found to rise as the number of accompanying health conditions increased in elderly individuals over 65. Similarly, De Oliveira et al. (2020) identified that comorbidities contribute to the progression of frailty in patients over 65 years of age [28]. As the number of diseases in the elderly population increases, so does the likelihood of frailty [7]. Our findings are consistent with the existing literature.

In our study, the prevalence of frailty was higher among singles (52.7%) compared to married individuals. Hiriscau et al. (2022) reported a frailty prevalence of 65% in single cardiovascular patients aged over 65. Similarly, Lisiak et al. (2016) found that the quality of life was lower in single cardiovascular patients over 65 years of age [27,30].

According to all research findings, it can be thought that the inadequacy of psychological and social support of singles causes a decrease in frailty and quality of life.

Our study found that the prevalence of frailty was higher (55.9%) among individuals living alone. In contrast, Liu et al. (2021) reported a higher frequency of frailty (64.6%) in hypertensive patients aged over 60 who lived with their families [24]. Retirement incomes are lower in our country. The elderly living alone meets their health and basic needs with low income. The elderly who participated in our study are thought to be more vulnerable to physical, mental and social effects due to low economic status and loneliness. It is thought that the frequency of frailty is higher than those who live with their families. The low frequency of frailty can also be explained by cultural factors. It is thought that interaction increases in those living with their families in our society and contributes positively to the healing processes. Socially and culturally, the elderly is supported in economic and social areas within the family. 86.7% of the participants in our study live with their families. In their study, Softa et al. (2016) determined that the higher the perceived social support of the elderly, the better their healthy lifestyle behaviors [31].

This study found a significant association between a history of falls in the past year and the development of frailty. In the research by Hiriscau et al. (2022), frailty was observed in 63% of cardiovascular patients over 65 who had experienced a fall in the previous year [27]. Frailty, including symptoms such as slowness, weakness, inactivity, and exhaustion, is known to contribute to an increased risk of falls in older adults [13].

The total score, all subscale scores, and mean rank values of the CAPS 19 quality of life scale were significantly lower in frail patients with cardiovascular disease than in their non-frail peers. In the study of Hiriscau et al. (2022), statistically significant differences between the EQ-5D-5L quality of life scale subgroups in elderly cardiovascular patients were found to be associated with mobility, self-care, and usual activities [27].

This study identified a negative correlation between the total score of the quality of life scale, its sub-dimension scores, and frailty. In the study of Lisiak et al. (2016), The MacNew quality of life scale and Tilburg Frailty Indicator were used in cardiovascular patients over 65 years of age. A negative correlation was found between patients' quality of life and the frequency of frailty [30]. In the study of Liu et al. (2021), the SF-36 quality of life scale and unintentional weight loss, self-recognized fatigue, weakness, slowness

and lack of activity, and frailty were evaluated in hypertensive patients over 60 years of age. A negative correlation was observed between the patients' quality of life and the prevalence of frailty [24]. In the study by Slawuta et al. (2020), the HRQoL scale and the Edmonton Frailty Scale were used to assess patients over 60 with atrial fibrillation. The analysis of total scores revealed that frail patients had significantly higher scale scores, indicating the impact of arrhythmia on quality of life [14]. Uchmanowicz et al. (2019) employed the WHOQOL-BREF quality of life scale and the Tilburg Frailty Indicator in cardiovascular patients aged over 65. They found a negative correlation between quality of life and frailty frequency [32]. Similarly, in the study by Qayyum et al. (2020), coronary artery patients aged over 80 were assessed with the SF-12 quality of life scale and the Edmonton Frailty Scale, and it was found that as frailty increased, quality of life decreased [15]. De Oliveira et al. (2020) also reported a decline in quality of life in frail patients over 60 years of age [28]. These findings align with the results of our study. Across the literature, quality of life and frailty frequency have been assessed using various scales in elderly cardiovascular patients, with frailty consistently shown to have a statistically negative effect on quality of life.

Study Limitations

As the study was conducted at a single center and relied on self-reported data collection tools, the findings may not be generalizable to the broader population.

Conclusion

This study explored the association between frailty and quality of life in older adults with cardiovascular disease. It was found that sociodemographic factors, particularly social support and economic status, have a significant impact on the frailty levels of elderly individuals. The rise in chronic conditions with age, along with their link to various geriatric syndromes, represents a critical factor to consider in the health management of older adults. The frequency of frailty and related sociodemographic variables can serve as useful indicators for evaluating the health status of elderly individuals and improving their quality of life. Increasing access to healthcare services for older adults, strengthening social support systems, and managing chronic diseases require further research and intervention. Such measures can improve the overall health of the elderly population and contribute to reducing the negative outcomes associated with frailty.

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Conflict of interest

The authors report no conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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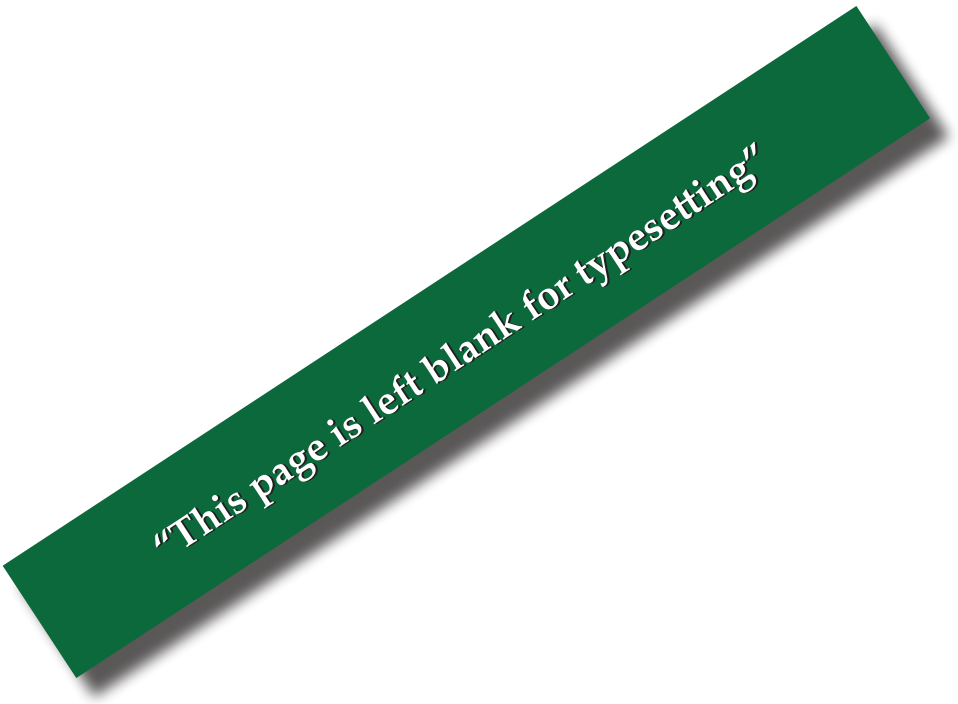
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ORIGINAL ARTICLE

