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Pre-treatment inflammatory and immune system parameters predicting cervical cancer metastasis

Rahim ağzı kanseri metastazını öngören tedavi öncesi enflamasyon ve bağışıklık sistemi parametreleri

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Abstract

Objective: This study aimed to evaluate the relationship between mannose-binding lectin-associated serine protease-2 as an immune system parameter and neutrophil lymphocyte ratio (NLR) as an inflammatory parameter to predict cervical cancer metastasis.

Materials and Methods: This cross-sectional study included 70 patients diagnosed with cervical cancer between January 2022 and February 2023 at Dr. Wahidin Sudirohusodo Hospital, Hasanuddin University Hospital, and Ibnu Sina Hospital, Makassar, Indonesia. Blood samples taken before therapy as well as clinical and histological data were gathered and examined. MASP-2 levels and NLR were measured by ELISA and flow cytometry respectively.

Results: The median age of the patients was 46 years (range, 24-72 years), with the majority of patients aged between 41 and 52 years. Statistical analysis showed that MASP-2 was associated with cervical cancer stage (p≤0.000), organ metastasis (p=0.011), and lymphovascular invasion (p=0.036). In addition, NLR was associated with cervical cancer stage (p=0.004), histopathology type (p=0.031), tumor size (p=0.019), and organ metastasis (p=0.013).

Conclusion: Pretreatment with MASP-2 as an immune system parameter and NLR as an inflammatory parameter is associated with cervical cancer metastasis. The NLR indicator can be applied in clinical practice because it is simple and reasonably priced.

Keywords: Cervical cancer, Mannose-binding lectin-associated serine protease-2, neutrophil lymphocyte ratio

Öz

Amaç: Bu çalışmada serviks kanseri metastazını öngörmek amacıyla bir bağışıklık sistemi parametresi olarak mannoz bağlayıcı lektin ilişkili serin proteaz-2 ile enflamatuvar bir parametre olarak nötrofil lenfosit oranı (NLR) arasındaki ilişkinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bu kesitsel çalışmaya Ocak 2022 ile Şubat 2023 tarihleri arasında Endonezya'nın Makassar şehrindeki Dr. Wahidin Sudirohusodo Hastanesi'nde, Hasanuddin Üniversite Hastanesi'nde ve İbnu Sina Hastanesi'nde rahim ağzı kanseri teşhisi konulan 80 hasta dahil edildi. Tedaviden önce alınan kan örneklerinin yanı sıra klinik ve histolojik veriler toplanıp incelendi. MASP-2 seviyeleri ve NLR sırasıyla ELISA ve akış sitometrisi ile ölçüldü.

Bulgular: Hastaların ortanca yaşı 46 (aralık, 24-72) olup, hastaların çoğunluğunun yaşı 41 ile 52 arasındaydı. İstatistiksel analiz MASP-2'nin rahim ağzı kanseri evresi (p≤0,000), organ metastazı (p=0,011) ve lenfovasküler invazyon (p=0,036) ile ilişkili olduğunu gösterdi. Ayrıca NLR'nin rahim ağzı kanseri evresi (p=0,004), histopatoloji tipi (p=0,031), tümör boyutu (p=0,019) ve organ metastazı (p=0,013) ile ilişkili olduğu görüldü.

Sonuç: Tedavi öncesi ölçülen bir bağışıklık sistemi parametresi olarak MASP-2 ve enflamatuvar bir parametre olarak NLR serviks kanseri metastazı ile ilişkilidir. NLR basit ve uygun fiyatlı olması nedeniyle klinik pratikte bir belirteç olarak kullanılabilir.

Anahtar Kelimeler: Rahim ağzı kanseri, Mannoz bağlayıcı lektin ilişkili serin proteaz-2, nötrofil lenfosit oranı

PRECIS: Pre-treatment MASP-2 as immune systems parameters and NLR as inflammatory parameters is a simple and inexpensive indicator to predict cervical cancer metastasis.

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Introduction

Particularly in developing nations, cervical cancer continues to be a major public health issue impacting women between the ages of 40 and 55. Oncogenic human papilloma virus (HPV) infection is the main cause of cervical cancer. It can be influenced by several factors such as smoking, number of parities, changing sexual partners, marriage, or intercourse from a young age. Chronic HPV infection causes suppression of the immune response, which can disrupt the immune system[1-4].

