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ORIGINAL STUDY

Neutrophil-to-lymphocyte ratio (NLR) distribution shows an advantage compared to C-reactive protein (CRP) for the early inflammation monitoring after total hip arthroplasty

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C-reactive protein (CRP) distribution has been used to monitor early inflammation after total hip arthroplasty (THA). Neutrophil to lymphocyte ratio (NLR) is a new and cheap inflammatory marker. This study aimed to verify whether Neutrophil to lymphocyte ratio (NLR) distribution has an advantage when compared to C-reactive protein (CRP) distribution for the inflammation monitoring after total hip arthroplasty (THA).

116 THA patients were retrospectively selected over a 2 years period. They all had available blood tests preoperatively and at postoperative days 2, 4 and 42. Median peak values were compared between CRP and NLR. The effect of demographics on CRP and NLR was tested.

At days 4 and 42, 100% and 16.3% of patients had not reached normal CRP (< 10mg/L) while 56.8% and 6.8% of patients had not reached normal NLR (<5) respectively. There was no effect of demographics on NLR except for age. Older patients had higher NLR (p 0.037).

NLR showed a quicker return to normal than CRP. Our results show that NLR seems to be a better marker to follow inflammation after THA than CRP.

Keywords : Total hip arthroplasty (THA) ; C-reactive protein (CRP) ; Neutrophil-to-lymphocyte ratio (NLR) ; inflammation.

INTRODUCTION

Total hip arthroplasty (THA) addresses pain and lack of mobility in the hip by restoring joint structure and function. On the other hand, it is a surgical trauma that implies invasion of body soft and bone tissues which induces physiological inflammatory response aiming to control tissue damage, to kill infective organisms and to induce a repair process. This acute phase response is initiated

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by macrophages and monocytes that produce pro-inflammatory cytokines which stimulate production and release of other cytokines such as Interleukine-6 (IL-6) *(17)*. IL-6 induces the production of acute phase proteins including C-reactive protein (CRP) *(7,11)*. Serum CRP is a marker used as reference in postoperative inflammation monitoring. The normal concentration in healthy adult human is inferior to 10 mg/L. After total hip arthroplasty, the CRP serum level increases rapidly to reach a peak value between 24 and 72 hours after surgery. Afterwards, it progressively decreases to reach normal values in a major number of patients between 3 and 6 weeks after surgery *(4,6,14,18)*. A persisting high level of serum CRP combined with suggestive symptoms can help detect postoperative complications, especially infection. Without clear symptoms, CRP positive predictive value remains limited *(21)*.

Systemic inflammatory response to surgical trauma leads to a raise in neutrophil blood count while lymphocyte count drops *(17)*. Neutrophil-to-lymphocyte ratio (NLR) has been recognised as a convenient, cheap and trustworthy parameter to assess inflammatory response as well as a predictor in cardiovascular, oncologic and infection monitoring and outcomes *(15,21)*. A postoperative NLR < 5 has been considered normal by several authors *(8,9,21)*. Literature concerning NLR distribution after arthroplasty is scarce. In a previous study, NLR distribution after total knee arthroplasty (TKA) showed a quicker return to normal than CRP. NLR was considered to be a better parameter to monitor inflammation and early infection after surgery *(21)*. To our knowledge, only one very recent study provides information on NLR distribution after THA, however limited to 5 days of follow-up and missing day 2 peak values which are important in normalization downslope appraisal *(19)*.

The purpose of this study was to compare postoperative distributions of NLR and CRP after THA with a 6 weeks follow-up. We hypothesised that NLR would show a faster return to normal than CRP.

PATIENTS AND METHODS

This was a retrospective study that included primary THA for osteoarthritis or osteonecrosis performed by two experienced surgeons in our university hospital from November 2014 to November 2016. In our institution all patients undergoing hip or knee arthroplasty are included in a cohort followed prospectively. In case of THA, routine blood samples are usually taken preoperatively and postoperatively at day 2, day 4 and day 42. The data were collected from our patients' medical files software (Medical Explorer v3r49b7). All blood samples were processed in our hospital laboratory. Serum CRP was detected using an immunoturbidimetric auto-analyser (Olympus), with a limit of detection of 0.14 mg/L. The blood cell counts were obtained after EDTA anticoagulation and processing by a blood analyser (Sysmex, TOA Medical Electronics, Kobe, Japan). The neutrophil-to-lymphocyte ratio was calculated by dividing the neutrophil by lymphocyte counts, obtaining a numerical value.

