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RESEARCH ARTICLE

Chemoradiotherapy Results Without Surgery in Patients with Locally Advanced Esophageal Squamous Cell Carcinoma

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Abstract

Introduction: It aimed to evaluate the overall survival (OS) results of chemoradiotherapy (CRT) without surgery in patients with locally advanced esophageal squamous cell carcinoma (ESCC).

Methods: Patients who received chemoradiotherapy with a diagnosis of ESCC at the Radiation Oncology Department of Ankara Bilkent City Hospitals were retrospectively analysed. The primary endpoint was OS.

Results: The results of 46 patients who underwent radiotherapy (RT) between 26.06.2012 and 21.03.2023 were analysed. Median follow-up was 14 (range 1-47) months. The localisation was upper thoracic in 8(17.4%), middle thoracic in 36(78.3%) and lower thoracic in 2(4.3%) patients. Surgery was considered at the time of admission to the radiotherapy clinic in 25 (54.3%) of our patient group, and neoadjuvant treatment was given, but no surgery was subsequently performed. Patients referred to the radiotherapy clinic for neoadjuvant chemoradiotherapy received a significantly lower total dose than those referred directly for definitive chemoradiotherapy (p0.006; Z-2.768). Patients were evaluated by endoscopic biopsy and computed tomography 6-8 weeks after the end of treatment, and clinical complete response (cCR) was observed in 15 (32.6%) patients. At last follow-up, 19 (41.3%) patients were dead and 27 (58.7%) were alive. Median OS was 25 months (range 1.5-47). 1-year OS was 66%; 2-year OS was 54.7%; 3-year OS was 40.4%. Significantly higher OS was observed in patients with cCR (HR 4.2; 95% CI 1.2-14.7).

Conclusion: Patients referred to the radiotherapy clinic for neoadjuvant therapy received a significantly lower total dose than patients referred for definitive chemoradiotherapy. Patients who received cCR after chemoradiotherapy had significantly higher OS.

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Introduction

Esophageal cancer (EC) is the 7th most common cancer worldwide. Esophageal cancer ranks 5th in terms of cancer-related deaths. 500,000 people die of esophageal cancer each year.[1] Esophageal cancer, which is more common in eastern countries, has a poor prognosis. Although a statistically significant but small improvement in the prognosis of esophageal cancer has been achieved, treatments do not achieve the expected high results and esophageal cancer is still considered to be one of the most aggressive malignancies.[1,2]

There are two main pathological subtypes of esophageal cancer: adenocarcinoma and squamous cell carcinoma (SCC). These two pathological subtypes differ in terms of localisation, spread and prognosis. Squamous cell carcinoma is more common in eastern countries, and smoking/alcohol consumption and dietary habits are important aetiological factors.[3,4]

Surgery is the main treatment for esophageal cancer, but the prognosis of surgery alone is poor. Neoadjuvant therapy has been shown to improve OS. According to the European Society for Medical Oncology (ESMO) guidelines[5] and the National Comprehensive Cancer Network (NCCN) guidelines,[6] the standard treatment for patients with locally advanced esophageal squamous cell carcinoma (ESCC) is surgery after neoadjuvant chemoradiotherapy. However, due to the effect of surgery on prolonged quality of life up to 20 years later,[7] omission of surgery is being considered for patients who have achieved a clinical complete response (cCR). Promising results for overall survival in patients who achieved cCR and did not undergo surgery have been reported in studies.[8,9]

The aim of this study was to evaluate OS outcomes in patients with locally advanced esophageal squamous cell carcinoma (ESCC) who received chemoradiotherapy without surgery.

Material and Methods

In the current study, patients who received chemoradiotherapy with a diagnosis of ESCC at the Radiation Oncology Department of Ankara City Hospital were retrospectively analysed. Patient interview information, patient records, dose-volume histograms and electronic system data were used for the data obtained. Patients' demographic status, admission complaints, clinical stages, radiotherapy (RT) and chemotherapy details, and treatment response status were recorded. Staging was performed according to the American Joint Committee on Cancer ver(version) 8.[25] The Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.[26]

Patient selection

Adult patients with pathological evidence of thoracic esophageal cancer, pathological subtype squamous cell carcinoma, undergoing curative chemoradiotherapy were included in the study. Patients without path)ological evidence, patients receiving palliative radiotherapy, patients with adenocarcinoma, cervical or gastroesophageal junction tumours and patients with Eastern Cooperative Oncology Group performance scale 4 (ECOG PS) esophageal cancer were excluded.

Primary and secondary endpoints

The objective was to analyse the oncological outcome of patients who received chemoradiotherapy without surgery. The primary endpoint of the study was overall survival (OS). OS was defined as the time from the end of radiotherapy to the patient's death or last follow-up. The secondary endpoint of the study was initial response status after chemoradiotherapy. All patients underwent endoscopy and biopsy 6-8 weeks after chemoradiotherapy. Patients whose tumour was found in the control endoscopic biopsy or who could not pass the probe due to stenosis were not considered to have a complete response. Patients underwent computed tomography (CT) scans within 6 to 8 weeks after completion of chemoradiotherapy and were compared with pre-treatment CT scans. Response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) criteria.[10] It was aimed to analyze the oncological outcomes of patients who underwent chemoradiotherapy without surgery. The primary endpoint of the study was overall survival. OS was defined as the period from the end of radiotherapy to the patient's death or the last control date. The secondary endpoint of the study was the first response status after chemoradiotherapy. All our patients underwent endoscopy and biopsy 6-8 weeks after chemoradiotherapy. Patients whose tumor was detected as a result of control endoscopic biopsy or who could not pass the probe due to stenosis were not considered to have a complete response. After chemoradiotherapy was completed, our patients were scanned with computed tomography (CT) within 6-8 weeks and a comparative evaluation was made with the pre-treatment computed tomography. Response

Evaluation Criteria in Solid Tumors (RECIST 1.0) criteria were used for response evaluation,[10]

Statistical analysis

Data were analysed using SPSS version 26. The conformity of the data to a normal distribution was evaluated with the Shapiro–Wilk test; as the data were not normally distributed, parametric tests were used. The Chi-squared test and Fisher's exact test were used to analyse categorical variables. The Mann–Whitney U test was used for independent two-group analyses. The Kruskal–Wallis test was used for the analysis of 3 or more independent groups and Tukey's post hoc test was performed in cases of significance. In the statistical analysis method section; Kaplan Meier is used for survival analysis and Cox regression analysis is used for ultravariate and multivariate analysis. The hazard ratios (HR) and 95% confidence intervals (CI) of results that were significant in our survival analyses were calculated. A HR > 1 denotes an increased relative risk compared to the reference category. The significance limit of this study was set to 0.05.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Ankara City Hospital No. 1 on 15.5.2023 with the number E1-23-3568.

Results

The results of 46 patients who were diagnosed with ESCC between 26.06.2012 and 21.03.2023 at the Radiation Oncology Department of Ankara Bilkent City Hospital were analysed (Table 1). The median follow-up was 14 (range 1-47) months. The median age of the patients undergoing chemoradiotherapy was 61 years (range 40-74). The clinical stage of the patients was stage 2 in 13(28.3%), stage 3 in 22(47.8%), stage 4 in 11(23.9%). There were 3 patients with brain, lung and cervical lymph node metastases. Intensity-modulated radiation therapy (IMRT) with 6 MV photons was applied to all patients. The median total radiotherapy dose was 50 (37.8-60) Gy. The median neoadjuvant prescription dose was 5000 cGy (4140-5600) and the median definitive prescription dose was 5040 cGy (3780-6000). Chemotherapy was given to all patients, and the most commonly used chemotherapeutic agents were carboplatin and paclitaxel in 37 patients (80.4%). Neoadjuvant chemoradiotherapy was planned in 25 patients (54.3%) and definitive chemoradiotherapy in 21 patients (45.7%). Patients referred to the radiotherapy clinic for neoadjuvant chemoradiotherapy received a significantly lower total dose than patients referred for definitive chemoradiotherapy (p0.006; Z-2.768) (Figure 3).

Table 1. Patients and Treatment Details

Age	Median(range)	61 (40-74)
Gender	Women	18(39.1%)
	Man	28(60.9%)
Localisation	Upper Thoracic	8 (17.4%)
	Middle Thoracic	36(78.3%)
	Lower Thoracic	2(4.3%)
Clinic T Stage	cT2	4(8.7%)
	cT3	33(71.7%)
	cT4	9(19.6%)
Clinic N Stage	cN0	16(34.8%)
	cN1	21(45.7%)
	cN2	6(13%)
	cN3	3(6.5%)
M Stage	M0	43(93.5%)
	M1	3(6.5%)
Stage	Stage2	13(28.3%)
	Stage3	22(47.8%)
	Stage4	11(23.9%)
RT Purpose (RT başlangıcında)	Definitive	21 (45.7%)
	Neoadjuvan	25(54.3%)
RT Total Dose	< 50 Gy	14 (30.4%)
	≥50 Gy	32 (69.6%)
Chemotherapy	Cisplatin	2 (4.3%)
	Cisplatin +5 FU	7 (15.2%)
	Carboplatin + Paclitaxel	37 (80.4%)
Clinic Response	cCR	15 (32.6%)
	cPR	18 (39.1%)
	Stabil	6 (13%)
	Progression	7 (15.2%)
Last Status	Ex	19 (41.3%)
	Alive	27 (58.7%)

RT: radiotherapy; cCR: clinic complete response; cPR: clinic partial response

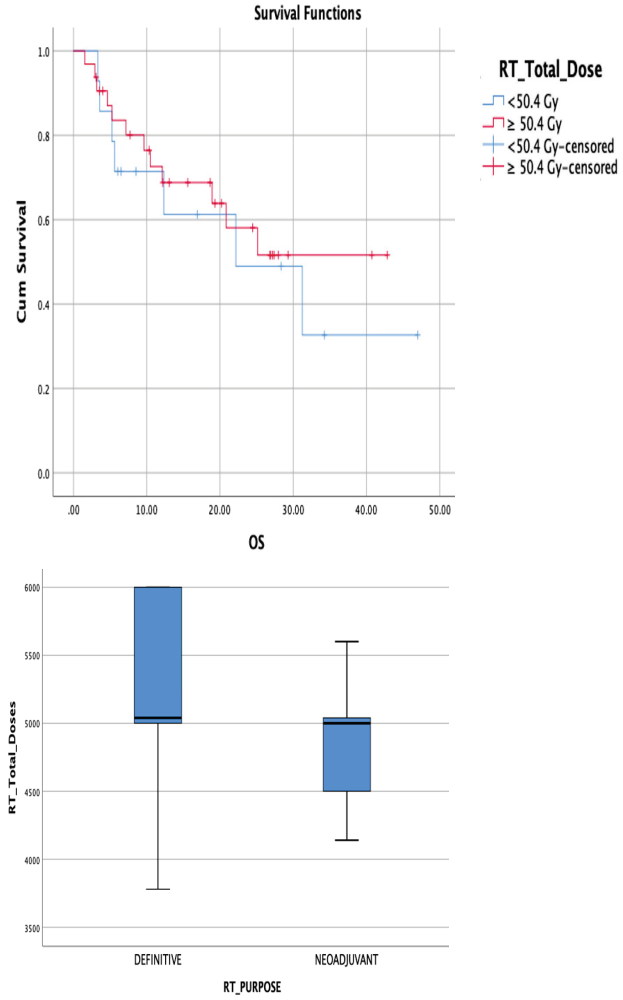

Figure 3. Similar overall survival rates were observed at doses greater than 50.4 Gy compared to lower doses.

Evaluation of clinical response after neoadjuvant therapy

After NA treatment, patients were evaluated by endoscopic biopsy and computed tomography. In patients receiving definitive radiotherapy, clinical complete response was observed in 8 (38.1%), clinical PR in 6 (28.6%), SD in 3 (14.3%) and progression in 4 (19%).

And in patients who received neoadjuvant radiotherapy, clinical complete response was seen in 7 (28%) of patients, clinical PR 12 (48%), SD in 3 (12%) and progression in 3 (12%) of patients.

Clinical response status was not significantly associated with age (p0.507), gender (p0.633), location (upper thoracic - middle thoracic - lower thoracic) (p0. 671), stage (p0.230), cT (p0.671), cN (p0.142), cM (p0.085), purpose of treatment (neoadjuvant or definitive) (p0.590) and total radiotherapy dose (< 50 Gy vs ≥50 Gy) (p0.634).

Overall Survival Result

During follow-up, 19 (41.3%) patients died; 27 (58.7%) patients were alive; median OS was 25 (range 1.5-47) months. 1-year OS is 66%; 2-year OS is 54.7%; 3-year OS is 40.4%. The following parameters were not significantly associated with overall survival (OS): age (p0.674); gender (p0.830); stage (p0.703); cT (p0.842); cN (p0.820), cM (p0.189); purpose of treatment (neoadjuvant or definitive) (p0.273); total radiotherapy dose (< 50 Gy vs ≥50 Gy) (p0.620). A significantly lower OS was observed in patients with lower thoracic localisation compared to upper and middle thoracic esophageal tumours (p0.012; HR 9.6; CI 95% 1.3-16.9)(Figure 1). However, only 2 patients had distal localisation and these patients were discharged at 3.1 and 3.5 months after NA treatment due to general discomfort and inability to eat. A significantly higher OS was observed in patients with cCR compared to others (p0.023; HR 4.2; 95%CI 1.2-14.7)(Figure 2). Patients with cCR did not achieve median survival (Figure 4).

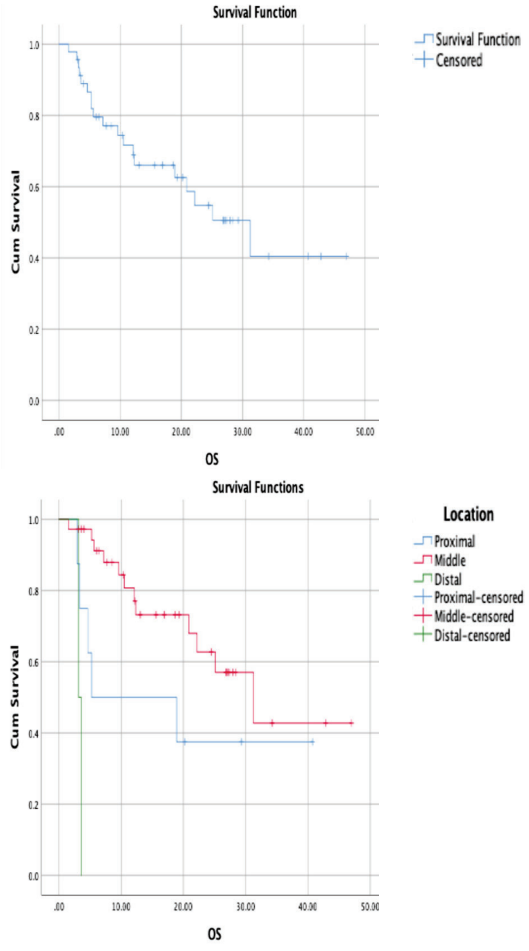

Figure 1. Kaplan Meier overall survival of the patients. According to the localization, no significant changes were observed in overall survival.