An evaluation of the wastes and obstacles within the context of lean management in emergency services

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Abstract

The objective of this study is to evaluate the types of waste within the context of lean management practices in emergency departments and to provide recommendations for addressing the challenges associated with their implementation. The vision is to enhance the effectiveness of performance improvement processes and to improve patient satisfaction. The opinions of eight experts in the field were collected and analysed using fuzzy AHP. The study followed the STROBE checklist to ensure comprehensive reporting to study. The analysis revealed that defects (29%) are the most common type of waste in emergency departments, with a significant impact on efficiency and patient safety. This is followed by extra handling (15%) and waiting time (13%). Addressing these issues, along with other types of waste such as wasted talent, movement, transportation, inventory, and overproduction, is critical to improving overall operational performance. The overcoming of integration challenges necessitates the implementation of a multifaceted strategy, which should encompass the commitment of leadership, the engagement of staff, multidisciplinary collaboration, process streamlining, the ability to navigate resistance to change, and the establishment of a culture of continuous improvement. Additionally, processes must be redesigned with the objective of enhancing their efficiency, and this endeavour must be supported by continuous training and regular monitoring of progress.

Keywords: Hospital emergency services, decision making, lean six sigma

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Introduction

The complex and multidisciplinary nature of healthcare services, their non-postponability and the necessity to be provided 24/7, the financial pressures faced by healthcare organizations and the goals to be achieved have made it necessary to make changes in existing management mechanisms [1,2]. Especially in units working under high demand such as emergency services, the increasing population, the spread of chronic diseases and the increase in the number of emergencies increase the workload day by day. This workload may lead to an increase in medical errors, decrease in service quality, and patient dissatisfaction. In order to reduce such negativities in health services, some practices regulate patient flow such as triage systems. While the triage system aims to meet more patient demand with limited resources, it also brings new problems such as long waiting times. This situation causes dissatisfaction and resistance to the system among patients and their relatives [3]. In this regard, the importance of lean management approach in healthcare services has increased as it provides a solution to operational inefficiencies, resistance to change, and process bottlenecks identified in emergency departments. Lean management is defined as a management system that aims to produce with fewer resources, in a shorter time, at low cost, and error-free production. As stated by Lopez et al. (2013), lean thinking is defined as a system that will best meet customer demand, minimize waste, and use production factors in the most efficient way [4].

Lean management implementations are used in the field of healthcare services, especially to improve emergency services, intensive care, and operating theatre processes, reduce waiting times, and improve service quality [5]. These practices are based on value, value flow, continuous flow, and excellence, the basic principles of lean thinking in hospitals [6]. This approach, called Lean Healthcare, has goals such as reorganizing patient flows, producing new care and management indicators in healthcare services, and improving service processes [7].

Lean management in healthcare aims not only to solve big issues but also to solve hundreds of small problems that hospitals face every day. Solving these small issues can lead to important results such as preventing delays in processes, ensuring patient safety, enabling healthcare organizations to grow and generate more revenue, and reducing costs [8]. Lean management also promotes operational changes that are necessary to make the delivery of healthcare services more efficient. In this process, identifying and eliminating waste is one of the most important goals of lean techniques [9].

Lean management is critical to minimizing waste in healthcare, improving service quality and ensuring patient satisfaction. Lean management is seen as an effective tool to optimize patient flow, reduce waiting times, and improve service quality, especially in emergency services. In this context, the design and management of healthcare organizations is considered as a complex multivariate problem where medical, technical, and social factors are considered together [10]. To overcome this complexity, lean philosophy and tools have been adopted as a solution in healthcare management [9].

Types of waste in lean management concept, examples and difficulties in implementation

In addition to the 7 types of waste defined by Toyota within the scope of the lean management concept, Liker (2014) defined underutilization of human potential and creativity as the eighth type of waste [11,12]. Explanations of waste types and examples specific to hospitals are shown in Table 1.

Although the advantages of integrating lean management and which wastes can be avoided are clear, some difficulties in implementation have been experienced and published in research. As a matter of fact, in some studies, many barriers such as the need to create a multidisciplinary team, and lack of senior management and leadership support, make it difficult to implement lean management in emergency services. These obstacles make it difficult to integrate lean principles into the organization and increase the training requirements of the staff [13-17]. However, operational factors such as difficulties in process redesign, health safety

concerns, management issues, and management of high patient flow further complicate the adoption of lean management in emergency departments [18]. These processes create the need for cost analysis and require rapid and accurate clinical assessments for effective management of emergencies, especially when dealing with critical cases such as traumatic injuries [19].

Other barriers to lean management in emergency departments include waiting times, procedural uncertainty, and resistance to change [13,15,17,20-22]. In addition, problems such as increasing patient demand and overcrowding in emergency services directly affect the quality of healthcare services, making it difficult to sustain improvements [15,22,23]. As stated above, the barriers to integrating lean management in emergency health services are shown in Table 2.

The study aims to evaluate the types of waste within the context of lean management practices in emergency departments and then uncover importance of challenges associated to lean management. By this way making performance improvement processes in emergency services more effective and increase patient satisfaction. In distinguishing itself from previous studies the

Table 1. Waste types in lean manufacturing and samples from healthcare.

Kod	Waste type	Explanation	Samples
OVP	Overproduction	The production of quantities exceeding the required levels is a common phenomenon.	Unnecessary diagnostic (tests, tests, *etc.*) procedures
INV	Inventory	Costs such as transport and storage by keeping excess stock	End of life of medicines and medical consumables, increase in depreciation of other consumables
EXP	Extra processing	Carrying out non-value-creating works and transactions	Use of patient forms not included in the evidence processing process, need for re-examination
MOT	Motion	Actions of staff that do not add value to the process within the organization	The necessity for staff to visit different areas or units as a result of architectural or legal regulations, movements to collect tools, materials, *etc*.
TRA	Transportation	Transport of the product in unnecessary places within the system	Long distances between patient registration, laboratory and data processing units
UNT	Unused talent	Lack of decision support systems that enable career development of the personnel and take their ideas into consideration	Waiting for the diagnostic results to start the patient's treatment
WAT	Waiting	The prolongation of the time in the transactions in the process keeps the subsequent transactions waiting	Waiting of patients due to delays in processes such as registration procedures, hospitalisation procedures, etc. in emergency services
DEF	Defects	In case of inaccuracies in processes and controls, the time spent for the related errors (detection and correction, *etc*.)	Injecting the wrong dose of medication to the patient or patients, giving the wrong medication to the wrong patient, wrong procedure, *etc*.

