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REVIEW

Zahorec index or Neutrophil-to-lymphocyte ratio, valid biomarker of inflammation and immune response to infection, cancer and surgery

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ABSTRACT

BACKGROUND: For many years, the physicians are searching for easily measurable marker of immune response to the stress and inflammation. More than, 20 years ago Zahorec (2001) proposed neutrophil-to-lymphocyte ratio (NLR) as an easy available and valid biomarker of inflammation, stress, and activation of immune system.

METHODS: In this narrative review we focused on the utility of neutrophil-to-lymphocyte ratio (Zahorec's index) in clinical practice of general medicine (inflammation and infection), intensive medicine (sepsis), oncology (prediction of prognosis in cancer of solid organs), surgery and perioperative medicine (diagnosis of complications, and prediction of clinical outcome).

RESULTS AND CONCLUSION: We provide many evidences of clinical research which confirm that Neutrophil-to-lymphocyte ratio is a very sensitive marker of inflammation, stress reliable and valid parameter in everyday clinical practice. NLR (Zahorec index) is an effective tool for diagnosis of infection and severity of disease of variable etiologies. NLR reflect the grade of inflammation in cancer disease, which has a significant impact on the prognosis of cancer patients. Zahorec index should be used routinely in emergency medicine, surgery and perioperative medicine as a marker of the severity of affliction, infection, and complications in general. NLR may help physicians in decision making process for early diagnosis and therapy. NLR should be investigated frequently in acute states (sepsis, shock, peritonitis, stroke, trauma) on a daily basis, in subacute states few times per week (during hospital stay), and few times per year in chronic disease (cancer, diabetes mellitus, ischemic heart disease, psychiatry disorders). NLR has a deep biological sense connecting together function of three suprasystems: immune, endocrinne and autonomous nervous system *(Tab. 2, Fig. 3, Ref. 86)*. Text in PDF *www.elis.sk*

KEY WORDS: Zahorec index, neutrophil-to-lymphocyte ratio, valid biomarker of inflammation, immune response to infection, cancer, surgery.

Introduction

The neutrophil-to-lymphocyte ratio (NLR) was established by Roman Zahorec (Zahorec, 2001) as a simple, easy available and cheap hematologic parameter, which is very sensitive to detect the intensity of endocrinne stress, infection, inflammation and severity of disease. The values of NLR are obtained from complete blood count (white blood cells differential) as a ratio between neutrophils count and lymphocytes count. Twenty years of research worldwire confirmed utility of NLR across clinical medicine (Zahorec, 2021). NLR is a marker which conjugates two arms of the immune system: the innate immune response (neutrophils) and adaptive response (lymphocytes) (Song et al, 2021). Never the less, NLR is a sensitive marker of activity of vegetative nervous system and endocrinne system as well, supported by animal experiments focused on various receptors for hormones (adrenalin, cortisol, prolactin, thyroid hormones) on the surface of neutrophils and lymphocytes (Kalelioglu, 2019, Reiske, 2020). NLR is a common sensor of in-

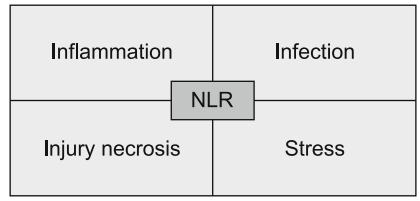

Fig. 1. Neutrophil to lymphocyte ratio reflects the intensity of immune activation (cell-mediated immune response) during to various noxious stimuli (endocrinne stress, injury, necrosis, infection)

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flammation and stress together. NLR is used for monitoring, stratification and prognosis of various clinical syndromes, and diseases: acute myocardial infarction (Tamhane, 2008, Bhat, 2013), viral, bacterial and fungal infection (Holub, 2012, Naess, 2017, Russel, 2019), acute stroke (Latanzzi, 2016), severe trauma (Park, 2017, Fisher et al, 2016), sepsis (Salciccioli, 2015, Riché, 2015, Ljungstrom, 2017, Farkas, 2020, Serrano, 2023), acute appendicitis and pancreatitis (Ishizuka, 2012, Suppiah, 2013, Kong, 2020). NLR is used nowadays for monitoring the course and outcome of several clinical entities regarding: infection, local and systemic inflammation, cancer of solid organs, stress and imbalance of homeostasis of various origin (Fig. 1) In this short narrative rewiev we focused on the three domains where Zahorec index (NLR) may be useful for clinical medicine: sepsis and infection, oncology, surgery and perioperative medicine.