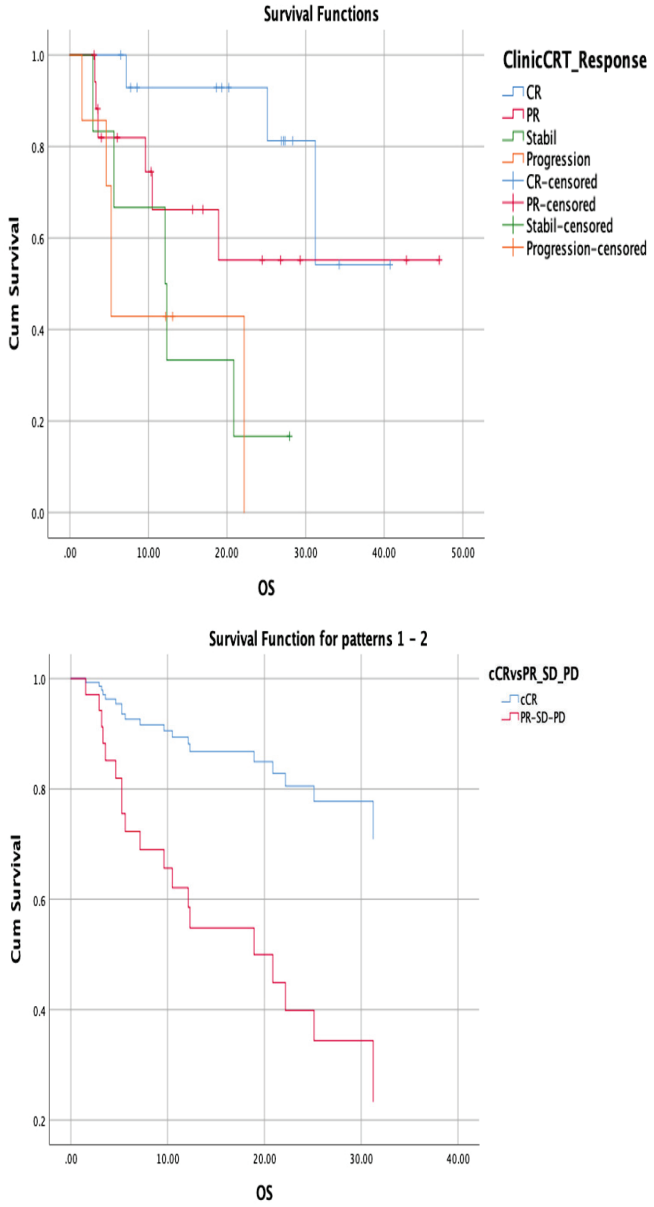

Figure 2. Significantly higher survival was achieved in the patient arm with clinical complete response.

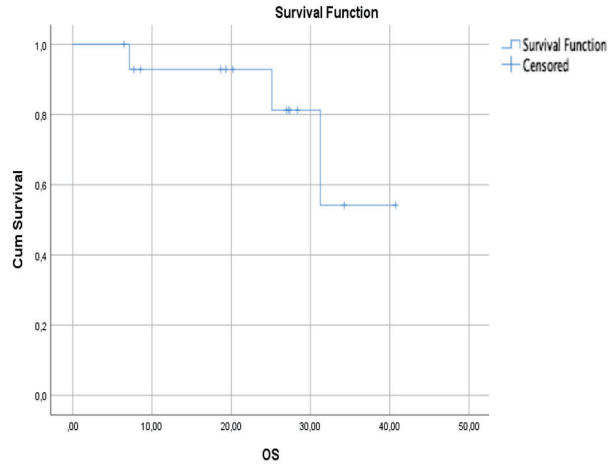

Figure 4. Cox regression analysis results of patients with cCR.

Discussion

In our study, we retrospectively analysed the results of 46 patients who received chemoradiotherapy without surgery for the diagnosis of ESCC, with a median follow-up of 14 months. Forty-six of the patients included in our study were referred to the radiotherapy clinic for neoadjuvant therapy, but did not subsequently undergo surgery. During the follow-up period, approximately 40% of the patients were excited and the median OS was 25 months. Of the parameters we evaluated, only CR had a significant impact on OS. In locally advanced ESCC, non-surgical follow-up is an alternative treatment for patients with cCR. According to Stahl et al, in a prospective randomised trial, patients were divided into two arms: those who received surgery after 40 Gy chemoradiotherapy and those who received chemoradiotherapy alone (60 Gy). The addition of surgery improved local tumour control but did not contribute to survival.[11] In the FFCD 9102 trial, patients were divided into 2 arms after 46 Gy of radiotherapy; those who underwent surgery and those who underwent definitive chemoradiotherapy (total 66 Gy).

Median survival was similar between the two arms (17.7 months in the surgery arm vs 19.3 months in the chemoradiotherapy arm). However, the 3-month mortality rate was significantly higher in the surgery arm (9.3% in the surgery arm versus 0.8% in the chemoradiotherapy arm (p0.002)).[12] In the prospective phase 2/3 SCOPE-1 trial using modern radiotherapy techniques, definitive chemoradiotherapy was used in ESCC patients and in this trial the 3-year OS was 47.2% and the median OS was 34.5 months.[13] Regarding this issue, Van Der Wilk et al in their review published in 2022 analysed 788 patients from 7 studies and found that 5-year survival was 58% and 2-year local regional control was 33% in patients without surgery after chemoradiotherapy.[14] According to Best et al. in a review published in 2016, which included 8 randomised trials, definitive chemoradiotherapy was compared with surgery after NA chemoradiotherapy; there was no significant difference between the two arms in terms of long-term mortality and recurrence.[15] However, according to Chow et al. in a meta-analysis comparing esophagectomy and definitive chemoradiotherapy arms after neoadjuvant chemoradiotherapy, which included 8 trials and 16,647 patients, higher survival rates were observed in the surgical arm, contrary to Best and colleagues.[16] Based on our current knowledge, nonsurgical treatment is an

appropriate alternative for locally advanced ESCC. Of the ongoing trials, SANO (NCT04886635), Esostrate (NCT02551458), PreSINO (NCT03937362); Needs trial (NCT04460352) will contribute to the standardisation of non-surgical regimens. In our trial, there was no surgical arm and no comparison could be made. And 46 ESCC patients who did not undergo surgery were followed for 14 months and our median OS was 25 months.

The contribution of surgical evaluation in patients with complete response after NA treatment is controversial. In the trials that set the standard of care, the treatment decision was not changed according to clinical response status, patients underwent surgery regardless of response status.[1,17] Patients with cCR have a better prognosis. A meta-analysis by Wang et al. of 648 patients with cCR (620 with squamous cell carcinoma and 28 with adenocarcinoma) showed that the addition of surgery contributed to 2-year disease-free survival. However, 5-year OS was similar between arms.[9] In a meta-analysis of 609 patients published by Park et al. in 2021, better OS was achieved in patients with cCR without surgery (HR = 0.80, 95% confidence interval [CI] 0.64-0.99, p = 0.04). The addition of surgery may increase morbidity and mortality and decrease quality of life. Therefore, chemoradiotherapy alone may be an appropriate approach for patients with cCR.[8]. In our study, cCR was achieved in 15 (32.6%) patients, and a significantly higher OS was observed in patients with CR compared to others (HR 4.2; 95% CI 1.2-14.7).

In our study, 54% of our patient group who were consulted for neoadjuvant therapy did not have surgery after NA chemoradiotherapy. Neoadjuvant and definitive radiotherapy doses are different (Figure 3). For this reason, each patient should be evaluated by the multidisciplinary tumour board to assess the patient's treatment in a multifaceted manner and select the most appropriate dose. 41.4 Gy is often preferred for neoadjuvant treatment and 50.4 Gy for definitive treatment. Dose escalation in radiotherapy for esophageal cancer has been attempted in the Intergroup 0123 and Artdeco trials. In the Intergroup 0123 study, 236 patients with esophageal cancer were divided into two arms: high dose (64.8 Gy) and standard dose (50.4 Gy). There was no significant difference between the two arms in median survival (13.0 vs 18.1 months), 2-year OS (31% vs 40%) and local regional disease continuity (56% vs 52%). In addition, 11 treatment-related deaths were observed in the high-dose arm compared to 2 treatment-related deaths in the 50.4 Gy arm.[18] The Artdeco trial was published in 2021 and used modern radiotherapy techniques. This study included patients diagnosed with esophageal cancer without surgery. The median follow-up was 50 months. 61.6 Gy was given with SIB (simultaneous integrated boost) in the high-dose arm and 50.4 Gy in the standard arm. There was no significant difference between the two arms for 3-year OS (70% vs 73%), 3-year local progression-free survival (52% vs 59%), grade 4 acute side effects (ASE) (12.5% vs 14.5%) and grade 5 ASE (3.3% vs 7.6%).[19]According to the results of these studies, higher doses did not provide better local control. Although there is a tendency to prescribe higher primary doses in boost/SIB, there is insufficient evidence to support the contribution of doses of 50.4 and above. In our study, a significantly lower total radiotherapy dose was administered to patients who presented to the clinic and underwent neoadjuvant planning. However, this dose difference did not show a significant effect on clinical response and OS.

The main limitation of our study is its retrospective nature and short follow-up. In our study, clinical response was assessed by computed tomography and endoscopy. PET-CT was not performed in all patients, so the metabolic response status was not included in the study. In addition, toxicity could not be assessed because not enough data were available in the records and system notes.

Conclusion

Definitive chemoradiotherapy is a viable option for patients diagnosed with locally advanced ESCC without surgery. In our own clinical experience, patients referred for neoadjuvant therapy receive lower doses. Patients should be assessed for operability and acceptance of surgery prior to radiotherapy. A complete response at week 6 after chemoradiotherapy is associated with improved survival.

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RESEARCH ARTICLE

Fetal Humerus Length Nomogram in Gestational Weeks 19-24: Clinical Significance, Gender and Turkish Ethnical Differences

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Abstract

Introduction: Objective To create a comprehensive fetal humerus length nomogram that is both gender- and ethnically relevant and applicable to the specified gestational weeks.

Methods: We conducted a retrospective cohort study that included singleton pregnancies between 19 and 24 weeks of gestation who were admitted to our clinic between 2021 and 2023. The study population comprised pregnant women who identified themselves as originating from the primary Turkish ethnic group and are between the age of 18 to 45. Ultrasonographic measurements were conducted by a single clinician using a General Electric Voluson E6 (USA) ultrasonography device with a transabdominal approach. Biometric evaluation of fetus was determined with measurements taken for Biparietal Diameter, Head circumference, Abdominal Circumference, Femur Lenght and Humerus Lenght.

Results: Gender-specific nomograms were constructed according to the gestational weeks. No significant differences were observed between the fetal genders,however, the humerus length of the fetuses was found to be greater than that documented in other populations, as evidenced in the WHO fetal growth charts.

Conclusion: The findings of our study demonstrate the necessity of ethnic-specific fetal HL nomograms. Furthermore, we anticipate that our results will contribute to the development of customised fetal nomograms for the Turkish population, in the future. In conclusion, by using a nomogram that accounts for ethnic differences, clinicians can better identify at-risk populations and provide targeted interventions, ultimately improving fetal outcomes.

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Introduction

The measurement of fetal humerus length (HL) during second trimester sonography provides essential insights into fetal growth and development. This period is particularly significant as it marks a phase of rapid skeletal development, where the accurate assessment of long bone lengths can serve as an important indicator of overall fetal health. The humerus becomes visible on ultrasound at 10 weeks of gestation. The optimal measurement of HL is taken between the two ends of the diaphysis.[1] Several studies have demonstrated that ultrasonographic measurement of HL can be employed to assess the fetal skeletal system and fetal growth and development in instances where conventional measurements such as Biparietal diameter (BPD) and Femur lenght (FL) cannot be obtained with sufficient accuracy. HL also plays an important role in the assessment of potential growth restriction, developmental abnormalities and aneuploidies, so it is very important to establish customised growth standards that incorporate maternal and fetal variables to improve the detection of abnormal conditions.[2]

The concept of a universal standard has been challenged on the grounds that a multitude of biological and cultural factors can exert an influence on fetal growth, including those pertaining to racial and ethnic backgrounds.[3] A cross-sectional study that compared fetal long-bone lengths across different populations, highlighting the necessity of considering demographic factors when interpreting fetal measurements.[4] It is therefore crucial to develop population and gender specific reference ranges in order to guarantee the precision of assessments.

The creation of HL nomograms for the evaluation of healty fetal development and the prediction of FGR and aneuploidy, with consideration of ethnic variations and fetal gender will enhance the clinical utility of these measurements. For this purpose, we created the HL nomograms of our patients evaluated at Selcuk Univercity Perinatology Clinic with the aim of contributing to the specific nomograms of the Turkish population.

Material and Methods

We conducted a retrospective cohort study that included singleton pregnancies between 19 and 24 weeks of gestation who were admitted to our clinic between 2021 and 2023. The study population comprised pregnant women who identified themselves as originating from the primary Turkish ethnic group and are between the age of 18 to 45. The last menstrual period was used to determine the gestational week. In pregnant women whose last menstrual period was not known, the gestational week was determined by first-trimester crown–rump length (CRL) measurement or second-trimester BPD. Pregnancies with structural and karyotype anomalies, preterm premature rupture of membranes, intrauterine growth retardation, maternal systemic diseases and multiple pregnancies were excluded from the study. The Local Ethics Committee of Selçuk University Rectorate gave permission to conduct the study with the document date and number 19.01.2023-E.440154.

Ultrasonographic measurements were conducted by a single clinician using a General Electric Voluson E6 (USA) ultrasonography device with a transabdominal approach. Biometric evaluation of fetus was determined with measurements taken for BPD, Head circumference (HC), Abdominal Circumference (AC), FL and HL. The fetal gender was assessed, and fetal anomaly screening was performed. HL was properly measured in the horizontal plane between the two ends of the diaphyseal portion of the bone in close proximity to the probe as recommended by ISUOG.[5] The percentile values of Göynümer et. Al. and Yorgunlar et. Al studies [6,7] and the WHO fetal growth chart study according to fetal HL are shown side by side with our study results

The statical analyses were performed using SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22. Descriptive data were presented as n, % values for categorical data, and mean±standard deviation (mean±SD) and percentile values for continuous data and the percentile values of Göynümer et. Al. and Yorgunlar et. Al studies and the WHO fetal growth chart study according to fetal HL are shown side by side with our study results. The suitability of continuous variables for normal distribution was assessed by the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare paired groups

The level of statistical significance in the analyses was accepted as $p<0.05$.

Results

The study included 660 pregnant women with a mean age of 27.5±3 (min=18 - max=45) years. Overall, 305 (46.2%) fetuses were female and 355 fetuses were (53.8%) male. The mean height of the

pregnant women was 164.9±5.4 cm, the mean weight was 70.8±12.5 kg and the mean BMI was 26.1±4.3 kg/m2. The mean gravida was 2.2±1.3 and the mean parity was 1,2±1.0 (Table 1). When the gestational weeks of the pregnant women were analyzed, 75 (11.4%) were in the 19th week, 207 (31.4%) in the 20th week, 199 (30.2%) in the 21st week, 106 (16.1%) in the 22nd week, 55 (8.3%) in the 23rd week and 18 (2.7%) in the 24th week.

Table 1. Main demographic features of study group

	n %
	Mean±SS
Maternal Age	27,5±5,3
Height (cm)	164,9±5,4
Weight (kilograms)	70,8±12,5
BMI (kg/m2)	26,1±4,3
Gravida	2,2±1,3
Parity	1,2±1,0

BMI:Body Mass Index

Comparision of all biometric measurements in terms of fetal gender is summarized by Table 2. The BPD measurements of female fetuses were found to be significantly lower than that of male fetuses (p=0.041). No significant difference was observed between the genders for remaining features (p>0.05 for all).

Table 2. Comparison of biometric measurements according to gender

	Female				Male				p*
	mean±SS	5p	50p	95p	mean±SS	5p	50p	95p	
BPD (mm)	50,8±4,5	44	50	58	51,6±4,9	45	51	60	**0,041**
HC (mm)	189,5±14,3	169	188	216	191,4±15,7	170	190	221	0,164
AC (mm)	165,6±16,8	144	163	191	166,8±16,6	144	165	198	0,245
FL (mm)	36,3±4,0	30	36	43	36,3±4,2	30	36	43	0,841
HL (mm)	34,9±3,5	30	34	41	34,8±3,8	30	35	41	0,626
EFW (grams)	446,5±102,8	312	427	636	453,8±109,5	319	434	677	0,461

* Mann Whitney U test was performed.

A second analysis was performed for each gestational week as shown in Table 3. BPD (p=0.018), HC (p=0.003) and EFW (p=0.023) of female fetuses at 21 weeks gestational age were significantly lower than those of male fetuses. At 22 weeks gestational age, BPD measurements of female fetuses were significantly lower than those of male fetuses (p=0.01). The BPD measurement of female fetuses at 23 weeks of gestation was significantly lower than that of male fetuses (p=0.005). The HC (p=0.006) and AC (p=0.035) measurements of female fetuses at 24 weeks' gestation were significantly lower than those of male fetuses (Table 3).

