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Research

Prevalence and Prognostic Significance of Anemia in Lymphoma

Lenfomada Aneminin Prevalansı ve Prognostik Önemi

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ABSTRACT

Objective: Anemia is common in cancer patients and has adverse effects on prognosis. In this study, we investigated the prevalence, etiological causes, and effects of anemia on the prognosis of patients with lymphoma.

Methods: We analyzed 153 newly diagnosed lymphoma cases. The hemoglobin (Hb) cut-off value for the diagnosis of anemia was set as Hb <12 g/dL in women and Hb <13 g/dL in men. Cases with anemia were classified as mild (Hb =10 g/dL-normal value), moderate (Hb =8-9.9 g/dL), and severe (Hb <8 g/dL) anemia. The relationship between the presence and degree of anemia and the revised international prognostic index (r-IPI) score, Eastern Cooperative Oncology Group performance score, Ann Arbor stage, presence of B symptoms, bulky mass, extra-nodal involvement, and life status was evaluated.

Results: Anemia was detected in 82 (53.6%) patients, and the most common cause of anemia was chronic disease anemia (30.5%). There was no significant relationship between the presence of anemia and the presence of bulky mass, r-IPI score, performance score, or Ann Arbor stage. A significant correlation was found between the degree of anemia and the presence of extranodal involvement and B symptoms (p<0.001, p=0.01, respectively). A significant correlation was found between the presence and degree of anemia and overall survival (p=0.011, p<0.001, respectively).

Conclusion: Anemia is common in Hodgkin and diffuse large B-cell lymphoma patients and is associated with some worse prognostic factors. Therefore, further studies examining more cases and including patients in all non-Hodgkin lymphoma subgroups are needed to better understand the importance of anemia in lymphoma cases.

Keywords: Anemia, diffuse large B-cell lymphoma, Hodgkin lymphoma, prognosis, prevalence

ÖZ

Amaç: Anemi kanser hastalarında sık görülür ve prognozu olumsuz etkiler. Bu çalışmada lenfoma hastalarında aneminin prevalansını, etiyolojik nedenlerini ve prognoz üzerindeki etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Yeni tanı almış 153 lenfoma olgusunu inceledik. Anemi tanısı için hemoglobin (Hb) eşik değeri kadınlarda Hb <12 g/dL, erkeklerde Hb <13 g/dL olarak kabul edildi. Anemisi olan olgular hafif (Hb =10 g/dL-normal değer), orta (Hb =8-9,9 g/dL) ve şiddetli (Hb <8 g/dL) anemi olarak sınıflandırıldı. Anemi varlığı ve derecesi ile revize edilmiş uluslararası prognostik indeks (r-IPI) skoru, Eastern Cooperative Oncology Group performans skoru, Ann Arbor evresi, B semptom varlığı, hacimli kitle, ekstra nodal tutulum ve yaşam durumu arasındaki ilişki değerlendirildi.

Bulgular: Seksen iki (%53,6) olguda anemi saptandı ve aneminin en sık nedeni kronik hastalık anemisiydi (%30,5). Anemi varlığı ile hacimli kitle varlığı, r-IPI skoru, performans skoru, Ann Arbor evresi arasında anlamlı bir ilişki yoktu. Anemi derecesi ile ekstranodal tutulum ve B semptomlarının varlığı arasında anlamlı bir ilişki bulundu (sırasıyla p<0,001, p=0,01). Anemi varlığı ve derecesi ile genel sağkalım arasında anlamlı bir korelasyon bulundu (sırasıyla p=0,011, p<0,001).

Sonuç: Hodgkin ve diffüz büyük B-hücreli lenfoma hastalarında anemi sıktır ve bazı kötü prognostik faktörlerle ilişkilidir. Bu nedenle lenfoma olgularında aneminin öneminin daha iyi anlaşılabilmesi için daha fazla olguyu inceleyen ve Hodgkin dışı lenfomanın tüm alt gruplarındaki hastaları içeren ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Anemi, diffüz büyük B-hücreli lenfoma, Hodgkin lenfoma, prognoz, prevalans