The inclusion criteria were primary THA for osteoarthritis or osteonecrosis and available blood tests preoperatively and at days +2, +4 and +42. Exclusion criteria were any clinical signs of infection, active neoplasia or inflammatory disease. Patients who underwent another surgery within 3 months prior or later than hip arthroplasty were excluded. Patients who experienced a postoperative complication within one year follow up were excluded as well. We also excluded patients who received allogenic blood transfusion in the postoperative settings.

From our database only 116 patients met the selection requirements. The operations were performed by 2 well trained surgeons, each using their own minimally invasive approach : anterolateral (Rottinger) and direct anterior (Hueter). The demographic characteristics from each patient included : age, sex, American Society of Anaesthesiology (ASA) score and body mass index (BMI). (Table 1)

Surgical technique

All surgeries were performed under general anaesthesia. Prophylactic intravenous antibiotics (cephalosporin) were administered 30 minutes before skin incision.

For Rottinger's approach, the patient was positioned in the contralateral decubitus position, the joint was accessed through the intermuscular

Table 1. — Characteristics of the study group

	Number	Median	Percentile	Minimum	Maximum
Age	116	76.26	66.0-81.2	26	94
BMI	116	27.53	24.7-30.1	17.9	51.1
Sex					
Males	39				
Females	77				
Laterality					
Right	69				
Left	47				
ASA Score					
ASA 1	7				
ASA 2	92				
ASA 3	17				

BMI body mass index, *ASA* American Society of Anesthesiologists

space between tensor fasciae latae and gluteus medius prior to capsulotomy. Hueter's approach was performed with the patient in a dorsal decubitus, and access to the joint was achieved through the intermuscular passage between the tensor fasciae latae on lateral aspect and the sartorius and rectus femoris on the medial aspect. The surgeon systematically detached the psoas muscle from the capsule prior to capsulotomy and performed a posterolateral capsule release to allow femoral exposure. The other steps were similar in both approaches including neck in situ osteotomy, acetabular reaming and implantation first, followed by femoral broaching and implantation in figure of four position.

All patients followed the same rehabilitation protocols consisting in daily walking practice with crutches which were progressively withdrawn before discharge. Daily medical examination was performed on each patient during hospitalisation which lasted 4 to 5 days. After discharge, the first check was done in the outpatients' clinic at day 42. Afterwards, all patients were controlled clinically and radiologically at 3, 6 and 12 months after surgery.

CRP and NLR were extracted from blood tests performed pre-operatively and postoperatively at days 2, 4 and 42. Given the two parameters are expressed in different units, we presented the results in percentage, 100% being the highest values observed in our database for each parameter.

For each patient, we plotted the relative values of CRP and NLR parameters in function of time (expressed in days), and we calculated up and down slopes (Fig 1). Upslope is the slope between the pre-operative value and the peak value (at day 2 or 4), and downslope is the slope between the peak value and the value of day 42.

Our institutional ethics committee stated that a written consent is not needed for analyses of anonymized databases coming from routine practice, as permitted by country and European laws. Consequently, our data was anonymously processed under authorization of our institutional ethical committee (N°B403201 111 562 CEBH of the Université Catholique de Louvain, Brussels, Belgium).

