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"Factors Associated with Mediastinal Lymph Node Positivity in Proximal Gastric Tumor Patients Undergoing Curative Surgery"

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Abstract

Background: Gastric cancer is the fifth most common cancer worldwide.
Objectives: This study investigated the risk factors associated with mediastinal lymph node metastases due to proximal gastric cancer.
Methods: The study included patients with curative surgical resection and transcural lymphadenectomy for proximal gastric tumors between January 2012 and January 2020. The patients (n=88) were divided into Group 1 (n=54, negative) and Group 2 (n=34, positive) according to the positivity of mediastinal lymph nodes. The diagnostic value of composite immunonutritional and inflammatory indices in predicting lymph node positivity was examined.
Results: It was found that only C-reactive protein (CRP) (P=0.044), the rate of postoperative respiratory complications (P=0.002), tumor size (P=0.0001), the total number of lymph nodes, and the number of metastatic lymph nodes were higher in Group 2. Moreover, pT stage (P=0.008) and pN stage (P<0.001) were more advanced in Group 2. Among the composite indices, only the neutrophil-to-lymphocyte ratio (NLR) had a diagnostic value, with a sensitivity of 67.65% and a specificity of 55.56% at a cut-off point of > 2.19. According to the multivariate analysis, a tumor size of > 3 cm, a CRP value of > 7, and tumor localization were independent risk factors.
Conclusion: Our study found that mediastinal lymph node positivity was associated with elevated CRP and that these patients had more advanced tumors and poor histopathological characteristics. Mediastinal lymph node positivity was also associated with increased postoperative respiratory complications. We established the diagnostic value of the NLR in predicting lymph node positivity. It is helpful to establish the relationship between clinicopathological characteristics and mediastinal lymph node positivity in proximal gastric tumors since it can be useful in determining the surgical strategy for esophagogastric junction tumors.

Keywords: Gastric adenocarcinoma, Immunonutrition, Mediastinal lymphadenectomy

1. Background

Gastric cancer is the fifth most common cancer worldwide and ranks fourth in cancer-related deaths (1). While gastroesophageal junction (GEJ) cancer is common in Western populations, it is still rare in Eastern populations, with an increasing incidence in recent years (2).

Several issues are involved in the surgical approach to the management of GEJ. The vague anatomical location of GEJ cancer gives rise to controversy about the esophagogastric resection range, staging system, and the extent of lymph node dissection, including mediastinal lymph nodes (MLNs) for this disease entity (3, 4).

Surgery is the mainstay of treatment; however, due to the anatomical complexity around the esophagogastric junction (EGJ), an optimal lymph node (LN) dissection or surgical approach remains controversial. Therefore, there are strategic differences between institutions and countries. An important factor in determining the surgical procedure is the presence of mediastinal lymph node metastases (MLNMs). The reported rate of MLNMs in patients with type II and III adenocarcinoma of the GEJ varies from 5% to 25% (3-8). Unfortunately, it is not possible to predict the number of metastatic lymph nodes before surgery. The accuracy of computed tomography and endoscopic ultrasonography in assessing positive lymph node metastases is not as high as necessary (9).

2. Objectives

Several previous studies described clinical indicators to predict MLNMs in patients with EGJ cancer (10-12). In addition, it has been a controversial issue whether MLN dissection has survival benefits (5-8). The present study was conducted to identify the factors associated with MLN positivity in patients with proximal gastric tumors who received curative surgical treatment.

3. Methods

3.1. Patient characteristics

After the study was approved by the Ethics Committee of the Faculty of Medicine of Çukurova University (IRB no Date:03.12.2021 and No: 117/14), patients who had curative surgical resection and

transcrural lymphadenectomy for proximal gastric tumor between January 2012 and January 2020 were included in the study. Transcrural lymphadenectomy was performed on all patients.