References: [8,11,12]

study doesn't merely entail the identification of wastes in the department; it's also a guide for decision makers on how to create customized solutions for these barriers related to their importance evaluated by experts from field.

Materials and Methods

The study design and reporting were guided by STROBE checklist, ensuring to key standards. Each checklist item was addressed to enhance the rigor and transparency of study.

Ethical Approval

Ethical approval for this study was granted by the İstanbul Medipol University Ethics Committee for Non-Interventional Clinical Studies (reference number E-10840098-202.3.02-6056, dated 26.09.2024).

Participants

This cross-sectional study was conducted between 29.09.2024-03.10.2024. The study involved an analysis of the evaluations of eight participants with at least ten years of experience

Table 2. The barriers to the integration of lean management in emergency departments.

Barriers	References
Multidisciplinary team formation	[13,14]
Lack of top management/leadership support	[13,15-17,24]
The need for process redesign	[15,18]
Health safety concerns	[18]
Governance issues	[13,18,20]
Intensive patient flow	[18,22,23]
Waiting times	[13,20-22]
Procedural uncertainties	[15,21]
Resistance to change	[15-17,21]
Lack of staff and/or irresponsible duties	[25]

Table 3. Decision makers' details.

Decision makers	Profession	Education	Position	Experience
DM1	Health Management	PhD	Prof. /University	15 years
DM2	Health Management	PhD	Assoc. Prof. /University	10 years
DM3	Health Management	PhD	Asst. Prof. /University	8 years
DM4	Manag. and Organisation	PhD	Prof. /University	11 years
DM5	Hospital Administration	Master's Degree	Administrator/Hospital	13 years
DM6	Hospital Administration	Master's Degree	Administrator/Hospital	18 years
DM7	Emergency Service	Bachelor	Nurse/Hospital	20 years
DM8	Emergency Service	Bachelor	Nurse/Hospital	20 years

in health management, hospital administration, and emergency service provision. Further details about the participants are presented in Table 3.

Fuzzy-AHP

The Analytic Hierarchy Process (AHP) method was employed for the assessment and analysis of participant views. In situations characterized by complexity and uncertainty, AHP provides a structured approach to the prioritization of options and the formulation of informed decisions. By the AHP method, a matrix is generated through the pairwise comparison of each alternative criterion on a scale of 1 to 9, in alignment with the expert opinions. In this comparison, 1 represents equal importance, and 9 represents the highest importance [26]. AHP is frequently an effective instrument for resolving the ambiguity of human judgment, particularly when decision-makers are required to assign exact numerical values to their preferences. However, AHP also has some disadvantages, as outlined [27]. For instance, the ordering of AHP outcomes is not exact due to the subjective assessment of decision-makers. To address this issue, numerous researchers have employed the Fuzzy AHP approach, which integrates fuzzy theory and the AHP [28,29].

Fuzzy AHP addresses this issue by enabling decision-makers to articulate their preferences through the use of linguistic terms, which are subsequently transformed into fuzzy numbers, typically triangular or trapezoidal, to reflect the inherent ambiguity in their judgments [30,31]. In other words, decision-makers are initially requested to provide linguistic terms and pairwise comparisons on a scale of 1–9. Subsequently, the pairwise comparisons provided by the decision makers are transformed into triangular fuzzy numbers, as illustrated in Table 4.

The application of fuzzy AHP usually involves several stages. These stages are completed by the following process [30-34];

1. A hierarchical structure is established, whereby the decision problem is decomposed into a set of criteria and sub-criteria.

2. Construction of Pairwise Comparison Matrices with Fuzzy sets.

3. Normalization of Fuzzy Pairwise Comparison Matrices

4. Calculation of Fuzzy Weights (With fuzzy sets, fuzzy priority weights are calculated for each criterion from pairwise comparison matrices.)

5. Defuzzification (Fuzzy numbers are converted into crisp scores for easy comparison and decision-making.)

6. Final weight calculation (The final ranking of alternatives is made.)

7. Consistency check (Verify the consistency of pairwise comparisons by the consistency ratio)

Results

By employing pairwise comparison matrices, the necessary information to use the Fuzzy AHP method was obtained. For example, overproduction (OVP) and transportation

Table 4. Triangular fuzzy sets and their reciprocal forms.

Linguistic term	Relative importance	Triangular fuzzy set	Triangular fuzzy set
Equal (E)	1	(1, 1, 1)	1,1,1
Moderate (M)	3	(2, 3, 4)	1/4,1/3,1/2
Strong (S)	5	(4, 5, 6)	1/6,1/5,1/4
Very Strong (VS)	7	(6, 7, 8)	1/8,1/7,1/6
Extremely Strong (ES)	9	(9, 9, 9)	1/9,1/9,1/9
Intermediate Values (IV)	2, 4, 6, 8	(1, 2, 3), (3, 4, 5), (5, 6, 7), (7, 8, 9)	(1/3, 1/2, 1), (1/5, 1/4, 1/3), (1/7, 1/6, 1/5), (1/9, 1/8, 1/7)

(TRA) were compared using the question *'How critical/important is "overproduction" compared to "transportation" for the integration of lean management in the delivery of emergency health services?'*. If the answer is linguistic 'Extremely strong', the corresponding cell in the triangular fuzzy scale matrices will have '9,9,9'. An example of the comparative evaluation of waste types is shown in Table 5.

As a result of the analysis, the CR (consistency ratio) value expressing the reliability of the AHS technique was calculated using the integrated matrix and found to be 0.082. This value is expected to be less than 0.10 [35]. It means that the obtained result indicates that the study is quite reliable.

After collecting the data through pairwise comparison matrices, the relevant matrices were transformed into triangular fuzzy numbers specified in Table 4. The integrated matrix was constructed using the geometric means of the evaluations of each expert (Table 6).

The fuzzy priority weights for each criterion and alternative were calculated using fuzzy arithmetic, based on the pairwise comparison matrices. The fuzzy weights were then aggregated to derive the fuzzy priority values for each alternative. The centroid method was employed for defuzzification, whereby the fuzzy numbers were converted into crisp scores, thus facilitating comparison and decision-making. The final weights are listed in Table 7.

Tablo 5. An example of a pairwise comparison matrix of waste types.