NLR, invasive systemic infection and sepsis

Sepsis is a life-threatening organ dysfunction with high mortality rate, when accompanied by shock, multiorgan failure and acute deterioration of homeostasis. Immune, reticulo-endothelial and hematological systems are playing central role in the pathogenesis of sepsis. Quantitative and qualitative activation of white blood cells during infection and sepsis are hallmarks which can be used for early diagnosis. 40 years ago Elebute and Stoner (1983) established Sepsis score to measure severity and intensity of systemic inflammation. Zahorec (2001) observed a specific pattern of dynamics of leukocytes subpopulations, simultaneously increase of neutrophils count and decline of lymphocyte counts „hand-in-hand“ but in opposite directions in early postoperative period of ninety oncosurgical patients. The most striking increase of neutrophils (more than 90 % of leukocytes) and sudden decrease of lymphocytes (less than 5 % of all WBC) were observed in patients with abdominal sepsis and septic shock. Zahorec (2001) first proposed neutrophil-lymphocyte stress factor calculated as a neutrophils count divided by lymphocytes count, now named neutrophil-to-lymphocyte ratio (NLR) or Zahorec index. Since the first citation of his paper by Aird (2003), plenty of articles on the role of NLR in sepsis and infection were issued (de Jager, 2010, Riche, 2015, Ljungstrom, 2017, Russel, 2019, Farkas, 2020, Marik, 2021). NLR is very sensitive but not specific marker for sepsis and differenet types of infection of variable etiologies (Naess, 2017, Russel et al, 2019). It can be used in a panel of inflammatory parameters like C-reactive protein (CRP), procalcitonin (PCT), interleukin 6, platelets count, NLR and lactate (Fig. 2). Ljungstrom (2017) compared all this markers on the cohort of 1,572 adult patients. NLR was superior to C-reactive protein but inferior to procalcitonin regarding specificity for sepsis. C. de Jager (2010) demonstrated priority of profound lymphocytopenia and high NLR over CRP and total white blood cell count for the diagnosis of bacteremia. Riché et al (2015) analyzed to an association between increased NLR values and the risk of death during the course of septic shock in a cohort of 130 ICU patients. High values of NLR (median 12.5) reflected the severity of septic shock, but as a paradox early death was associated with low

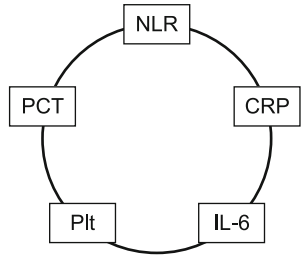

Fig. 2. Valid and reliable laboratory markers for diagnosis and monitoring of systemic infection and sepsis syndrome routinely used in clinical setting (CRP – C-reactive protein, IL-6 interleukin 6, Plt – platelets, PCT – procalcitonin, NLR – neutrophil to lymphocyte ratio)

NLR values (median 6.2). Probably due to inappropriate response of innate cellular response, eg. in leukopenia /neutropenia. Late death after 5 days was associated with dynamic increase of NLR values. Others confirmed that in ICU patients we should follow up NLR values on a daily basis to evaluate the severity of sepsis, inflammation, and risk of death. The survivors and responders to ICU therapy had a significantly decline of NLR between 3rd and 5th day. Non-responders or non-survivors had on ICU day 3 very high NLR above ≥ 15, the mortality odds ratio was 6.96 (Sari, 2019). Hemogram, complete blood count and easy calculated values of NLR are reliable and helpful markers for diagnosis, stratification of severity, prediction and prognosis of sepsis syndrom (Farkas, 2020, Zahorec, 2021a). The gold laboratory standard for monitoring sepsis and septic shock are up-to-day following basic three parameters: **C-reactive protein, procalcitonin and NLR** (Fig. 2). In ICU setting they should be measured every day in the morning from peripheral venous blood, in general ward setting in acute state every second day (1st, 3rd, 5th and 7th day). Not only absolute values, but dynamic changes of NLR, PCT, CRP values and immature granulocytes count reflect the course of sepsis syndrome and are crucial for prediction and prognosis of sepsis and septic shock (Nierhaus, 2013, Riché et al, 2015, Salciccioli, 2015, Zahorec, 2021). High /low values of inflammatory markers (NLR, CRP, PCT, albumin) and tendency of increased /decreased levels of acute phase proteins can provide an objective tool which may help physicians in decision making process for early and precise diagnosis (Buonacerra, 2022, Serrano, 2023).

