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Neutrophil - Lymphocyte Ratio as a Reliable Predictor of Postoperative Outcome And Mortality In Delayed Cases Of Peripheral Arterial Embolism

Abstract

Introduction: Peripheral arterial embolism (PAE) continues to pose a challenge to vascular surgeons and remains to be characterized by high morbidity, limb threat and mortality, often requiring urgent revascularization. Contemporary untreated arterial embolism is among the leading causes of morbidity and mortality within the vascular field. Detection of a fast and reliable biomarker for risk stratification and early post-treatment prognosis is important for those with PAE, so that individuals at high risk can be accurately treated and targeted for prevention.

Complete blood count is inexpensive, comparatively routine, and is a practical laboratory test that gives important information about the patient's formed blood contents. Routine peripheral blood counts may be useful in diagnosis and prognosis of many disorders, including peripheral vascular ischemic incidents. Neutrophil - lymphocyte ratio (NLR) has been shown to be an independent predictor of early and midterm amputation in patients with acute limb ischemia after revascularisation.

Methods: Data was collected retrospectively from hospitalised patients, in the Vascular Surgery Clinic of University Hospital, Stara Zagora, Bulgaria, who had a diagnosis of PAE, from January 2010 to January 2019. Inclusion criteria were clinical data of an ischemic embolic incident of the limbs,

untreated at least 12 hours from the onset of symptoms.

Results: A single cutoff point was chosen to better inform clinical practice at a value of NLR 4.55, to maximize sensitivity and specificity. The majority of patients from the group

Who had a NLR under 4.55 had mild symptoms. Older patients however, were significantly more likely to have an elevated NLR. The incidence of diabetes and hypertension were not significantly higher in any group. There was a higher incidence of primary major amputations in the elevated NLR group. Of the 25 deaths during the course of the study, which were specifically attributed to cardiac causes, twelve (13.8%) occurred within the elevated NLR group and thirteen (8.7%) in the low NLR group.

Conclusion: NLR is an easily accessible biomarker that conveys important information about the patient's inflammatory activity and can be easily calculated from the differential WBC count, which is routinely performed on admission and is universally available.

An elevated NLR could potentially be included in addition to the most common risk factors for mortality and poor post-treatment outcome including cardiac causes, age >70 years, history of stroke or previous MI, renal failure, and smoking history (at any time).

Subject: Medicine, Vascular surgery

Keywords: Peripheral, Arterial, Embolism, Neutrophil, Lymphocyte, Ratio

Introduction

Peripheral arterial embolism (PAE) continues to pose a challenge to the vascular surgeons and is still characterized by high morbidity, limb threat or mortality and often requires urgent revascularization (Creager, Kaufman, Conte, 2012).

Contemporary untreated arterial embolism is among leading causes of morbidity and mortality in vascular surgery (Van, Boesmans, Defraigne, 2018). Detection of a fast and reliable biomarker for risk stratification and early post-treatment prognosis in PAE is important so that individuals at high risk can be accurately treated and targeted for prevention.

Complete blood count is inexpensive, comparatively routine, and a practical laboratory test that gives us important information about the patient's formed blood contents (Zahorec, 2001). Routine peripheral blood counts may be useful in diagnosis and prognosis of many disorders, including peripheral vascular ischemic incidents.

This paper reviews the association of the NLR, with post-treatment outcome and mortality in contemporary untreated peripheral arterial embolism of the limbs.

NLR has been shown to be an independent predictor of early and midterm amputation in patients with acute limb ischemia after revascularisation (Spark, Sarveswaran, Blest, Charalabidis, Asthana, 2010).

The ratio is measured by dividing the number of neutrophils by the number of lymphocytes. Relevant studies were analysed with NLR as a study factor. An elevated NLR was significantly associated with an increased risk of coronary arterial disease, acute coronary syndrome, stroke, and composite cardiovascular events. Even when white blood cell count is in normal range, NLR has been demonstrated to play a predictive role in the prognosis of chronic and acute cardiovascular events (Bhat, Afari, Garcia, 2016).

The aim of this study was to examine the predictive ability of the NLR for post-treatment outcome and survival in patients who received delayed treatment (12 hours from onset of symptoms) in PAE.

Methods

Retrospectively collected data of hospitalised patients in Vascular Surgery Clinic of University Hospital, Stara Zagora, Bulgaria with a diagnosis of PAE untreated at least 12 hours from onset of symptoms from January 2010 to January 2019.