The patients were divided into Group 1 (Negative) and Group 2 (Positive) according to the positivity of MLNs. These groups were compared for demographic data, body mass index, American Society of Anesthesiologists score, comorbidities, neoadjuvant therapy status, preoperative laboratory parameters (tumor markers [CEA, Ca19,9], C-Reactive protein [CRP], lymphocyte count, platelet count, albumin, and hemoglobin), length of surgery, type of surgery, intraoperative complications, pathological data (tumor grade, mucinous histology, signet-ring cell component, tumor size, tumor localization, number of total and metastatic lymph nodes dissected, the P, T, PN, and PTNM stages, and lymphovascular and perineural invasion), postoperative complications, postoperative respiratory complications, anastomotic leaks, length of postoperative hospital stay, postoperative reoperation and 90-day unplanned hospital admission, survival, and composite indices (the neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], CRP-to-albumin ratio, and HALP score). The ratio of the composite indices to predict positive lymph nodes was calculated separately.

3.2. Definitions

The study patients received proximal gastrectomy with distal esophagectomy and proximal gastrectomy or radical total gastrectomy plus D2 lymph node dissection according to the criteria defined in the Japanese Classification of Gastric Cancer by the Japanese Gastric Cancer Association (13). Stations No. 110, 111, 112, 19, and 20 (as defined in the Japanese Classification) were dissected by transcrural lymphadenectomy. The pathological stage of the disease was determined according to the 7th or 8th tumor, node, metastasis classification (14, 15). The tumor localization was identified using the Siewert classification.

Patients with non-adenocarcinoma tumor histology and endoscopic submucosal dissection before the surgery were excluded from the study. Patients with distant metastases, positive intraoperative cytology, or those who had palliative surgery were also excluded.

The HALP score was calculated by the following formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L) / platelets (/L). Blood samples for laboratory examination were collected at the admission of the patient for the surgery.

This study was conducted in line with the principles of the Declaration of Helsinki. All methods were performed in accordance with the relevant guidelines and regulations.

3.3. Statistical Assessment

Statistical analysis of the data was performed using SPSS v23.0. Categorical measurements were summarized using numbers and percentages, and continuous measurements using mean, standard deviation, and minimum-maximum. The normality of the data was analyzed by the Shapiro-Wilk test. Categorical variables were compared using the Chi-square and Fisher's tests. Independent Samples (Student's) t-test was used for the normally distributed groups and Mann-Whitney U test for non-normally distributed groups. The sensitivity and specificity of the NLR, PLR, CRP/Albumin, and HALP were calculated based on the lymph node positivity of the study patients, and cut-off points were established by examining the area under the ROC curve. The Cox regression analysis was used for multivariate evaluations. The Kaplan-Meier analysis and Log-Rank tests were conducted for survival analysis. The statistical significance level was set at 0.05 for all tests.

4. Results

Our study included 88 patients with 54 patients in Group 1 and 34 patients in Group 2. Among the laboratory parameters, only CRP was higher in Group 2 (4.58 vs. 10.7, P=0.044) and other parameters were similar in the groups. The results are presented in Table 1.

The rate of postoperative complications (9.3% vs. 35.3%, P=0.003), the rate of postoperative respiratory complications (5.6% vs. 29.4%, P=0.002), and the length of hospital stay (9 vs. 12 days, P<0.001) were higher in Group 2. The operative variables are presented in Table 2. The tumor size (25.3 mm vs. 33 mm, P= 0.0001), the total number of lymph nodes, the number of metastatic lymph nodes, and the rate of Siewert type 2 tumor localization (35.2% vs. 73.5%, P<0.002) were higher in Group 2. The rate of lymphovascular invasion (64.8% vs. 97.1%, P<0.001) and the rate of perineural invasion (40.7% vs. 94.1%, P<0.001) were higher in Group 2. The pT stage (P=0.008) and the pN stage (P=<0.001) were more advanced in Group 2. Tumors were more advanced in Group 2 (P<0.001). The results are tabulated in Table 3. Among the composite indices, only NLR had a diagnostic value, with a sensitivity of 67.65% and a specificity of 55.56% at a cut-off point of > 2.19. The results are presented in Table 4 and Figure 1.