NLR and cancer, utility of Zahorec index in oncology

Zahorec index (NLR) may serve as a reliable parameter of cancer-induced inflammation (Guthrie, 2013, Zahorec, 2021b). Cancer as a systemic disease is associated with local inflammation. There is a large body of evidence showing the links of inflammation to both oncogenesis and tumor biology (Coussens, Werb, 2002, Grivennikov, 2010). Inflammation is now considered a hallmark of cancer (Colotta, 2009, Hannahan, 2011). Systemic inflammation results form immunological pathways that govern the interplay between immune cells, inflammatory cytokines and mediators and their cellular targets including cancer cells and tu-

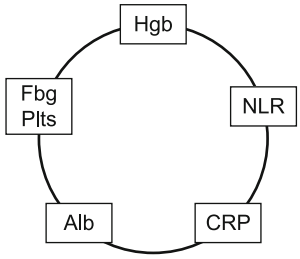

Fig. 3. Inflammation based parameters for diagnosis, stratification, prediction and prognosis of cancer of solid organs: hemoglobin, fibrinogen, platelets count, albumin, C-reactive protein, and neutrophil to lymphocyte ratio.

mor stroma (microenviroment). Tumor associated immune response is recognized as a fundamental process in cancerogenesis (Hannahan, 2011). Tumor-associated local inflammation is a double edged sword which may influence the favorable and poor outcome of cancer. Favorable outcomes are associated with proper regulation of anti-cancer immune response, which is characterized by a strong local infiltration with N1-neutrophils, high density of T-lymphocytes, and M1 – monocytes driven innate immune response (Chanmee, 2014, Hibino, 2021). Key role are playing NK cells and CD8+ cytotoxic T-lymphocytes (CTL) promoting anti-tumor effect. Opposite is a tumor-promoting immune response, which may be driven by a T-helper-2 (Th2) adaptive immune response and M2 innate immune reponse (Chanmee, 2014, Motomura, 2013, Hibino, 2021). Local inflammation inside solid cancer may established even systemic inflammatory response, which is manifested with anemia, paraneoplastic thrombocytosis, mild leukocytosis (above 8.0 thousand/µl) with neutrophilia (higher count than 6.0 thousand/µl) and lymphocytopenia (less < 1,800/µl, Zahorec, 2021b), acute phase response (elevated concentration of C-reactive protein, decreased concentration of albumin in the plasma) and activation of coagulation system (higher fibrinogen concentration ≥ 3.8 g/l, and INR ≥ 1.3). Markers of systemic inflammation and poor prognosis of cancer are elevated CRP, low serum albumin and high NLR (McMillan, 2013, Guthrie, 2013), high concentration of fibrinogen, and low hemoglobin (Lam, 2015, Palaj, 2018). Monitoring of inflammation-based systemic reponse in colorectal cancer patients which may have a negative influence (impact) on outcome are following parameters: hemoglobin, NLR, fibrinogen, C-reactive protein, albumin, platelets count (Zahorec et al, 2021) (Fig 3). Neutrophil-to-lymphocyte ratio has a strong statistical power to predict outcome in various types of cancer since Walsh et al (2005) demonstrated that NLR greater than 5 was significantly associated with poorer overall and cancer specific survival in colorectal cancer patients of two years after radical surgery. They observed significant differences in the mean NLR values associated with different Dukes stage (NLR 4.0–4.83 in Dukes stage A, B, C, and NLR 6.12 in Dukes stage D). Preoperative NLR represents a simple surrogate marker for identifying colorectal cancer patients at high risk of death with poor prognosis. NLR is very sensitive parameter of cellular immunity which may detect low-grade cancer associated inflammation, or subclinical systemic inflammatory response to the growing malignant tumor (Zahorec, 2021). Developing cancer is associated with mild increase of **NLR greater than 2.4–4.5** (normal values of NLR are between 1.1–2.3). At present, NLR is broadly use as a cheap and easy available parameter for stratification of advanced cancer and prognosis of oncological disease of various origin. The cut-off

Tab. 1. Inflammation based scores (CIPS, HALP, SII) or ratio (CAR, CLR, FAR, NLR) used for monitoring of inflammation in the course of cancer development (stratification, diagnosis, prognosis), according Zahorec 2001, 2021, Lu 2023.

