

# Correlation between Neutrophil-to-lymphocyte ratio and Euthyroid Sick Syndrome in elderly patients with proximal femur fractures

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**Abstract. – OBJECTIVE:** Proximal femur fractures are among the most common type of trauma in elderly patients, and Euthyroid sick syndrome has already been related to fractures and trauma. The evidence of a consistent inflammatory state occurring during hip fracture, made us consider as a potential marker also the neutrophil-to-lymphocyte ratio (NLR), which is already in use to measure the prognosis and guide the therapeutic management in various conditions.

**PATIENTS AND METHODS:** A retrospective observational analysis on patients affected by proximal femur fractures was conducted. Patients were divided between affected and non-affected by Euthyroid Sick Syndrome (ESS). Standard follow up was conducted at 1, 3, 6 and 12 months.

**RESULTS:** 79 patients were enrolled in this study. There were 19 males and 60 females, the mean age was  $83.8 \pm 6.5$  y.o., and 44 patients were affected by ESS. Affected patients showed higher NLR values ( $10.2 \pm 9.4$  vs.  $6.9 \pm 3.9$ ;  $p=0.001$ ) and higher decrease in fT3 values in the 1st post-operative day ( $1.8 \pm 0.4$  vs.  $2.2 \pm 0.3$ ;  $p=0.001$ ), higher values of PTH ( $97.9 \pm 46.2$  vs.  $70.1 \pm 36.2$ ;  $p=0.004$ ) and lower levels of Vitamin D ( $18.8 \pm 7.8$  vs.  $23.5 \pm 12.9$ ;  $p=0.04$ ). As regards complications, we found them in 27% of patients in group A, while only in 8% in Group B, with a statistically significant difference ( $p=0.03$ ).

**CONCLUSIONS:** ESS and NLR are promising prognostic markers in PFF in the elderly patients. If used together, they could help in the pre- and post-operative management of the patients.

## Key Words:

Euthyroid Sick Syndrome, Nonthyroidal Illness Syndrome, Neutrophil-to-lymphocyte ratio, Proximal femur fractures.

## Introduction

Nowadays the incidence of proximal femur fractures (PFF) is increasing due to the aging of the population and the increased incidence of osteoporosis in the elderly patients. This represents a current health burden with high social and economic costs because they frequently require surgery with long hospitalizations, which is also affected by the relevant rate of secondary fracture following the primary treatment<sup>1-3</sup>.

PFF is often an end-of-life phenomenon in elderly patients, and it is linked to a high rate of complications, early mortality and disability, especially in patients affected by chronic diseases<sup>4-6</sup>. Many factors have been identified as predictors of bad clinical outcome, including anemia and euthyroid sick syndrome (ESS)<sup>4,5</sup>.

In fact, ESS could represent a reliable indicator to monitor and predict an unfavorable outcome in chronic diseases, such as renal failure, diabetes mellitus and diseases characterized by a state of chronic inflammation<sup>7</sup>.

Recently, the Neutrophil-to-lymphocyte ratio (NLR) has emerged in literature<sup>8,9</sup> as an inflammatory index used to measure the prognosis and guide the therapeutic management in various conditions, such as diabetes mellitus (DM), systemic lupus erythematosus, infections, neoplasms, gouty arthritis and ischemic heart disease. NLR represents an easily calculable value, affordable and immediately available from the full blood count routinely performed in emergency settings<sup>9</sup>.

The aim of the present study was to evaluate the correlation between NLR and ESS in a cohort of elderly patients with PFFs and estimate its influence on perioperative complications.

## Patients and Methods

### *Study Setting and Design*

The present investigation is a retrospective observational analysis performed according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines<sup>10</sup>. Clinical records of patients admitted to our Emergency Unit (EU) from 1 January 2018 to 31 December 2018 with diagnosis of proximal femur fractures (AO classification: 31A or 31B)<sup>11</sup> consecutively treated were potentially eligible for this study.

This study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A written informed consent for scientific purposes and clinical data collection was obtained according to institutional protocol.

### *Inclusion and Exclusion Criteria*

Patients with age > of 65 years with diagnosis of proximal femur fracture requiring surgical treatment (AO classification: 31A or 31B)<sup>11</sup> managed in our institution were potentially enrollable in this study.