Table 3. Comparison of measurements by gender according to gestational weeks

		Female		Male		p*
		mean±SS	5p-50p-95p	mean±SS	5p-50p-95p	
19. w	BPD	46,5±2,8	42-47-52	46,7±2,5	42-47-50	0,793
	HC	173,0±8,6	158-172-188	172,9±7,0	160-174-182	0,856
	AC	151,0±7,6	136-150-166	149,1±9,4	134-150-162	0,602
	FL	32,0±2,1	28-32-36	31,7±2,0	29-32-34	0,784
	HL	30,7±2,1	27-31-34	30,9±2,2	27-31-35	0,884
	EFW	342,7±37,0	274-340-404	335,0±37,6	266-333-388	0,392
20. w	BPD	48,2±2,7	44-49-52	49,6±4,6	45-50-54	**0,004**
	HC	179,9±7,5	167-180-190	183,2±9,0	169-184-197	**0,005**
	AC	156,0±10,6	142-155-173	159,1±12,2	145-160-173	**0,001**
	FL	33,5±2,4	29-33-37	34,6±3,7	30-34-38	**0,032**
	HL	32,7±2,1	29-33-36	33,1±2,3	30-33-37	0,108
	EFW	374,6±49,0	299-373,5-452	397,9±48,4	320-399-480	**0,001**
21. w	BPD	50,6±2,6	46-50-55	51,5±2,7	48-52-56	**0,018**
	HC	188,5±8,1	175-189-203	192,1±7,7	180-192-206	**0,003**
	AC	165,2±8,9	154-163-183	167,3±10,7	151-168-182	0,145
	FL	36,1±2,2	32-36-40	36,5±2,5	32-37-40	0,131
	HL	34,9±2,3	32-35-39	35,1±3,6	31-35-39	0,865
	EFW	433,7±53,0	355-438-522	450,0±58,8	349-456-548	**0,023**
22. w	BPD	53,5±2,9	49-53,5-58	55,1±2,8	50-55-60	**0,010**
	HC	201,8±8,8	185-201,5-216	204,7±7,7	194-205-218	0,090
	AC	174,2±15,8	161-175,5-194	178,5±9,6	165-177-198	0,117
	FL	39,9±2,2	36-40-45	39,2±2,3	35-39-42	0,172
	HL	37,8±2,2	34-38-41	37,5±2,3	34-37-41	0,357
	EFW	531,1±64,3	422-533,5-639	540,3±61,7	452-534-651	0,530
23. w	BPD	56,9±6,3	52-56-59	58,2±3,9	50-59-63	**0,005**
	HC	210,7±7,6	203-209-223	213,8±12,2	187-214,5-232	0,172
	AC	190,4±20,0	173-187-208	189,1±9,9	167-190-202	0,284
	FL	41,9±2,3	39-42-46	41,8±3,1	37-41-47	0,819
	HL	39,4±2,7	36-39-45	39,4±2,6	35-39-43	0,852
	EFW	607,6±61,9	517-600-702	617,6±91,0	437-614-754	0,414
24. w	BPD	58,7±4,5	50-60-63	61,2±2,8	55-61-66	0,285
	HC	214,9±6,1	202-216-221	228,7±14,4	216-227-265	**0,006**
	AC	193,4±9,3	183-191-211	204,5±10,2	184-203-224	**0,035**
	FL	43,3±2,4	40-44-46	44,3±2,8	40-45-48	0,425
	HL	40,0±2,3	37-40-43	41,5±2,5	36-41-45	0,246
	EFW	680,3±86,6	569-657-803	755,2±86,1	594-797-862	0,085

* Mann Whitney U test was performed.

The main findings of the HL percentiles for each Gestational week are shown in Table 4, regardless of gender.

Table 4. HL percentiles acording gestational weeks, regardless of gender

	Percentiles								
Gestational week	**2,5**	**5**	**10**	**25**	**50**	**75**	**95**	**97,5**	**99**
19.w	25,9	27,0	28,0	30,0	31,0	32,0	34,0	35,0	35,0
20.w	28,2	30,0	30,0	31,0	33,0	34,0	36,0	37,0	37,0
21.w	31,0	31,0	32,0	33,0	35,0	36,0	39,0	39,0	43,0
22.w	32,7	34,0	35,0	36,0	38,0	39,0	41,0	42,0	42,0
23.w	34,4	36,0	36,0	37,0	39,0	41,0	44,0	45,0	45,0
24.w	35,9	36,0	36,9	40,0	41,0	43,0	45,0	45,0	45,0

A significant positive correlation was observed between HL and BPD, HC, AC, FL and gestational week (Table 5, Figure 1-4)

Table 5. Correlation of Humerus Lenght with other parameters

	HL (mm)	
	r	p
BPD (mm)	0,741	<0,001
HC (mm)	0,813	<0,001
AC (mm)	0,748	<0,001
FL (mm)	0,834	<0,001
Gestational week	0,753	<0,001

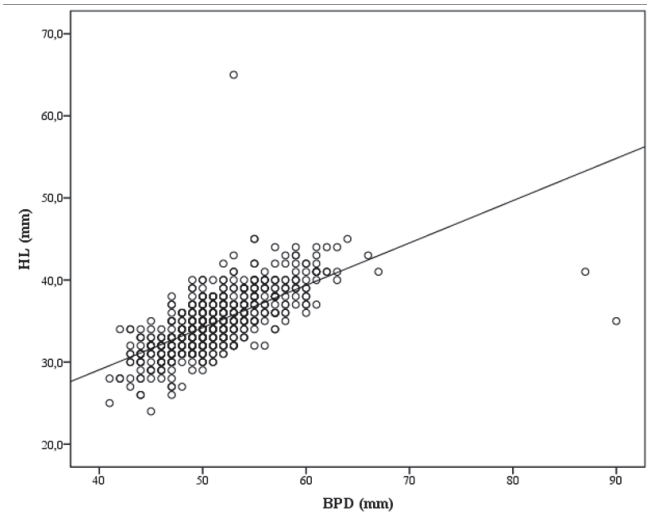

Figure 1. Correlation between HL and BPD measurments

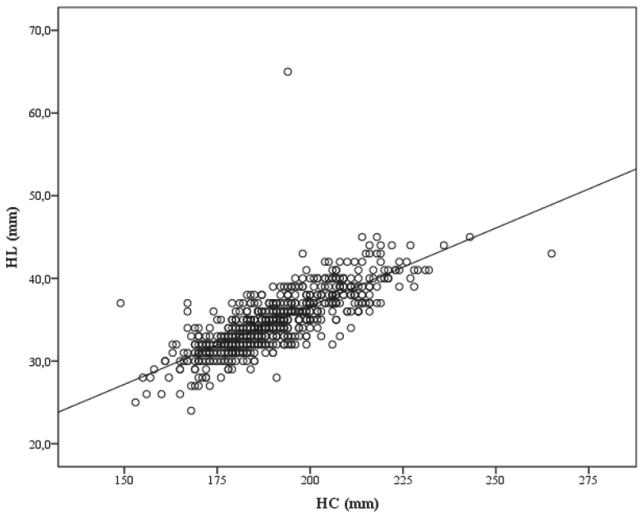

Figure 2. Correlation between HL and HC measurments

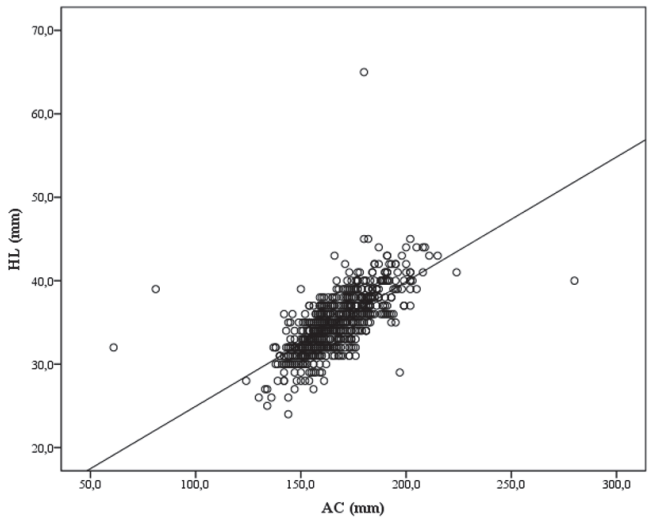

Figure 3. Correlation between HL and AC measurments

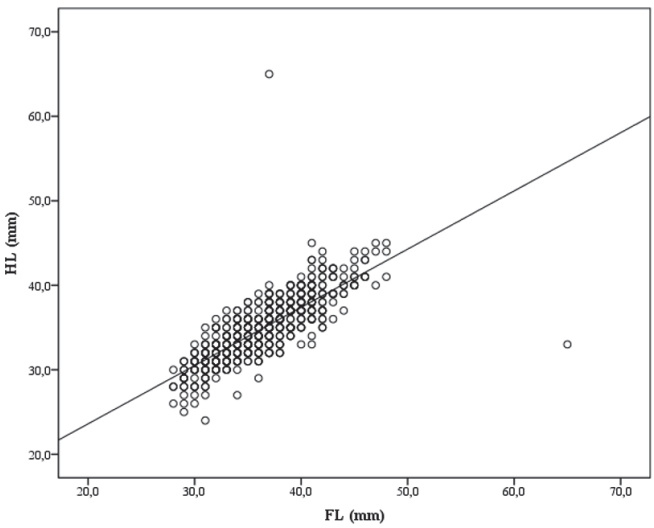

Figure 4. Correlation between HL and FL measurments

Comparision of our findings with previous Turkish studies and WHO fetal growth charts are summarized in Table 6

Table 6: Table showing HL percentiles by Gestational week (GW) in studies conducted in different Turkish populations and WHO Fetal Growth Charts.

GW	Our study				WHO Fetal Growth Charts			Göynümer et. Al.			Yorgunlar et. Al.		
	2,5p	5p	50p	95p	5p	50p	95p	5p	50p	95p	5p	50p	95p
19.w	25,9	27	31	34	25	28	31	25	29	32	22	29	33
20.w	28,2	30	33	36	28	31	33	29	32	35	26	31	35
21.w	31	31	35	39	31	34	36	30	33	37	30	32	37
22.w	32,7	34	38	41	33	36	39	33	36	39	32	35	38
23.w	34,4	36	39	44	35	38	41	34	38	41	34	37	41
24.w	35,9	36	41	45	37	41	43	35	39	45	36	39	42

Discussion

Fetal HL at 19-24 weeks of gestation is a critical parameter in prenatal assessments, serving as a reliable indicator of fetal growth and development. Furthermore, it is used to predict aneuploidy and FGR. Therefore, it is essential to investigate whether HL nomograms differ regionally, racially and between fetal genders. Integrating these demographic factors into clinical practice not only supports individualized patient care, but also contributes to better prenatal monitoring, diagnosis and fetal health outcomes.[4]

The findings presented by Kasraeian et al., in their study on fetal long-bone length provide crucial insights into the development of a nomogram for fetal HL. Their research highlights that variations in long-bone measurements among different populations can significantly influence the accuracy of gestational age assessment and the identification of potential congenital anomalies, thereby underscoring the necessity of spesific reference standards in obstetric practice.[8] Similarly; another study established nomograms for all the fetal limb bones in the Chinese ethnic population, which showed lengths comparatively shorter than Caucasian and Afro-Caribbean nomograms. They antipiciated that this would reduce the false alarm of short fetal limb bone lengths and the consequent anxiety and intervention.[9]

Our study revealed that the length of the humerus is greater than that observed in other populations, as documented in the WHO fetal growth charts. Additionally, it was noticed that there can be regional variations in this phenomenon. When the literature was reviewed, only 2 studies in terms of HL measurement from Turkey was found.[6,7] Both previous studies provided a comprehensive analysis of fetal HL during gestational weeks 18-24 in the İstanbul region and their HL nomograms are different from ours but very similar to the WHO growth charts.[10] The percentile values of these two studies and the WHO fetal growth chart study according to fetal HL are shown in Table 6 side by side with our study results. In particular, when the 2.5 percentile values of all gestational weeks in our nomogram were considered, these values were found to be consistent with the 5 percentile values in other studies, and when the 5 percentile values were considered, these HL values were found to be 1.2 mm longer on average across all gestational weeks compared with other studies. This result may be based on the fact that the population of Istanbul is diverse and consists of many different ethnic groups. While the greater HL measurements in our study may be attributed to the participation of a perinatologist, the utilisation of advanced ultrasound equipment, or advancements in prenatal care and nutrition, it remains possible that ethnic and geographic differences still exist and emphasises the need for the development of customised nomograms as literature indicates.

Fetal gender differences in fetal measurements have also been studied previously. Literature indicates that while there may be variations in fetal growth patterns between male and female fetuses, the differences in HL specifically may not be as pronounced as in other measurements. Hassan's study highlighted that fetal HL and femur length were comparable in estimating fetal age among Saudi fetuses, suggesting that while gender may play a role in overall fetal growth, it may not significantly impact HL length.[11] Similar to the literature, we found no statistically significant difference between HL measurements in terms of fetal gender.

The clinical utility of a fetal HL nomogram extends beyond mere measurement; it can also facilitate early detection of FGR and aneuploidies. The findings presented by Carvalho et al. highlighted the importance of utilizing spesific fetal HL nomograms, particularly in the context of identifying growth restrictions. The research findings indicated that fetuses with shortened HL may require closer monitoring especialy for FGR;[2] also the association between fetal bone lengths and chromosomal abnormalities, such as

Down syndrome, has also been well-documented.[12] Y. Tannirandorn et al. confirm that HL is significantly shorter in Down syndrome fetuses than in normal fetuses also support the previous literature about Asian population ,that second trimester fetuses in Asian population have shorter HL compared with caucasian and Afro-American fetuses.[13,14] Additionally, these studies suggest that gender and ethnic differences may impact the accuracy of FGR and congenital genetic anomalies and accordingly fetal outcomes.

The limitations of our study are that it was performed in a single center, the number of patients was small and it was retrospective.

Our study provides a comprehensive analysis of fetal humeral length between 19 and 24 weeks of gestation, with particular consideration of the ethnic and gender characteristics of the fetuses. The findings of our study demonstrate the necessity of ethnic-specific fetal HL nomograms. Furthermore, we anticipate that our results will contribute to the development of customised fetal nomograms for the Turkish population, in the future. In conclusion, by using a nomogram that accounts for ethnic differences, clinicians can better identify at-risk populations and provide targeted interventions, ultimately improving fetal outcomes.

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RESEARCH ARTICLE

Is plasminogen activator inhibitor-1 level a prognostic marker in COVID-19?

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Abstract

Introduction: We aimed to investigate the relationship of plasminogen activator inhibitor-1 (PAI-1) level, which is the main inhibitor of the fibrinolytic system, with COVID – 19 severities.

Methods: A total of 88 cases diagnosed with COVID – 19, 42 with mild pneumonia and 46 with severe pneumonia, were prospectively included in the study. Serum PAI-1 level was studied by ELISA method. COVID – 19 diagnosis was made by reverse transcriptase-polymerase chain reaction test.

Results: PAI – 1 level was found to be higher in the group with severe pneumonia compared to the group with mild pneumonia (72.1 ng/mL vs 64.1 ng/mL, respectively; p=0.005). In the multivariate regression analysis high level of serum PAI – 1 was associated with severe pneumoniae (OR: 1.073; CI: 1.003 – 1.147; p=0.040). The cut off value of PAI – 1 for severe pneumoniae was determined as 65.8 ng/mL with 52.2% sensitivity, specificity of 78.6%, positive predictive value of 72.7% and negative predictive value of 60%. The patients whose PAI – 1 level were over 65.8 ng/mL were found to have 4.646 times increased risk of severe pneumoniae compared to the ones who had PAI – 1 lower than 65.8 ng/mL (OR: 4.646; CI: 1.186 – 18.202; p= 0.027).

Conclusion: In this study, we found out that the serum level of PAI – 1 was higher in patients with severe pneumoniae than the ones with mild pneumoniae. High level of serum PAI – 1 was associated with severe pneumoniae.

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Introduction

Coronavirus disease (COVID-19) prognosis can vary from asymptomatic infection to Acute Respiratory Distress Syndrome (ARDS), multiple organ failure and death.[1] In severe COVID – 19 cases, it is known that the coagulation system is active. In the pathogenesis of hypercoagulability in patients with COVID-19; there is direct invasion of endothelial cells by virus, cytokines causing systemic inflammatory response, especially Interleukin (IL) – 6, neutrophil extracellular traps and activated complement system.[2] The frequency of thromboembolic events has increased in patients with severe COVID-19. In a study evaluating the frequency of thromboembolic events in COVID – 19 patients receiving prophylactic doses of anticoagulants followed in the Intensive Care Unit (ICU) thromboembolic events were detected at a rate of 31% .[3] These findings show that the coagulation system is active in COVID – 19 and coagulation markers have prognostic significace in the disease.