	OVP	**INV**	**EXP**	**MOT**	**TRA**	**UNT**	**WAT**	**DEF**
OVP	1	1/ES	1/ES	S	1/S	1/S	ES	E
INV		1	1/VS	1/ES	E	1/MS	VS	E
EXP			1	VS	E	MS	ES	E
MOT				1	E	ES	E	1/ES
TRA					1	ES	ES	1/ES
UNT						1	1/VS	1/VS
WAT							1	1/ES
DEF								1

Table 6. The integrated matrix.

	OVP	**INV**	**EXP**	**MOT**	**TRA**	**UNT**	**WAT**	**DEF**
OVP	(1.00, 1.00, 1.00)	(0.31, 0.37, 0.45)	(0.36, 0.41, 0.46)	(0.87, 1.08, 1.30)	(0.43, 0.52, 0.63)	(0.30, 0.36, 0.42)	(0.48, 0.60, 0.73)	(0.22, 0.24, 0.27)
INV	(3.22, 2.70, 2.25)	(1.00, 1.00, 1.00)	(0.30, 0.35, 0.41)	(0.95, 1.17, 1.39)	(0.66, 0.78, 0.90)	(0.39, 0.47, 0.59)	(0.23, 0.27, 0.33)	(0.22, 0.24, 0.26)
EXP	(2.81, 2.46, 2.17)	(3.29, 2.88, 2.45)	(1.00, 1.00, 1.00)	(1.59, 1.85, 2.10)	(1.15, 1.29, 1.44)	(0.87, 1.04, 1.21)	(0.95, 1.15, 1.36)	(0.59, 0.65, 0.73)
MOT	(1.15, 0.93, 0.77)	(1.05, 0.85, 0.72)	(0.63, 0.54, 0.48)	(1.00, 1.00, 1.00)	(2.14, 2.35, 2.54)	(1.59, 1.97, 2.33)	(0.54, 0.66, 0.79)	(0.25, 0.29, 0.35)
TRA	(2.33, 1.91, 1.59)	(1.51, 1.29, 1.11)	(0.87, 0.78, 0.70)	(0.47, 0.42, 0.39)	(1.00, 1.00, 1.00)	(2.52, 2.79, 3.08)	(0.64, 0.74, 0.87)	(0.14, 0.16, 0.18)
UNT	(3.29, 2.79, 2.36)	(2.59, 2.14, 1.71)	(1.15, 0.96, 0.82)	(0.63, 0.51, 0.43)	(0.40, 0.36, 0.32)	(1.00, 1.00, 1.00)	(0.96, 1.12, 1.32)	(0.50, 0.60, 0.71)
WAT	(2.07, 1.68, 1.36)	(4.27, 3.67, 3.06)	(1.05, 0.87, 0.73)	(1.86, 1.53, 1.27)	(1.57, 1.36, 1.15)	(1.04, 0.89, 0.76)	(1.00, 1.00, 1.00)	(0.32, 0.37, 0.44)
DEF	(4.49, 4.08, 3.64)	(4.56, 4.21, 3.83)	(1.70, 1.53, 1.36)	(3.97, 3.44, 2.85)	(7.14, 6.36, 5.50)	(2.00, 1.68, 1.41)	(3.11, 2.67, 2.28)	(1.00, 1.00, 1.00)

Table 7. The final weights.

Code	**Waste type**	**Weight**	**Rank**
OVP	Overproduction	0,056144	8
INV	Inventory	0,069968	7
EXP	Extra processing	0,151494	2
MOT	Motion	0,097720	5
TRA	Transportation	0,093644	6
UNT	Unused talent	0,105825	4
WAT	Waiting	0,130536	3
DEF	Defects	0,294670	1

As revealed by the analysis, defects (DEF) represent the most prevalent type of waste encountered in emergency departments, accounting for 29% of the total waste generated in such settings. This finding indicates that deficiencies in quality represent a critical factor impeding the efficiency of processes within emergency departments. Defective procedures and errors have been demonstrated to have a detrimental effect on patient safety and service quality, underscoring the necessity for enhancements in this domain.

Furthermore, the category of extra processing (EXP) waste represents 15% of the total waste, ranking as the second most crucial type. This indicates that superfluous steps or an excessively heavy workload in the processes are impeding the effective utilization of resources, thereby necessitating a process of streamlining. The third most significant type of waste is waiting time (WAT), which accounted for 13% of the total waste. This result underscores the fact that delays in patient flow and operational bottlenecks are major sources of waste.

Other notable waste types, in descending order, are unused talent (UNT) (11%), motion (MOT) (10%), Transportation (TRA) (9%), inventory (INV) (7%), and finally, OVP (5%). These results demonstrate that while each type of waste is critical in the operational processes, some types are more significant than others in terms of prioritization for improvement.

This ranking provides valuable insight into which areas should be prioritized for improvement in emergency department operations. Particularly, addressing defects and errors has the potential to significantly enhance emergency department performance, while optimizing other waste types will further increase operational efficiency.

Discussion

The integration of lean management in emergency departments presents a complex challenge, particularly considering the diverse forms of waste identified through expert assessment. Here, study aims investigate wastes and obstacles for lean management. Then evaluate them for implementation on emergency department. The relative weights assigned to the various types of waste serve to identify critical areas for improvement, with defects and errors being the most significant, followed by excessive handling and waiting times. This emphasizes the necessity for targeted interventions that address the underlying causes of wastage, which can impede the efficiency and effectiveness of emergency services. Furthermore, the integration of lean management presents additional complexities, including the challenges of multidisciplinary collaboration, the need for leadership, and the necessity of process redesign.

Defects have the potential to result in considerable delays and the misallocation of resources within emergency departments. The presence of defects has been demonstrated to affect patient outcomes, as well as to result in increased operational costs and lower staff morale. The principles of lean management place a strong emphasis on the necessity of maintaining quality at each stage of the process and advocate for the pursuit of continuous improvement and the reduction of defects. However, this integration process is often met with resistance, particularly in environments characterized by high stress and rapidly changing conditions, such as those encountered in emergency services [36,37]. It is imperative that a robust leadership framework is established which promotes a culture of quality and accountability. This will ensure that all team members are aligned with lean goals [37,38]. Indeed, with the backing of senior management and efficacious leadership strategies pertaining to this category of waste, it is feasible to surmount the errors identified as the most significant type of waste [13,15-17,24].