Ratio, index or score	Name, of index or ratio	Calculation / equation	Normal value range in health	**Pathology, and disease severity**	Citations of original article
CAR	C-reactive protein to albumin ratio	CRP (mg/L)x 10^3/ALB (g/L)	< 0.2	**≥ 0.3** **≥ 1.0** **≥ 3.0**	Fairclough 2009
CLR orthopaedic surgery	CRP to lymphocyte ratio	CRP (mg/l) : lymphocyte count / µl	< 5.0	**≥ 7** **≥ 15** **≥ 50**	Zhu 2022
CIPS score in cancer	Cancer inflammation prognostic score	(NLR x CRP x Fbg x Plts) /: (hbg x alb)	< 1.6	**≥ 2.5** **≥ 5.0** **≥ 10.0**	Zahorec 2021
HALP score In cancer	Hemoglobin x albumin / lymphocyte x platelets score	(hbg x Alb) : / (Lymph x Plt)	≥ 10	**< 9.0** **< 8.0** **< 6.0**	Chen 2016, Benli 2023
FAR	Fibrinogen to albumin ratio	Fbg / Alb g/L :/ g/L	< 0.1	**≥ 0.1** **≥ 0.15** **≥ 0.2**	Papila 2021, Wang 2022, Jiang 2023
NLR	Neutrophil to lymphocyte ratio	Neutrophils : lymphocytes count	1.0 – 2.0	**≥ 3.0** **≥ 7.0** **≥ 11.0**	Zahorec 2001, Zahorec 2021
SII	Systemic inflammation score	Platelet count x NLR	< 500	**≥ 600** **≥ 1,000** **≥ 4,000**	