The systemic immune inflammation index has been recognized as a reliable indicator of both systemic and local immunological responses based on peripheral neutrophil, platelet, and lymphocyte counts. The tumor microenvironment (TME) depends on several inflammatory cells and mediators. Acute-phase proteins, platelets, neutrophils, lymphocytes, and peripheral leukocytes can be observed and are involved in the inflammatory response[5].

Cell production and exudates from capillary leaks in the TME activate the complement system. It has been proposed that complement is crucial for cancer immunity. Mannose-binding lectin (MBL), a component of the complement system's lectin pathway that participates in cytolysis, opsonization, and inflammatory reactions, is a component of the natural immune system[6].

MBL interacts with antigen-presenting cells in the tumor microenvironment, which affects their activity/proliferation and thus influences the outcome of the anti-tumor immune response system. It also directly interacts with neoplasm cells by inhibiting metalloproteinases from degrading the extracellular matrix of carcinogenic agents. Interactions with MBL-associated serine protease (MASP) enable MBL to initiate the complement cascade. MASP-2, a mannose-binding lectin-associated serine proteinase, is involved in the survival and recurrence of many malignancies. A lack of MASPs is linked to an increased risk of infection, whereas an abundance of MASPs is associated to tissue damage[7,8].

The complement system will also have an impact on the TME, which will increase tumor-associated macrophages, tumor-associated neutrophils, and myeloid-derived suppressor cells, leading to the release of pro-inflammatory cytokines that increase neutrophils and suppress T-cells, NK cells, and lymphocytes. This increases neutrophil lymphocyte ratio (NLR) in the blood. Increased NLR is a marker that predisposes tumors to proliferation and metastasis through apoptosis inhibition, angiogenesis promotion, and DNA damage[9,10]. This study aims to determine how to predict cervical cancer metastasis by comparing the mannose-binding lectin-associated serine protease-2 and NLR.

Materials and Methods

Study Design

This article was generated in accordance with the strengthening the reporting of observational studies in epidemiology 2007 (STROBE)[11]. A cross-sectional study was conducted at the Hasanuddin University Hospital, Ibnu Sina Hospital, and Dr Wahidin Sudirohusodo Hospital, Makassar, Indonesia between January 2022 and February 2023.

Population and Study Setting

The participants were women newly diagnosed with cervical cancer based on histopathological examination from cervical biopsy and agreed to participate, attending the gynecology clinic during the data collection period. The following conditions had to be met for inclusion in the study: (1) Cervical cancer as determined by histopathological examination; (2) no concurrent malignancy; (3) no prior history of blood transfusion within 60 days; (4) no prior history of chemotherapy or radiation; and (5) full access to medical records. The following were the exclusion criteria: (1) being pregnant; (2) taking immunosuppressants; and (3) having a hematologic condition, an autoimmune condition, organ dysfunction, an acute or chronic infection, or another disease.

Variables

The MASP-2 level and NLR were independent variables in this study. In addition, the International Federation of Gynecology and Obstetrics (FIGO) stage[12], histopathology subtype, histological grade, tumor size, lymph node metastasis, organ metastasis, and lymphovascular invasion were the dependent variables.

MASP-2 is a zymogen that initiates the innate immune response by binding to the MBL and activating the lectin complement pathway. MASP-2 was measured using a Microplate Reader Biorad model 680 (ELISA) and expressed in ng/ml with the following cut-off values >291.9 ng/mL from the previous study[7]. Using flow cytometry analysis, NLR compares the number of neutrophils and lymphocytes from differential count calculations. The results of the comparison of the two are expressed as percentages.

The stage of cervical cancer is assessed according to the FIGO classification (2021) based on data from clinical examinations, ultrasonography, chest radiography, and computed tomography (CT) scans. Cervical cancer stages are divided into early (IA1-IB2), locally advanced (IB3-IIA2) and advanced (IIB-IVB) stages[12]. Histopathological subtypes are cell and tissue morphology types that are visible microscopically and are grouped into squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma. Histopathological grades were grouped based on the level of cell differentiation into three categories: G1 (good differentiation), G2 (moderate differentiation), and G3 (poor differentiation). Lymphovascular invasion was assessed on the basis of the presence of intralymphatic cancer cells or intravascular cervical tissue on histopathological examination. All histopathological examinations were performed by one pathologist blinded to the patient's clinical information.