The prevalence of excessive procedures and prolonged waiting times is closely associated with the inefficiencies that are pervasive within emergency departments. The lean philosophy advocates the implementation of processes that aim to minimize unnecessary steps and optimize patient flow. However, the integration of lean practices is often impeded by procedural ambiguities and governance issues that can create confusion and impede decision-making [39,40]. For instance, the absence of transparent protocols may result in over-processing as staff navigate ambiguous processes, which could

ultimately lead to prolonged waiting times for patients. In order to address these challenges, it is necessary to adopt a comprehensive approach that encompasses the redesign of processes and the establishment of transparent governance structures. This will facilitate effective communication and coordination between multidisciplinary teams [40,41].

It is essential to acknowledge and utilize the diverse skills and expertise of team members to optimize patient care and operational efficiency. The tenets of lean management place considerable emphasis on the necessity of engaging all personnel in the process of improvement. However, instances of resistance to change frequently emerge when employees perceive a lack of appreciation for their abilities or a disregard for their input [42,43]. Such resistance can be further compounded by concerns pertaining to health and safety, particularly in high-risk environments such as emergency departments, where the ramifications of errors can be grave. It is of the utmost importance to surmount these obstacles and guarantee that all members of the team are empowered to contribute to lean initiatives [42,43]. It is similarly possible to circumvent this type of wastage, particularly through the implementation of effective leadership processes.

The inefficient movement of people and materials serves to compound the inefficiencies that are endemic to emergency departments. The objective of lean management is to eliminate these movements through process optimization and layout redesign. However, implementing such changes can face significant challenges. The necessity for effective patient flow management frequently results in a reactive rather than a proactive approach to process improvement, thereby creating a cyclical pattern of inefficiency that is challenging to break [44,45]. Furthermore, the implementation of lean principles necessitates a paradigm shift in the mindset of the staff, who may be accustomed to traditional workflows that prioritize speed over efficiency. Such a cultural shift necessitates robust leadership and continuous training to guarantee that all team members comprehend and adopt lean methodologies [42,45].

While less heavily weighted in the assessment, excess inventory and overproduction nonetheless represent critical areas for improvement. The lean philosophy advocates the implementation of just-in-time inventory management practices with the objective of reducing waste and improving responsiveness to patient needs. However, the complexity of emergency department operations, characterized by fluctuating demand and unpredictable patient flow, can present challenges to the effective implementation of these principles [46,47]. The challenge is to achieve a balance between the need for adequate resources and the imperative to minimize waste. This requires careful planning and coordination among the various stakeholders involved [48,49].

Conclusion

In conclusion, the integration of lean management in emergency departments is beset with challenges arising from both operational inefficiencies and resistance. An assessment of the types of waste reveals critical areas for intervention and highlights the necessity for a comprehensive approach that addresses leadership, process redesign, and team dynamics. The integration of lean management principles into emergency departments represents a crucial endeavour, to enhance operational efficiency and improving patient care. An evaluation of the types of waste, as identified through expert judgment, indicates that defects and errors represent the most significant area of concern, followed by excessive handling and waiting times.

By cultivating a culture of continuous improvement and engaging all staff in the lean journey, emergency departments can enhance their operational efficiency, improve patient outcomes, and, ultimately, establish a more sustainable healthcare environment. The integration of lean management presents several challenges, including the formation of multidisciplinary teams, the lack of leadership, the redesign of processes, and resistance to change. These factors serve to illustrate the complexity of implementing these principles in high-risk settings. The overcoming of these integration challenges necessitates the implementation of a

multifaceted strategy, which should encompass the commitment of leadership, the engagement of staff, and the establishment of a culture of continuous improvement.

This study presents a discussion of the critical strategies for the successful integration of lean management practices in emergency departments. The success of lean management is contingent upon several factors, including leadership support, multidisciplinary collaboration, process streamlining, and the ability to navigate resistance to change. Additionally, exploring the role of leadership in driving lean initiatives and fostering cross-disciplinary collaborations may be crucial for successful implementation. The fundamentals of these processes are the reinforcement of senior management's commitment to lean principles and the promotion of effective collaboration among employees. Furthermore, processes must be redesigned with the objective of enhancing their efficiency, and this endeavour must be supported by continuous training and regular monitoring of progress. The integration of lean management into a culture of health, safety, and quality will make a significant contribution to the improvement of patient outcomes and the enhancement of operational efficiency.

Future studies further explore the underlying reasons for resistance to lean management principles and figure out pathways to overcome barriers. Authors could also focus on evaluating the long-term sustainability of lean practices in emergency departments and the use of artificial intelligence tools for both creating data and managing them. Also, examining the influences of lean management on patient-centred outcomes would provide novel perspectives.

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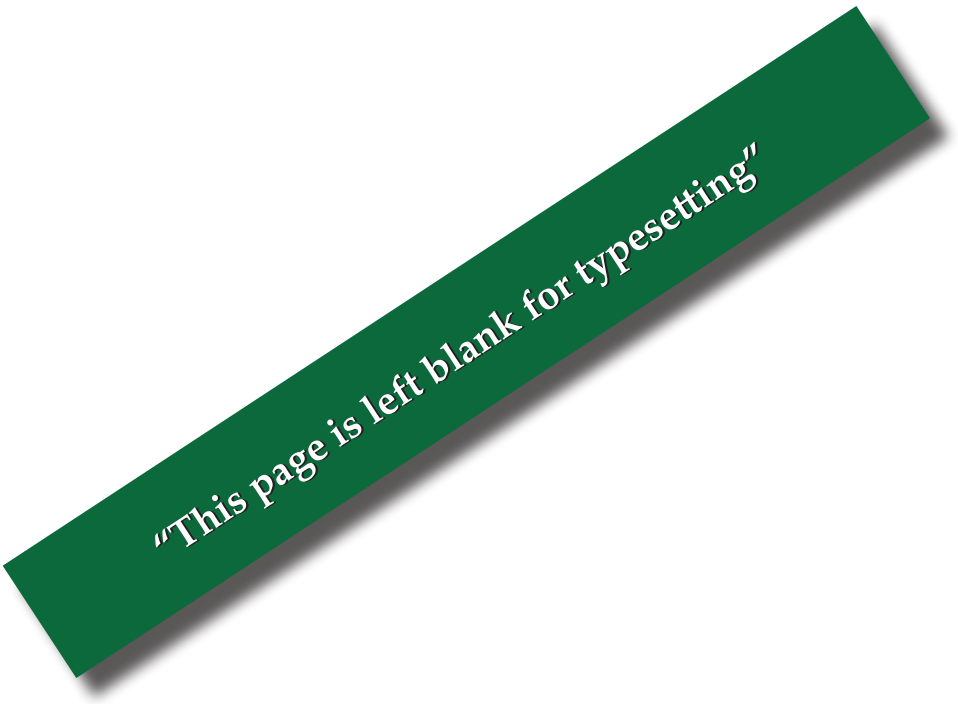
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ORIGINAL ARTICLE