Fibrinolysis is the breakdown of fibrin by plasmin.[4] In fibrinolysis, inactive plasminogen is converted into active plasmin with the effect of plasminogen activator. The main enzyme of the fibrinolytic system is plasmin. Plasmin is a serine protease responsible for the degradation of fibrin and extracellular matrix proteins. There are two types of plasminogen activators in humans: Tissue – type Plasminogen Activator (tPA) and Urokinase-type Plasminogen Activator (uPA). The main regulator of these plasminogen activators is the Plasminogen Activator Inhibitor – 1 (PAI-1) molecule. PAI – 1 is the principal inhibitor of the fibrinolytic cascade. There are many publications in the literature in which PAI – 1 is used as a prognostic marker in patients with sepsis and ARDS.[5-7] Studies have also evaluated the relationship between COVID – 19 and the fibrinolytic system. In the study of Wright et al. with 44 severe COVID – 19 patients, fibrinolytic activity was evaluated by thromboelastography and it was observed that fibrinolytic activity stopped in 57% of the patients participating in the study.[8] This condition was associated with an increased risk of thromboembolic events. In vitro studies have shown that IL – 6 induces PAI – 1 production and inhibition of IL – 6 mediated signaling with tocilizumab reduces PAI – 1 levels.[9] In another in vitro study, it was determined that the spike protein of SARS – COV – 2 stimulated PAI – 1 production in human pulmonary microvascular endothelial cells.[10]

Therefore, in this study, we aimed to investigate the effect of plasma PAI – 1 level on disease prognosis in patients diagnosed with COVID – 19.

Material and Methods

Study Population

This study was designed as a prospective cross-sectional study in Ankara Bilkent City Hospital Internal Medicine Clinic. Ethics committee approval was obtained from Ankara City Hospital Ethics Committee for the study (approval number: E2-20-117). Written and verbal informed consent was obtained from the patients included in the study.

The study included patients over the age of 18 who applied to our clinic with COVID-19 symptoms and were diagnosed with COVID – 19 through a reverse transcriptase-polymerase chain reaction (RT – PCR) test. The cases were divided into two groups: mild and severe pneumonia. Patients with diagnosis of pregnancy, chronic restrictive or obstructive pulmonary disease, chronic renal failure, malignancy, rheumatological disease, diabetes mellitus, obesity, coronary artery disease, cerebrovascular accident history, peripheral artery disease history, chronic liver disease, hematological disorder and anticoagulant and immunosuppressive therapy (Pulse steroid, anakinra, tocilizumab) were not included in the present study.

In line with the COVID-19 Diagnostic Guidelines of the Turkish Ministry of Health; patients were divided into two groups; i.e., mild and severe pneumonia according to their clinical condition at hospital admission. Mild pneumonia; was defined as patients having a respiratory rate <30/minute and a room air oxygen saturation (SpO2) level >90%. Severe pneumonia was defined as patients having respiratory rate ≥30/minute and/or SpO2 level ≤ 90% in room air (PaO2/FiO2<300 in the patient receiving oxygen).

Demographic, clinical characteristics and laboratory findings of the patients were recorded from the patient files. In addition to routine tests, blood samples were taken from the patients for the plasma PAI – 1 level.

Plasma Plasminogen Activator Inhibitor – 1 Level

Peripheral blood samples were taken from the patients during their hospitalization to measure plasma PAI-1 levels, and the samples were centrifuged for 5 minutes after collection. The obtained plasma samples were preserved until analysis at -80°C. PAI

– 1 level; Human PAI – 1 elisa kit (Elabscience Biotechnology Inc, Houston, Texas) (Catalogue Number: E-EL-H2104, LOT number: A4CCIFTMP6) and were measured with 96 test kit according to manufacturer's instructions. The lyophilized standard available in the kit was dissolved and diluted. Standards were obtained at different concentrations. Compliant with kit procedure of the samples, absorbances were measured at 450 nm. standard curve graph ng/mL, in which all absorbances corresponding with the formula obtained with the help of concentrations were calculated. The measurable range is 0.16-10 ng/mL and the sensitivity is 0.1 ng/ml.

COVID – 19 Reverse Transcriptase-Polymerase Chain Reaction Test

Samples were taken from the upper respiratory tract (nose and throat) by swab or sputum. In Ankara City Hospital Clinical Microbiology Laboratory; Severe Acute Respiratory-associated Coronavirus – 2 (SARS – CoV – 2) RNA detection is made with Bio Speedy Bioeksen COVID – 19 RT-qPCR diagnostic kit (Istanbul, Turkey).

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL). The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Numerical variables showing normal distribution were expresssed with mean ± standard deviation, and numerical variables not showing normal distribution were expresed with median (min-max). Categorical variables were expressed with numbers and percentages. Student's T test or Mann-Whitney U test was used to compare numerical variables between the two groups. Chi-square test was used to compare categorical variables. The relationship between numerical variables was examined by Pearson and Spearman correlation analysis. Multivariate logistic regression analysis was used to identify risk factors affecting severe pneumonia. The ability of PAI – 1 level to distinguish severe pneumonia from mild pneumonia was evaluated with Receiver Operating Charecteristic (ROC) curve analysis, and the predictive values were determined according to the Youden index method. $P < 0.05$ (*) value was considered as significant in statistical analysis.

Results

The study population consisted of 88 patients, 42 with mild pneumonia and 46 with severe pneumonia. 68.2% of the patients was male (n:60) and their mean age was 55.5±16.2 years (range: 20-88 years). The median symptom duration of the patients was 12 days (range: 4-27). There was cough in 37.5% (n:33), headache in 10.2% (n:9), low back pain in 4.5% (n: 4), dyspnea in 46.6% (n:41), myalgia in 8% (n:7), anosmia in 1.1% (n:1), atralgia in 8% (n:7)) and 11.4% (n:10) had nausea symptoms. While 17% (n:15) of the patients received nasal oxygen, 21.5% (n:19) reservoir oxygen, 9.1% (n:8) high-flow oxygen support and 11.4% (n:10) were intubated, 41% (n:36) did not require oxygen. In the follow-up of the patients, the rate of need for ICU was found to be 33% (n:29). While no death was detected in mild pneumonia patients, the fatality rate was found to be 39.1% (n:18) in severe pneumonia patients (Table 1).

Table 1. Demographic and clinical characteristics of COVID-19 patients.

Variables	Patients n (%)
Age, years	55.5±16.2
Male, n (%)	60 (68.2)
Symptoms, n (%)	
Fever	33 (37.5)
Cough	33 (37.5)
Headache	9 (10.2)
Backache	4 (4.5)
Dyspnea	41 (46.6)
Myalgia	7 (8.0)
Anosmia	1 (1.1)
Arthralgia	7 (8.0)
Nausea- diarrhea	10 (11.4)
Symptom duration, day	12 (4-27)
10 and below	34 (38.6)
>10	54 (61.4)
Severe pneumonia, n (%)	46(52.3)
Respiratory status, n (%)	
Room air	36(41.0)
Nasal Cannula	15(17.0)
Reservoir oxygen	19(21.5)
High flow oxygen	8(9.1)
Mechanical ventilation	10(11.4)
Hospitalization duration, day	12(1-58)
ICU need, n (%)	29(33.0)
Exitus, n (%)	
Mild pneumonia	0(0)
Severe pneumonia	18(39.1)

Numerical variables were shown as mean±standard deviation or median (min-max) according to their normal distribution. Categorical variables were shown as numbers (%).
Abbreviations: ICU: Intensive Care Unit

Laboratory findings according to pneumonia severity are shown in Table 2 in detail. The mean PAI-1 level (72.1±15.8 ng/mL vs 64.1±9.5 29, respectively; p=0.005) was found to be higher in severe pneumonia cases compared to mild pneumonia cases.

Table 2. Distribution of laboratory findings according to pneumonia severity

Variables	Pneumonia		p
	Severe n=46	Mild n=42	
AST (U/L)	44.5(11-125)	36.5(17-211)	0.345
ALT (U/L)	48(8-291)	41.5(18-454)	0.917
Troponin (ng/L)	4.5(1-5037)	1(1-37.8)	0.001*
CK (U/L)	70(12-873)	59.5(12-614)	0.547
ALP (U/L)	91.5(30-210)	62(30-144)	<0.001*
GGT (U/L)	46(10-827)	28.5(8-194)	0.002*
Total bilirubin (mg/dL)	0.5(0.2-3.1)	0.4(0.2-0.9)	0.003*
Albumin (g/L)	32.8±6	39.7±4.2	<0.001*
Urea (mg/dL)	47(21-173)	32.5(17-71)	<0.001*
LDH (U/L)	442(209-873)	261(153-670)	<0.001*
Creatinine (mg/dL)	0.7(0.4-2.9)	0.8(0.5-1.6)	0.025*
WBC (x109/L)	10(4.8-22.4)	6.3(1.7-29.4)	<0.001*
Neutrophil (x109/L)	8.7(4-20.7)	4.3(1.3-26.5)	<0.001*
Eosinophil (x109/L)	0.04(0-0.43)	0.05(0-0.39)	0.563
Lymphocyte (x109/L)	0.6(0.1-3.2)	1.4(0.3-2.9)	<0.001*
Hemoglobin (g/dL)	12.5±2.1	13.9±1.6	0.001*
Thrombocyte (x109/L)	302(31-681)	236(105-599)	0.232
CRP (g/L)	0.05(0-0.2)	0.01(0-0.17)	<0.001*
Procalcitonin (µg/L)	0.07(0.02-20.65)	0.02(0.02-1.62)	<0.001*
Ferritin (µg/L)	654(20-3369)	243.5(19-1711)	<0.001*
Fibrinogen (g/L)	4.8±1.5	4.1±1.4	0.022*
aPTT (second)	22.5(18-127)	23.7(19.5-29.6)	0.204
D-Dimer (mg/L)	1(0.2-16.9)	0.4(0.2-6)	<0.001*
INR	1.1±0.3	1.0±0.1	0.025*
PAI-1 (ng/mL)	72.1±15.8	64.1±9.5	0.005*

Numerical variables were shown as mean±standard deviation or median (min-max) according to their normal distribution. Categorical variables were shown as numbers (%). *p<0.05 indicates statistical significance.

Abbreviations: AST: Aspartate aminotransferase, ALT: Alanine aminotranferase, CK: Creatinine kinase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, LDH: Lactate dehydrogenase, WBC: White blood cell, CRP: C – reactive protein, aPTT: Active partial thromboplastin time, INR: International normalized ratio, PAI – 1: Plasminogen activator inhibitor-1

Factors predicting severe pneumonia in patients were analyzed by univariate and multivariate logistic regression. Accordingly, low albumin (OR:0.843; p=0.045), high lactate dehydrohenase (LDH) (OR:1.010; p=0.002), low hemoglobin (OR:0.666; p=0.044), and high PAI – 1 (OR:1.073; p=0.040) were factors associated with severe pneumonia in the multivariate analysis. Univariate and multivariate regression analyzes for factors predicting severe pneumonia are shown in Table 3.

Table 3. Parameters predicting severe pneumonia in univariate and multivariate regression

Variables	Univariate analysis			Multivariate analysis		
	OR	%95 confidence interval	p	OR	%95 confidence interval	p
Age	1.052	1.020-1.085	0.001			
LDH	1.013	1.007-1.018	<0.001	1.010	1.004-1.016	0.002
Albumin	0.761	0.673-0.862	<0.001	0.843	0.714-0.996	0.045
ALP	1.029	1.013-1.045	<0.001			
Neutrophil	1.266	1.112-1.442	<0.001			
WBC	1.215	1.081-1.366	0.001			
Ferritin	1.002	1.001-1.003	0.001			
Hemoglobin	0.649	0.499-0.844	0.001	0.666	0.449-0.989	0.044
Urea	1.057	1.023-1.093	0.001			
PAI-1	1.059	1.014-1.106	0.009	1.073	1.003-1.147	0.040

Only parameters that were significant (p<0.05) in the univariate regression model were included.

Abbreaviations: LDH: Lactate dehyrogenase, ALP: Alkaline phosphatase, WBC: White blood cell, PAI – 1: Plasminogen activator inhibitor – 1

The ability of PAI – 1 level to distinguish severe pneumonia from mild pneumonia was evaluated by ROC Curve analysis. In multivariate analysis, the ability of factors associated with severe pneumonia to distinguish severe pneumonia from mild pneumonia was evaluated by ROC Curve analysis and the area under the curve (AUC) was calculated (Figure 1). Accordingly, AUC values for LDH, albumin, hemoglobin, and PAI – 1, respectively, were 0.855 (95% CI: 0.774-0.936), 0.821 (95% CI: 0.735-0.908), 0.686 (95% CI: 0.575- 0.797) and 0.688 (95% CI: 0.576-0.799).

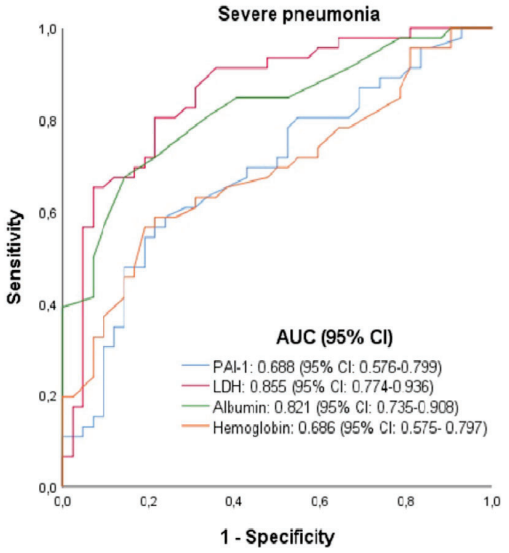

Figure 1. ROC curve evaluating the ability to distinguish factors associated with severe pneumonia from mild pneumonia in multivariate analysis

Appropriate cut-off values were calculated for these four parameters using the Youden index with ROC curve analysis. Accordingly, the appropriate cut-off values for LDH, albumin, hemoglobin, and PAI-1 were determined as> 401.5 U/L, <35.5 g/L, <12.9 g/dL, and >65.8 ng/mL, respectively. Multivariate logistic regression analysis was performed again with the cut-off values of these predictors. Accordingly, those with LDH>401.5 U/L had 21,643 times higher risk of severe pneumonia than those with LDH<401.5 U/L, those with albumin <35.5 g/L had 5.721 times higher risk than those with albumin> 35.5 g/L, those with hemoglobin <12, 9 g/dL had 5.328-fold increased risk of severe pneumonia compared to those with hemoglobin>12.9 g/dL, and those with PAI – 1>65.8 ng/mL had a 4.646 – fold increased risk compared to those with PAI – 1<65.8 ng/mL. Multivariate regression analysis with predictors' cut-off values is shown in Table 4.

Tablo 4. Predictors of severe pneumonia according to appropriate cut-off values in multivariate regression

Variables	OR	%95 confidence interval	p
LDH (>401.5 U/L)	21.643	4.312-108.620	<0.001
Albumin (<35.5 g/L)	5.721	1.520-21.530	0.010
Hemoglobin (<12.9 g/dL)	5.328	1.378-20.599	0.015
PAI-1 (>65.8 ng/mL)	4.646	1.186-18.202	0.027

Abbreaviations: LDH: Lactate dehyrogenase, PAI – 1: Plasminogen activator inhibitor – 1

In patients with severe pneumoniae it was also found that the PAI – 1 level was positively correlated with the levels of alkaline phosphatase (ALP) (r= 0.290; p=0.050), urea (r=0.410; p=0.005), neutrophil (r=0.310; p=0.036), and D – Dimer (r=0.321; p=0.030) (Table 5).