values of NLR range are **between 2.4–5.0** for shorter disease free survival and overall survival (Cook, 2009, Ohno, 2010, Pichler, 2012, Guthrie, 2013, Motomura, 2013, Sun X, 2016, Kantola, 2012, Yoshida, 2020). Several meta-analyses have explored the prognostic value of NLR various solid tumors. Howard et al (2019) explored group-specific cut-off values of NLR in different types of cancer for precise validation as a tool for risk stratification. A total of 5,363 patients were included in the final analysis where 1,024 were out of colorectal cancer. They measured optimal cut-off value for good prognosis NLR < 3.2 for overall survival. Patients with NLR higher than median had poorer clinical outcome with shorter overall survival (Howard et al, 2019). Bowen et al (2017) analyzed 144 studies comprising 45,905 patients with gastrointestinal cancers. Evidence suggests that NLR greater than the median of the cut-off value NLR ≥ 3.0 (IQR 2.5–5.0) reduces over all survival, independently of stage of cancer. NLR is a sensitive marker of cancer-associated systemic inflmammation together with acute phase proteins like a C-reactive protein, fibrinogen, platelets count and negative correlation with hemoglobin and albumin concentrations (Seong, 2015, Lam, 2015, Arigami, 2016). NLR can be used as a surrogate marker for monitoring the response to oncological therapy, decreasing post-treatment NLR values are associated with better clinical outcome (Ferruci, 2015, Capone, 2018, Shindo, 2019, Ishihara, 2021). It is highly recommended to follow-up NLR values together with onkomarkers or with acute phase proteins during the course of anti-cancer treatment. Seong (2015) suggested prognostic inflammatory score (PIS) to measure risk of recurrence and death in patients with CRC. PIS consists of two biomarkers – NLR and C-reactive protein. Combination of CRP, albumin and NLR is very useful and effective tool for monitoring the immune-inflammatory response in cancer patients (Proctor, 2012, Guthrie, 2013, Kubo, 2014, Pine, 2015). The progress in the research of microenviroment and immune-inflammation processes in the pathogenesis of cancer approved the central role of immune cells (NK cells, T-lymphocytes, neutrophils N1/N2, monocytes/macrophages M1/M2), acute phase response (APPs – albumin, fibrinogen, CRP), cancer induced anemia (low hemoglobin) and thormbocytosis (high platelets count ≥ 300 thousand/μl). Hematologic and reticuloendothelial system (bone marrow, endothelium, spleen, liver) with acute phase response (liver) are activated during cancer disease. The blood and complete blood count may serve as easy available and reliable source of „cancer inflammation-based markers“ such like: hemoglobin, albumin, fibrinogen, neutrophil count, lymphocytes count ratio (NLR – Zahorec index), platelet count, eosinophils count and C-reactive protein (Fig. 3) (Jiang, 2023, Zhang et al, 2023, Akiyama, 2023, Iaciu et al, 2023). Nowadays several ratios /scores were used to estimate the intensity of inflammation in the develompent of cancer: fibrinogen to albumin ratio (FAR, Sun, 2020, Wang, 2022), C-reactive protein to albumin ratio (CAR, Fairclough, 2009), C-reactive protein to lymphocytes count (CLR), hemoglobin x albumin concentration divided by lymphocyte and platelets count (HALP score), or CIPS score (Zahorec et al, 2021) (Tab. 1). NLR is a moderate prognostic factor to monitor long-term clinical outcome after oncological treatment (onco-surgery, chemotherapy and biological therapy and radiotherapy). Many retrospective studies evaluated the efficacy of pretreatment NLR values and post-treatment NLR values on clinical outcome, overall survival (OS) and disease free interval (DFI). Both the preoperative and postoperative NLR have been proposed to predict long-term prognosis in some cancers, including gastric cancer (Kim, 2023). On the cohort of 1,277 patients with gastric cancer who underwent total R0 gastrectomy they followed-up NLR values preoperatively – before surgery and then 6 months after surgery. The main goal of the study was 5-year overall survival (OS). The preoperative median of NLR was 2.0, the postoperative median of NLR was 1.70 6th month after onco-surgery. The strength of the study was its use of reliable NLR cut-off values based on a large pool of data for gastric cancer patients. Both the high NLR group of pretreatment value ≥ 2.0, and postreatment value high NLR ≥ 1.7 6th months after gastrectomy were associated with poor clinical outcome and shorter overall 5 year survival in mutlivariate analysis with hazard ratio 1.817 (p = 0.003). They concluded that preoperative NLR, postoperative NLR and dynamic changes in NLR both were significant prognostic factors in patients with gastric cancer (Kim et al, 2023). The NLR is a systemic reflection of cancer-associated inflammation and a valid prognostic factor for breast cancer. The study on the cohort of 146 patients with breast cancer receiving neoadjuvant chemotherapy explored the relationship between systemic immune respone (pre-chemotherapy and post-surgery NLR), local immune mircoenviroment (pre-chemotherapy biopsy, and post-surgery specimens were assessed for TILs and TAMs. Pre-CHT and post-surgery NLR at a cut-off value of 2.6 were positevely associated with necrosis on biopsy and excision and TAMs on excision. High NLR values one-year post-surgery were associated with high tumor stage and low histologic grade (p < 0.008). TIL count in tumor was lower in NLR-high cases. In multivariate analysis post-surgery NLR is an independent predictor of overall survival, cancer specific survival and disease free survival (Hazard ratio 9.52, 10.0 and 2.82 respectively) (Li et al, 2023).

Neutrophil-to-lymphocyte ratio (NLR) in surgery and perioperative medicine

NLR is a valid hematological parameter to support clinical diagnosis like acute appendicitis (Ishizuka, 2012, Toktas, 2017, Hajibandeh, 2020), cholecystitis, cholangoitis (Xu, 2023) or acute pancreatitis (Suppiah, 2013, Kong, 2020), endometriosis (Drobny, 2020). NLR may help physicians in decision making process for early diagnosis of intraabdomninal infection and inflammation. NLR is available and reliable index for monitoring intensity of inflammation in the whole perioperative period. NLR as a marker of cellular immune activity can be used for evaluation a possible risk in postoperative period, in prediction of postoperative complication, as well as a prognostic index of clinical outcome six to twelve months after surgery.