Statistical analysis was performed using Sigmaplot 14.0 software of SPSS. Descriptive statistical analysis of the subject's characteristics included numbers, medians, percentiles 25 and 75 and minimum and maximum values (table 1). The normality Test (Shapiro-Wilk) and Equal Variance Test (Brown-Forsythe) did not allow computing a parametric test. Therefore, all data were expressed in terms of median and percentiles (25 and 75) and the Mann-Whitney Rank Sum test was used to compare 2 groups. A p-value of 0.05 or less was considered statistically significant. We analysed the effect of CRP vs NLR for up and downslopes. The effects of BMI (<=30 vs >30), age (<=75 vs >75 yrs), ASA score (1-2 vs 3), surgical approach

Table 2. — Median (percentile 25 and 75%) of CRP and NLR values over 42 days after THA in absolute and relative (expressed in percent of highest level of all patients)

	CRP (mg L^{-1})		NLR	
Absolute	Median	Percentile	Median	Percentile
Pre	3.0	1-5	2.63	2.1-3.5
Day-2	143.0	94-197	5.50	4.2-7.3
Day-4	115.0	82-162	4.17	3.2-5.8
Day-42	3.0	2-7	2.45	1.9-3.2
		CRP (%)		NLR (%)
Relative (%)	Median	Percentile	Median	Percentile
Pre	0.56	0-1.1	9.22	6.7-13.2
Day-2	40.11	25.6-53.9	22.35	16.8-30.3
Day-4	31.92	21.8-44.7	16.45	11.7-23.8
Day-42	0.56	0.3-1.7	8.53	6.0-11.8

(Rottinger vs Hueter) on CRP and NLR values were tested. The Chi Square test was used to evaluate the proportions of patients above reference values on days 2, 4 and 42.

RESULTS

The medians (percentiles 25-75) for both serum parameters are represented in Table 2 in absolute and relative values. Preoperative median CRP was 3 mg/L (Normal <10 mg/L). The maximal median elevation was reached on day 2 (143 mg/L),

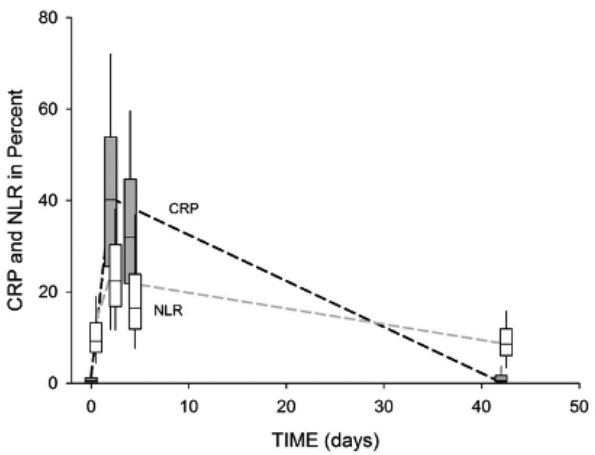

Figure 1. — CRP and NLR in relative values.
Box plot of CRP (gray) and NLR (white) level (expressed in %) as function of time (expressed in days). Dashed lines represent up and downslope.