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INTRODUCTION

Anemia is a decrease in the erythrocyte mass or hemoglobin (Hb) value from the normal range according to age and gender (1). It is defined by the World Health Organization as <12 g/dL in women, <13 g/dL in men, and <11 g/dL in pregnant women (2). The prevalence of anemia was reported to be 22.8% in the population in 2019 (3). However, the prevalence of anemia in cancer patients is 30%-90% (4). One of the most important reasons for this variability in the prevalence of anemia in cancer patients is the different Hb cut-off values accepted for anemia. In cases with Hodgkin lymphoma (HL), the prevalence of anemia is 7% when Hb <9 g/dL is accepted as anemia, and it is 86% when Hb <11 g/dL is accepted (4). The European Cancer Anemia Research Group reported the prevalence of anemia (Hb <12 g/dL) as 52.5% in lymphoma and multiple myeloma cases (5).

The most important cause of anemia in cancer patients is increased inflammatory mediators such as tumor necrotizing factor-alpha, interleukin (IL)-1, IL-6, and tumor necrotizing factor gamma (6). These mediators cause shortening of erythrocyte lifespan, impaired iron utilization, suppression of erythropoietin (EPO) secretion, inadequate response of bone marrow precursor cells to EPO, and inhibition of erythroid precursor cells. Therefore, chronic disease anemia is a common cause of anemia in lymphoma cases. The causes of anemia in lymphoma cases are nutritional anemia, autoimmune hemolytic anemia (AIHA), anemia associated with bleeding caused by tumor tissue, anemia secondary to bone marrow infiltration, and chemotherapy treatment. Anemia is associated with poor prognosis in patients with lymphoma (7). In addition, it worsens the quality of life of cancer patients due to fatigue, decreased exercise capacity, and cognitive functions. Anemia treatment positively affects both the quality of life of cancer patients and their response to cancer treatment (8,9). However, only approximately 40% of cancer patients with anemia receive anemia treatment (6). In this study, we investigated the prevalence, causes, and prognostic significance of anemia.

METHODS

In our study, 153 cases of newly diagnosed HL and diffuse large B-cell lymphoma (DLBCL) followed up in our clinic were examined. Ethical approval was obtained from the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee for this study (decision no: 50, date: 30.09.2021). In addition, written informed consent was obtained from the participants.

Patients who were pregnant at the time of diagnosis and were treated for anemia, had a history of blood transfusion, were diagnosed with congenital anemia, and had active infection were excluded from this study. The diagnosis and classification of lymphoma cases were made by histopathological examination according to the 2016 criteria of the World Health Organization. HL with anemia cases who received adriamycin, bleomycin, vinblastine, and deticine chemotherapy and DLBCL with anemia cases who received rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone treatment were included in our study. Bone marrow biopsy was performed in all patients.

Anemia was accepted as Hb <12 g/dL in women and Hb <13 g/dL in men. Patients with anemia were divided into 3 groups according to their Hb values: severe (Hb <8 g/dL), moderate (Hb =8-9.9 g/dL), and mild (Hb =10 g/dL-normal value) grade anemia. Cases with low serum iron levels increased iron-binding capacity and low ferritin levels were considered to have iron deficiency anemia. Patients were accepted as having B12 deficiency anemia if serum vitamin B12 <200 µg, folic acid deficiency anemia if folate level <4 µg, anemia secondary to bone marrow involvement if bone marrow infiltration, AIHA if the direct Coombs test was positive with laboratory findings of hemolysis.

The files of all patients were reviewed retrospectively and age, gender, hemogram parameters (mean corpuscular volume, mean corpuscular Hb and mean corpuscular Hb concentration), lactate dehydrogenase (LDH), iron, iron-binding, ferritin, vitamin B12, folate, and reticulocyte levels, direct and indirect Coombs tests, bone marrow infiltration status, revised international prognostic index (r-IPI) score of DLBCL cases, Eastern Cooperative Oncology Group (ECOG) performance score, and Ann Arbor stage were recorded. When determining the r-IPI score, 1 point was given for each parameter if age >60, LDH value higher than normal, ECOG score ≥2, Ann Arbor stage 3 or 4, and area of extranodal involvement >1. The cases were divided into 3 groups according to their total scores (0 points = very good, 1-2 points = good, and ≥3 points = poor risk group).