Walsh et al (2005) were first who observed that adult patients with colorectal cancer and elevated NLR above 5 pre-operatively had significantly higher ocurrence of complications, recurrence of

cancer and shorter over all survival one year after colorectal surgery. In a prospective cohort study Cook et al (2007) followed up the NLR on the first postoperative day in 100 colorectal surgical patients, They recorded pre-defined post-operative complications. They found out that NLR above 9.3 on the first postoperative day is associated with significant higher occurrence of complications. NLR is helpful marker for diagnosis of post-operative complications in abdominal surgery, cardiac and thoracic surgery, othopedic and oncological surgery (). In a single center retrospective study Kwak et al (2022) reviewed 212 patients with gastric cancer who underwent total gastrectomy. They followed up perioperative neutrophil-to-lymphocyte ratio as a early predictor of major postoperative complications. According ROC analysis for NLR on second postoperative day the cut off was 9.6. In multivariate analysis the NLR on POD 2 of ≥ 9.6 and ASA classification ≥ 3 were significant predictors of major postoperative complications (Kwak et al, 2022). NLR is a very effective biomarker in postoperative wound infections (Duran, 2022).

Preoperative NLR is a simple cheap and easy available index (Zahorec, 2001, 2021) for postoperative complications and clinical outcome, either 1 year after surgery (Sung, 2021, Zhu, 2023, Tzikos, 2023). Korean retrospective trial on a cohort of 7,089 adult patients undergoing plastic and reconstructive surgery extensively studied the association between preoperative value NLR and postoperative outcomes 1 year after surgery. The preoperative median of NLR was 1.84. This observational study showed that mortality during the first year after plastic and reconstrucxtive surgery was significantly increased in the high NLR group. The estimated threshold of preoperative NLR was 2.5. Like in the Walsh study (2005) preoperative NLR was associated with 1-year mortality (Sung, 2021). Assessment of prognostic value of preoperative NLR for postoperative morbidity and mortality were done in Sichuan, China. They conducted a cohort analysis on adult patients who underwent surgery. Multivariable regression analysis were used to determine optimal cutoff value of NLR obtained preoperatively from 136,347 patients. The optimal cutoff of preoperative NLR ≥ 3.6 confirmed valid predictive value of high NLR in multiple surgical subgroups. This robust study confirmed association of elevated NLR (≥ 3.6) preoperatively with higher mortality and ICU admission postoperatively (Zhu et al, 2023). NLR and platelet-to-lymphocyte ratio (PLR) were investigated on the day of cardiac surgery, and 3rd, 5th and 7th postoperative day. Analysis was performed on 179 patients who underwent cardiac surgery, 11 of whom (6.15 %) died within 90-day mortality interval. They found out that the optimal thresholds of NLR for major complications and high risk of death is POD5 when NLR5 ≥ 7.7 and POD7 when NLR7 ≥ 6.6. They concluded that elevated postoperative NLR value (NLR7 ≥ 6.6) after cardiac surgery and the ICU length of stay are independent risk factors for increased 90-day mortality (Tzikos et al, 2023). The NLR is extensively analyzed prognostic index in cardiac surgery patients. Very important for prediction of complication is the dynamic course of NLR values before and after surgery, which can be expressed as delta NLR (ΔNLR): Dynamic changes of NLR values can represent the intensity of stress and inflammatory response induced by surgery. Bae et al (2023) in single-center retrospective study followed perioperative data including NLR values from 1,322 adult patients undergoing off-pump cardiac surgery. The primary endpoint were postoperative complications 90 days after surgery and secondary endpoint was longterm mortality. The median preoperative NLR values of 2.2 were significantly increased on the first and third postoperative day (POD3) to 7.4 (5.4–10.3). The overall mortality rate was 5.3 % (70 patients out from 1,322). All deaths occurred after POD3. Higher risk for major complications and death had a group with delta-NLR = NLR3 – NLR-1 ≥ 5.0. Multivariable Cox regression analysis for long-term post-operative complications and mortality rate showed a significant correlation (high hazard ratio) with high delta-NLR ≥ 5.0 group, age, history of anemia (low hemoglobin pre-and post-operatively). In conclusion delta-NLR (NLR3 on POD3 diminished by preoperative NLR-1 value) was an independent risk factor for longterm mortality (Bae et al, 2023). Lu et al (2023) explored the predictive value of perioperative blood circulating markers on surgical complications in patients undergoing robotic-assisted surgery. In terms of the systemic inflammatory markers identified several markers as critical predictors for surgical complications in peripheral venous blood, among which, NLR and CRP played a pivotal role, together with RBCs count and hemoglobin level preOP, and on POD1 and POD3 (Lu et al, 2023). They concluded that elevated values of NLR and CRP concentration in postoperative period predict and increased risk of grade II and major complications after robotic-assisted radical prostatectomy (Lu et al, 2023).

