The Association of Neutrophil-Lymphocyte Ratio with Medical Treatment Failure in Patients with Tubo-ovarian Abscess

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Background: Pelvic inflammatory disease (PID) is an acute infection of the upper female genital tract, which may involve the uterus, fallopian tubes and ovaries. Tubo-ovarian abscess (TOA) is a complication of Pelvic Inflammatory Disease. Different methods are being utilized to predict the failure of medical management of TOA. Neutrophil-lymphocyte ratio (NLR) has been proposed as a significant marker for diagnosis in PID.
Objective: To compare NLR and sonographic TOA volume between patients who responded to medical management versus patients with failed medical management, and who eventually underwent surgery.
Methods: This is a cross-sectional study done by reviewing the hospital records of patients admitted for TOA in a tertiary hospital, from 2014 to 2018. Demographic details of the patients, computed NLR values and TOA volumes were gathered and analyzed.
Results: There was no statistical difference between the group who responded to treatment (medical group) versus the group of patients with failed medical management (surgical group) in terms of age, gravidity, parity and mean volume of the TOA. There was a statistically significant difference between the mean NLR of the two treatment groups.
Conclusion: Patients diagnosed with TOA, and with failed medical management have significantly higher levels of NLR compared with patients who responded to medical treatment. This positive association can be explored in future researches to validate NLR as a predictor of medical treatment failure for patients with TOA. NLR can also be potentially utilized as novel marker to indicate need for earlier surgical management to decrease the patient's risk for sepsis.

Key words: Tubo-ovarian abscess, neutrophil-lymphocyte ratio, pelvic inflammatory disease

Introduction

Tubo-ovarian abscess (TOA) is an inflammatory disease which involves the fallopian tubes, ovary and adjacent pelvic organs. The causative agents of TOA are polymicrobial which usually involve *Escherichia coli*, *Aerobic streptococci*, *Bacteroides fragilis*, Prevotella, and other anaerobes, such as *Neisseria gonorrhea* and *Chlamydia trachomatis*.

The treatment of TOA includes: a) broad-spectrum antibiotic therapy, b) minimally invasive drainage procedures, c) invasive surgery.[1]

The mortality rate associated with TOA prior to the introduction of broad-spectrum antibiotics is reported to be as high as 50%.[1] However, with the advent of antibiotics targeting anaerobes and gram-negative aerobes, the success rate of antibiotic treatment alone is qpproximately 70%, and is now considered the first-line treatment for TOA.[1]

According to the Sexually Transmitted Disease Guidelines (2021) of the Centers for Disease Control and Prevention (CDC)[3], the recommended parenteral therapy in PID are the following: a) Ceftriaxone 1 gram every 24 hours plus Doxycycline 100 mg

orally every 12 hours plus Metronidazole 500 mg orally every 12 hours; b) Cefotetan 2 grams every 6 hours plus Doxycycline 100 mg every 12 hours; or c) Cefoxitin 2 grams every 6 hours plus Doxycycline 100 mg every 12 hours. Alternative parenteral regimens include a) Ampicillin-Sulbactam 3 grams intravenously every 6 hours plus Doxycycline 100 mg every 12 hours, b) Clindamycin 900 mg intravenously every 8 hours plus Gentamicin 2 milligram per kilogram as loading dose followed by maintenance dose of 1.5 milligram per kilogram every 8 hours antibiotic therapies are the first-line therapies for TOA.

The recommended intramuscular or oral therapy for PID based on the CDC STD Guidelines (2021) are the following: a) Ceftriaxone 500 mg intramuscularly in a single dose plus Doxycycline 100 mg 2 times a day for 14 days with Metronidazole 500 mg 2 times a day for 14 days; b) Cefoxitin 2 gram intramuscularly and Probenecid 1 gram orally administered concurrently in a single dose plus Doxycycline 100 mg 2 times a day for 14 days with Metronidazole 500 mg 2 times a day for 14 days; c) Ceftizoxime or Cefotaxime plus Doxycycline 100 mg 2 times a day for 14 days with Metronidazole 500 mg 2 times a day for 14 days. The addition of metronidazole to these regimens provides extended coverage against anaerobic organisms and will also effectively treat BV, which is frequently associated with PID.[3] Patients who are not responsive with the medical treatment are advised surgical treatment options in the form of abscess drainage, laparoscopy or laparotomy.[4]

The measurement of the neutrophil-lymphocyte ratio (NLR) is a convenient and low cost method that has been proposed as a significant marker for diagnosis and prognosis of PID. Some studies have demonstrated that NLR values tend to be higher among patients who need surgical treatment, compared to those who were successfully treated medically.[1] A study by Akopuz et. al showed that NLR was a useful marker for treatment follow-up of patients with PID. An NLR .cut-off value of 2.92 demonstrated a sensitivity of 81.5% and specificity of 98.4%.[5] A study by Alay, et al.[1] showed that the NLR can be used to predict medical failure and can be used as a novel predictor of medical treatment failure in patients with TOA.