Tumor size was evaluated by rectovaginal examination, abdominopelvic ultrasound, CT, and magnetic resonance imaging (MRI) based on the largest distance in centimeters. Tumor sizes were categorized into <2 cm, 2-4 cm, >4 cm, and null (not included in the examination results). The spread of other organs is assessed on the basis of mucosal involvement of the bladder, rectum, lungs, liver, bones, and/or other organs on ultrasound examination, CT scan, and MRI.

MASP-2 Level and NLR Measurement

The two main parameters were measured using a venous blood sample (5 cc) from the cubital vein. After the blood specimen is put into the SST tube, it is inverted 5-10 times until homogeneous. The sample was sent to the Prodia laboratory for testing with the Human MASP-2 SimpleStep ELISA Kit (Abcam, Cambridge, UK). Measurements were performed using the Microplate Reader Biorad model 680 (Bio-rad Laboratories Inc., CA, USA) with Microplate Manager software ver 5.2.1 (Bio-rad Laboratories Inc., CA, USA).

Some blood samples were also taken for the NLR examination. A complete blood count was performed using an automated hematological examination device (Yumizen H1500/2500, Kyoto, Japan) to obtain a differential leukocyte count. Next, the neutrophils and leukocytes were divided to measure the NLR.

Data Collection

The patient's medical records and pathology reports were used to gather data. Clinical information for the patient included clinicopathological statistics (age, histologic grade, tumor size, lymph node metastases, lymphovascular space invasion, and FIGO stages) and the outcomes of a pre-treatment routine blood test. All patients had venous blood drawn, which was then sent to Prodia Laboratory for testing with the Human MASP-2 SimpleStep ELISA Kit Reagent and NLR, which is the neutrophil count divided by the lymphocyte count.

Sampling Size

A purposive sampling method was employed to obtain the samples. The calculation formula for single-population proportion studies was used to estimate the sample size. The sample size (n) was 62 when using a proportion of 50%, a 95% confidence interval, and a degree of precision of 10%; after adding an additional 10% for the non-response rate, the total sample size was 67.

Statistical Analysis

SPSS 24.0 was used for statistical analysis after gathering and logging the main data. The data distribution was determined using the Kolmogorov-Smirnov method, and the median and interquartile range were used to express the central tendency. For variables with two unpaired groups, the Mann-Whitney U test was employed, whereas the Kruskal-Wallis test was used for variables with more than two unpaired groups. A p-value <0.05 is the limit for determining significant test results.

Results

Subject Characteristics

There were a total of 85 patients with recently diagnosed cervical cancer. The final analysis comprised 70 patients who met the eligibility requirements (Figure 1). Table 1 displays the clinicopathological characteristics of the patients. Most patients were between the ages of 41 and 52 years, with a median age of 46 (ranging from 24 to 72). To be more precise, there were 37 cases (52.8%) who were over 45 years old and 33 cases (47.2%) who were under 45 years old.

Association Between MASP-2 and Clinicopathological Parameters

The association of MASP-2 with clinicopathological parameters is shown in Table 2. Histopathological type (p=0.798), histological grade (p=0.194), tumor size (p=0.121), and lymph node metastasis (p=0.100) were not significantly associated with MASP-2 levels. In contrast, cervical cancer stage (p≤0.000), organ metastasis (p=0.011), and lymphovascular invasion (p=0.036) were significantly associated with MASP-2 levels.

Association Between NLR and Clinicopathological Parameters

The results of the analysis of the relationship between NLR and cervical cancer clinicopathology are presented in Table 3. Statistical results showed no significant correlation between NLR level and histological grade (p=0.718), lymph node metastasis (p=0.404), and lymphovascular invasion (p=0.992), whereas cervical cancer stage (p=0.004), histopathology type (p=0.031), tumor size (p=0.019), and organ metastasis (p=0.13) showed significant association with NLR.