The positivity of MLNs significantly reduced survival (43.2±8.11 (27.29-59.11) vs. 77.92±10.39 (57.59-98.33), P=0.013). The results are provided

Table 1. Demographic and clinical data

	Group 1	Group 2	Total	P
	n (%)	n (%)	n (%)	
BMI[a]	27.6±6.6	29.9±5.5	28.5±6.3	0.089
Age[a]	59.4±11.1	57.1±12.9	58.5±11.8	0.381
ASA				
1	5 (9.3)	0 (0)	5 (5.7)	0.166
2	30 (55.6)	22 (64.7)	52 (59.1)	
3	19 (35.2)	11 (32.4)	30 (34.1)	
4	0 (0)	1 (2.9)	1 (1.1)	
Comorbidities	26 (48.1)	19 (55.9)	45 (51.1)	0.480
DM	16 (29.6)	7 (20.6)	23 (26.1)	0.347
HT	8 (14.8)	8 (23.5)	16 (18.2)	0.302
CAD	1 (1.9)	6 (17.6)	7 (8.0)	0.008
Neoadjuvant therapy	39 (72.2)	27 (79.4)	66 (75)	0.448
Neutrophil count[b]	4055 (350–14670)	4435 (1930–19490)	4280 (350–19490)	0.217
Lymphocyte count[b]	1945 (300–500)	1755 (850–2940)	1780 (300–5000)	0.406
Platelet count[a]	274.8±87.5	281.9±73.7	277.5±82.1	0.696
Hemoglobin[b]	12.7 (7.6–15.6)	12.8 (8–17.6)	12.7 (7.6–17.6)	0.451
Albumin[b]	4.1 (2.5–4.98)	3.9 (2.73-4.87)	4.0 (2.5–4.98)	0.643
CRP[b]	4.58±5.5	10.7±2.1	6.96±1.4	0.044
CEA[b]	2.7 (0.25–259)	2.4 (0.41–59.5)	2.5 (0.25–259)	0.684
Ca 19.9[b]	7.9 (0.6–135.8)	9.6 (0.6–1523)	8.7 (0.6–1523)	0.166
NLR[b]	2.08 (0.7–28.7)	2.67 (0.9–17.6)	2.32 (0.7–28.7)	0.053
PLR[b]	159.7 (45.4–436.7)	161.6 (79.3–425.8)	161.6 (45.4–436.7)	0.619
CRP/Albumin[b]	0.67 (0.09–8.11)	1.3 (0.01–40.69)	0.77 (0.01–40.69)	0.100
HALP[b]	0.35 (0.09–1.2)	0.29 (0.11–0.68)	0.31 (0.09–1.2)	0.368

BMI: Body mass index, ASA: The American Society of Anesthesiologists, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio
* P<0.05, [a] Independent Student's t-test, [b] Mann-Whitney U test

Table 2. Operative parameters

	Group 1	Group 2	Total	P
	n (%)	n (%)	n (%)	
Surgical procedure				
Proximal	6 (11.1)	4 (11.8)	10 (11.4)	0.550
Proximal + distal	15 (27.8)	6 (17.6)	21 (23.9)	
Radical total	33 (61.1)	24 (70.6)	57 (64.8)	
Intraoperative complications	1 (1.9)	0 (0)	1 (1.1)	0.425
Length of surgery[a]	189.0±26.6	197.0±32.4	192.1±29.0	0.212
Postoperative complications	5 (9.3)	12 (35.3)	17 (19.3)	0.003
Postoperative respiratory complications	3 (5.6)	10 (29.4)	13 (14.8)	0.002
Length of postoperative hospital stay[b]	9 (7–15)	12 (7–25)	10 (7–25)	<0.001