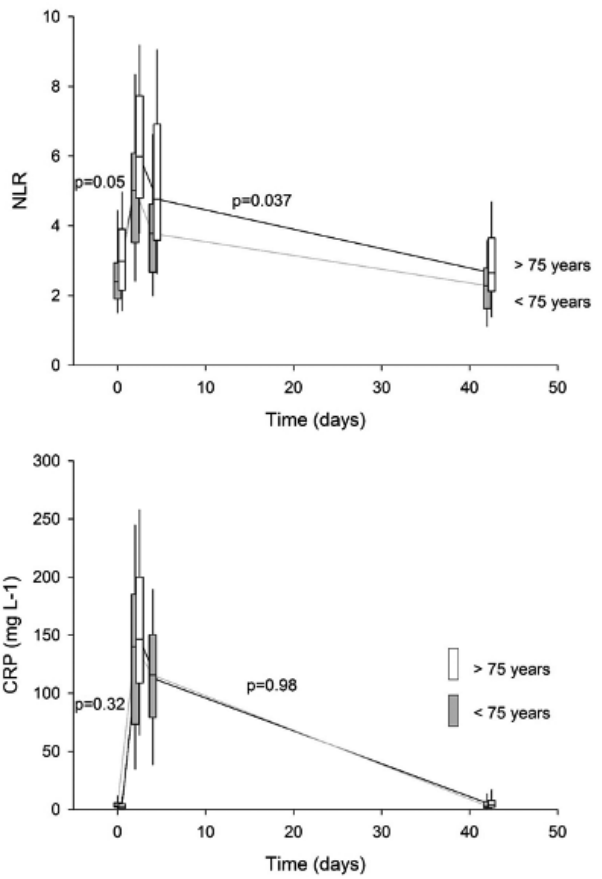

Figure 2. — Effect of age.
Box Plot of NLR (first graph) and CRP (lower graph) level as function of time (expressed in days). Grey symbols represent subjects <= 75 years and white symbols represent subjects > 75 years.

Table 3. — Proportion of pathological values at Day-2, Day-4 and Day-42

	Day-2	Day-4	Day-42
CRP >10 mg/L	100 %	100 %	16.3 %
NLR >5	62.9 %	56.8 %	6.8 %
Chi-Square	**<0.001**	**<0.001**	**0.024**

followed by a decrease that reached 3.0 mg/L at day 42. Regarding NLR, preoperative median was 2.63(Reference <5), highest mean peak was reached on day 2 (5.5) and the subsequent decrease reached median of 2.45 at day 42.

Median (percentiles 5, 25, 75 and 95) relative values of CRP and NLR expressed in function of time (days) are plotted in Fig 1. From preoperative status to day 2, CRP significantly showed a much higher increase than NLR (more than 40 times its baseline versus about 2.5 times respectively). During decrease phase, NLR reached baseline earlier than CRP ($p<0.0001$). At day 4, 100% of subjects kept abnormal CRP level (> 10mg/L) while NRL was abnormal for 56.8%. At day 42, the results were 16.3% versus 6.8% respectively, with a chi-square test showing significance (Chi-square test, p-value=0.024) (Table 3).

Regarding demographics, age showed a significant effect on NLR (Fig. 2). Older patient had higher values than younger ones, with a cut-off at 75 years. ASA score and BMI affected neither NLR nor CRP levels.

There was no difference between the two surgical approaches for NLR. However, Hueter group showed a significantly higher CRP level ($p=0.032$) than Rottinger group (median 155 versus 130 mg/L respectively) only at day 2. No difference was observed on other days of the timeline.

DISCUSSION

Our main finding is that NLR returned to preoperative baseline values earlier than CRP in standard THA postoperative settings. At day 4 after surgery, return to baseline had occurred for nearly half of our subjects for NLR versus none for CRP. Median value at day +4 was below cut-off 5 for NLR while still quite high for CRP (115 mg/L). Considering the steep negative slope of NLR from day +2 to day +4, these results suggest that most of our patients normalized NLR quickly after day +4 while keeping a high level of CRP. It was impossible to specify the day NLR reached baseline because of lack of daily postoperative blood samples.

This observation is consistent with the literature. In a previous study in TKA patients, Yombi et al *(21)* concluded that NLR normalization occurred between day +4 and day +21 and rather quickly after day +4. In a recent study, Wasko et al. *(19)* prospectively collected blood samples in 235 patients undergoing THA at day -1, day +3 and day +5. At day +5, 95.7% of their patients had a normalized NLR with a mean value of 2.7. The authors observed NLR returning to preoperative values within 5 days. Their study also included a TKA group and no difference in NLR distribution was observed between TKA and THA groups. CRP kinetics were not different between the two techniques either, as it had been observed by other authors *(20)*.

The CRP level can remain abnormally high until 3 to 6 weeks after surgery *(4,6,14,18)* or even later. Some authors have observed a high CRP after 150 days *(2)*. In our study, 16.3% of patients kept an abnormally high CRP (>10mg/dl) at day 42, versus 6.8% for NLR (>5).