The effect of blood parameters measured in the emergency department on 30-day mortality in patients with proximal femur fractures: A retrospective analysis

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Abstract

Proximal femur fractures (PFF) are a common and significant health problem in the elderly population, often leading to morbidity and mortality. This study aims to investigate the association between hematological and biochemical parameters measured at admission and 30-day mortality by retrospectively evaluating patients diagnosed with PFF in the emergency department. This retrospective study includes 344 patients over the age of 65 who admitted to the Emergency Medicine Department of Afyonkarahisar Health Science University Faculty of Medicine Hospital and were diagnosed with PFF between January 1st, 2018, and July 1st, 2023. The patients' demographic characteristics, PFF-related features, and their hematological and biochemical parameters at presentation, were recorded. Specific parameters were proportionally analyzed in accordance with relevant literature. The relationship between these findings and 30-day mortality was evaluated. Of the included patients, 59.6% were female, with a mean age of 81.88 ± 7.76 years. The 30-day mortality rate was 7%. A significant difference was observed in the mortality group regarding ICU admission history, length of hospital stays, glucose/potassium ratio, WBC, neutrophil, hemoglobin, and RDW levels. According to ROC analysis, the AUC for hemoglobin was 0.641 (95% CI: 0.589–0.690), with a cutoff value of <12.8, yielding a sensitivity of 87.5% and specificity of 36.0% (p=0.01). For RDW, the AUC was 0.721 (95% CI: 0.672–0.767), with a cutoff value of >16.2, resulting in a sensitivity of 54.2% and specificity of 86.7% (p=0.001). Hemoglobin, red cell distribution width, and glucose/potassium ratio levels in the emergency department are associated with 30-day mortality in patients diagnosed with PFF. Evaluating these parameters in clinical practice may aid in the early identification of high-risk patients and facilitate the planning of appropriate treatment strategies. Future research should validate these findings through larger-scale studies.

Keywords Proximal femur fracture, glucose/potassium ratio, hemoglobin, RDW, 30-day mortality

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Introduction

Proximal femur fractures (PFF) represent a significant health concern, particularly prevalent in the elderly population, and are a major cause of morbidity and mortality. These fractures typically result from high-energy trauma in younger individuals, while in older adults, they are primarily associated with low-energy trauma [1]. Osteoporosis is a leading cause of hip fractures in the elderly, with approximately 70% of these fractures occurring in women [2]. Around 18% of women and 6% of men are diagnosed with a hip fracture at some point in their lives [3]. Globally, the mortality rate associated with hip fractures is approximately 7% [4]. According to estimates by the World Health Organization, the elderly population is projected to reach 1.2 billion by 2025 and 2 billion by 2050 [5]. This demographic shift indicates that PFFs will become an increasingly critical public health issue.

Emergency departments serve as crucial points for the initial diagnosis and assessment of hip fractures. Rapid and accurate diagnosis is essential for effective treatment and patient comfort [6]. Surgical intervention is the primary approach to managing these fractures, encompassing reduction, fixation, and arthroplasty [7]. Prolonged hospital stays and the need for subsequent home care services create a medical and socioeconomic burden [3].

Various biomarkers have been investigated to predict mortality and morbidity in PFF cases. Serum glucose is an easily obtainable and cost-effective parameter, with significant associations between elevated glucose levels and post-traumatic mortality [8,9]. However, the prognostic value of the glucose/potassium ratio in hip fractures has yet to be thoroughly studied. Parameters such as low hemoglobin [10], albumin levels [11,12], elevated C-reactive protein [13], neutrophil/lymphocyte ratio [14], and platelet/lymphocyte ratio [15] have demonstrated prognostic value in various clinical contexts. Nevertheless, more research is needed on the specific role of these parameters in PFF cases.

This study aims to retrospectively evaluate patients with PFF who presented to the emergency department and to investigate the relationship between routinely assessed hematological and biochemical parameters—and specific ratios of these parameters (*e.g.*, glucose/potassium, neutrophil/lymphocyte, platelet/lymphocyte, monocyte/lymphocyte ratios) - and 30-day (short-term) mortality. A distinctive aspect of this study is its focus on examining the prognostic value of the glucose/potassium ratio. Ultimately, this research seeks to contribute to more effective management of the growing PFF burden in emergency settings and to identify potential risk factors in an aging population.

Materials and Methods

Ethical approval for this study was obtained from the Ethics Committee Afyonkarahisar Health Sciences University on April 19, 2024, with protocol number 2024/2. This retrospective study examined patients diagnosed with proximal femur fractures (PFF) who admitted to the Emergency Medicine Department of Afyonkarahisar Health Sciences University Faculty of Medicine Hospital. The study included 344 patients aged 65 and older who visited the hospital between January 1, 2018, and July 1, 2023 and were diagnosed with PFF according to the International Classification of Diseases-10 (ICD-10). Inclusion criteria were being over 65, having an isolated traumatic femur fracture, presence of a femur fracture record in the hospital system, and accessible post-discharge patient information. Exclusion criteria included being under 65, missing information in the hospital system, a history of hematologic disease or malignancy, signs of acute infection, multiple traumas, inaccessible post-discharge data, and a diagnosis of Diabetes Mellitus or chronic kidney failure.

Patient characteristics (*e.g.*, gender, age, medical history, medication use, side of the fracture, and fracture type), length of hospital stay, intensive care unit (ICU) admissions, ICU stay duration, and one-year mortality status were recorded in a data collection form. Hematologic and biochemical parameters collected at the time of emergency admission - hemoglobin, leukocytes, neutrophils, lymphocytes, monocytes, platelets, RDW (red cell distribution width),

glucose, potassium, CRP (C-reactive protein), albumin, and total protein - were documented. Additionally, ratios such as neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte (MLR), platelet-to-lymphocyte (PLR), and CRP-to-albumin (CAR) were calculated and included in the data form. These parameters were analyzed for their association with 30-day mortality. The glucose-to-potassium ratio was also calculated and evaluated for its relation to mortality within the first 30 days.

Mortality data were obtained from the Ministry of Health's death notification system and through follow-up calls to patients' registered contact numbers. Additional necessary data were retrieved from the hospital's automation system (Nucleus v9.40.69 and Interpacs imaging application) and recorded in the data collection form.