Chae et al (2021) on the robust retrospective study on the cohort of 21,150 cases of non-cardiac surgery evaluated a risk scoring system integrating postoperative factors on the early postoperative mortality rate focused on the laboratory parameters and markers of inflammation. The independent risk factors were: age ≥ 65 y/o, type of surgery (urgent/emergent), ASA classification ≥ 3, blood loss and need for transfusions, and the postoperative dynamic course of hemoglobin, higher NLR values, high C-reactive concentration and low albumin concentration with significant differences on 5th postoperative day (POD5). The high risk for mortality rate on POD5 were NLR ≥ 7,0, CRP ≥ 100 mg/l, platelets count < 100,000 /ul, albumin < 27 g/l, and low hemoglobin < 85 g/l (Chae et al, 2021). Integrating the data and results of previous studies few hematological and biochemical parameters obtained preoperatively like NLR ≥ 3.0, ≥ 3.3, ≥ 3.6 (Sung, 2022, Zhu, 2023), albumin < 36 g/l, hemoglobin < 110 g/l, have significant impact on postoperative major complication and even on mortality rate (Chae, 2021, Zhu, 2023). Many retrospective robust studies verified the importance of NLR in post-operative period on the short-term (per hospital or 30 day mortality) and long-term mortality (6-months or 1-year mortality). Crucial condition is a serial measurment of white blood cells differential and calculation of NLR values automatically before, and every day after surgery on the POD1, POD2, POD3, POD5 and POD7. The significant differences between uncomplicated postoperative course and major postoperative complications were observed in various cohort of surgical patients on POD2 of NLR ≥ 9.3–9.6 (Cook, 2007, Kwak, 2022), on POD3 of NLR ≥ 7.5 and delta NLR ≥ 5.5 (Bae, 2023,

Tab. 2. Results of threshold NLR values pre-operatively and post-operatively for evaluation of hospital short-term (30, 90 days) and long-term (1 year, 2 years) post-operative complications and mortality rate.

Diagnosis, type of surgery, number of patients in the cohort	**Pre-operative** cut off NLR values	**Post-operative cut-off** NLR at POD2, POD3, POD5, POD7	Reference
CRC surgery, 203 pts	**≥ 5.0**	**N.A.**	Walsh 2005
CRC surgery, curative resection, 100 pts	**≥ 3.5**	**≥ 9.3 on POD1** **≥ 9.6 on POD2**	Cook 2007, Kwak 2022
General surgery, cohort 136,347 pts	**≥ 3.6**	**N.A.**	Zhu et al 2023
Cardiac surgery, 179 pts	**≥ 2.5**	**≥ 7.1 on POD5,** **≥ 6.6 on POD7**	Tzikos et al 2023
Cardiac surgery off-pump, 1,322 pts	**≥ 2.2**	**≥ 7.5 on POD3, delta NLR ≥ 5.0 on POD3**	Bae et al 2023
General non-cardiac surgery 21,150 pts	**≥ 3.3**	**≥ 7.0 on POD5**	Chae et al 2021
Plastic Reconstructive surgery, 7,089 pts	**≥ 2.5**	**N.A.**	Sung et al 2021

Lu, 2023), or on POD5 of NLR ≥ 7.1–7.7 or on POD7, when NLR values are above ≥ 6.6 (Chae, 2021, Tzikos, 2023). The overview of cutoff values of NLR for high risk of postoperative complication and death rate are summarized on the Table 2. Regarding laboratory parameters which have significant impact preoperatively as well as postoperatively on the clinical outcome except NLR are hemoglobin levels, albumin and C-reactive protein concentrations, and platelets count (Fig. 3).