However, a local retrospective, study published by Santos and Jose (2020)[6] showed data that were not consistent with those published in foreign literature. The authors concluded that more studies need be done about NLR as a predictor of treatment failure in patients with TOA.

Because of these inconsistencies in local data and the small population of previous studies on the use of NLR as a possible predictor for failure of medical management, this study was conducted to further investigate the association of NLR with medical treatment failure among patients with TOA.

The objective of the study was to show the association of NLR with medical treatment failure of TOA among patients admitted at a tertiary hospital in the Philippines.

Methods

The protocol was reviewed and approved by the Research Ethics Board of the institution prior to the conduct of the study. This study was done in a tertiary hospital in the Philippines. Data were collected from hospital records from January 1, 2014 to December 31, 2018. All patients with TOA that were confirmed by transvaginal ultrasound and with baseline complete blood count (CBC) on admission were included. Patients' demographic data were collected. The size of the TOA and NLR values prior to and after medical treatment were computed for each patient and entered into the excel sheet. The patients who responded to medical treatment were grouped under "medical treatment", while the patients with failed medical management and underwent surgery were grouped under "surgical treatment". The data collected were analyzed by computing for mean, standard deviation, frequency and percentage using Microsoft Excel 2019. The difference in outcome measures between the two treatment groups was determined using independent t-test for quantitative variables and chi-square test for qualitative variables. All analyses were conducted using SPSS version 22 with a report of p- values, at an alpha of 0.05 and 95% confidence level.

Results

From 2014 to 2018, a total of 82 patients with TOA were admitted. Forty five (54.9%) patients were

responsive to medical treatment (grouped under "medical treatment") and 37 (45.1%) patients had failed medical mangement and underwent surgery (grouped under "surgical management"), Table 1 shows the demographic data of the participants including the age, gravidity, parity, volume of TOA and the NLR. The mean age of patients with TOA who had successful medical management was 30.36 years, while the mean age of patients who underwent surgical management was 35.65 years. Age range of all patients was 15 to 50 years old. Table 2 shows the mean NLR and the mean volume of the TOA. The mean TOA volume among patients who responded to medical intervention was 141.9 cc, while those who eventually underwent surgical management had a higher mean volume of 351.9 cc. The mean difference however, was not significant. The mean NLR of patients who responded to medical treatment was 5.6, versus a mean value of 13.4 for patients who were eventually managed surgically. The mean NLR between groups showed a significant difference.

Discussion

PID is an inflammatory disease spectrum that affects upper female genital system. Risk factors include young and early age of first coitus, multiple sexual partners, presence of bacterial vaginosis, vaginal douching, intrauterine contraceptive device use, and sexually transmitted disease.[2] TOA mostly affects women in reproductive age and approximately 60% are nulliparous. Around 15-35% of women being treated for PID will be diagnosed with TOA.[7]

PID is a polymicrobial disease that if left untreated, may cause serious complications such as tubo-ovarian abscess.[1] The infection activates interleukins (IL-3, IL-6, IL-11), granulocyte stimulating factor (G-CSF) and cytokines, hence, there is release of mature granulocytes from the bone marrow. The first response is the arrival of neutrophils in the affected area. The increase in neutrophil count causes decline of lymphocyte count and results in an increase in NLR. Thus, NLR reflects the severity of the disease or condition.[3] Endogenous cortisol

Table 1. Demographic data and laboratory results of the patients between the two treatment groups.

Parameters	Medical Treatment (n=47)	Surgical Treatment (n=37)	p-value
	Mean	Mean	(2-tailed)
Age	30.36	35.65	0.666
Gravidity	1.82	2.00	0.568
Parity	1.49	1.78	0.789

Significant if $p < 0.05$

Table 2. Mean NLR value and mean TOA volume of the patients between the two treatment groups.

Parameters	Medical Treatment (n=47)	Surgical Treatment (n=37)	p-value
	Mean	Mean	(2-tailed)
Volume TOA	141.92502	351.87203	0.075
NLR	5.5867	13.3973	0.037*

Significant if $p < 0.05$

and catecholamines serve as major drivers of the NLR. When there is an increase in the cortisol levels, there will be an increased neutrophil count which concurrently causes a decrease in the lymphocyte count. The endogenous catecholamines, such as epinephrine, may cause lymphopenia and leukocytosis.