[a] Independent Student's t-test, [b] Mann-Whitney U test

Table 3. Pathological data

	Group 1	Group 2	Total	p
	n (%)	n (%)	n (%)	
Tumor size[b]	25.3 (9–57.5)	33 (18.5–65)	30 (9–65)	0.001
Total number of lymph nodes[b]	34 (17–63)	43.5 (21–108)	37 (17–108)	<0.001
Number of metastatic lymph nodes[b]	2 (0–10)	8 (2–31)	3 (0–31)	<0.001
Total number of mediastinal lymph nodes[b]	3 (2–11)	4 (3–8)	4 (2–11)	0.004
Tumor localization			0 (0)	
Siewert 1	0 (0)	0 (0)	0 (0)	0.002
Siewert 2	19 (35.2)	25 (73.5)	44 (50)	
Siewert 3	21 (38.9)	7 (20.6)	28 (31.8)	
Proximal stomach	14 (25.9)	2 (5.9)	16 (18.2)	
Grade				
1	8 (14.8)	1 (2.9)	9 (10.2)	0.022
2	29 (53.7)	13 (38.2)	42 (47.7)	
3	17 (31.5)	20 (58.8)	37 (42)	
Mucinous pattern	7 (13.0)	8 (23.5)	15 (17.0)	0.199
Signet-ring cell	7 (13.0)	10 (29.4)	17 (19.3)	0.057
Lymphovascular invasion	35 (64.8)	33 (97.1)	68 (77.3)	<0.001
Perineural invasion	22 (40.7)	32 (94.1)	54 (61.4)	<0.001
pT				
1	7 (13.0)	0 (0)	7 (8.0)	0.008
2	19 (35.2)	5 (14.7)	24 (27.3)	

3	25 (46.3)	24 (70.6)	49 (55.7)	
4	3 (5.6)	5 (14.7)	8 (9.1)	
pN category				
0	19 (35.2)	0 (0)	19 (21.6)	
1	13 (24.1)	0 (0)	13 (14.8)	
2	20 (37.0)	11 (32.4)	31 (35.2)	<0.001
3a	2 (3.7)	17 (50.0)	19 (21.6)	
3b	0 (0)	6 (17.6)	6 (6.8)	
Stage category				
1a	6 (11.1)	0 (0)	6 (6.8)	
1b	10 (18.5)	0 (0)	10 (11.4)	
2a	7 (13.0)	0 (0)	7 (8.0)	
2b	14 (25.9)	1 (2.9)	15 (17.0)	<0.001
3a	16 (29.6)	14 (41.2)	30 (34.1)	
3b	1 (1.9)	11 (32.4)	12 (13.6)	
3c	0 (0)	8 (23.5)	8 (9.1)	

[a] Independent Student's t-test, [b] Mann-Whitney U test

in Table 5 and Figure 2.

The multivariate analysis revealed that a tumor size of > 3 cm, the presence of lymphovascular and perineural invasion, a CRP value of > 7, an elevated CA19.9 level, the pT and pN stages, and tumor localization were independent risk factors for MLN positivity. The results are presented in Table 6.

Table 4. Predictivity of NLR for lymph node positivity

	Cut-off	Sensitivity (%95 CI)	Specificity (%95 CI)	PPV (%95 CI)	NPV (%95 CI)	AUC (%95 CI)
NLR	>2.19	67.65 (49.5–82.6)	55.56 (41.4–69.1)	48.9 (39.6–58.3)	73.2 (61.3–82.4)	0.623 (0.513–0.724)

NLR: Neutrophil/lymphocyte ratio, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve

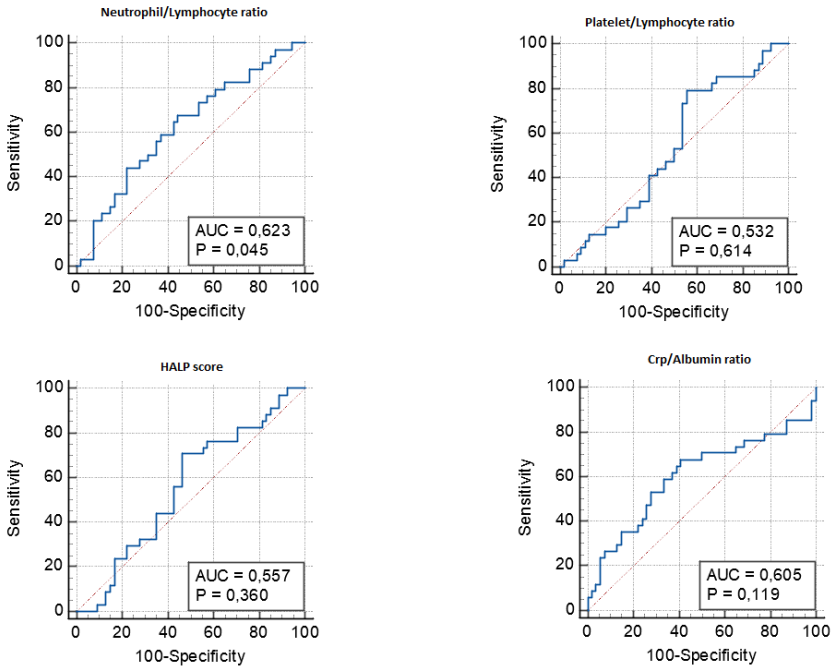

Figure 1. Receiver operating characteristic curve analysis of the mediastinal lymph node positivity