Discussion

This study shows that MASP-2 levels were associated with cervical cancer stages statistically. In the pathophysiology of cancer, the complement system can have two functions. Initially, it can regulate the removal of cells that can potentially cause

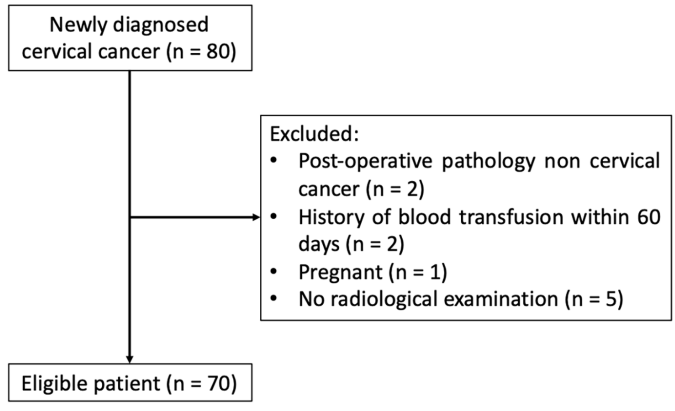

Figure 1. Flowchart of patient screening

Table 1. The clinicopathological characteristics of patient

Characteristics	n*	(%)
FIGO stage		
Stage I		
IA1	0	0
IA2	0	0
IB1	2	3.0
IB2	1	1.0
IB3	2	3.0
Stage II		
IIA1	1	1.0
IIA2	0	0
IIB	31	44.0
Stage III		
IIIA	2	3.0
IIIB	22	31.0
IIIC1	4	6.0
IIIC2	0	0
Stage IV		
IVA	4	6.0
IVB	1	1.0
Histopathology		
Squamous cell carcinoma	60	85.7
Adenocarcinoma	7	10.0
Adenosquamous carcinoma	3	4.3
Histological grade		
G1	15	21.4
G2	30	42.9
G3	25	35.7
Tumor size		
<2 cm	-	-
2-4 cm	11	15.7
>4 cm	47	67.1
Unknown	12	17.1
Lymph node metastasis		
Positive	24	34.3
Negative	46	65.7
Organ metastasis		
Positive	28	40.0
Negative	42	60.0
Lymphovascular invasion		
Positive	13	18.6
Negative	31	44.3
Unknown	26	37.1

*n=70, FIGO: International Federation of Gynecology and Obstetrics

tumors and have dangers or pathogen-associated molecular patterns or pathogens (DAMPs or PAMPs). Furthermore, complement activation may promote the growth of tumors[6]. Mannan-binding lectin (MBL) and collectin-LK, as well as ficolins, are pattern recognition molecules that can bind to carbohydrates on the surface of microbes or damaged tissue and activate the complement system through the lectin pathway. When the aforementioned occurs, two MBL-associated proteins (MAp44 and MAp19) serve as endogenous competitive inhibitors, whereas three MBL-associated proteases (MASP-1, -2, and -3) activate the complement system. Tumor tissue may release mediators that can increase serum MASP-2 levels, which are associated with poor prognosis, disease recurrence, and mortality in cervical cancer[7,8]. MASP-2 levels may facilitate or inhibit malignancy progression through complement factor C5a, which may influence the microtumor environment. However, the observed MASP-2 levels may also result from chronic inflammation, which is an ongoing acute phase associated with tumor growth[13-15].

This study also found that NLR was associated with cervical cancer stages. Neutropenia, thrombocytosis, and lymphocytopenia are signs that cancer has progressed to an advanced stage. As a result, the interaction of lymphocytes, neutrophils, and platelets has been investigated as a prognostic factor in predicting the course of malignancy. Previous studies have illustrated that an increase in NLR aligns with more advanced severity (advanced stage)[9,10].

This study showed no statistical association between MASP-2 levels and the histopathological type of cervical cancer. There was an association between NLR and the histological type of cervical cancer. However, MASP-2 levels were highest in adenosquamous carcinomas, followed by adenocarcinoma types and squamous cell carcinomas.