The established gold standard for the diagnosis of PID is laparoscopy. However, due to its invasive nature and high costs, it is not usually done.[2,8]

The diagnosis of tubo-ovarian abscess that was diagnosed clinically can be confirmed by transvaginal ultrasound, and it may appear as a complex solid or cystic mass, may be unilateral or bilateral, with features of acute tubal inflammatory disease including dilated tubal shape, abnormal wall structure, increased wall thickness (≥5mm), and presence of pelvic peritoneal fluid (free fluid or inclusion cyst).[9] 'Cogwheel sign' is also seen via ultrasound due to the thickened endosalpingeal folds which is a sensitive marker for TOA.[7]

In cases of failed medical management, surgery such as laparoscopy or laparotomy with drainage of abscess, unilateral or bilateral adnexectomy, or hysterectomy is done. Surgical intervention of cases with TOA is necessary if there is no clinical response or improvement after more than 72 hours of antibiotic treatment or in cases of ruptured abscess. The recurrence rate after antibiotics alone is high and one-third of patients with TOA or pelvic abscess will eventually undergo drainage or surgery.[5,10,11]

A local retrospective study done by Santos and Jose published in 20206 (n= 49 patients) showed that age ≥ 40 years old was a predictor of medical treatment failure. The results of the study further showed that tubo-ovarian abscess size of > 7 cm was associated with increased incidence of medical treatment failure.[7] However, contrary to the findings from published international literature, the study by Santos and Jose (2020)[6] showed that the NLR values were not found to be significantly associated with medical treatment outcomes. This current study, on the other hand, showed that indeed, there was a significant difference between the mean NLR value of the group with good response to medical treatment versus the group with failed medical management who eventually underwent surgery. The non-significant difference of the NLR between the 2 treatment groups in the study of Santos and Jose (2020) can be attributed to their small sample size (n=49).

Results of this study are consistent with other previously published studies. A study by Akopuz, et al. (2016)[5], which included 65 patients with PID and 65 patients as control group, established an NLR cut-off value of 2.92 (sensitivity of 81.5% and specificity of 98.4%) as a useful predictor of response to medical regimen on treatment follow-up. Among all CBC parameters, NLR was found to be the most sensitive and specific marker. Another study by Coskun, et al.[4] in 2019 (n = 96 patients) showed that NLR values were significantly higher in the group of patients with TOA who underwent surgery, versus patients who underwent medical treatment only. A similar study done by Alay, et al.[1] in 2019 (n = 81 patients) also showed a significant difference between the medical treatment group versus the group who eventually underwent surgical treatment. The area under the curve (AUC) for NLR was 0.69 with sensitivity of 79.1% and specificity of 57.9%.[1] NLR can be calculated as absolute neutrophil count (10^9/L) divided by absolute lymphocyte count (10^9/L).

The results of this study showed that patients who responded to medical treatment have low baseline neutrophil values which resulted to lower NLR values, and a lower TOA volume (mean value of 142 cc). On the other hand, patients who failed medical management and were treated surgically have higher NLR values (mean value of 13.4) due to higher baseline neutrophil counts, and with higher TOA volume (mean volume of 352 cc) . The increase in neutrophil count causes decline of lymphocyte count which result in an increase in NLR. This study however did not find a significant difference between the mean TOA volumes of the 2 treatment groups. Nevertheless, the local study done by Santos and Jose (2020) showed that a tubo-ovarian abscess volume measuring at least 120 cc was predictive of medical treatment failure. The lower mean value for NLR and TOA volume among patients who responded to medical treatment may signify a lower degree of inflammatory response.

The NLR is an inexpensive and convenient method in determining a systemic inflammatory response of the body and can be used to identify the severity of the disease or condition.[1] The NLR values can be correlated with the degree of the inflammatory

process and the prognosis of the disease. This can be potentially used as a predictor for early surgical intervention correlated with other factors such as the size of the TOA and the age of the patient.

Conclusion

Patients diagnosed with TOA, and with failed medical management have significantly higher levels of NLR compared with patients who responded to medical treatment. This positive association can be explored in future researches to validate NLR as a predictor of medical treatment failure for patients with TOA. NLR can also be potentially utilized as novel marker to indicate need for earlier surgical management to decrease the patient's risk for sepsis.

Limitations

The retrospective design of this study limits the results to what was already recorded such as the transvaginal ultrasound and CBC. This also limits the study to a smaller population size since the population used were the admitted patients at a tertiary hospital in the Philippines.

Recommendations

A prospective design of this study and a larger sample size is recommended. A data analysis of the value and cut off for NLR can be done in the local setting to help predict the level of NLR that is expected to have a higher risk of medical management failure.

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