Increased neutrophil-to-lymphocyte ratio is associated with higher incidence of acute kidney injury and worse survival after transcatheter aortic valve implantation

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Abstract

Background: Although considered a minimally invasive procedure, transcatheter aortic valve implantation (TAVI) generates an inflammatory response which is related to post-procedural complications including acute kidney injury (AKI). The aim of the present study was to analyze the association between simple, easily available post-operative morphological parameters of inflammatory status such as neutrophil-to-lymphocyte ratio (NLR) and AKI as well as post-discharge survival.

Methods: The study group was comprised of 203 consecutive patients (102 females and 101 males, mean age 78 ± 6.9 years) who underwent TAVI between January 2013 and March 2017. Demographic and clinical data were collected. Baseline and subsequent post-procedural blood samples (at 8, 24, 48, 72 h and at discharge) were taken. Blood morphology (including NLR) and creatinine concentration were assessed. Long-term survival was also analyzed.

Results: Seventy-four (36.5%) patients developed AKI. Baseline morphological parameters did not differ between subject with and without AKI. Those reflecting post-procedural inflammatory response, including leucocytes, neutrophils and NLR increased significantly following TAVI in both subgroups and the rise was more pronounced in AKI patients ($p < 0.001$). A comparison of Kaplan-Meier curves for patients with the lowest (NLR 1; below 25th percentile) and highest NLR (NLR 3; above 75th) revealed a significant difference in the log-rank test ($p = 0.049$). Estimated probability of 1-, 2- and 5-year survival were 100% vs. 79%, 94% vs. 77% and 75% vs. 46%, respectively in subgroup NLR 1 and NLR 3.

Conclusions: Inflammatory response after TAVI, estimated by means of NLR, is more pronounced in patients with AKI. A higher value of NLR is associated with a lower probability of long-term survival after TAVI. (Cardiol J)

Key words: transcatheter aortic valve implantation, inflammatory response, acute kidney injury, survival

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Introduction

Transcatheter aortic valve implantation (TAVI) has become an alternative for patients with aortic stenosis at low to high perioperative risk. Experience of TAVI teams together with progress in technology resulted in improved patient safety and a marked decrease in operative risk. However, some complications cannot be completely excluded, including acute kidney injury (AKI), access site injury or stroke. Every attempt for a better understanding and improvement in procedural technique is of crucial clinical importance.

Acute kidney injury may occur both after cardiac surgery and transcatheter procedures. However, patients with aortic stenosis selected for the latter one are usually elderly, with many comorbidities, thus both can additionally contribute to AKI development. The prevalence of this complication is estimated on 8 through 58% of cases after TAVI [1] and negatively influences the prognosis [2, 3]. Of note, some patients require temporary or permanent kidney replacement therapy. Several factors were linked with AKI development, including pre-operative kidney disease, peri-operative blood transfusions, hypertension, chronic obstructive pulmonary disease (COPD), contrast medium application [2, 4, 5]. Moreover, TAVI although considered a minimally invasive procedure still generates inflammatory response and increases oxidative damage [6] which may lead to post-procedural complications with AKI as the most prominent one. A significant increase in pro-inflammatory cytokines including C-reactive protein, interleukin-6 and tumor necrosis factor alpha were reported [6]. Though pronounced, the redox imbalance is lesser and recovery of antioxidant capacity is faster after TAVI compared to surgical aortic valve replacement [7].

Routine assessment of oxidative stress is impossible due to the complex methodology and sophistication of the laboratory equipment. However, inflammatory reaction following interventional procedures that reflects redox imbalance is an easily available method of oxidative stress estimation. In turn, neutrophil counts are considered as the markers of inflammatory reaction following invasive and not only cardiac procedures [8].

Therefore, the aim of the present study was to analyze if simple and easily available post-operative blood morphological parameters of inflammatory status such as leukocyte counts, or neutrophil-to-lymphocyte ratio (NLR) may be associated with AKI and post-discharge survival.

Methods

Patients

The study group was comprised of 203 consecutive patients (102 females and 101 males) with the mean age of 78 ± 6.9 who underwent TAVI between January 2013 and March 2017 in our hospital. All of them were qualified for TAVI after careful analysis of clinical history and examination results. Examined patients were retrospectively divided into two subsets based on the occurrence of AKI defined according to Valve Academic Research Consortium 3 (VARC-3) criteria [9], AKI and non-AKI groups, respectively. Baseline characteristics is presented in Table 1. Patients who died during the procedure were excluded from further analysis.

The study was approved by the Institutional Ethics Committee and respected the principles outlined in the Declaration of Helsinki.