Patients with: (I) any thyroidal pathology, (II) active infective disease, (III) concomitant or previous neoplastic disease, (IV) home medications with drugs that could modify the thyroidal function (such as: Calcium carbonates, Sulfonylurea, Dopamine-agonists, Spironolactone, Estrogens, Growth Hormones, Octreotide), (V) surgery performed over 72 hours from admission, and (VI) refusal of surgical treatment were excluded from this study.

### *Outcomes*

The primary outcome was the correlation between the ESS and NLR. The secondary outcome was the perioperative compliance rate.

### *Institutional Database and Data Collection*

All patients with diagnosis of proximal femur fracture treated in the emergency unit (EU) of our institution were managed using a standardized data collection system. From each patient the following data were collected and stored: age, gender, clinical history, body mass index (BMI), American Society of Anesthesiologists (ASA) scale, routine blood tests, type of fracture

according to AO classification<sup>11</sup>, type of surgery performed, thyroid function obtained through fT3, fT4, TSH, PTH and D vitamin dosage.

### *Patients' Management and Group Settings*

All patients enrolled in the study underwent surgery within 48 hours from EU admission. All blood tests were performed at EU arrival, on the first and third day after surgery. The ESS diagnosis was made when fT3 values were < 2.3 pg/ml and fT4 and TSH values were normal.

The surgical indication was established by an experienced orthopedic and trauma surgeon according to the AO trauma indication<sup>11</sup>. Generally, the same surgical technique was performed to treat the same type of fracture<sup>12</sup>. In this case, patients underwent two different types of surgery: intramedullary nailing (Synthes PFNA<sup>®</sup>) or partial hip replacement surgery using Implantcast<sup>®</sup> hip prosthesis.

Urinary catheter was positioned before surgery, in the emergency room or in the operating room, and it was removed during the first post-operative day in all patients.

Starting by the first post-operative day, all patients followed a physiotherapy protocol including partial and then progressive load.

Based on the diagnosis of ESS, all enrolled patients were divided in two groups. In Group A, we included patients with ESS, while in Group B we collocated patients without ESS.

As standard of care in our institution, all patients with diagnosis of proximal femur fractures surgically treated were systematically monitored at 1, 3, 6 and 12 months after diagnosis and then once a year after surgery. The complication rate was recorded during the follow-up period. According to the overtime appearance, the complications were divided as intraoperative, early (within 6 postoperative months), and late (more than 6 months after surgery) complications.

The NLR value was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained by blood sample performed<sup>13</sup>.

### *Statistical Analysis*

GraphPad QuickCalcs (GraphPad Software, San Diego, CA, USA) was used for data analysis. The data were reported as mean and standard deviation (+ SD). The asymmetry was calculated to evaluate the normality of the different param-

**Table I.** Anthropomorphic data.

	Total population	Group 1	Group 2
Total patients	79	35	44
Gender	60 females 19 males	26 females 9 males	34 females 10 males
Age (years old)	83.8 ± 6.5	83.8 ± 6.4	83.9 ± 6.7
BMI	23.5 ± 3.7	23.5 ± 4.1	23.5 ± 3.5
Pattern of Fracture	38 medial 41 lateral	19 medial 16 lateral	19 medial 25 lateral
Surgical time (minutes)	78.2 (71 ± 31.9)	71 ± 27.6	83.9 (71 ± 34.2)

eters. An unpaired *t*-test was used to compare unrelated, continuous, variable. Chi-square test was performed for evaluation of complication in the two group. Significance was set for  $p < 0.05$ .

### Results

According to inclusion and exclusion criteria, 79 patients were considered eligible and were finally included in the study. 44 patients were affected by ESS and were assigned to Group A, while 35 patients were assigned to group B (without ESS).

There were 19 males and 60 females, the mean age was  $83.8 \pm 6.5$  y.o., and the mean BMI was  $23.5 \pm 3.7$ . There were 41 lateral fractures that underwent intramedullary nailing, and 38 medial fractures that underwent endoprosthesis surgery.

Anthropomorphic data and routine lab test are reported in Table I and Table II. No statistical difference was noted between the two group.

The group of patients with euthyroid sick syndrome demonstrated lower lymphocyte values upon arrival in the emergency room ( $1.2 \pm 0.6$  vs.  $1.4 \pm 0.5$ ;  $p = 0.02$ ) and consequently higher NLR values ( $10.2 \pm 9.4$  vs.  $6.9 \pm 3.9$ ;  $p = 0.001$ ). As regards the hormonal axis, patients in group A showed a further decrease in fT3 in the first postoperative day ( $1.8 \pm 0.4$  vs.  $2.2 \pm 0.3$ ;  $p = 0.001$ ), higher values of PTH ( $97.9 \pm 46.2$  vs.  $70.1 \pm 36.2$ ;  $p = 0.004$ ) and lower levels of Vitamin D ( $18.8 \pm 7.8$  vs.  $23.5 \pm 12.9$ ;  $p = 0.04$ ) (Table II). No statistical difference was noted among group about ADL and IADL (Table II).