Statistical Analysis

Data were evaluated using SPSS software (version 21.0, Chicago, USA). Categorical variables are given as percentages and continuous variables as mean ± standard deviation. The independent t-test was used to determine the difference between the two groups if there was a normal distribution, and the Mann-Whitney U test was used in the other groups. One-way analysis of variance was used to compare the three groups. Survival curves were evaluated

using the Kaplan-Meier method. The log-rank test was used to determine univariate relationships between progression-free survival and prognostic variables, and multivariate analysis tests were performed using the cox proportional hazards model. P-value <0.05 for all analyses was considered statistically significant.

RESULTS

In this study, 153 cases followed up in our clinic with the diagnoses of HL (n=40) and DLBCL (n=113) were examined. Anemia was detected in 82 (53.6%) patients (20 patients with HL, 62 patients with DLBCL). The mean age of our patients with anemia was 50.32±18.73 years; 37 (45.1%) patients were female and 45 (54.9%) were male. The age and gender distribution of the groups with and without anemia were similar (p=0.8 and p=0.6, respectively). The most common cause of anemia in our cases was chronic disease anemia, and other causes of anemia are shown in Table 1.

The hemogram parameters, LDH, and β2 microglobulin levels of the groups with and without anemia are reported in Table 2. The presence of bulky mass, extranodal involvement status, presence of B symptoms, r-IPI score (for DLBCL cases), ECOG score, and Ann Arbor stage in the groups with and without anemia are indicated in Table 3.

Fifty-eight (70.7%) patients had mild anemia, 18 (22%) had moderate anemia, and 6 (7.3%) had severe anemia. The relationship between the degree of anemia and clinical parameters such as disease stage, IPI score (in DLBCL cases), ECOG score, extranodal involvement, presence of B symptoms, and bulky mass are shown in Table 4.

The mean follow-up period was 37.91±7.45 months. Three of the patients with mild anemia, 10 with moderate anemia, and 6 with severe anemia died during the follow-up period. Six patients died in the without anemia group. A significant correlation was found between the presence and degree of anemia and overall survival (p=0.011, p<0.001, respectively) (Figures 1, 2, respectively). The results of univariate and multivariate analyses of some factors affecting survival are shown in Table 5.

Table 1. Anemia causes our cases

Type of anemia	HL, n (%)	DLBCL, n (%)	Total, n (%)
Chronic disease anemia	6 (30%)	19 (30.6%)	25 (30.5%)
Anemia secondary to bone marrow infiltration	5 (25%)	14 (22.6%)	19 (23.2%)
Autoimmune hemolytic anemia	4 (20%)	13 (21%)	17 (20.7%)
Iron deficiency anemia	2 (10%)	7 (11.3%)	9 (11%)
Multifactorial anemia	2 (10%)	5 (8%)	7 (8.5%)
Vitamin B12 deficiency anemia	1 (5%)	4 (6.5%)	5 (6%)

HL: Hodgkin lymphoma, DLBCL: Diffuse large B-cell lymphoma

Table 2. Hemogram parameters, LDH, and β2 microglobulin levels of anemia and non-anemia groups

Parameters	Group					p-value
	Group with anemia				Group without anemia	
	Mild	Moderate	Severe	Total		
Hb (g/dL)	11.42±0.78	9.18±0.49	7.9±0.86	10.67±1.41	14.58±1.42	<0.001
Hct (%)	35.12±2.75	28.53±2.36	25±3.77	32.93±4.44	43.88±3.92	<0.001
MCV (fL)	82.01±9.36	82.11±6.61	87.83±8.63	82.45±8.82	85.4±4.41	0.01
MCH (pg)	26.59±2.68	26.11±3.12	27.33±3.38	26.54±2.81	28.14±1.93	<0.001
MCHC (g/dL)	31.95±1.59	31.5±1.5	31±1.78	31.78±1.59	32.8±1.51	<0.001
RBC (10^6/μL)	4.23±0.46	3.47±0.49	2.86±0.54	3.97±0.64	5.09±0.46	<0.001
LDH (IU/L)	366.38±329.8	544.28±521.69	242.83±62.54	397.14±376.78	307.23±164.62	0.067
β2 (μg/mL)	2.86±0.64	3.47±0.49	4.24±0.46	4.74±0.89	3.97±0.64	<0.001

Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RBC: Red blood cell, LDH: Lactate dehydrogenase, B2: β2 microglobulin

Table 3. Bulky mass, extranodal involvement, B symptoms, r-IPI score, ECOG score, and Ann Arbor stage of anemia and non-anemia groups

Parameters	Anemia group n (%)	Non-anemia group n (%)	p-value
Bulky mass	14 (17%)	7 (9.9%)	0.15
Extranodal involvement	9 (11%)	5 (7%)	0.23
Presence of B symptoms	38 (46.3%)	25 (35.2%)	0.10
r-IPI score			
Very good	28 (34.1%)	23 (32.4%)	
Good	30 (36.6%)	29 (40.8%)	0.73
Bad	24 (29.3%)	19 (26.8%)	
ECOG performance score			
ECOG 1	27 (32.9%)	17 (23.9%)	
ECOG 2	34 (41.5%)	35 (42.3%)	0.57
ECOG 3	16 (19.5%)	16 (22.5%)	
ECOG 4	5 (6%)	3 (4.2%)	
Ann Arbor stage			
Stage 1	15 (18.3%)	6 (8.5%)	
Stage 2	26 (31.7%)	27 (38%)	0.39
Stage 3	29 (35.4%)	24 (33.8%)	
Stage 4	12 (14.6%)	14 (19.7%)	

r-IPI: Revised international prognostic index score, ECOG: Eastern Cooperative Oncology Group

Table 4. The relationship between the degree of anemia and disease stage, IPI score, ECOG score, extranodal involvement, presence of B symptoms, and bulky mass

Parameters	Anemia grade			p-value
	Mild n (%)	Moderate n (%)	Severe n (%)	
Ann Arbor stage				
Stage 1	12 (20.7%)	3 (16.7%)	0 (0%)	
Stage 2	17 (29.3%)	7 (38.9%)	2 (33.3%)	0.73
Stage 3	19 (32.8%)	7 (38.9%)	3 (50%)	
Stage 4	10 (17.2%)	1 (5.6%)	1 (16.7%)	
r-IPI score				
Very good	22 (37.9%)	4 (22.2%)	2 (33.3%)	
Good	24 (41.4%)	4 (22.2%)	2 (33.3%)	0.73
Bad	12 (20.7%)	10 (55.6%)	2 (33.3%)	
ECOG score				
ECOG 1	21 (36.2%)	4 (22.2%)	2 (33.3%)	
ECOG 2	25 (43.1%)	7 (38.9%)	2 (33.3%)	0.63
ECOG 3	10 (17.2%)	5 (27.8%)	1 (16.7%)	
ECOG 4	2 (3.4%)	2 (11.1%)	1 (16.7%)	
B symptoms				
Present	14 (24.1%)	18 (100%)	6 (100%)	<0.001
Absent	44 (75.9%)	0 (0%)	0 (0%)	
Bulky mass				
Present	10 (17.2%)	2 (11.1%)	2 (33.3%)	0.45
Absent	48 (82.8%)	16 (88.9%)	4 (66.7%)	
Extranodal involvement				
Present	1 (1.7%)	4 (22.2%)	4 (66.7%)	0.01
Absent	57 (98.3%)	14 (77.8%)	2 (33.3%)	

r-IPI: Revised international prognostic index score, ECOG: Eastern Cooperative Oncology Group

DISCUSSION

Anemia is common in patients with lymphoma (10). In a study conducted in India, the prevalence of anemia was reported to be 42.4% in patients with lymphoma (7). In our study, this rate was 53.4% and which was higher than the study conducted in India. While Moullet et al. (10) reported the prevalence of anemia as 32% in patients with NHL, Morel et al. (11) reported this rate as 35.3%. In our study, anemia prevalence was 40.3% in DLBCL cases, which was higher than that reported in the literature. The reason for this situation may be the difference in the number of cases in the studies or the inclusion of only DLBCL cases in our study. Yasmeen et al. (12) examined 422 lymphoma cases and reported the prevalence of anemia as 53.23% in cases with HL and 40.3% in cases with DLBCL. We found the prevalence of anemia in HL cases to be similar to that reported by Yasmeen et al. (12), and it was higher than the rate reported by Yasmeen et al. (12) in our DLBCL cases. This may be due to the small number of cases in our study. In another study, 422 patients with solid organ malignancy were examined, and the prevalence of anemia was reported as 29%. In this study, it was stated that 83.5% of the cases had mild- moderate anemia (13). In our study, mild to moderate anemia was found in 92.7% of the cases. This rate was higher than the anemia prevalence in cases with solid organ malignancy. This may be because bone marrow infiltration is more common in lymphoma cases than in solid organ malignancies.