Table 5. Relation of parameters with PAI-1 Level in Severe Pneumonia Patients

Variables	PAI	
	r	p
Age	0.102	0.498
Symptom duration	0.274	0.065
Hospitalization duration	-0191	0.204
AST	0.268	0.072
ALT	0.142	0.347
Troponin	0.256	0.086
CK	0.169	0.261
ALP	0.290	0.050*
GGT	0.183	0.223
T. bilirubin	0180	0.231
Albumin	-0.275	0.064
Urea	0.410	0.005*
LDH	0.251	0.092
Creatinine	0.102	0.499
WBC	0.281	0.058
Neutrophil	0.310	0.036*
Eosinophil	0.082	0.588
Lymphocyte	-0.075	0.620
Hemoglobin	-0.171	0.257
Thrombocyte	-0.040	0.791
CRP	-0.106	0.481
Procalcitonin	0.128	0.397
Ferritin	0.064	0.670
Fibrinogen	-0.094	0.536
aPTT	0.145	0.336
D-Dimer	0.321	0.030*
INR	0.164	0.275

Abbreviations: AST: Aspartate aminotransferase, ALT: Alanine aminotranferase, CK: Creatinine kinase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, LDH: Lactate dehydrogenase, WBC: White blood cell, CRP: C – reactive protein, aPTT: Active partial thromboplastin time, INR: International normalized ratio, PAI – 1: Plasminogen activator inhibitor-1

Discussion

In this study, we examined whether PAI - 1 is associated with the prognosis of COVID - 19 infection. In our study, PAI - 1 levels were found to be higher in COVID - 19 cases with severe pneumonia compared to cases with mild pneumonia. We found that PAI - 1 levels are associated with severe pneumonia due to COVID - 19.

Hypofibrinolytic state associated with elevated PAI-1 levels has been observed in SARS-COV coagulopathy.[11,12] Studies perfromed previously supports impaired fibrinolysis in COVID-19 disease. [8] In in vitro studies, the spike protein of SARS-COV-2 has been shown to stimulate PAI-1 production in human pulmonary microvascular endothelial cells.[10] However, in COVID-19 infection; Angiotensin converting enzyme-2 (ACE-2) expression, which is the receptor of the virus, decreases and the amount of angiotensin-2 increases. There are also studies reporting that increased angiotensin-2 promotes hypercoagulant state by increasing PAI-1 level.[13]

In the present study, according to the multivariate regression, high PAI-1 and LDH and low hemoglobin and albumin levels are factors associated with severe pneumonia in COVID-19. There are few studies in the literature examining the relationship between PAI-1 level and pneumonia severity in patients diagnosed with COVID-19. Zuo et al evaluated this relationship in patients with COVID-19.[14] In their study examining plasma PAI-1 level in 118 COVID 19 patients, it was determined that the patients in need of oxygen had a higher plasma PAI-1 level compared to the patients followed up with room air. Results of the same study showed a negative correlation between plasma PAI-1 level and arterial oxygen saturation/percentage of oxygen in inspired air. In the present study, high PAI-1 level was found to be a predictor for severe pneumonia, and those with PAI-1>65.8 ng/ml were associated with a 4.646-fold increased risk of severe pneumonia compared to those with PAI-1 level of <65.8 ng/ml. In the study by Masi et al., the mean PAI-1 value was found to be 95.2 ng/mL in COVID-19 patients with severe pneumonia.[15] In our study, mean PAI-1 level was found to be 72.1 ng/mL in severe pneumonia patients. The reason for the higher level of PAI-1 in their study may be related to the inclusion of patients with comorbidity in the study. Because previous studies in the literature have shown that diabetes mellitus, atherosclerotic disease, stroke, cardiovascular disease, malignancy and obesity are associated with high PAI-1 levels.[4,16] In the study of Umemura et al., in which serum PAI-1 levels were examined in 24 patients with ARDS caused by COVID-19 and in patients with ARDS caused by non-COVID-19 diseases, PAI-1 levels (median: 28 ng/ml) were found in the normal range in patients with a diagnosis of COVID-19.[17] According to the results of the study, it was argued that there is no suppression of systemic fibrinolysis in COVID-19, where coagulopathy of COVID-19 and sepsis are different from each other. However, low number of patients with a diagnosis of COVID-19 participating in the study may be the reason why the PAI-1 value was found within the normal range.

In the present study, low albumin level was found to be a factor associated with severe pneumonia, and those with albumin level of <35.5 g/L were associated with a 5.721-fold increased risk of severe pneumonia compared to those with albumin >35.5 g/L. When previous studies were examined, it was determined that low albumin level was associated with mortality and disease severity in severe inflammation conditions such as sepsis and ARDS.[18,19] In this context, low albumin level was found to be associated with disease severity in many studies conducted in COVID-19 patients with severe systemic inflammation.[20] Our results are in agreement with the available literature data.

In the present study, low hemoglobin level was found to be associated with severe pneumonia. Those with hemoglobin level of <12.9 g/dL had a 5.328-fold increased risk of severe pneumonia compared to those with hemoglobin>12.9 g/dL. Anemia is commonly encountered in patients followed up for pneumonia. In the study of Bellmann-Weiler et al., the frequency of anemia in COVID-19 was found to be 24.7%.[21] In the presence of anemia, the oxygen carrying capacity decreases, thus increasing the severity of respiratory diseases. In the study of Wang et al. in COVID-19 patients, low hemoglobin level was found to be an independent predictor for severe disease.[22]

In the present study, high LDH level was established to be a factor associated with severe pneumonia. The LDH cut-off value for severe pneumonia was determined to be>401.5 U/L. Those with LDH>401.5 U/L had a 21,643-fold increased risk of severe pneumonia compared to those with LDH<401.5 U/L. In

the study of Li et al. in COVID-19 patients, high LDH level at the time of admission to the hospital was found to be an independent risk factor for severe illness and death.[23] The high LDH level in patients with severe pneumonia can be explained by the fact that plasma LDH level reflects lung injury and tissue damage.

It was found that plasma PAI-1 level was positively correlated with neutrophil, urea, ALP and D-Dimer levels in severe pneumonia patients. Neutrophils are an important factor in the occurrence of organ damage in COVID-19.[17] One of the hallmarks of COVID-19-induced ARDS is the sequestration of neutrophils in lung microvascularity.[24] This local proinflammatory environment is further enhanced by the formation of neutrophil extracellular traps (NETs), resulting in the release of proinflammatory cytokines. These cytokines probably promote the release of PAI-1 by endothelial cell activation. Zuo et al.'s study in COVID-19 patients found a positive correlation between PAI-1 and absolute neutrophil count.[14] In our study, as mentioned above, a positive correlation was found between PAI level and neutrophils in severe pneumonia patients.

Organ damage in COVID-19 patients with severe pneumonia is not limited to the lung. Severe COVID-19 affects many organs and systems with its severe inflammation, cytokine storm and coagulopathy.[25] Liver and kidney dysfunction is a common condition associated with poor prognosis in critically ill COVID-19 patients.[18,19] Indeed, in our study, a positive correlation was found between plasma PAI-1 level, which is an indicator of severe pneumonia in COVID-19, and ALP and urea levels, which are liver-kidney function tests.

D-dimer is a fibrin degradation product produced during fibrinolysis. In a study conducted by Oualim et al in COVID-19 patients, it was revealed that high D-Dimer levels are associated with poor prognosis.[26] In the current study, the D-dimer level was found to be higher in patients with severe pneumonia compared to those with mild pneumonia, and a positive correlation was shown between PAI-1 level and D-dimer level in patients with severe pneumonia. This can be explained by the fact that both molecules are predictors of the prothrombotic state. In a study conducted in patients with breast cancer, a positive correlation was found between PAI-1 and D-Dimer levels.[27]

The small number of patients and the fact that the PAI-1 level was not determined in the clinical follow-up of the patients are the limitations of our study. In addition, another limitation is that anticoagulant drugs and low-dose steroid treatments administed in the treatment of the disease can affect PAI-1 level, which may change plasma PAI-1 levels.

Conclusions

In Conclusion, in our study, plasma PAI-1 level was found to be associated with disease prognosis. If this result is supported by larger-scale studies, early identification of patients who are thought to have a poor prognosis may make it possible for these patients to be treated earlier and more aggressively.

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RESEARCH ARTICLE

The Evaluation Of Dysmenorrhea, Quality Of Life, And Sexual Functions In Patients With And Without Conization

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Abstract

Introduction: Conization is a surgical procedure performed to treat precancerous lesions. HPV is the most predisposing cause known. In our study, we aimed to evaluate and compare patients who were followed up as HPV positive and had conization due to cervical pathology in terms of dysmenorrhea, quality of life and sexual function.

Methods: HPV positive patients who underwent conization at Selcuk University Faculty of Medicine Obstetrics and Gynecology Department were evaluated.4 main surveys were used in the study. Personal and Demographic Information Form, Dysmenorrhea Scale - Visual Analogue Scale (VAS), Female Sexual Function Index (FSFI); It was evaluated using (Turkish Female Sexual Function Scale), and European Organisation for Research and Treatment of Cancer Quality of Life (Turkish EORTC QLQ-C30 (version 3.0)). In our study, we considered two groups: those without hpv positive conization and those with hpv positive conization.

Results: Dysmenorrhea scores of patients who underwent conization are higher than those of patients who did not undergo conization. Female sexual function scores of patients who underwent conization are higher than those of patients who did not undergo conization. There was no significant difference between the QoL scores of patients who underwent conization and those who did not.

Conclusion: The cervix has an anatomically important neurovascular network. Care should be taken at this point in terms of conization procedures. Surgical complications should be carefully evaluated in the treatment of precancerous lesions. HPV is a sexually transmitted disease and the treatment of lesions caused by it can affect anxiety, quality of life, sexual function and menstrual cyclus.

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Introduction

The loop electrosurgical excision procedure (LEEP), utilizes a skinny wire in the shape of a loop and an electrosurgical tool that allows accurate and selective blending of the current. Conization is performed with a scalpel, almost always under general or regional anesthesia. The patient is placed in the dorsal lithotomy position. It is the removal of the cervical pathological area, including the transformation zone. This cervical surgical procedure may be used to obtain excisional biopsies or to surgically treat high-grade ıntraepithelial lesions (HSIL) or persistent low-grade intraepithelial lesions (LSIL) and can be used to determine treatment modalities before cervical cancer surgery. Like any surgical procedure, conization has risks and complications. In this study can classify them as obstetric and nonobstetric. These are excessive bleeding after the postoperative period, excessive bleeding due to the operation, dysmenorrhea, and poor quality of life.[1] Especially depending on the depth of conization, premature birth, prematurity, and cervical insufficiency may develop.[2] At this point, Human Papilloma Vırus (HPV) is known as the pathogenic virus in the group that creates the most indications. Regarding social and sexual life, it can be thought that there is a decrease in sexual functions and quality of life in both men and women.[3-4] An increase in sexual life after conization can be detected, compared to HPV.[5]

In this study, we aimed to score the quality of life, dysmenorrhea, and sexual function of patients with HPV-positive preinvasive lesions who underwent conization and to compare these parameters in patients without HPV-positive preinvasive lesions.

Material and Methods

Patients who underwent conization/LEEP due to cervical pathologies at Selçuk University Faculty of Medicine, Department of Gynecology and Obstetrics, between 01/01/2021 and 30/12/2024 were evaluated. Two main groups were formed in the study. Those who were HPV positive and those who were HPV positive but developed HSIL or persistence LSIL and conization. Pathological specimens included approximately 0.5 cm areas of the conization material transformation zone to the excision margin were evaluated, and cases with intraoperative complications were not included. Patients between the ages of over 45 years who were diagnosed with high-grade intraepithelial lesions or persistent low-grade lesions and who were therefore planned for conization/leep surgery are the main sample of the study. In patients who develop secondary dysmenorrhea, those who are found to have no additional adnexal or other organ pathologies that may cause pelvic pain will be included. Patients with a known history of endometriosis, tuba-ovarian abscess and pelvic inflammatory disease, intrauterine device use, current pregnancy, or abortion, and those who wish to withdraw from the study will excluded from the study. Patients who did not use hormonal and surgical contraceptive methods, used barrier methods, or had unprotected sexual intercourse were evaluated. The questionnaires were evaluated when the patients were called for control. Since this was our routine evaluation, the patients were called by phone for missing forms. It was retrospectıvely evaluated because ıt was our routıne clınıc survey. Those who smoked, used substances, and had multiple partners were high-risk patients. HPV was not grouped separately; evaluation was made based on those that caused high-grade lesions and those that did not. The non-conization group consists of positive patients and those whose smear and cervical biopsy have no pathology if indicated and who are followed up. The conization group consists of patients who are HPV-positive and have pathology that requires conization.

Personal and Demographic Information Form, Dysmenorrhea Scale - Visual Analogue Scale (VAS), Female Sexual Function Index (FSFI); It was evaluated using (Turkish Female Sexual Function Scale), and European Organisation for Research and Treatment of Cancer Quality of Life (Turkish EORTC QLQ-C30 (version 3.0)).

The TFSFI survey has 19 questions; It evaluates 6 main factors: sexual desire, sexual arousal, lubrication, orgasm, satisfaction, and pain/discomfort. The highest total raw score that can be obtained in this scale is 95, the lowest raw score is 4, and after multiplying the coefficients, the highest score is 36 and the lowest score is 2. Impact coefficients were used to score the entire scale; It was determined as 0.6 for sexual desire, 0.3 for sexual arousal and lubrication, and 0.4 for orgasm, satisfaction, and pain/discomfort. A TFSFI score below 26.55 was defined as compatible with sexual dysfunction.[6] VAS scales pain intensity on a scale of 1-10.[7] T-EORTC; taken from this section means high scores indicate that the quality of life has increased, while low scores indicate that the quality has decreased.[8] Postoperative evaluation was made in the 8th week.

Selçuk University Faculty Of Medicine Ethical approval: 25.09.2024-E837694 2024/16

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Congress, Hyatt Istanbul Atakoy, It was presented by me as an oral presentation.

Statistics

For power analysis, power values for different sample numbers were calculated with G*Power software. The data was analyzed through the Statistical Package for the Social Sciences (SPSS) 26.0 Statistics package program. Categorical variables of patients with and without conization are given as numbers and percentages, and numerical variables are given as mean and standard deviation. The compliance of the patients' dysmenorrhea, and female functionality normal distribution was determined by looking at the skewness and kurtosis values. It was observed that not all variables followed the rules of normal distribution. The Chi-Square Test was used to compare the descriptive characteristics of the patients according to the status of conization. Paired Sample T Test was used to compare the preoperative and postoperative dysmenorrhea, female sexual function, and anxiety levels of each group, and the Independent Sample T Test was used to compare the preoperative and postoperative dysmenorrhea, female sexual function and anxiety levels according to the conization status. In the entire study, significance levels were determined by taking into account the values of 0.05 and 0.01.

Results

Descriptive Data

In the study 1.2% of the patients who underwent conization were under the age of 45, 3.8% were aged 45 and over, and 100% of the HPV-positive patients who did not undergo conization were under the age of 45. According to these results, the age distribution and mean age of patients who underwent and did not undergo conization differed ($p<0.05$). 49% of patients who underwent conization and 74.5% of patients who did not undergo conization use protection methods. According to these results, there is no difference in contraceptive method use rates between patients with and without conization ($p<0.05$). The rate of using protection methods in patients who underwent conization is lower than in patients who did not undergo conization. When HPV status is examined; While 65.3% of the conization group had HPV 16 or 18, 45.5% of the non-conization group had these high-risk types. While the low-risk or negative HPV rate was 8.2% in the conization group, this rate was 29.1% in the non-conization group. 24.5% of patients who underwent conization and 43.6% of patients who did not undergo conization smoke. According to these results, the smoking rates of patients who underwent and did not undergo conization were similar ($p>0.05$). The rate of those with negative cervical pathology was 18.4% in the conization group and 65.5% in the non-conization group. The rate of unvaccinated individuals is 69.4% in the conization group and 92.7% in the non-vaccinated group. The rate of vaccinated individuals is 30.6% in the conization group and 7.3% in the non-vaccinated group. According to these results, the vaccination rates of patients who underwent and did not undergo conization differed ($p<0.05$) (Table 1).