In total, 15 complications were recorded, accounting for 18% of the population. It mostly consisted in medical complications (14/15) and only in one case of a surgical complication with surgical site infection (Table III).

In group A, there were 12/44 complications (27%), while only 3/35 in group B (8%), with a statistically significant difference ( $p = 0.03$ ). All infections were treated with antibiotic therapy

**Table II.** Groups' comparison.

	Total population	Group 1	Group 2	<i>p</i> -value
Haemoglobin (g/dL)	12.3 ± 1.7	12.4 ± 1.4	12.1 ± 1.9	0.7
White blood cells ( $\times 10^9/L$ )	10.4 ± 3.4	10.2 ± 3.2	10.6 ± 3.6	0.6
Neutrophils ( $\times 10^9/L$ )	9.1 ± 4.6	8.6 ± 3.3	9.2 ± 4.9	0.5
Lymphocytes ( $\times 10^9/L$ )	1.2 ± 0.6	1.4 ± 0.5	1.2 ± 0.6	0.02
Platelet ( $\mu L$ )	244.8 ± 81.8	253.6 ± 93.1	237.8 ± 71.8	0.3
NLR	8.7 ± 7.6	6.9 ± 3.9	10.2 ± 9.4	0.001
PLR	223.4 ± 130.6	200.1 ± 115.1	242.2 ± 140.5	0.1
Sodium (mmMol/L)	139.0 ± 3.2	139.6 ± 2.9	138.5 ± 3.4	0.1
Potassium (mmMol/L)	4.2 ± 0.6	4.2 ± 0.6	4.3 ± 0.6	0.9
Calcium (mg/dL)	10.3 ± 8.4	11.6 ± 12.6	9.3 ± 0.5	0.2
Albumin (g/L)	28.5 ± 3.5	28.6 ± 3.6	28.4 ± 3.6	0.7
Creatinine (mg/dL)	1.0 ± 0.5	0.9 ± 0.3	1.0 ± 0.7	0.3
fT3 (pMol/L)	2.0 ± 0.4	2.2 ± 0.3	1.8 ± 0.4	0.001
PTH (pg/mL)	85.6 ± 44.0	70.1 ± 36.2	97.9 ± 46.2	0.004
Vitamin D (ng/mL)	20.9 ± 10.5	23.5 ± 12.9	18.8 ± 7.8	0.04
ADL	4.9 ± 2.0	5.1 ± 1.8	4.7 ± 2.1	0.4
IADL	4.9 ± 3	5.4 ± 2.8	4.6 ± 3.2	0.2

**Table III.** Groups' comparison.

	Total population	Group 1	Group 2	p-value
Pneumonia	5	1	4	/
Urinary Tract Infections	7	2	5	/
Wound Infections	2	/	2	/
Others	1	/	1	/
Number of complications	15	3	12	0.03

with benefit. The surgical site infection was treated with advanced wound care and antibiotic therapy and did not need further interventions.

### Discussion

ESS is a widely known disease that usually affects patients with many acute and chronic illnesses, described as a decrease in T3 level and increased levels of rT3<sup>14</sup>.

The reduction of thyroid hormones that is observed in this kind of patients is related to an inflammatory state that leads to a lower rate of conversion of T4 and T3 by muscle deiodinases<sup>15</sup>.

Considering the great relevance of thyroid hormones in the global homeostasis, many authors found it interesting to analyze the correlation between the levels of T3 and T4 and how they can affect the outcomes in surgical patients.

Several studies<sup>16,17</sup> observed how the presence of ESS in patients undergoing coronary artery bypass-grafting (CABG) has detrimental effects on short-term outcomes<sup>16</sup>. ESS, moreover, appears to have the same correlation in patients undergoing elective coronary procedures<sup>17</sup>.

Aside from cardiac diseases, it is interesting to underline how ESS is capable of influencing the prognosis of elderly patients undergoing emergency intervention<sup>18</sup>.

ESS has also been recently studied during the COVID-19 emergency. Indeed, it has been shown that patients with ESS who had contracted COVID-19 had a longer hospital stay, more complications, higher frequency of intubation and transfer to the intensive care unit<sup>19</sup>.