Ghosh et al. (7) examined 316 cases consisting of patients with chronic lymphocytic leukemia, HL, and NHL and reported the prevalence of anemia as 42.4%. Of these cases, 71.7% had chronic disease anemia, 39.1% had iron deficiency anemia, 21.7% had vitamin B12 and/or folic

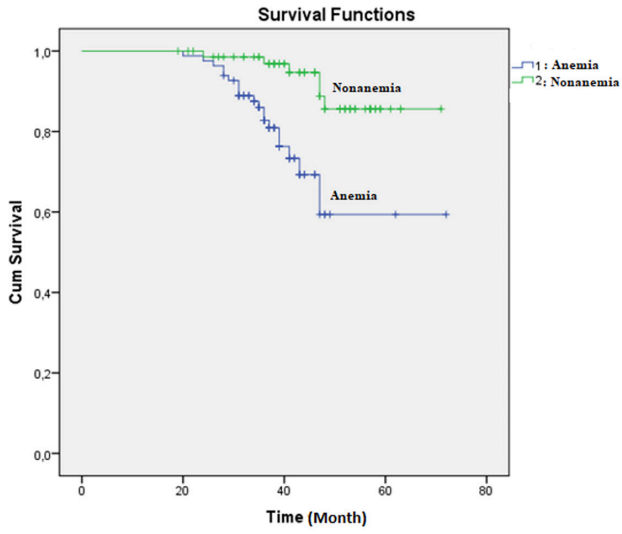

Figure 1. The correlation between the presence of anemia and overall survival

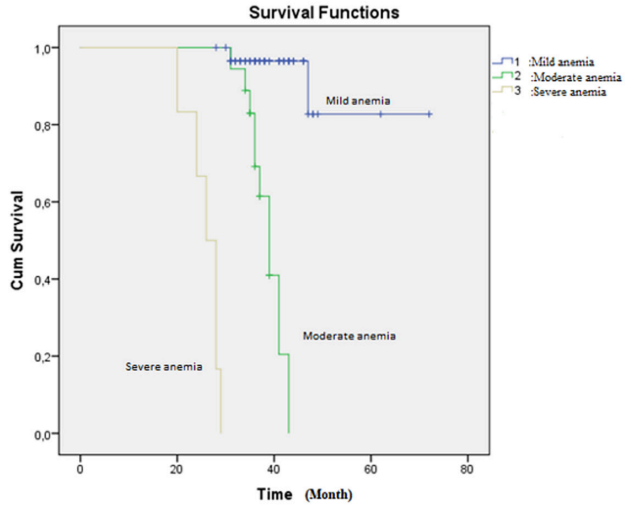

Figure 2. The correlation between degree of anemia and overall survival

Table 5. The results of univariate and multivariate analyzes of some factors affecting the survival