Histologically, squamous cell carcinoma is the disease's most prevalent subtype, followed by adenocarcinoma of the cervix, with a percentage of approximately 75% and 15%, respectively. Adenosquamous carcinoma and neuroendocrine tumors are uncommon histological subtypes. Cervical adenosquamous carcinoma is a rare malignant epithelial neoplasm characterized by squamous and glandular cell differentiation[16]. In more than 80% of instances, HPV infection -particularly HPV type 16 and HPV 18- causes cervical cancer. The virus can stimulate the complement system cascade, which is fully activated only during the inflammatory process, opsonization, phagocytosis, and pathogen elimination. This process activates the adaptive immune response and promotes cancer development[17]. In contrast to HPV-positive cervical cancer, people with HPV-negative cervical carcinoma are discovered more frequently at an advanced stage and frequently have non-squamous histology. The difference in prognosis between HPV-positive and HPV-negative cervical cancer depends on histology and not HPV status[18,19]. According to the limited number of

Table 2. Association of MASP-2 with clinicopathological parameters

			MASP-2	
		n	Median (IQR)	p-value
FIGO stage	Early	3	256.88 (244.69-323.71)	<0.000**
	Locally advanced	3	274.69 (257.34-286.42)	
	Advance	64	639.68 (485.47-738.24)	
Histopathology	Squamous cell carcinoma	60	590.09 (447.11-740.3)	0.798**
	Adenocarcinoma	7	697.26 (573.61-709.91)	
	Adenosquamous carcinoma	3	732.50 (540.93-735.78)	
Histological grade	G1	15	586.35 (465.22-696.87)	0.194**
	G2	30	549.25 (443.22-737.42)	
	G3	25	703.56 (550.46-754.82)	
Tumor size	<2 cm	-	-	0.121**
	2-4 cm	10	549.25 (461.85-653.88)	
	>4 cm	48	579.57 (424.19-741.12)	
	Unknown	12	704.74 (654.18-762.78)	
Lymph node metastasis	Positive	24	700.02 (507.35-749.00)	0.100*
	Negative	46	566.83 (414.28-723.56)	
Organ metastasis	Positive	28	704.74 (520.65-798.71)	0.011*
	Negative	42	555.66 (430.79-698.83)	
Lymphovascular invasion	Positive	13	703.56 (653.88-791.35)	0.036**
	Negative	31	560.87 (405.48-695.76)	
	Unknown	26	600.69 (465.22-743.18)	

*Mann-Whitney U, **Kruskal-Wallis, IQR: Interquartile range, FIGO: International Federation of Gynecology and Obstetrics, MASP: Mannose-binding lectin-associated serine protease

studies investigating the association between MASP-2 and histopathological types of cervical cancer, the present results can be used for further research to determine the cut-off for MASP-2.

Previous studies have shown that adenosquamous cervical carcinoma has the worst outcomes[20,21]. In addition, most studies examining NLR as a predictor of cervical cancer patient survival reported no association between NLR and histological type[22-24]. The present study had contrary findings and may be argued as follows: (1) The number of cases included was different, the size was small, (2) There were significant differences in baseline characteristics between the two groups, and (3) The comparison of the number of the three histopathological types was significantly different.

This study showed no statistical relationship between MASP-2 and NLR levels and the degree of cervical cancer differentiation but MASP-2 and NLR levels were found to be higher in poor differentiation than in good differentiation. The results demonstrate that MASP-2 and NLR can facilitate neoplastic transformation by triggering unregulated complement activation, which increases tumor cell proliferation, motility, and invasiveness as well as angiogenesis, growth factor synthesis, and host suppression[25]. Poor differentiation indicates a worse prognosis than excellent differentiation. According to this study's NLR findings and Wang et al.'s research[26], there is no association between NLR and the degree of differentiation of cervical cancer. Further study should be conducted to identify the cut-off value of MASP-2 to predict cervical cancer differentiation.

This study showed no statistical relationship between MASP-2 levels and tumor size, but MASP-2 levels were higher in tumors measuring more than 4 cm than those measuring less than 4 cm. In addition, there was an association between NLR and tumor size. A previous study revealed that patients with a tumor size 2 cm showed an almost two-fold lower risk of mortality from cervical cancer than patients with tumors measuring 2-4 cm, and tumors >4 cm showed unexpected distant metastasis[27]. This may suggest that excessive inflammation activates the complement system, resulting in increased levels of MASP-2, which activates the lectin pathway and releases proinflammatory cytokines that stimulate an increase in neutrophils and suppress lymphocytes, which increase the proliferation, migration, and