5. Discussion

Our study investigated the positivity of MLNs in proximal gastric cancer and identified positive MLNs in 40% of the patients. The tumor size, elevated CRP, and Siewert type 2 tumor localization were associated with and independent risk factors for lymph node positivity. We found that only the NLR, one of the immunonutritional composite indices, was diagnostically valuable in predicting lymph node positivity. The patients with positive MLNs exhibited poor histopathological characteristics, such as increased tumor size, advanced T and N stages, increased lymphovascular invasion, and perineuronal

Table 5. Overall survival by mediastinal lymph node groups

		Mean Mean±SD (Min-Max)	P
Mediastinal lymph nodes	(-)	77.92±10.39 (57.59–98.33)	0.013
	(+)	43.2±8.11 (27.29–59.11)	

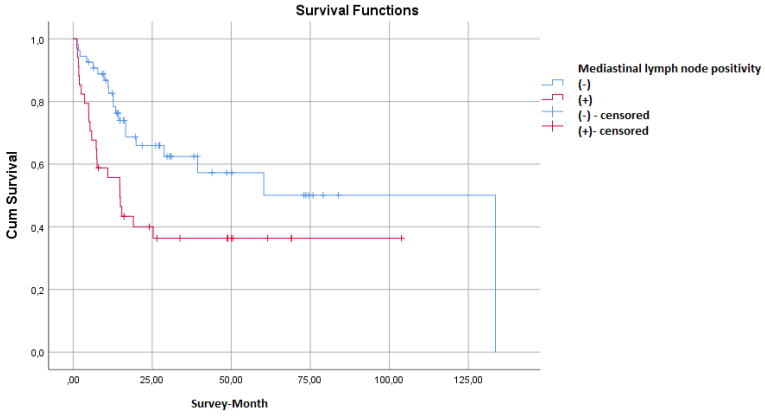

Figure 2. Overall survival by mediastinal lymph node groups

Table 6. Independent risk factors for mediastinal lymph node positivity

	Uni	Multivariate	
	p	OR (95% CI)	P
BMI			
≤25	0.130	1.000	0.139
>25		2.068 (0.790–5.417)	
Age			
≤65	0.700	1.000	0.701
>65		0.833 (0.329–2.111)	
Gender			
Male	0.932	1.000	0.93
Female		1.041 (0.415–2.611)	
ASA			
≤2	0.992	1.000	0.994
>2		1.005 (0.409–2.467)	
Neoadjuvant treatment	0.444	1.484 (0.534–4.125)	0.450
Tumor size			
≤3	0.002	1.000	0.003**
>3		3.990 (1.609–9.893)	
Mucinous	0.216	2.066 (0.673–6.343)	0.205
Signet-ring	0.060	2.798 (0.946–8.270)	0.063
Lymphovascular invasion	<0.001	17.914 (2.269–141.450)	0.006**
Perineural invasion	<0.001	23.273 (5.048–107.286)	<0.001**
NLR			
≤2	0.074	1.000	0.081
>2		2.299 (0.903–5.852)	
CRP			
≤7	0.030**	1.000	0.033*
>7		3.211 (1.101–9.370)	
CEA			
≤3	0.954	1.000	0.944
>3		1.031 (0.436–2.437)	
Ca19,9			
≤37	0.007**	1.000	0.010**
>37		5.208 (1.481–18.316)	
pT			
≤2	0.001**	1.000	0.002**
>2		5.386 (1.813–16.001)	
pN			
≤2	<0.001**	1.000	<0.001**
>2		54.364 (11.147–265.141)	
Tumor localization			
Siewert			
2	0.001**	1.000	0.003**
Siewert 3		0.253 (0.089–0.719)	0.010**
Proximal stomach		0.109 (0.022–0536)	0.006**

BMI: Body mass index, ASA: The American Society of Anesthesiologists, NLR: Neutrophil/lymphocyte ratio

invasion. In these patients, the stage was more advanced and survival was significantly reduced. The patients with positive MLNs were at an increased risk of postoperative complications.