Inclusion criteria were clinical data of an ischemic embolic incident of the limbs untreated at least 12 hours from the onset of symptoms.

Patients were identified through the administrative hospital database using the International Classification of Diseases (ICD-10) codes: I74.2 - "Embolism and thrombosis of arteries of the upper extremities", I74.3 - "Embolism and

thrombosis of arteries of the lower extremities”, I74.5 - “Embolism and thrombosis of the iliac artery” and I74.0 - “Embolism and thrombosis of the abdominal aorta”.

Demographic characteristics, medical histories, laboratory studies (including WBC counts and automated peripheral differential counts), and outcomes of the data were collected using a standardized hospital database - Gama Codemaster.

Any subsequent surgical or other intervention was also documented as follows: primary surgery (limb salvage), primary surgery (amputation), or a combined procedure.

Results

432 patients were analysed, of which 236 (54.6%) met the inclusion criteria and participated, including 155 male (65.6%) and 81 female (34.4%) with a mean age of 67.5 ± 6.85 years. Average hospital stay was 8.7 days. In all of the cases, post-treatment outcome (including mortality) during the hospital stay was recorded.

A single cutoff point was chosen to better inform clinical practice, using a value of NLR 4.55, to maximize sensitivity and specificity.

149 patients (63.1 %) were with a NLR < 4.55 and 87 patients (36.9%) with NLR > 4.55.

The majority of patients from the former group were with mild symptoms. Older patients were significantly more likely to have an elevated NLR, with a mean age in the high NLR group of 72.5 ± 9.85 versus low NLR group 64 ± 10.15 .

The incidence of diabetes and hypertension were not significantly higher in any of the groups. Medications use (antiplatelet, vasoactive, analgesics etc.) differed between groups (43.5% in the low NLR group vs 19.8% in the high NLR group).

83.9% (73 patients) of the higher NLR group had present or past cardiac incidents or comorbidities (including atrial fibrillation, coronary artery disease, congestive heart failure or episodes of past myocardial infarction) versus 57.3 % of the lower NLR group.

Table I. Analysis of risk factors for patients with late peripheral embolism.

	<i>NLR < 4.5</i> <i>(n=149)</i>	<i>NLR > 4.5</i> <i>(n=87)</i>
<i>Age >70 years (127)</i>	<i>71 (47.6%)</i>	<i>56 (64.4%)</i>
<i>Hypertension (146)</i>	<i>91(61.07%)</i>	<i>55(63.2%)</i>
<i>Diabetes (93)</i>	<i>59(39.5%)</i>	<i>34(39%)</i>

<i>Smokers (162)</i>	<i>113(75.8%)</i>	<i>49(56.3%)</i>
<i>Cardiac pathology (AF, CAD, CHF, incl.past myocardial infarction) (171)</i>	<i>98(57.3%)</i>	<i>73(83.9%)</i>
<i>Cerebrovascular disease (84)</i>	<i>51(34.2%)</i>	<i>33(37.9%)</i>
<i>Chronic kidney failure (29)</i>	<i>13(8.7%)</i>	<i>16(18.3%)</i>
<i>Medication use (prior to admission)</i>	<i>63(42.2%)</i>	<i>21(24.1%)</i>

There was a significantly higher incidence of primary major amputations in the elevated NLR group (16.1% vs 7.4%). A higher number of patients with lower NLR underwent embolectomy alone (69.8% vs 46%). There was no difference in necessity of combined surgical revascularizations in both groups (18.1% vs 18.4%). A significant difference was evident in the rates of nonsurgical or conservative management between the groups (4.7% in lower group vs 19.5% in higher NLR group).

Table II. Analysis of primary procedures.

	<i>NLR < 4.5 (n=149)</i>	<i>NLR > 4.5 (n=87)</i>
<i>Embolectomy alone (n=144)</i>	<i>104 (69.8%)</i>	<i>40 (46%)</i>
<i>Combined procedure (embolectomy + bypass, or embolectomy + minor amputation) (n=43)</i>	<i>27 (18.1%)</i>	<i>16 (18.4%)</i>
<i>Primary major amputation (n=25)</i>	<i>11 (7.4%)</i>	<i>14 (16.1%)</i>
<i>Conservative/palliative (n=24)</i>	<i>7 (4.7%)</i>	<i>17 (19.5%)</i>

102 patients (68.4%) of the lower group had no complaints when being discharged, versus 51 patients (58.6%) of the higher NLR group.