Table 1. Descriptive characteristics of patients according to conization procedure

Descriptive Characteristics		Conization (n:49)		No conization (n:55)		p
		no	%	no	%	
Age	<45	30	61,2	55	100,0	**0,000****
	>45	19	38,8	0	0,0	
Smoking	No	37	75,5	31	56,4	0,065
	Yes	12	24,5	24	43,6	
Contraception Methods	No	25	51,0	14	25,5	**0,013***
	Yes	24	49,0	41	74,5	
HPV	Low risk	4	8,2	16	29,1	**0,000****
	HPV 16,18	32	65,3	25	45,5	
	Another HR-HPV	13	26,5	14	25,5	
Smear	Negative	19	38,8	38	69,1	**0,000****
	ASCUS	7	14,3	9	16,4	
	LSIL	2	4,1	5	9,1	
	HSIL	21	42,9	3	5,5	
Cervical pathology	Negative	9	18,4	36	65,5	**0,000****
	LSIL	5	10,2	14	25,5	
	HSIL	34	69,4	5	9,1	
	AGC	1	2,0	0	0,0	
Vaccination	No	34	69,4	51	92,7	**0,005****
	Yes	15	30,6	4	7,3	
		med±S.D (Min.-Max.)		Med.±S.D (Min.-Max.)		
Age		43,63 ± 9,05 (25-72)		37,24 ± 5,48 (23-44)		**0,000****

Ort.: Median, S.D.: Standard Deviation a, Min.: Minimum, Max.: Maximum.
Categorical data statistics: chi-squared test, t: Independent Sample T Test
HR HPV= High-Risk HPV , lSIL=Low grade intraepithelial lesion , HSIL= High-Grade intraepiteial Lesion, ASCUS= atypical squamous cells of undetermined significance AGC= Atypical glandular cells

Dysmenorrhea Status

There was a significant difference between the dysmenorrhea scores of patients who underwent conization and those who did not ($p<0.05$). The average dysmenorrhea score of patients who underwent conization is 4.97, and the average dysmenorrhea score of patients who did not undergo conization is 0.27. According to these data, dysmenorrhea scores of patients who underwent conization are higher than those of patients who did not undergo conization (Table2).

Table 2. Examination of dysmenorrhea, female sexual selectivity, and QoL levels of patients according to conization status

Parameters	Conization (n:49) Med .±S.D	No conization (n:55) Med.±S.D	p
Dysmenorrhea Score (VAS)	4,97 ± 3,03	0,27 ± 0,45	**0,000****
T-FSFI	18,38 ± 6,93	13,53 ± 9,73	**0,006****
T-QoL Score	5,21 ± 4,11	5,31 ± 6,29	0,927

*p<0,05, **p<0,01. p: Independent Sample T Test
Dysmenorrhea Scale - Visual Analogue Scale (VAS), Turkish Female Sexual Function Index (TFSFI); T-QoL Quality of Life (Turkish EORTC QLQ-C30 (version 3.0))

Examination of Female Sexual Functioning Levels

There was a significant difference between the female sexual function scores of patients who underwent conization and those who did not ($p<0.05$). The average female sexual function score of patients who underwent conization is 18.38, and the average female sexual function score of patients who did not undergo conization is 6.93. According to these data, female sexual function scores of patients who underwent conization are higher than those of patients who did not undergo conization (Table 2).

Quality Of Life (QoL) Score

There was no significant difference between the QoL scores of patients who underwent conization and those who did not. The average preoperative QoL score of patients who did not undergo conization was 2.89 and the average postoperative QoL score was 5.31. There was a significant difference between before-diagnostic and post-diagnostic QoL scores of patients without conization ($p<0.05$) (Table 3).

Table 3. QoL Levels Before and After Surgery According to Conization Status

Parameters		Conization (n:49) Md.±S.D	No conization (n:55) Md.±S.D	p1
QoL score	Preop-Dt	5,53 ± 4,75	2,89 ± 3,63	0,003**
	Postop	5,21 ± 4,11	5,31 ± 6,29	0,927
	p2	0,657	**0,000****	

*p<0,05, **p<0,01.
p1: Paired Sample T Test
p2: Independent Sample T Test
Dt= Diagnosis time

Discussion

As a result, the rate of postoperative dysmenorrhea in patients who underwent conization is higher than in those who did not undergo surgery. While there was no difference in sexual scoring in patients after conization, there was a decrease after the moment of diagnosis in patients without conization. While there was no preoperative and postoperative difference in patients with conization, there was a significant difference between the pre-and post-diagnostic quality of life scores of patients without conization. When the literature was examined in the light of this information, it was examined especially in terms of meaningful results. There was a significant difference in postoperative dysmenorrhea scores depending on the conization performed ($p<0.05$). According to these data, dysmenorrhea scores of patients who underwent conization are higher than those of patients who did not undergo conization. In a study, complications of trachelectomy were examined, especially in the young population where fertility preservation was desired. Although our study was a conization examination, similarities such as ulceration, cervical stenosis, and obstetric complications should be kept in mind.[9-10] In a randomized controlled study, dysmenorrhea, profound dyspareunia, amenorrhea, vaginal bleeding, and cervical stenosis clinics were evaluated after conization.[11] Although it is associated with painful syndromes such as HPV vulvodynia / vulvovestibulitis, its direct relationship with dysmenorrhea has not been shown.[12-13] According to the data of the study, female sexual function scores of patients who underwent conization were found to be higher than those who did not undergo conization. In another study in the sexual function and conization evaluation performed on 55 women, no significant decrea-

se was observed in sexual function scores.[14] In our findings, a decrease was found in the scores of those without conization. We think that the reason for this is that the patients can have a more comfortable sexual life after conization because they have HPV and lesion treatment, while the other group has a decrease in their scores because they carry HPV and are afraid to infect it or have partner problems. In a review article, the results of 9 centers were examined and, unlike our study, a negative decrease in scores was detected.[15] In a case-control series, no change in FSFI scores was observed along with an increase in anxiety level.[16] In this series, a 6-month follow-up was made, in our case this period was 2 months, but the same scales were used. In a study conducted ın Korea, including 66 cases, no significant difference was shown after leep.[17] Although it is an old study, it is important to inform patients because of the reproductive period age range.[18] Based on this study, sexual counseling may be recommended, although we do not practice it routinely. The average female sexual function score before diagnosis of patients without conization is 16.40 and the average female sexual function score after diagnosis is 13.53. A significant difference was observed between the female sexual function levels before and after diagnosis in patients who did not undergo conization ($p<0.05$). In a study conducted on patients with genital warts and a control group consisting of a total of 74 patients, an evaluation was made with the ENRICH Marital Satisfaction Scale and Arizona Sexual Experience Scale, and the score was found women with warts had lower scores than men.[19] Another study; ıt has revealed that HPV positivity causes a significant deterioration in women's psychological and sexual health.[20] This study, which showed that HPV increases in direct proportion to the number of partners but did not detect any difference in sexual function, was conducted in the form of a telephone interview and is reliable in that it covers a long-term process. Data was collected by scanning the archives of the tests we routinely perform in our clinic and by calling patients who could not be reached.[21] In a study with similar results Even several years after LLETZ or Conization women may suffer from impaired Emotional Well-Being and reduced HRQoL. Awareness and assessment of these long-term consequences should be part of surveillance after excisional treatments for cervical dysplasia. Although it is essential to administer the vaccine before infection occurs, it may also be recommended to administer it as soon as the patient is detected. New infections and the bimodal peak status of cervical cancer should be explained to the patient. Although it is essential to administer the vaccine before infection occurs, it may also be recommended to administer it as soon as the patient is detected. New infections and cervical cancer bimodal peak status should be explained to the patient. Depending on the patient's age group, 2 or 3 doses of vaccine may be recommended (nanovalan is preferred).[22]

Conclusions

When patients encounter the HPV result, they realize that it is a sexually transmitted virus, and this can cause problems in the couple's relationship and the patient's self-confidence. In this respect, patients can be directed to family therapy and individual psychotherapy. Detailed information about HPV, vaccination, and protection methods can be provided by avoiding speculation. Although patients' quality of life and sexual functions may be affected, suitable patients should be encouraged for the treatment of precancerous lesions. Large case series are needed to investigate the effects and complication profiles of many surgical procedures such as conization, LEEP, LLETZ (Large loop excision of the transformation zone), trachelectomy, and cervical amputation, both obstetrically and nonobstetrically.

No conflict of interest.

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RESEARCH ARTICLE

Definitive Radiotherapy/Chemoradiotherapy Results in Geriatric Non-Small Cell Lung Cancer Patients with Multiple Comorbidity

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Abstract

Introduction: It was aimed to evaluate the definitive radiotherapy (RT)/ chemoradiotherapy outcomes in geriatric non-small cell lung cancer (NSCLC) patients with multiple comorbidities.

Methods: Patients who received RT 06.03.2019 and 24.10.2022 in XXX Hospital were analyzed retrospectively. The primary endpoints were RT compliance, acute adverse events (AAE), completeness of treatment. The secondary endpoints were overall survival (OS), disease-free survival (DFS).

Results: The results of 62 patients who received definitive RT/CRT were analyzed. Median follow-up time was 16 (2-55) months. The median age of the patients was 75(70-89) years. The median number of comorbidities was 3(2-6). Thirty-seven (59.7%) patients received concurrent chemotherapy (CRT);12(19.4%) patients received induction chemotherapy. One patient (1.6%) could not complete the RT and RT was interrupted in 6 (9.7%) patients. RT interruption was more common in patients with cerebrovascular disease (CVD) (p=0.002; OR5.5; CI %954,3-7). AAE were noted in 20 (32.3%) patients and AAEs increased with CRT (p=0.006; OR 6.2;95%CI1.5-24.4). Eighteen (29%) patients relapsed, 11(17.7%) of relapses were locoregional while 7 (11.3%) were distant. Median DFS was 12 (range1-50) months. Significantly higher DFS was observed in patients with squamous cell cancer (SCC) (p=0.021; HR 2.8;95%CI1.12-7.18). Thirty-three (53.2%) patients have died. Twenty-seven (81.8%) patients died without relapse, 6(17.2%) died after relapse. Median OS was 14 (2-50) months. Patients who interrupted RT had lower OS (p=0.003; HR5.96;95%-CI2.23-15.9). Patients with 3≥ comorbidities had lower OS (14 vs10 months) (p=0.053; HR2.3;CI95%0.98-5.8).

Conclusion: Definitive RT/CRT is an effective treatment with acceptable toxicity in geriatric NSCLC patients with multiple comorbidities.

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Introduction

According to GLOBOCAN 2020 statistics, an estimated 2,206,771 patients were diagnosed with lung cancer (LC) and 1,796,144 people die due to lung cancer.[1] The world population is aging, and more geriatric patients are refering oncology clinics. Consequently, an increase in lung cancer in the geriatric population is predicted.[2,3] However, treatment approaches are mostly based on studies of non-geriatric patient groups. It is an important problem that the treatment protocols obtained by excluding the geriatric patient group are applied directly to geriatric patients.[4]

In non-small cell lung cancer (NSCLC) patients, surgery is in the foreground in the early stage, while chemoradiotherapy (CRT) is indicated in locally advanced stages. Radiotherapy (RT) is an important part of local treatment in patients who are medically and surgically inoperable.[4] In elderly cancer patients with comorbidities who are not suitable for systemic therapy or surgery, radiotherapy is an effective treatment that can be used for both palliative and curative purposes.[5-8] CRT is a more effective treatment than only RT in this patient group, but it also causes a significant increase in advers effects.[9] It is important to consider the benefit/harm balance in the treatment decision.

The patient's chronological age should not be the only parameter for geriatric – fragile patient identification. In addition to chronological age, comorbidities, polypharmacy, functional status, life expectancy, psychological and mental status should also be evaluated.[10,11] Although the available data are limited, it has been reported that standard treatments are well tolerated, and oncologic outcomes are similar in elderly patients with good general condition.[12] There is no standard treatment approach in geriatric cancer patients with comorbidities, clinicians determine the treatment schemes according to the patient's condition and the extent of the disease. Evaluation of every geriatric patient admitted to the oncology clinic with geriatric scales and evaluation of these results together with oncological outcomes can guide the determination of treatment protocols.[13] Clearly, studies are needed for more standardized approaches. Patients should be evaluated from many aspects and clinics should routinely establish a scoring system for every geriatric patient.[12]

In this study, definitive RT/CRT results in NSCLC patients over 70 years of age and with at least 2 internal comorbidities were analyzed. It was aimed at evaluating the parameters affecting the tolerance of RT therapy and oncologic outcomes in geriatric NSCLC patients with multiple comorbidities.

Material and Methods

Geriatric patients who received curative dose RT with the diagnosis of NSCLC between 01.01.2019 and 30.12.2022 in the XXX Clinic of XXX Hospital were analyzed retrospectively. Patient files, dose volume histograms and medical records from electronic systems were used to obtain data. Patient demographics, complaints, radiological and pathological results, treatment details, acute adverse effects, recurrence status and final status were noted. Staging was performed according to American Joint Committee on Cancer (AJCC) ver 8., Common Terminology Criteria for Adverse Events (CTCAE) ver. 5 was used for acute adverse effect assessment.

Patient Selection

Patients with a diagnosis of NSCLC with pathological evidence, at least two internal comorbidities, age> 70years, receiving RT for curative purposes, and ECOG 0-3 were included in the study. The patients who could not complete radiotherapy were also included in the study. Under 70 years of age, without pathological evidence, with one or no internal comorbidity, patients receiving palliative RT and ECOG 4 were excluded. Patients with relapse or who underwent RT for adjuvant purposes were also excluded from the study.

Primary and Secondary Endpoints of the Study

The geriatric group is considered fragile, clinicians avoid aggressive treatments due to toxicity concerns. The primary endpoints of the study were interruption and completion of RT and acute RT toxicities. The secondary endpoints of the study were the evaluation of overall survival (OS) and disease-free survival (DFS) in this patient group. The end date of RT was accepted as the start date for the overall survey and DFS. The endpoint for OS was the last control date for surviving patients and the exitus date for those who died. The endpoint for DFS was the date of first event for patients with relapse, the date of last control for patients without relapse.

Statics

SPSS ver. 26 was used to note and analyze the data in the study. The conformity of the variables to the normal distribution was evaluated with histogram, detrend blot and Shapiro Wilk test. Non-para-

metric tests were preferred since its did not fit the normal distribution. Kaplan Meier and log rank test were used for univariate survival analysis. The significance limit of the study was accepted as 0.05.

Results

The results of 62 patients who received RT for curative purpose between 06.03.2019 and 24.10.2022 in our clinic were analyzed. Median follow-up time from diagnosis was 16 (2-55) months. The median age of the patients was 75 (range 70-89) years and 54 (87.1%) patients were male; 9 (12.9%) patients were women. The median number of comorbidities was 3.[2-6] There was a history of malignancy in 6 (9.7%) patients. The most frequently preferred RT technique was intensity modulated radiotherapy (IMRT) (n=53; 85.5%). RT total dose was median 60 (range 50-66) Gy. Concurrent chemotherapy was applied to 37 (59.7%) patients and induction chemotherapy (ind-CT) was applied to 12 (19.4%) patients. Concomitant chemotherapy was also applied in all patients receiving induction chemotherapy. Twenty-one (33.9%) of patients received no induction or concurrent chemotherapy. Patient and treatment details were summarized in Table 1.

Table I. Patient and treatment details

Parameters		n	%
Gender	Female	8	12.9
	Male	54	87.1
Age	Median (range)	75 (70-89)	
Localisation	Right	35	56.5
	Left	27	43.5
Stage	1	10	16.1
	2	6	9.7
	3	36	58.1
	4	10	16.1
Pathology	SCC	48	77.4
	Adenocancer	14	22.6
Chemotherapy	Induction CT+C-RT	8	12
	Induction CT+RT	4	6
	CRT	29	46
	Only RT(without CT)	21	33
Number of Comorbid Diseases	Median (range)	2 (0-6)	
	2 comorbidities	17	27.4
	3 or more comorbidities	45	72.6
COPD	No	33	52.2
	Yes	29	46.8
CAD	No	32	51.6
	Yes	30	48.4
CVD	No	58	93.5
	Yes	4	6.5
Malignancy anamnesis	No	56	90.3
	Yes	6	9.7 Lymphoma 1 (1.6) Laryngeal cancer 2 (3.3) Colon Cancer 1 (1.6) Prostate Cancer 2 (3.3)
RT Technique	3D	1	1.6
	IMRT	53	85.5
	VMAT	2	3.3
	SRT	6	9.7
RT Total Dose	Median (range)	60 (50-66)Gy	
RT Interruption	Interrupted	6	9.7
	Not interrupted	56	90.3
RT Complete Status	Completed	61	98.4
	Not completed	1	1.6
Concurrent CT	Yes	37	59.7
	No	25	40.3
Induction CT	Yes	12	19.4
	No	50	80.6
Acute Adverse Effect	No	42	67.7
	Yes	20	32.3 Dysphagia 18 (29) Leukopenia 2 (3.3)
Recurrence	No	44	71
	Yes	18	29 Locoregional 11 (17.7) Distant 7 (11.3)
Last Status	Alive	29	46.8
	Ex	33	53.2

SCC: Squamous cell cancer; RT:Radiotherapy; CT: Chemotherapy; 3D: Conformal RT; IMRT: Intensity Modulated RT; VMAT: Volumetric arc RT; SRT: Stereotactic RT; COPD : Chronic obstructive pulmonary disease; CAD: Coronary artery disease; CVD: Cerebrovascular disease

Radiotherapy Tolerance

RT compliance of the patients was high. RT was interrupted in only 6 (9.7%) patients. The treatment interruption durations were as follows; 22 days, 21 days, 19 days, 9 days, 6 days and 5 days. The reason for the interruption was the deterioration of the general condition of the patients. There was no significant relationship between RT-interruption and gender (p=0.420); right and left primary (p=0.220); pathology (SCC vs adenocancer) (p=0.590); malignancy anamnesis (p=0.528); number of comorbidity(2 vs 3 and higher)(p=0.176), chronic obstructive pulmonary disease(COPD) (yes or no)(p=0.868), coronary artery disease (CAD) (yes or no)(p=0.099); stage (p=0.866); RT technique (p=0.770); applying CR

T (p=0.678); applying ind-CT (p=0.586) or RT total dose (0.638). RT was interrupted more frequently in patients with cerebrovasculary disease (CVD) (p=0.002; OR 5.5; CI %95 4.3-7). Treatment was interrupted in 3 of 4 patients with CVD.