Statistical analyses were conducted using SPSS 27 for Windows. Distributions of nominal and ordinal variables were assessed via frequency analysis, while continuous data were reported as mean ± SD or patient count (%). Non-normally distributed variables were described using median and interquartile range (IQR). The normality of distribution was assessed using analytical methods (*Kolmogorov-Smirnov/ Shapiro-Wilk* tests). Student's *t*-test and paired *t*-test were applied to normally distributed continuous variables, while the *Mann-Whitney U* and *Wilcoxon* tests were used for non-normally distributed variables. Categorical data were analyzed using *Pearson's* chi-square test. ROC analysis was employed to determine thresholds for hemoglobin, RDW, and glucose/potassium ratio values concerning 30-day mortality and to evaluate their performance parameters (specificity and sensitivity). All analyses were performed with a 95% confidence interval, and a *p*-value of less than 0.05 was considered statistically significant. Following the statistical analyses, data were processed and tabulated using Microsoft Excel.

Results

A total of 344 patients were included in the

Table 1. The basic and clinical characteristics of the patients.

Sex, n (%)	
Male	139(40.4)
Female	205(59.6)
Mean age (Mean ± SD)	81.88±7.76
Age group, n (%)	
65-74	25 (7.3)
75-84	113 (32.8)
85 and over	206 (59.9)
Fractured Side, n (%)	
Right	183 (53.2)
Left	161 (46.8)
Fracture Type, n (%)	
Intracapsular	88 (25.6)
Extracapsular	256 (74.4)
Hospital length of stay, median (IQR)*	7 (5-9)
Hospitalization History at ICU, n (%)	
Yes	56 (16.3)
No	288 (83.7)
Hospitalization at ICU (days) (IQR)*	5 (3-16)

ICU: Intensive Care Unit IQR: Interquartile Range

Table 2. Mortality status of the patients.

Mortality Status	Number of Patients, n (%)
Mortality within One Year	37 (10.8)
Early Phase (First 30 Days) Mortality	24 (7)
Late Phase (30 Days to 1 Year) Mortality	13 (3.8)
Survivors at One Year	307 (89.2)
Day of Mortality, Median (IQR)	24 (8-86.5)

IQR: Interquartile range

Table 3. Comparison of basic and clinical parameters between mortality and non-mortality groups.

Parameter	Non-Mortality	30 Day Mortality	*p*-value
Sex, n (%)			0.064
Male	125 (39.1)	14 (58.3)	
Female	195 (60.9)	10 (41.7)	
Age	81.82±7.83	82.67±6.94	0.613
Fracture type, n (%)			0.418
Intracapsular	81 (25.3)	7 (29.2)	
Extracapsular	239 (74.7)	17 (70.8)	
ICU History, n (%)			<0.001
Yes	37 (11.6)	19 (79.2)	
No	283 (88.4)	5 (20.8)	
Hospitalization duration	8.82±12.22	12.17±8.34	0.008
ICU duration	17.03±30.75	9.75±8.05	0.482
Glucose	155.13±54.2	176.89±73.73	0.104
Potassium	4.62±0.61	4.35±0.63	0.039
Glucose/potassium	33.90±11.34	40.92±16.09	0.005
WBC	11.48±4.24	9.19±4.61	0.002
Neutrophil	9.51±4.19	7.44±4.34	0.002
Lymphocyte	1.17±0.6	1.02±0.54	0.177
Monocyte	0.68±0.25	0.64±0.30	0.242
Hemoglobin	12.09±1.91	10.92±2.04	0.004
RDW	14±2.38	16.32±2.8	0.022
Platelet	226.43±82.32	220.04±86.69	0.231
CRP	20.56±41.93	17.67±26.38	0.202
Albumin	3.6±0.47	3.46±0.66	0.317
NLR	10.58±8.32	9.12±7.11	0.251
PLR	238.47±151.74	287.12±199.5	0.544
MLR	0.72±0.52	0.77±0.55	0.956
CAR	3.19±8.57	1.99±2.43	0.122

ICU: Intensive Care Unit, RDW: Red Cell Distribution Width, NLR: Neutrophil to Lymphocyte Ratio

PLR: Platelet to Lymphocyte Ratio, MLR: Monocyte to Lymphocyte Ratio, CRP: C-reactive Protein CAR: CRP to Albumin Ratio

study. Of these, 205 (59.6%) were female, and 139 (40.4%) were male. The mean age was determined to be 81.88±7.76 years, with the majority of patients (59.9%) aged 85 years or older. Regarding fracture type, 74.4% of the patients had extracapsular fractures. The median length of hospital stay was 7 days (IQR: 5-9). A history of admission to the intensive care unit (ICU) was present in 16.3% of patients, with a median ICU stay of 5 days (IQR: 3-16) (Table 1).

In terms of mortality, 10.8% of the patients (37 patients) died within one year. Among these, 7% (24 patients) passed away within the first 30 days, while 3.8% (13 patients) died between 30 days and one year. The median time to death for deceased patients was 24 days (IQR: 8-86.5) (Table 2).

Comparing patient groups who died within the first 30 days to other patients, statistically significant differences were observed in ICU admission history (p<0.001), length of hospital stay (p=0.008), glucose/potassium ratio (p=0.005), white blood cell count (WBC, p=0.002), neutrophil count (p=0.002), hemoglobin level (p=0.004), and red cell distribution width (RDW, p=0.022). Among those who died, the ICU admission rate was higher (79.2%), the hospital stay was more extended (12.17±8.34 days), and the glucose/potassium ratio was elevated (40.92±16.09). Additionally, in this group, hemoglobin levels were lower (10.92±2.04 g/dL), and RDW values were higher (16.32±2.80) (Table 3).

According to ROC analysis, the area under the curve (AUC) for RDW was 0.721 (95% CI: 0.672–0.767) with a cutoff value of >16.2, yielding a sensitivity of 54.2% and specificity of 86.73% (p=0.001). For hemoglobin, the AUC was 0.641 (95% CI: 0.589–0.690), with a cutoff value of <12.8, resulting in a sensitivity of 87.5% and specificity of 36% (p=0.01) (Table 4).

Discussion

Proximal femur fractures (PFF) are a common occurrence, particularly among elderly patients presenting with low-energy trauma. With the increasing aging population, the prevalence of these fractures has risen, making them significant contributors to mortality and morbidity worldwide.

This study aimed to retrospectively analyze the fundamental and clinical characteristics of elderly patients with PFF and evaluate the impact of hematological and biochemical parameters measured in the emergency department on 30-day mortality. We included 344 patients, of whom 59.6% were female and 40.4% were male. Matos et al. reported that 65.5% of 119 patients with hip fractures were women, while Belmont et al. demonstrated that 62% of 44,419 hip fracture cases were female [4,16]. Osteoporosis is a major risk factor for fractures. In women, a decrease in bone mineral density is observed with menopause. The risk of fractures in women is higher than in men due to lower muscle mass and osteoporosis [17]. The distribution of patients by sex in our study aligns with findings from the literature.