The incidence of recurrent PAE was significantly more frequent in the higher group, 10.3% versus 3.3% in lower NLR group.

In higher NLR group the incidence of recurring thrombosis (with or without revascularisation options) was more common 37.9% vs 20.1% in lower NLR group.

Of the 25 deaths during the course of the study which were specifically attributed to cardiac causes, twelve (13.8%) occurred within the elevated NLR group and 13 (8.7%) in the low NLR group.

Table III. Analysis of post-treatment outcomes

	<i>NLR < 4.5</i> <i>(n=149)</i>	<i>NLR > 4.5</i> <i>(n=87)</i>
<i>Free of complains at discharge</i>	<i>102 (68.4%)</i>	<i>51 (58.6%)</i>
<i>Minimal complains (numbness, coldness etc.)</i>	<i>20 (13.5%)</i>	<i>9(10.3%)</i>
<i>Rethrombosis followed by revascularisation</i>	<i>16 (10.7%)</i>	<i>18(20.6%)</i>
<i>Rethrombosis followed by amputation</i>	<i>14 (9.4%)</i>	<i>15(17.3%)</i>
<i>Reccurent embolism</i>	<i>5 (3.3%)</i>	<i>9(10.3%)</i>
<i>Fasciotomy</i>	<i>17 (11.4%)</i>	<i>7 (8%)</i>
<i>Infection of operative side</i>	<i>8 (5.3%)</i>	<i>6 (6.8%)</i>
<i>Death (during hospital stay or 30 days follow up period.)</i>	<i>13 (8.7%)</i>	<i>12 (13.8%)</i>

Discussion

Cole (et al 1954) stated more than 50 years ago, that patients with myocardial infarction and elevated WBC counts had a higher risk of death compared to those with WBC counts in the normal range. Since then, many studies have demonstrated and suggested a relationship between higher total leukocyte counts and cardiovascular events. (Friedman, Klatsky ,Siegelaub, 1974; Hajj-Ali, Zareba, Ezzeddine, Moss, 2001).

Patients suffering from acute PAE bear a considerable risk of recurrent embolic incidents including MI, stroke, or cardiovascular incidents (Dormandy & Rutherford, 2000).

The number of neutrophils correlated primarily and constantly in a positive manner with the atherosclerotic load and ischemic condition in most of the cohort studies that have provided information on differential WBC count (Gurm, Bhatt, Lincoff, Tchong, Kereiakes, Kleiman, 2003; Sweetnam, Thomas, Yarnell, Baker, Elwood, 1997; Wheeler, Mussolino, Gillum, Danesh, 2004).

Neutrophils mediate the inflammatory response by numerous biochemical mechanisms, such as release of arachidonic acid metabolites and platelet-aggravating factors, cytotoxic oxygen-derived free radicals, and hydrolytic enzymes such as myeloperoxidase, elastase, various hydrolytic enzymes, and acid phosphatases. The NLR therefore reflects both the neutrophilia of inflammation and the relative lymphopenia of cortisol-induced stress. (Tamhane, Aneja, Montgomery, Rogers, Eagle, Gurm, 2008).

NLR is also correlated with other markers of a pro-inflammatory state; recent studies of long-term outcome in cardiac disease as well as oncologic resections have shown associations of elevated NLR with poor long-term outcome (Walsh, Cook, Goulder, Justin, Keeling, 2005; Gomez, Farid, Malik, Prasad, Toogood, Lodge, 2008; Halazun, Malik, Al-Mukhtar, Prasad, Toogood, Lodge, 2008).

The impact of cardiac pathology on survival and postoperative outcomes has long been known, thus medications, such as statins, play an undisputed role in the quest of increasing both the quantity and quality of life.

To conclude, it can be summarized that NLR is an easily accessible biomarker that conveys important information about the patient's inflammatory activity. NLR can be easily calculated from the differential WBC count, which is routinely performed on admission and is universally available.

NLR is an inexpensive and readily available marker that delivers an additional level of risk stratification beyond that provided by conventional methods in predicting and anticipating in-hospital and post-treatment outcome and mortality.

An elevated NLR could potentially be included in addition to the most common risk factors for mortality and poor post-treatment outcome including cardiac causes, age >70 years, history of stroke or previous MI, renal failure, and smoking history (at any time).

Moreover, it is available preoperatively and may be of use in informing patients with regard to treatment options and possible outcomes.

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