Only 1 patient (1.6%) could not complete their treatment. The patient who could not complete the RT scheme was an 87-year-old T3N0 SCC male patient. This patient did not receive induction or concomitant CT. The patient, who was planned 60 Gy, did not continue the treatment due to deterioration of the general condition while at the 54 Gy. Local progression was observed at 14 months of follow-up. He died in the 21st month after RT.

Acute Adverse Effect Assessment

Acute adverse events were noted in 20 (32.3%) patients. The most common acute adverse effect was dysphagia, and it was seen in 18 (29%) of patients. There was no significant relationship between acute adverse effects and gender (p=0.705); right and left primary (p=0.544); pathology (SCC vs adeno) (p=0.495); stage (p=0.097) malignancy anamnesis (p=0.495); number of comorbidity (2 vs 3 and higher)(p=0.265); COPD (yes or no)(p=0.458); CAD (yes or no)(p=0.262); CVD (yes or no)(p=0.201); RT technique (p=0.150); applying ind-CT (p=0.591) or RT total dose (0.833).

Acute adverse events were observed in 45.9% of patients receiving concomitant chemotherapy and in 12% of patients who did not receive concomitant chemotherapy. Acute adverse events significantly increased with CRT (p=0.006; OR 6.2; 95% CI 1.5-24.4).

According to AJCC TNM staging nodal stage of the patients included in our study were as follows: N3: 14 patients, N2: 19 patients, and N0-1: 29 patients. Unexpectedly, it was observed that 2 of the N3 patients (14%) and 5 of the N2 patients (26%) started treatment with induction chemotherapy. Oligometastatic patients evaluated as M1 constituted 16% (n=10) of all patients.

DFS Analysis

During the follow-up period, 18 (29%) patients relapsed, and the disease was under control in 46 (73.1%) patients. While 11 (17.7%) of the relapses were locoregional, 7 (11.3%) were distant. Median DFS was 12 (range 1-50) months (Figure 1). There was no significant relationship between DFS and gender (p=0.665); right and left primary (p=0.417); malignancy anamnesis (p=0.848); number of comorbidity (2 vs 3 and higher)(p=0.215); COPD (yes or no)(p=0.063); CAD (yes or no)(p=0.081); CVD (yes or no)(p=0.241); stage (p=0.740); RT technique (p=0.102); RT interruption (p=0.448); applying CRT (p=0.564); applying induction CT (p=0.936) or RT total dose (p=0.052).

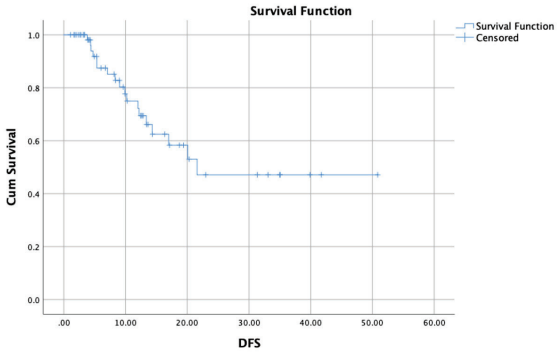

Fig.1. Disease free survey Kaplan Meier analysis

A significantly higher DFS was observed in patients with primary SCC who received definitive RT compared to adenocancer. The median DFS of SCC patients was 13 (range 1-41) months and it was 9 (range 1-50) months in adenocancer patients (p=0.021; HR 2.8; 95% CI 1.12-7.18)(Figure 2).

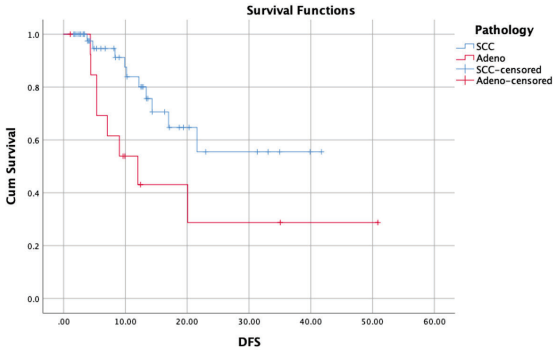

Fig.2. A significantly higher DFS was observed in patients with primary SCC than adenocancer.

OS Analysis

During the follow-up period, 33 (53.2 %) patients have died, 29 (46.8%) patients were alive. Of the 33 patients who died, 27 (81.8%) died without relapse, 6 (17.2%) died after disease relapse. Median OS was 14 (range 2-50) months (Figure 3). There was no significant relationship between OS and gender(p=0.393); right and left primary (p=0.412); pathology (SCC vs adenocancer) (p=0.602); stage (p=0.063); malignancy anamnesis (p=0.333); COPD (yes or no)(p=0.420); CAD (yes or no)(p=0.148); CVD (yes or no)(p=0.153);RT technique (p=0.191); applying CRT (p=0.065); applying induction KT (p=0.795) or RT total dose (p=0.055).

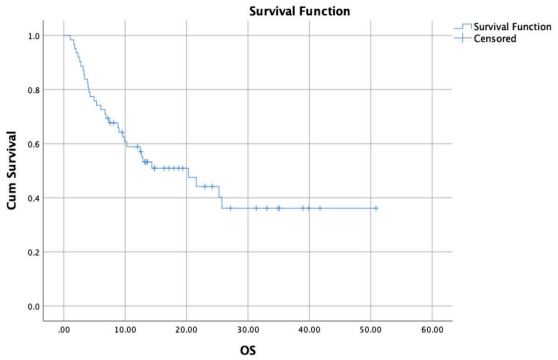

Fig. 3. Overall survey Kaplan Meier analysis

A significantly lower OS was observed in patients who interrupted RT (p=0.003; HR 5.96; 95% CI 2.23-15.9). Median OS was 15.4 (range 2-50) months in patients who did not interrupt RT and median OS was 4 (2-46) months in patients with RT interruption (Figure 4).

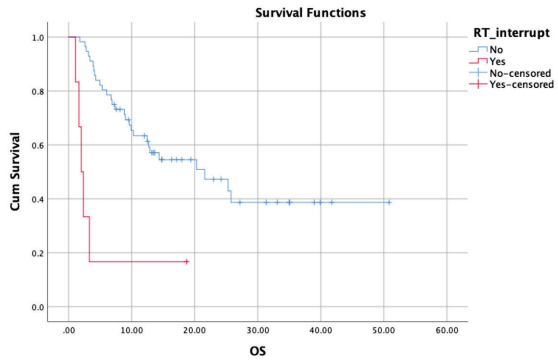

Fig.4. A significantly lower OS was observed in patients who interrupted RT compared to those who did not.

The relationship between the number of comorbidity and OS was close to the limit of significance (2 vs 3 and higher) (p=0.053; HR 2.3;CI95% 0.98-5.8). The median OS in patients with 2 internal comorbidities was 14 (range 3-39) months. The median OS value was 10 (range 1-50) months in patients with three or more comorbidities (Figure 5).

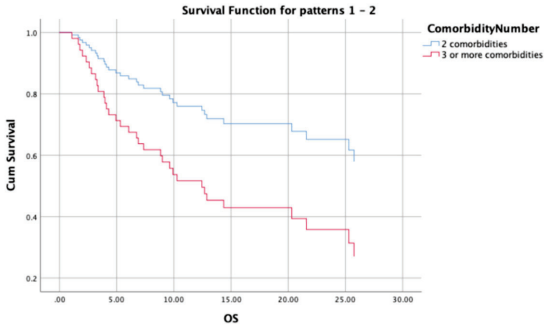

Fig.5. The relationship between the number of comorbidity and OS was close to the limit of significance (p0.053).

Discussion

Sixty-two geriatric patients with multiple comorbidities were analyzed. Treatment compliance of the patients was excellent, only 1 (1.6%) patient could not complete the RT scheme. RT was interrupted in only 6 (9.7%) patients. RT was interrupted more frequently in patients with CVD. Acute adverse events were significantly higher in patients receiving concomitant chemotherapy. No increase in acute adverse effects was observed in patients who received induction chemotherapy before concomitant CRT. There was a 4-month DFS difference in SCC patients compared to adenocancer, and this difference was significant (13 vs. 9 months). Patients who interrupted RT had dramatically lower OS (15.4 vs 4 months). OS was lower in patients with 3 or more internal comorbidities (14 vs 10 months) and the difference was close to the limit of significance (p=0.053).

Due to the changing demographic structure of the world, more geriatric patients are admitted to RT clinics. However, this patient group is underrepresented in clinical studies and is treated with a protocol that is not tailored to them. Considering lung cancer, comorbidities, which are more common with increasing age, may cause a decrease in RT tolerance.[12] The standard approach in early-stage NSCLC is surgery, and SBRT can be applied in patients who are not suitable for surgery. A pooled analysis of prospective randomized STARS and ROSEL studies showed improved survival with SABR than surgery in resectable patients, although not focusing on elderly patients.[14] Updated results of the STARS trial, published in 2021, stated that SABR is an effective short-term cu-

rative therapy with acceptable toxicity for frail or elderly patients, too.[15] In 772 patients with early stage I-II NSCLC (T1-T3N0M0) Brooks et al evaluated the effectiveness of SABR (50 Gy in 4 fractions or 70 Gy in 10 fractions).[16] While 442 of the patients were aged <75 years; 330 patients were aged ≥75 years. In this study, which had a median follow-up of 55 months, there was no significant difference between time-to-progression (p=0.419), lung cancer-specific survival (p=0.275), or toxicity (p=0.536) in the patient arm aged below 75 years and older. No patient ≥75 years of age experienced any grade 4 or 5 toxicity. In OS analysis, 1- and 3-year OS values were similar, but 5-year OS was lower in the advanced age group.[16] In the SEER-based study of Sigel et al, 6468 geriatric unresectable NSCLC patients who had undergone RT alone were analyzed. The OS contribution was observed with RT, but the patients had an increased risk of hospitalization for pneumonitis and esophagitis. These results suggest that the use of RT alone may improve outcomes in elderly patients with unresected stage III NSCLC. However, severe toxicity was significantly higher in the RT-treated group. They commented that the potential risks and benefits of RT should be carefully discussed with eligible elderly NSCLC patients.[17] In current study, the median follow-up period was 16 months and the median OS was 14 months. During the follow-up period, 33 (53.2 %) patients have died. Our remarkable result was that 27 (81.8%) of 33 patients died without recurrence. In our geriatric patient population with multiple comorbidities, a significant portion of our patients died while the disease was under control. Due to the retrospective nature of our study, long-term treatment adverse effects and the relationship between these adverse effects and the exact cause of death could not be reached. However, the high mortality rates that occur while the disease is under control clearly show that a treatment decision should be made considering the profit and loss balance, whether it is treatment-related or not.

Comorbidities are predicted as a very important determinant of lung cancer survival, and this importance is more pronounced in geriatric patients.[18] There are not enough studies to evaluate multiple comorbidities in geriatric NSCLC patients. One of the most interesting studies on the subject has been done by Cardia et al.[19] The results of 90 lung cancer (SCLC + NSCLC) patients over 70 years of age were evaluated in the study. In this study, groups were analyzed according to those with and without comorbidity. There was no significant difference in survival between the two arms.[19] Janssen-Heijnen et al evaluated the relationship between age, comorbidity and survival in NSCLC patients. In patients with comorbidities, despite less aggressive treatment, comorbidity seemed to have a negligible effect on survival of patients with lung cancer.[20] In the study of Fırat et al, 112 stage 3 NSCLC patients from 4 Radiation Therapy Oncology Group (RTOG) studies (RTOG 83-11, 84-03, 84-07, and 88-08 nonchemotherapy arms) were evaluated in terms of the relationship between comorbidity and survival.[21] In this study, comorbid diseases were evaluated with The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and Charlson scales. And they found that, comorbidities were defined as important independent prognostic factors in Stage III NSCLC.[21] Unlike other studies,[19,20] Fırat used a score that takes into account not only the presence or absence of comorbid disease, but also the number and severity of comorbid diseases.[21] Therefore, while comorbidity did not have a significant effect on survival in other studies,[19,20] it may have been significant in the study of Fırat et al.[21] It would be more accurate to evaluate the relationship between comorbidities and survival with scales that include the number, degree and severity of diseases. In our study, the number of diseases was evaluated, but a scoring that also evaluated the severity of the disease was not performed. According to our results, lower OS was observed in patients with three or more comorbidities. However, the number of patients in our study was small and the follow-up period was short. It is thought that this difference may become significant in larger series and longer follow-up.

RT interruption should not be acceptable unless necessary. The most common causes of RT interruption are public holiday, linak breakdown and treatment-resistant acute adverse events. It has been proven that prolonging the overall treatment time in many cancers such as cervical cancer, head and neck squamous cell carcinoma and anal squamous cell carcinoma adversely affects local control and survival.[22-24] There are limited studies evaluating the relationship between treatment interruption and survival in NSCLC patients. In these studies, it was observed that the prolongation of the treatment period worsened the local control and survival.[25-27] In the study

of Jeremic et al, the relationship between treatment interruption and oncologic outcomes was evaluated in NSCLC patients undergoing hyperfractionated RT (69.6 Gy, 1.2 Gy b.i.d.).[29] Patients with RT- interruptions had statistically significantly lower OS, local recurrence free survey (LRFS) and cause specific survival (CSS).[25] McMillan et al evaluated the relationship between prolonged radiation treatment and survival in NSCLC patient.[30] In this study, 14,154 patients were screened from The National Cancer Database, and the RT prolongation was observed in 6262 (44.2%). It was emphasized that prolongation of RT duration was an independent risk factor for OS in NSCLC patients and RT interruption should be minimized.[30] In this study, treatment was interrupted by approximately 10% of our patients. Like the literature, RT interruption resulted in a decrease in OS (15.4 vs 4 months). Another significant result of RT interruption is that it was observed more frequently in patients with CVD. Although RT interruption to treatment was observed in 75% of patients with CVD in our study, acute adverse effects, DFS and OS were not significantly affected. However, only 6.5% of our patients have a history of CVD. For a more accurate interpretation, the relationship between CVD and oncologic outcomes should be evaluated in larger series.

In patients with NSCLC who are scheduled for definitive RT, CRT improves oncologic outcomes compared to RT alone, while increasing adverse effects.[5,31,32] Especially because of cardiopulmonary comorbidities, patients are not suitable for systemic treatment. In this patient arm, sequential therapy is more appropriate than concurrent therapy, and the oncological results of sequential chemotherapy are better in geriatric patients compared to younger patients.[5,33] In the Japan Clinical Oncology Group studies, RT concomitant low-dose carboplatin was evaluated in geriatric patients. Confirmed the survival benefits of CRT in elderly patients with locally advanced NSCLC. No increase in late toxicity was observed with CRT compared to RT alone.[34-36] In this study, there was no patient arm who received sequential chemotherapy. Concurrent chemotherapy was applied to all 12 patients who received induction. A significant increase in acute toxicity was observed with concomitant CT, but the presence of induction did not cause an increase in RT toxicity.