In the specific field of orthopedics, ESS has been related to a higher risk of developing post-operative anemia in patients undergoing surgery for hip fractures<sup>4</sup>.

Among the other biological markers, CRP has been for a long time the first choice to evaluate patients at high risk of mortality after surgery, although, on the other hand, neutrophil-to-lym-

phocyte ratio (NLR) appeared to be a more reliable and easier marker to use<sup>20</sup>. NLR is an easy tool to obtain, since a simple WBC count is necessary, and it is a reliable marker of subclinical inflammation<sup>21</sup>. Neutrophils and lymphocytes play an important role in inflammatory response: the count of neutrophils increases resulting in a release of cytokines and molecular mediators while lymphocytes undergo demargination and apoptosis, which lead to lymphocytopenia. NLR reflects the balance between these two mechanisms and thus is a reliable index of inflammation and stress<sup>22</sup>.

While considering the different mortality rate of their patients, Temiz and Ersözlu<sup>23</sup> found a significant correlation between admission NLR values and poor prognosis, independently from the diagnosis.

On the other hand, in our study we observed how high NLR values are significantly related to post-operative complications (27%), compared to the control group (8%).

NLR is also useful to predict 30-days, 6- and 12-months outcomes after emergency abdominal surgery in the elderly<sup>24</sup> and risk of death 2 years following vascular surgery<sup>25</sup>. According to the abovementioned studies, though, NLR is to be considered as a risk factor more than a predictive one, and it should be used in addition to other well-known risk factors such as age, male sex, and comorbidities. This is true, considering the values of NLR after 5 days after surgery<sup>26</sup>.

As we also observed in our study, both ESS and NLR seem to be related to the risk of developing an infection in the postoperative period. These two factors already came out as helpful prognostic biomarkers both in sepsis<sup>27</sup> and COVID19<sup>28</sup>. It could be interesting to investigate if they could be implemented in clinical practice among the already well-known risk factors of infection in PFF<sup>29</sup>.

Despite that, NLR has been found to be a good predictive factor, easy to obtain and to under-

stand, to evaluate the patient before surgery as higher admission NLR values relate to a higher rate of post-operative complications.

As mentioned before both ESS and NLR found several applications as prediction markers of poor prognosis in a wide variety of patients. Despite that, they failed to become standardized parameters due to the weak feedback and the lack of consensus from physicians. Recognizing their role in the inflammatory processes, we suggested a cross analysis of the two factors to increase their reliability<sup>30</sup>.

In particular, elderly patients with hip fractures show a persistent inflammatory state in the post-operative period associated with a higher risk to develop complications such as anemia and cardiovascular issues<sup>31</sup>.

As emerged from the literature and our study itself, both ESS and NLR are alone helpful predictive factors in elderly patients undergoing surgery. For this reason, we decided to analyze the association between ESS and NLR as negative predictive factors in patients with proximal femur fractures.

Our analysis showed how ESS group presented not only a higher risk of complications (27%), compared to the control group (8%), but also a higher NLR.

Femur fractures alone already bear a high-mortality rate and having a predictive index can be decisive for the management of surgical planning<sup>32</sup>.

In our specific case, the ESS group showed a significant increase ( $p=0.001$ ) of the NLR compared to the control group. Moreover, the patients in the ESS group who also showed higher NLR values, came out with a statistically significant rate of complications ( $p=0.03$ ).

### Limitations

One of the limitations of our study was the size of the sample. A larger number of patients, especially in the context of a multicenter study, could have brought more reliability to the results. Moreover, ours was a retrospective study, so it is clear the need of an observational study to validate the results.

Another aspect that should be considered is that we had no data regarding the pre-operative thyroid hormonal axis of the patients. It could be interesting to analyze if ESS was present before the trauma or if it was triggered by the trauma itself.

### Conclusions

Despite the limitations of this study, the results observed by now are promising and point out how both ESS and NLR are related to a higher risk of complications and mortality in patients with hip fractures. Our hope is to validate these two values as standardizes predictive factors to use in the preoperative evaluation of elderly with hip fractures.

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### Conflict of Interest

The Authors declare that they have no conflict of interests.

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### Data Availability Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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### Informed Consent

A written informed consent for scientific purposes and clinical data collection was obtained according to institutional protocol.

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### Ethics Approval

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Orthopedic and Traumatology Institute.

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