The difference between NLR and CRP distributions could be useful for patients with a suspected complication in the early postoperative course, especially infection. In a context of re-rise of CRP level after normalisation, it is obvious to suspect a complication. But before normalisation, CRP levels may be difficult to include in a clinical diagnostic algorithm due to the slow return to normal postoperatively, which can trigger unnecessary investigations or surgery, especially if clinicians are not aware of the usual CRP distribution. In such situations, NLR could help in decision making. It is a simple test that does not require additional health costs, given white cell count is widely part of routine blood checks. Our observation combined with literature data suggests that a high NLR (>5) later than 5 days after surgery is likely to be linked to a postoperative complication such as infection or deep venous thrombosis *(1,3)*. Outside a surgical context, a NLR > 10 was shown

to substantially predict bacteraemia by de Jager et al *(13)* who compared serum markers between patients with positive bacterial cultures and a control group of matched patients with negative bacterial cultures. The sensitivity, specificity, positive and negative predictive values obtained for NLR were respectively 77.2%, 63%, 67.6% and 73.4%, and were stronger than those for CRP : 75%, 37%, 54.3% and 59.6% respectively. Gurol and co-authors *(10)* concluded that NLR was more convenient at detecting bacteraemia than CRP in a study where they demonstrated the correlation between procalcitonin (PCT) levels and NLR in patients with suspected infection.

Nevertheless, like all biological markers, NLR should be handled with caution when investigating a suspected periprosthetic infection in the early postoperative period : the complete clinical picture must be considered.

Another observation from this study is the difference in NLR level according to age. Older patients (>75yo) showed significantly higher levels than younger ones. The main explanation is the decrease of lymphocyte absolute count related to age that has been demonstrated by several authors *(12,16)*. In our study, neutrophil counts were similar while lymphocytes showed significantly lower counts in the older patients' group when compared to the young patients' group. Nevertheless, despite the difference, NLR distribution kept the same tendency, showing normalized median value (<5) before day 5 in the older patients' group (see Fig 2). Therefore, this finding does not have a significant repercussion on NLR distribution.

The higher CRP level at day +2 in Hueter group compared to Rottinger group could be theoretically explained by the additional steps of psoas detachment from the capsule and femoral release during Hueter's approach. Besides, Hueter's approach is inter-muscular and inter-nervous, and was performed with patient in supine position, whereas Rottinger's approach is inter-muscular but not inter-nervous and was performed with patient in contra-lateral decubitus. However, the importance of the difference in soft tissue management could have been proven more accurately if we had had information on creatine kinase (CK) distribution as well. Bergin et al *(5)* used serum CK to compare inflammation and muscle damage after a direct anterior approach (Hueter) versus a posterior approach for THA. They observed significantly higher CK values after the posterior approach, which indeed caused more muscle damage to access the joint when compared with Hueter's approach. Unfortunately, our patients' blood samples did not include CK tests. Therefore, we cannot provide a consistent clinical interpretation of this result.

The present study had some limitations. First, though from a prospective cohort, the data was analysed retrospectively, resulting in a relatively small number of subjects with available blood samples and fitting the selection criteria. Second, patients were operated by 2 senior surgeons using 2 different techniques. However, both consisted in mini invasive approaches which we theoretically assumed to have the same surgical aggression impact. Third, implants were variable depending on patient's age and bone quality. Nevertheless, all implants required a similar amount of bone resection. Some authors have found no difference in CRP levels according to bleeding, transfusion and fixation (cemented/uncemented implants) *(18)*.

One other limitation is that we did not include patients with complications and our number of subjects was relatively small. Therefore, we could not show the predictive value of NLR as a test to detect periprosthetic infection. More precisions would come out from a wider and longer study, carried out prospectively and including patients with complications after arthroplasty.

The strength of our study is that all selected patients had blood samples collected at the same intervals, allowing comparison of CRP and NLR before and up to 6 weeks after THA. The day 2 blood samples corresponding to NLR peak values allowed a good appraisal of distribution downslope. Despite our limited sample size compared to similar studies, our results were highly significant. Unlike in previous studies, slopes were calculated considering each patient individually.

CONCLUSION

In the present study, we have observed that NLR distribution has an advantage of a quicker return to

normal than CRP after hip arthroplasty. NLR is a recent, simple and promising biomarker that should keep researchers' attention. Further investigations should be carried out to determine the accurate strength of NLR in predicting periprosthetic infection.

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