Table 4. Performance parameters of hemoglobin and RDW as a predictor of 30-day mortality.

Performance parameters	Hemoglobin	RDW
Cutoff value	<12.8	>16.2
Sensitivity	87.5	54.2
Specificity	36	86.7
AUC	0.641	0.721
95% CI for AUC	0.589 - 0.69	0.672 -0.767
p	**0.01***	**0.001***

AUC: Area Under the Receiver Operating Characteristic Curve

RDW: Red Cell Distribution Width

CI: Confidence Interval

*p<0.05

The mean age of the patients was 81.88 ± 7.76 years, comparable to the ages reported by Zhang et al. (77.12 ± 5.88) and Dubljanin et al. (77.6 years) [18,19]. It has been reported that the risk of PFF increases with age due to factors such as worsening osteoporosis, decreased physical activity, and comorbidities [20]. The fact that the majority of our patients (59.9%) were aged 85 years and older supports this observation.

Regarding fracture type, our study demonstrated that extracapsular fractures (74.4%) were more prevalent than intracapsular fractures (25.6%) [21]. This finding is consistent with the study by Morita et al. Similarly, Guerra et al. reported that extracapsular fractures were more common (61.8%) [22].

The median hospital stay was 7 days (interquartile range: 5-9), shorter than reported in other studies. Matos et al. reported an average length of stay of 20 days, while Astur et al. and Eschbach et al. reported 10.65 days and 13.5 days, respectively [4,23,24]. This difference may be attributed to recent improvements in the quality of healthcare services and the implementation of more effective treatment protocols.

In our study, it was demonstrated that 10.8% of patients diagnosed with PFF in the emergency department died within one year, with a substantial proportion (7.1%) of patients passing away within the first 30 days (short-term).

Similar studies reported short-term mortality rates as 5% by Ariza-Vega et al. and 8.7% by Tarazona-Santabalbina et al. [25,26]. Moran et al. examined 2,660 patients with hip fractures and determined the short-term mortality rate to be 9% and the one-year mortality rate to be 30% [27]. Differences in mortality rates may depend on the methodologies employed in the studies and the levels of healthcare system development in different countries.

Mortality rates are high among patients with PFF. Epidemiological characteristics and hematological and biochemical parameters potentially associated with short-term mortality were examined. A history of intensive care unit admission, length of hospital stays, leukocyte count, neutrophil count, hemoglobin levels, red cell distribution width (RDW), and glucose/potassium ratios were all shown to correlate with short-term mortality. In this study, we specifically investigated the role of hemoglobin and RDW levels and the glucose/potassium ratio in predicting short-term mortality.

An analysis of the relationship between hemoglobin levels and early mortality indicated a significant association between low hemoglobin and increased mortality. Julian Karres et al. demonstrated that low hemoglobin levels increased the risk of 30-day mortality following a hip fracture [28]. Zhang et al. identified an association between low hemoglobin levels and mortality in a study of 2589 patients [29]. Receiver operating characteristic (ROC) analysis indicated an area under the curve (AUC) of 0.641 for hemoglobin levels in predicting 30-day mortality (p=0.01), with the most discriminative hemoglobin threshold being <12.8 g/dL (sensitivity: 87.5%, specificity: 36.0%). Additionally, some studies relate mortality to preoperative and postoperative transfusion complications. Anemia is a common problem among the elderly and is a significant contributor to the poor prognosis of PFFs. Therefore, preventive healthcare services aimed at osteoporosis management and identifying the etiologies of anemia, followed by appropriate interventions, may effectively reduce the incidence of proximal femur fractures and associated mortality.

RDW (Red Cell Distribution Width) describes the red blood cell volume variability [30]. Our study found a statistically significant relationship between RDW levels and 30-day mortality. The ROC curve analysis identified a cutoff value of RDW>16.2 for predicting 30-day mortality (p=0.001, AUC=0.721, sensitivity: 54.2%, specificity: 86.7%). In the literature, RDW is a reliable indicator of disease severity and mortality prediction in conditions such as pneumonia, heart failure, renal failure, and acute pancreatitis [31,32]. Elevated RDW is considered an unfavorable prognostic factor. Two studies in the literature, like ours, have also found an association between high RDW levels and 30-day mortality in patients with PFF [33,34]. It has been demonstrated that RDW values increase with oxidative stress and inflammation. A meta-

analysis suggested that elevated RDW levels at presentation and thereafter may correlate with both short- and long-term mortality in PFF patients [35]. In clinical practice, alongside factors such as age, patient history, fracture type, and hemoglobin levels, RDW can also be utilized as a critical determinant for patient management in PFF cases.

Several studies have investigated the relationship between serum glucose/potassium (Glu/K) ratios and mortality in different clinical scenarios. The Glu/K ratio is obtained by comparing the levels of glucose and potassium, which are routinely measured biochemical parameters in all patients presenting to the emergency department without additional burdens on healthcare staff. Due to the sympathetic activity increased by trauma, the release of catecholamines is expected to raise serum Glu/K ratios, potentially influencing patient prognosis. Previous studies have examined Glu/K ratios in patients with blunt abdominal trauma, acute intracerebral hemorrhage, and severe traumatic brain injury, finding associations particularly with early mortality [36,37]. While various studies have explored hyperglycemia and hypoglycemia concerning hip fractures, ours is the first to investigate the relationship between Glu/K ratios and mortality in patients presenting with PFF. In our cohort, patients who experienced early mortality (within the first 30 days) had higher glucose/potassium ratios at presentation. This suggests that elevated Glu/K ratios at presentation may be associated with early mortality in patients with PFF. Correcting hyperglycemia and potassium disturbances at presentation could represent a novel strategy to improve the prognosis of patients with PFF.

Our study specifically examined the relationship between hemoglobin, RDW, and glucose/potassium ratios and short-term mortality. Our findings indicate that these parameters are associated with mortality. These results suggest that routine evaluation of these parameters in the emergency department may play a significant role in the early detection and treatment planning for high-risk patients.

The strengths of our study include its large patient cohort and the comprehensive examination of the association between routinely measured hematological and biochemical parameters and short-term mortality. Additionally, focusing on the relatively new glucose/potassium ratio parameter concerning short-term mortality enhances the study's uniqueness. However, the study's retrospective design presents limitations in establishing causality, and its execution at a single center may restrict the generalizability of the findings. Potential confounding factors, such as chronic diseases within the study population, may not have been fully controlled. Future research should validate these findings in multiple centers with larger patient groups.

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Conflict of interest

The authors declare no conflict of interest.

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