SCC and adenocarcinoma are two distinct subtypes that differ in histology, anatomical localization and prognosis.[37] Adenocancer and SCC are also radiosensitive, although not as much as small cell lung cancer (SCLC).[38] Nomori et al evaluated CRT outcomes of adenocarcinoma and SCC.[36] More residual tumor, worse clinical and pathological responses were observed in adenocancer patients compared to SCC patients. In addition, recurrence-free survival was worse in adenocarcinoma patients, while OS was similar in both pathologies.[39] The results of our study are also in agreement with the results of Nomori et al. Higher DFS is observed after definitive RT in SCC patients compared to adenocancer. However, there was no significant difference in overall survival.

The study was single-center and retrospective. Because of its retrospective nature, geriatric examination or any geriatric scoring was not performed. The number of patients was low, the follow-up period was short, and long-term adverse effects could not be evaluated. Evaluation of immunological agents was not performed. A comparison of concurrent and sequential CRT could not be made. The exact cause of death could not be determined for every patient. Lastly, the number of diseases was evaluated, but a scoring that also evaluated the severity of the disease was not performed.

Conclusions

Definitive RT/CRT is an effective treatment with acceptable toxicity in geriatric NSCLC patients with multiple comorbidities. The treatment compliance of the patients is excellent. Higher DFS is observed after definitive treatment in SCC patients compared to adenocancer. OS is significantly reduced when RT is interrupted and in patients with three or more comorbidities.

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RESEARCH ARTICLE

The Relationship Between Sleep and Quality of Life in Older People Living in Nursing Homes

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Abstract

Introduction: Sleep problems are more prevalent in older adults compared to the general population. This study aims to assess the relationship between sleep quality, sleep propensity and quality of life among nursing home residents.

Methods:A total of 107 nursing home residents who attended the geriatric outpatient clinic between May and July 2016 were included in the study. Demographic data and comorbidities were recorded. Sleep quality and sleepiness were evaluated using the Pittsburgh Sleep Quality Index (PSQI) and Stanford Sleepiness Scale (SSS), with higher scores indicating worse sleep quality and increased sleep propensity. Quality of life was measured using the SF-36 Quality of Life Scale. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Windows 21. Correlation analysis was performed using Spearman's rho, with statistical significance set at $p < 0.05$.

Results: Among the 107 participants, 67 (62.6%) were women. The mean score of PSQI in the study population was found to be 6.33 ± 4.03. Of the participants, 65.3% were classified as having poor sleep quality. A positive and statistically significant correlation was observed between PSQI scores and all sub-dimensions of the SF-36 scale except pain. The correlation between the SSS and each sub-dimension of the SF-36 scale is statistically significant except pain and mental health status.

Conclusion: Our study demonstrates that poor sleep quality and daytime sleepiness are common among nursing home residents and are associated with lower quality of life. Dementia was identified as the most common comorbidity related to sleep problems. To improve the quality of life in nursing home residents, addressing sleep disturbances should be a key focus of care.

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Introduction

The older population is the fastest-growing demographic globally, with the World Health Organization defining old age as a period marked by a decreased ability to adapt to environmental factors.[1] Aging is commonly associated with changes in circadian rhythms and sleep homeostasis which contribute to alterations in sleep patterns.[2] The prevalence of sleep disturbances is notably higher in older adults compared to the general adult population, with over 50% of older individuals reporting sleep problems.[3] A study conducted in Turkey further highlighted that the incidence of sleep disorders is significantly higher in older adults residing in nursing homes.[4]

Deterioration in sleep quality among older adults can have profound consequences on emotional, cognitive, and physical health. Poor sleep is linked to a range of negative outcomes, including emotional disturbances, mental health disorders, and a loss of motivation. Individuals who experience inadequate sleep often face physical, emotional, and cognitive decline.[5] Additionally, poor sleep quality is closely associated with daytime sleepiness, fatigue, depression, anxiety, irritability, increased pain sensitivity, muscle tremors, and a decline in both mental functions and overall health status.[6] Daytime sleepiness, also referred to as excessive sleep propensity, is characterized by difficulty maintaining wakefulness, which can result in feelings of drowsiness and the urge to nap.

Excessive daytime sleepiness can lead to a range of functional impairments and further exacerbate sleep problems, creating a cycle of poor sleep. The older people, particularly those aged 65 and older, are affected by poor sleep quality in nearly every biopsychosocial domain. Despite the widespread nature of these issues, there is a relative scarcity of studies focusing on sleep quality among nursing home residents in Türkiye.

Therefore, the aim of this study is to examine the correlation between sleep quality, sleep propensity, and quality of life among nursing home residents. By investigating the relationship between sleep disturbances and quality of life, this study seeks to provide insight into the challenges faced by individuals in institutional care settings and highlight the importance of addressing sleep issues to enhance their quality of life.

Material and Methods

Study Design

This cross-sectional study, conducted at the Geriatrics Outpatient Clinic of Ankara Ataturk Hospital (May-July 2016), included 107 older nursing home residents, selected from 300. Eligibility required being 65 or older, residing in the nursing home, and having sufficient cognitive function. Participants with advanced dementia were excluded. Written consent was obtained from literate, voluntary participants. Participants were grouped into three age categories: 65-74, 75-84, and 85+. Data on demographics, comorbidities, medications, and fall history were collected

Sleep Quality Evaluation

The Pittsburgh Sleep Quality Index (PSQI) is a reliable, valid, and standardized tool used to assess sleep quality. It contains 24 questions, 19 of which are self-reported by the participant, while 5 are answered by a spouse or roommate for clinical purposes without affecting the overall score. A score of 5 or higher on the PSQI indicates poor sleep quality.[7]

The Stanford Sleepiness Scale (SSS) is a subjective measure of daytime sleepiness, evaluating the level of "fogginess" and the tendency to lose interest in staying awake. The scale ranges from 1 (mildest) to 7 (most severe), with a score above 3 indicating excessive daytime sleepiness or sleep propensity.[8]

Quality of Life Assessment

The 36-Item Short Form Health Survey (SF-36) is a widely used tool to assess health status and quality of life. It contains 36 items that cover two main dimensions (physical and mental health) and eight concepts: physical function, role limitations due to physical problems, pain, vitality, social function, role limitations due to emotional problems, mental health, and general health perception. Scores on the SF-36 range from 0 to 100, with higher scores reflecting better health-related quality of life.[9]

Statistical Evaluation

Descriptive statistics were calculated for all study variables. The normality of the data was assessed using the Shapiro-Wilk test. For comparing categorical variables, chi-square tests were used. The Spearman rho coefficient was employed for correlation analysis to assess relationships between sleep quality, sleepiness, and quality of life. A p-value of <0.05 was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows version 21.

Results

Of the study participants, 62.6% (n=67) were female, with a mean age of 82.40 ± 6.33 years. Tables 1 summarize demographic data and comorbidities.

Table 1: Descriptive Statistics of Participants

Variables	n (%)
Sex	
Female	67 (62.6%)
Male	40 (37.4%)
Educational Status	
Elementary School- No Education	36 (46.7%)
Middle School- High School	57 (53.3%)
Age Groups	
Group 1 (Age 65–74)	12 (11.2%)
Group 2 (Age 75–74)	58 (54.2%)
Group 3 (Age 85+)	37 (34.6%)
Number of Drugs*	5.98 ± 2.84
Comorbidities	
Fall	29 (27.9%)
Obesity	29 (27.9%)
Hypertension	82 (76.6%)
Coronary Artery Disease	37 (34.6%)
Diabetes Mellitus	83 (77.6%)
Cerebrovascular Accident	15 (14.0%)
Dementia	24 (22.4%)
Parkinson's Disease	10 (9.3%)
Depression	29 (27.1%)
Chronic Obstructive Pulmonary Disease	11 (10.3%)
Heart Failure	12 (11.2%)
Cancer	8 (7.5%)

* Number of drugs is presented as a mean ± standard deviation

The mean score of PSQI in the study population was found to be 6.33 ± 4.03. Of the participants, 65.3% were classified as having poor sleep quality. The individual subcomponents of the PSQI were also assessed, with the following mean scores: Subjective Sleep Quality: 0.99 ± 0.86 Sleep Latency: 1.66 ± 1.13 Sleep Duration: 0.91 ± 0.92 Sleep Efficiency: 0.67 ± 0.93 Sleep Disorders: 0.79 ± 0.57 Medication Use: 0.50 ± 1.05 Daytime Function: 0.82 ± 1.21 The subcomponent of sleep latency had the highest mean score, suggesting that difficulty in falling asleep was a prominent issue among participants. The median PSQI scores for the different age groups were as follows: Group 1: 6.00 Group 2: 6.00 Group 3: 5.00 No statistically significant difference in the PSQI scores was observed across the age groups (p = 0.433), indicating that age did not significantly affect overall sleep quality. The median score on SSS was: Group 1: 6.00 Group 2: 2.00 Group 3: 3.00 The SSS scores showed a statistically significant difference between the age groups (p = 0.009), with advanced-age individuals (Group 3) having higher SSS scores than the other groups, suggesting greater sleep-related issues with increasing age.

When evaluating the relationship between comorbidities and sleep scales, dementia was significantly associated with the SSS score (p = 0.026), while cerebrovascular accidents and dementia were both significantly related to the PSQI score (p = 0.004 and p = 0.015, respectively). However, no significant relationship was found between polypharmacy or falls and the sleep scales.

The correlation between PSQI and each sub-dimension of the SF-36 scale is presented in Table 2. The strongest correlations were observed with Physical Function (0.522), Vitality (0.523), and General Health Status (0.480), all of which show significant associations with poorer sleep quality. The pain sub-dimension had a very weak negative correlation (-0.041) and was not statistically significant (p=0.692).

Table 2. Correlation analysis of PSQI with SF 36 scale sub-dimensions

Variables	Spearman's Rho Coefficient	p-value
Physical Function	0.522	<0.001
Physical Role	0.450	<0.001
General Health Status	0.480	<0.001
Vitality	0.523	<0.001
Social Function	0.437	<0.001
Emotional Function	0.476	<0.001
Mental Health Status	0.287	0.003
Pain	-0.041	0.692

The correlation between the SSS and each sub-dimension of the SF-36 scale is presented in Table 3. While Vitality (−0.349) and Physical Function (−0.307) showed the strongest negative correlations with SSS, both with p-values <0.01 Mental Health Status (−0.118) and pain (−0.038) showed very weak correlations and were not statistically significant (p>0.05).

Table 3. Correlation analysis of SSS with SF 36 scale sub-dimensions

Variables	Spearman's Rho Coefficient	p-value
Physical Function	-0.307	0.002
Physical Role	-0.136	0.174
General Health Status	-0.274	0.006
Vitality	-0.349	<0.001
Social Function	-0.242	0.015
Emotional Function	-0.248	0.012
Mental Health Status	-0.118	0.241
Pain	-0.038	0.354

Discussion

Our findings indicate that poor sleep quality and high sleep propensity are prevalent among older adults residing in nursing homes and are significantly associated with a lower quality of life. One of the strengths of our study is the use of two sleep scales simultaneously to evaluate individuals' sleep quality, which provides a comprehensive assessment of sleep disturbances in this population. With normal aging, sleep changes occur due to effects of an aging suprachiasmatic nucleus that leads to circadian rhythm changes. Along with many other physiological alterations in normal aging, sleep patterns change with aging, independent of many factors including medical comorbidity and medications. Our study supports the finding that sleep propensity tends to be higher in individuals over the age of 85, a group particularly vulnerable to sleep disturbances. Sleepiness may dramatically affect a patient's quality of life and is linked to changes in neurocognitive function, such as memory loss, impaired fine motor skills and abnormal executive function.[10] Patients whose complaints appear consistent with normal aging need not be further investigated. Daytime napping may be normal or even beneficial, but excessive daytime sleepiness should not be considered normal in the healthy old people. Any patient who appears to be getting a reasonable amount of sleep who has difficulty staying awake should have further evaluation. Sleep disorders, dementia, depression, chronic diseases and medications may contribute this problem as people ages. In line with these observations, several studies have investigated the prevalence of sleep disorders among older adults. For example, a study by Chiu et al,[11] conducted in China, found that 75% of 1,034 older individuals reported sleep disturbances. In another study of 400 nursing home residents in Iran, 83% were found to have poor sleep quality, and 29% experienced excessive daytime sleepiness.[12] Similarly, Çalık's study[13] reported that 48% of older adults had poor sleep quality, while 77% experienced excessive daytime sleepiness. These findings underscore the widespread nature of sleep disturbances in aging populations and the importance of addressing sleep-related issues to improve quality of life in older individuals.

In our study, we found that the most significant factor contributing to sleep disorders among older adults was sleep onset latency. Contrary to common belief, which assumes that the ability to initiate sleep declines markedly with age, current evidence does not fully support this assumption. Research suggests that both sleep latency and the ability to return to sleep after nocturnal awakenings demonstrate only minimal increases after the age of 60 years. While sleep latency has been shown to increase with age, the magnitude of this change is modest, as indicated by results from two meta-analyses.[14,15] In these studies, sleep latency remained relatively stable from childhood through adolescence, with a notable increase only occurring between young adults and older adults. A study by Fadıloğlu et al.[3] conducted in a nursing home population found that 23% of older residents had difficulty falling asleep, 47% reported frequent awakenings after initially falling asleep, and 32% were able to fall back asleep after waking up.[3] However, in contrast to these findings, our study identified sleep onset latency as the most prevalent sleep-related issue among the seniors. The discrepancy between our findings and those of previous studies may reflect differences in study design, population characteristics, or measurement methods.

The data obtained from the two scales used in our study indicate that poor sleep quality and daytime sleepiness have a negative impact on the quality of life of old individuals residing in nursing homes. A statistically significant correlation was observed between the quality of life scale and the PSQI scores across all sub-dimensions, with the exception of the pain. Similarly, a strong and statistically significant correlation was found between the SSS and the sub-dimensions of quality of life, with exceptions of mental health and pain. These findings suggest that while sleep disturbances significantly affect most aspects of quality of life, the relationship may be less

pronounced in the areas of pain and mental health. Many studies have found that mental health, physical illnesses, and quality of life may be related to sleep quality.[16-19] This suggests that while sleep quality affects most domains of quality of life, pain and mental health may be influenced by additional factors beyond sleep disturbances, such as underlying chronic conditions, medication use, or psychosocial factors. Further research is needed to explore these relationships in more detail, including potential moderating or confounding variables that could explain the weaker associations observed.

When examining the relationship between comorbidities and sleep scales, dementia was significantly associated with the SSS score, while both cerebrovascular accidents and dementia were significantly related to the PSQI score. The significant association between dementia and both sleep scales highlights the complex interplay between cognitive decline and sleep disturbances. Studies estimate that between one-quarter and one half of older adults with dementias suffer from some form of sleep disruption.[20] Dementia is known to disrupt the sleep-wake cycle, contributing to poor sleep quality and increased daytime sleepiness. Additionally, cerebrovascular accidents, which often result in neurological deficits, may exacerbate sleep-related issues by affecting brain regions involved in regulating sleep patterns. Increasing daytime activity and physical exercise are known to enhance sleep in persons with dementia, as they may correct the circadian rhythm disturbances that these persons experience.[21] This finding warrants further exploration into how these two conditions interact and contribute to the decline in both cognitive and physical health in affected individuals.

Interestingly, no significant relationship was observed between polypharmacy and the sleep scales, suggesting that medication use may not be the primary factor influencing sleep disturbances in this population. However, this does not rule out the potential role of specific medications, and further studies exploring the impact of individual drugs on sleep are warranted.

In our study, we observed that 29% of senior participants had experienced at least one fall within the past year. However, when examining the relationship between sleep disturbances and fall incidents, we found no statistically significant correlation. This lack of association may be explained by the relatively high degree of independence among the study participants, as many were not severely limited in their mobility or daily functioning.

The strength of this study is its use of two validated sleep scales which provide a comprehensive evaluation of both sleep quality and daytime sleepiness. Another strength is the clear focus on a specific and vulnerable population allowing for targeted insights into the relationship between sleep disturbances and quality of life in older adults, with potential for improving care and interventions. Future research should consider larger, more diverse populations that include individuals with varying levels of physical and cognitive impairment.

Conclusions

In conclusion, addressing sleep problems should be a priority in the care of nursing home residents, particularly those with dementia and cerebrovascular accidents. By improving sleep hygiene and managing underlying medical conditions, healthcare providers can help improve the overall well-being of nursing home residents, ultimately enhancing their quality of life. Targeted interventions, such as individualized sleep management plans, may be beneficial in reducing the negative impact of sleep disturbances on old individuals' health and daily functioning.

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Ethics:

Ethics committee approval was obtained from XXXX University Faculty of Medicine with decision number 215.

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