Table 3. Association of NLR with clinicopathological parameters

			NLR	
		Median (IQR)	Median (IQR)	p-value
FIGO stage	Early	3	2.03 (1.51-2.09)	0.004**
	Locally advanced	3	1.53 (1.46-2.34)	
	Advance	64	4.2 (2.97-7.71)	
Histopathology	Squamous cell carcinoma	60	4.02 (2.81-7.96)	0.031**
	Adenocarcinoma	7	2.58 (2.13-3.04)	
	Adenosquamous carcinoma	3	4.94 (4.68-5.53)	
Histological grade	G1	15	3.60 (2.52-6.42)	0.718**
	G2	30	3.86 (3.01-8.00)	
	G3	25	3.91 (2.58-5.70)	
Tumor size	<2 cm	-	-	0.019**
	2-4 cm	10	2.18 (1.49-3.77)	
	>4 cm	48	3.89 (2.88-7.71)	
	Unknown	12	4.73 (3.84-7.06)	
Lymph node metastasis	Positive	24	4.67 (2.43-11.73)	0.404*
	Negative	46	3.81 (2.83-5.62)	
Organ metastasis	Positive	28	4.52 (3.18-13.64)	0.013*
	Negative	42	3.51 (2.29-4.94)	
Lymphovascular invasion	Positive	13	3.48 (3.15-8.73)	0.992**
	Negative	31	4.42 (2.62-6.81)	
	Unknown	26	3.83 (3.02-6.96)	

*Mann-Whitney U, **Kruskal-Wallis. IQR; Interquartile range, FIGO: International Federation of Gynecology and Obstetrics, NLR: Meutrophil lymphocyte ratio

invasion activities of tumor cells[28]. This finding is also in line with that of Huang et al.[29], who explained that NLR is positively associated with tumor size. The insignificant results for MASP-2 levels in this study may be related to tumor sizes that had not been identified through radiological examination. Although there was no statistically significant correlation between MASP-2 and NLR levels and lymph node spread in this study, participants with lymph node spread had higher MASP-2 and NLR levels. This study found an association between MASP-2 and NLR levels and organ metastasis, but not between NLR and LVSI involvement. However, there was an association between MASP-2 levels and LVSI involvement. The activation of the complement system is part of the immune system, which also affects the TME and stimulates the proliferation of macrophages and neutrophils and suppresses myeloid cells, thereby stimulating the release of pro-inflammatory cytokines, which increase neutrophil proliferation and suppress lymphocytes, T-cells, and NK cells. Therefore, elevated blood NLR is a marker that predisposes tumors to proliferation and metastasis by inhibiting apoptosis, promoting angiogenesis, and causing DNA damage[17]. An earlier study also discovered a relationship between NLR and carcinoma metastasis and higher MASP-2 levels in unsurvived patients as opposed to those who survived[7]. The predictive value of NLR is highly substantial for LVSI, which contrasts with the findings of this study[30,31].

Study Limitations

The insignificant results in this study may be due to some histopathological results not including the presence or absence of LVSI involvement, thus possibly contributing to the results obtained. Recently, no study has linked MASP-2 levels with LVSI involvement; therefore, this study can be used to develop MASP-2 cut-off values.

Conclusion

This study showed that pretreatment with MASP-2 as an immune system parameter is significantly associated with organ metastasis and lymphovascular invasion in cervical cancer. Moreover, NLR as an inflammatory parameter is significantly associated with FIGO stage, histopathology, tumor size, and organ metastasis in cervical cancer. The NLR indicator can be applied in clinical practice because it is simple and reasonably priced.

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Ethics

Ethics Committee Approval: Ethical approval was obtained from Institute for Research and Community Services LPPM Hasanuddin University, protocol number UH21090607 and date of approval 16 November 2021.
Informed Consent: Informed consent was obtained.
Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., N.U.P., A.R., Concept: N.U.P., Design: M.A., N.U.P., A.R., Data Collection or Processing: M.A., N.U.P., A.R., S.R., N.R., Analysis or Interpretation: M.A., N.U.P., A.R., S.R., N.R., F.H., Literature Search: M.A., Writing: M.A., N.U.P., A.R., S.R., N.R., F.H.
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