Parameters	HL		DLBCL	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Univariate analyses				
Age >40 (HL group) Age >60 (DLBCL group)	1.02 (0.51-1.15)	0.04	1.06 (0.32-1.35)	0.03
Sex	0.79 (0.68-1.31)	0.08	0.39 (0.29-1.61)	0.6
Elevated lactose dehydrogenase	1.34 (0.82-1.68)	0.04	1.44 (0.72-2.18)	0.02
ECOG performance status ≥2	0.65 (0.38-1.51)	0.2	1.21 (0.28-2.18)	0.04
Presence of bulky mass	0.97 (0.28-2.51)	0.04	0.69 (0.23-2.11)	0.06
Presence of B symptoms	1.49 (0.38-1.51)	0.02	0.95 (0.38-1.51)	0.04
Ann Arbor stage ≥3 (DLBCL) Ann Arbor stage =4 (HL)	0.31 (0.24-2.38)	0.3	1.23 (0.94-2.28)	0.04
Extranodal sites ≥2	0.74 (0.41-1.92)	0.4	1.2 (0.84-1.82)	0.02
BM involvement	1.32 (0.98-2.31)	0.01	1.18 (0.49-2.17)	0.03
Number of nodal areas ≥3	1.34 (1.1-2.24)	0.04	1.26 (0.86-1.77)	0.03
Presence of anemia	1.23 (0.92-2.35)	0.01	1.29 (0.78-1.65)	0.02
Presence of moderate or severe anemia	0.97 (0.57-1.47)	0.001	1.25 (0.87-1.92)	0.002
Multivariate analysis				
Presence of anemia	1.39 (0.71-1.43)	0.02	1.22 (0.84-1.46)	0.02
BM involvement	1.35 (0.69-2.22)	0.04	1.38 (0.92-1.83)	0.03
Presence of moderate or severe anemia	1.25 (0.83-2.1)	0.001	1.12 (0.91-1.86)	0.02

HL: Hodgkin lymphoma, DLBCL: Diffuse large B-cell lymphoma, BM: Bone marrow, ECOG: Eastern Cooperative Oncology Group, HR: Hazard ratio, CI: Confidence interval

acid deficiency anemia, 10.9% had AIHA, and 40% had anemia secondary to bone marrow infiltration. In addition, multifactorial anemia was in 39.1% of the patients. Yasmeen et al. (12) determined that the most common cause of anemia in patients with lymphoma was chronic disease anemia (33.1%). They reported that anemia secondary to bone marrow infiltration was 27.17%, iron deficiency anemia was 7.6%, vitamin B12 deficiency anemia was 1.6%, and

AIHA was 0.54%. In our study, the most common cause of anemia was chronic disease anemia, and the second most common cause was anemia secondary to bone marrow infiltration. The frequencies of chronic disease anemia and bone marrow infiltration-related anemia in our study were consistent with the results of Yasmeen et al.'s study (12). The frequency of anemia of chronic disease was lower in our cases than in the study by Ghosh et al. (7) This may be because of the small number of cases in our study.

AIHA is seen in 7-10% of lymphoma cases (14). The cause of AIHA is chronic antigenic stimulation. Zhou et al. (15) examined 20 cases with concomitant AIHA and NHL (15). They reported that AIHA is most commonly associated with angioimmunoblastic T-cell lymphoma. In our study, the frequency of AIHA was higher than that reported in the literature. This may be because we included only HL and DLBCL cases in our study.

Yasmeen et al. (12) reported a relationship between anemia and disease stage in lymphoma. In addition, this relationship has been reported in other studies (7,16). In our study, no correlation was found between the stage of the disease and the presence and degree of anemia. We found a relationship between the presence of anemia and the level of LDH, which is a prognostic marker in patients with lymphoma. We also determined a correlation between the severity of anemia and the presence of extranodal involvement and B symptoms. Anemia has been reported as a negative prognostic marker in patients with NHL (15,17). Moullet et al. (10) examined 1077 cases with NHL and considered anemia as Hb ≤12 g/dL for men and women over 50 years and Hb ≤11 g/dL for women aged 50 years. They stated that anemia is an unfavorable prognostic factor for overall survival and progression-free survival. In our study, we found a relationship between overall survival and the presence and degree of anemia.

CONCLUSION

Anemia, which is a treatable condition, is frequently observed in patients with lymphoma. It has adverse effects on patient prognosis. Therefore, careful evaluation of lymphoma cases in terms of anemia and early diagnosis and treatment of anemia may contribute positively to disease surveillance.

ETHICS

Ethics Committee Approval: Ethical approval was obtained from the Atatürk University Faculty of Medicine Clinical Researches Ethics Committee for this study (decision no: 50, date: 30.09.2021).

Informed Consent: Written informed consent was obtained from the participants.

Authorship Contributions

Surgical and Medical Practices: G.S., S.S., F.E., Concept: G.S., A.F.K., S.S., Design: G.S., A.F.K., S.S., F.E., Data Collection or Processing: G.S., A.F.K., Analysis or Interpretation: G.S., S.S., Literature Search: A.F.K., S.S., Writing: G.S., A.F.K., S.S., F.E.

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