Maatouk et al. were the first to publish a systematic review and meta-analysis examining predictive parameters for MLN positivity. In the mentioned meta-analysis, the researchers identified the undifferentiated type (OR=1.82, 95% HR=1.07-3.10, P=0.03) and esophageal invasion length (OR=10.95, 95% HR=6.37-18.82, P<0.00001) as the most important predictors. The researchers further divided patients into groups according to an age of 65 years and found that an age of > 65 years and gender were not associated with lymph node positivity (12). Similar to the literature, our study established no association with age and gender, while the tumor size and grade were associated with the positivity of MLNs (12).

In their study evaluating the risk factors for MLNs in EGJ tumors, Sugita et al. identified esophageal involvement (P<0.001), esophageal involvement greater than 30 mm (P<0.001), pathological tumor size greater than 40 mm (P=0.037), and Siewert type I (P<0.001) as risk factors for MLNMs (11). Shiraishi et al. retrospectively examined the risk factors for and prognostic impact of MLNMs in EGJ cancer with an epicenter of 2 cm below and above the macroscopically defined EGJ. The researchers reported that MLNMs were closely associated with the esophageal invasion length, and an esophageal invasion length of > 20 mm was a risk factor for MLNMs. Lymphatic tumor invasion did not differ according to histological type. In addition, an MLNM was not a poor prognostic factor, and some patients achieved long-term survival despite having MLNMs (10).

The common risk factor identified based on the studies in the literature was the length of the tumor extending to the esophagus in EGJ tumors. If the endoscopically-detected tumor extends to the esophagus, it would require mediastinal lymphadenectomy. Large-size and undifferentiated tumors with poor histological characteristics would also require mediastinal lymphadenectomy.

CRP may also be an indicator of the immunological response against the tumor (16, 17). The meta-analyses in the literature showed that an increased serum level of CRP before treatment was significantly associated with poor prognosis in gastric cancer patients, at an early or advanced stage (18, 19). Considering this evidence, an elevated CRP level is an expected finding in patients with positive MLNs, which was confirmed in our study.

Screening for effective markers to identify high-risk patients helps improve the prognosis and individualized treatment of EGJ tumors. Urabe et al. reported that preoperative NLR and PLR were associated with overall survival and disease-free survival in patients with EGJ tumors (20). In our study, immunonutritional and inflammatory indices had a limited value in detecting the positivity of MLNs. Only the NLR was proven to have a diagnostic value.

A study by Han et al. from the Far East divided EGJ tumors into two groups of those receiving and not receiving MLN dissection and reported a slightly higher rate of postoperative complications in the MLN dissection group (3). Recent studies suggest that delaying or skipping adjuvant chemotherapy may affect survival in GEJ cancer (21, 22). Since we performed MLN dissection on all patients in our series, we could not determine the relationship between dissection and complications. However, the patients with positive MLNs in our series had an increased rate of complications. The patients who are subjected to mediastinal lymphadenectomy should be chosen. Potential complications affect the long-term oncological outcomes of the patients.

The most important limitation of our study was its retrospective design and the inclusion of only the adenocarcinoma histological type. However, we believe that this study will contribute to the literature due to the scarcity of research in the literature on predicting MLN positivity.

6. Conclusion

It is a major challenge to determine the ideal prophylactic extent of the MLN dissection in patients without MLNMs. Knowing the relationship between clinicopathological characteristics and MLN positivity in proximal gastric tumors can be useful in determining the surgical strategy for EGJ tumors. Predicting patients who will require mediastinal lymphadenectomy would allow for individualized treatment.

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None.

Footnotes

Conflicts of Interest: The authors declare that there are no conflicts of interest regarding the publication of this article.

Supplementary Information: ETHICAL APPROVAL.The manuscript complies with the ethical standard guidelines of the journal. Collection and registration of the original database were performed according to the regulations and with the approval of the institutional review board of Cukurova University (IRB Date:03.12.2021 and No: 117/14)

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