Zahorec index (NLR), homeostasis, stress, and holistic approach to biomarkers and indexes

NLR has a deep biological function connecting together function of three suprasystems: immune, endocrinne and autonomous nervous system. Neutrophil-to-lymphocyte ratio has a deep sense and importance regarding holistic approach and regulation of biological systems with the outstanding role of biomarkers (Hedayat, 2020). The theory of endobiogeny emphasizes the central role of neuroendocrine system as the manager of metabolism and integrity of the whole body in health and disease. The autonomic nervous system calibrates and sequences timing, duration, amplitude and intensity of endocrine function. The biology of physiological functions of the human organism in its dynamic state of phenotypic expression can be explored by serum biomarkers obtained by venous blood (Lapraz, 2013). The essential ones are: red blood cells (RBC), hemoglobin level, leukocytes and its subpopulations (neutrophils, lymphocytes, eosinophils, and monocytes), platelets, serum ions – sodium, potassium, calcium and chloride, total protein and albumin, thyroid stimulatign hormone (TSH), and few enzymes lactate dehydrogenase (LDH), creatine kinase (CK) total, osteocalcin and alkaline phosphatase (AP bone isoenzyme). The special position has TSH serum concentrations in regulation of metabolism and for interpretation of indexes. Once serum biomarkers have been resulted, they are combined by ratios to form direct indexes. Direct indexes my be combined with other indexes or additional biomarkers to form indirect or meta indexes (like genital ratio, thyroid index, or genito-thyroid index, discussed later). The initial index value represents the general current capabilities of the orgasnism during normal metabolism in health or during adaptive metabolism in physical excercise or during the disease. In the scope of the theory of endobiogeny there are several advantages to using biomarkers to mirror upstream regulation of the terrain of metabolism, immunity and other physiologic functions. First, quantifiable biomarkers allow for objective, repeatable evaluations of key physiological function across time. Secondly, it allows for qualitative, polyfactorial assessment. Third, it allows for personalization of treatment by evaluating the specific elements, most implicated for disequilibrium (Hedayat, 2020). According to the theory of endobiogeny some direct indexes were created on the activity of sex hormones (androgens, estrogens) and thyroid gland hormones: the Genital ratio is defined as the relative activity of androgens (RBC count) on tissue mertabolism and bone marrow during adaptation in relationship to the estrogen activity (WBC count). Genital ratio = RBCs x 10^3 / Leukocytes = 0.8–0.95 for men, and 0.7–0.85 for women. It is very interesting that founder of the theory of endobiogeny developed genito-thyroid index (GTi) as a ratio of relative count of neutrophil granulocytes to relative count of lymphocytes, and the normal value is **1.5**–**2.5** in men and women. It was defined as the relative activity of estrogenes in relationship to that of the thyroid gland. Estrogens proliferate neutrophils and TSH proliferates T-lymphocytes in the thymus (Hedayat, 2020). An isolated rise in neutrophil count, and consequently an increased values of NLR were observed in many clinical conditions like bacterial and viral infection including COVID-19, acute stroke, myocardial infarctzion and acute coronary syndrom, severe trauma, cancer, in post-surgery complications, in schizophrenia and depression. NLR is characterized by an increase of neutrophils count and a decline of lymphocytes count at the same time „synchronous dynamics“. NLR can predict mortality in the general population, in cancer and ICU patients NLR is associated with higher overall mortality (Buonacera et al, 2022). The early increase of NLR following acute physiological insult and stress can confer on NLR to be a marker of neuroendcrinne stress as well as very senzitive biomarker of inflammation, injury and infection. NLR should be used with other biomarkers (IL-6, CD64), positive acute phase proteins (C-reactive protein, procalcitonin, fibrinogen, ferritin, serum amyloid A), (Serrano et al, 2023) and negative acute phase proteins (albumin, hemoglobin, transferin, HDL-cholesterol lipoproteins). There are some confounding factors that can determine false increase in NLR, age, intake of corticosteroids, leuke-

mia and hematooncological diagnosis, chronic psychoemotional stress, profound anemia, endogenous sexual hormones activity, endogenous or exogenous catecholamines, cytokines and other hormones (Karakonstantis et al, 2018)

Conclusion

This short review would like to emphasize the importance of neutrophil-to-lympohcyte ratio or Zahorec index (Zahorec, 2001, 2021) across the disciplines of clinical medicine, physiology and immunity. The utility and efficacy of NLR were demonstrated in more than 4,000 articles published in the last, 20 years.

Neutrophil-to-lymphocyte ratio is easy available, cheap, reliable and valid parameter for objective evaluation of various diagnosis, syndromes in many medical disciplines including internal medicine, surgery, intensive care, perioperative medicine, oncology, psychiatry, gynecology and pediatrics. We suggest that it should be used routinely in everyday clinical practice in hospitals and ambulances. The evaluation of NLR and its dynamic changes may be helpful and useful in decision making process in clinical medicine.

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