TAVI procedures

All procedures were performed by the same experienced TAVI team in the hybrid room under fluoroscopic and echocardiographic guidance. A majority of patients ($n = 184$, 90.6%) had transfemoral access and 19 other (one trans-carotid, 12 transapical and 6 by direct aorta). In 74.4% of procedures ($n = 151$) general anaesthesia was used, while 52 (25.6%) patients had local anaesthesia with sedation. In patients with percutaneous femoral access, ProstarTM system or two ProglidesTM were introduced. In transapical access, left anterolateral minithoracotomy was performed through the 5th or 6th intercostal space. Aortic balloon valvuloplasty was performed in 101 (49.8%) patients before prosthesis implantation. Self-expandable prostheses were used, including Medtronic CoreValve and CoreValve Evolut R ($n = 151$), Boston Scientific Lotus ($n = 38$) and Symetis Accurate ($n = 14$). The procedural details were previously described [10].

Analyzed clinical and laboratory data

Demographic and clinical data were collected and analyzed. Baseline and post-procedural (on regular basis) blood samples were collected, and the following parameters which evaluated counts of white blood cells (WBC), neutrophils (NEU), lymphocytes (LYMPH), red blood cells (RBC), platelets (PLT) and creatinine concentration (CREA). Moreover, the NLR was also calculated. Estimated glomerular filtration rate (eGFR) was calculated based on Modification of Diet in Renal Disease (MDRD) formula. AKI was diagnosed according to

Table 1. Demographics, preoperative clinical characteristics and procedural details.

Parameters*	Whole group (n = 203)	AKI group (n = 74)	Non-AKI group (n = 129)	P [#]
Male	101 (49.8)	36 (48.6)	65 (50.4)	0.811
Age	78 ± 6.9	78.8 ± 6.4	77.6 ± 7.2	0.518
Body mass index [kg/m ²]	28.0 ± 4.5	28.1 ± 4.0	27.9 ± 3.8	0.681
EuroSCORE II [%]	5.0 (3.0–9.5)	6.4 (3.4–10.3)	4.6 (2.7–8.8)	0.042
STS score [%]	5.3 (3.3–14.0)	6.0 (3.6–14.2)	5.0 (3.3–13.8)	0.159
Diabetes mellitus	69 (34.0)	29 (39.2)	40 (31.0)	0.236
Hypertension	146 (71.9)	56 (75.7)	90 (69.8)	0.367
Atrial fibrillation	76 (37.4)	27 (36.5)	49 (38.0)	0.832
Chronic obstructive pulmonary disease	43 (21.2)	14 (18.9)	29 (22.5)	0.550
Myocardial infarction in history	73 (36.0)	32 (43.2)	41 (31.8)	0.101
Stroke or TIA in history	34 (16.7)	13 (17.6)	21 (16.3)	0.813
GFR [mL/min/1.73 m ²]	57.6 ± 17.7	51.5 ± 19.1	61 ± 15.9	< 0.001
GFR ≤ 60 mL/min/1.73 m ² [n]	121 (59.6)	55 (74.3)	66 (51.2)	0.0012
Mean pressure gradient [mmHg]	58.7 ± 20.5	57.1 ± 18.0	59.6 ± 21.9	0.844
Peak pressure gradient [mmHg]	89.9 ± 26.8	90.2 ± 23.9	89.8 ± 28.3	0.809
Left ventricular ejection fraction [%]	51.4 ± 11.7	50.9 ± 11.8	51.7 ± 11.7	0.828
Predilatation	101 (49.8)	34 (45.9)	67 (51.9)	0.411
Prosthesis:				0.086
Medtronic CoreValve and CV Evolut	151 (74.4)	61 (82.4)	90 (69.8)	
Lotus	38 (18.7)	11 (14.9)	27 (20.9)	
Symetis	14 (6.9)	2 (2.7)	12 (9.3)	
Anesthesia:				0.514
General	151 (74.4)	57 (77.0)	94 (72.9)	
Local	52 (25.6)	17 (23.0)	35 (27.1)	
Access:				0.257
Femoral and carotid	185 (91.1)	69 (93.2)	116 (89.9)	
Apical	12 (5.9)	2 (2.7)	10 (7.8)	
Direct-aorta	6 (3.0)	3 (4.1)	3 (2.3)	
TAVI time [min]	85.6 ± 27.7	87.0 ± 32.0	84.9 ± 24.9	0.446
Volume of contrast media [mL]	197.6 ± 66.1	199.2 ± 66.0	196.7 ± 66.0	0.801
Blood transfusions	74 (36.5)	39 (52.7)	35 (27.1)	< 0.001

*Continuous variables are expressed either as the means with standard deviations (SD) (if normally distributed) or the medians with interquartile range (IQR) (the others) whereas categorical ones as the numbers (n) with percent (%). #It refers to the comparison between acute kidney injury (AKI) and non-AKI subgroups; GFR — glomerular filtration rate; TIA — transient ischemic attack TAVI — transcatheter aortic valve implantation

VARC-3 criteria [9] (> 1.5 × or increase of ≥ 0.3 mg/dL [≥ 26.4 mmol/L] within 48 h or hemofiltration). Post-procedural in-hospital outcome was also assessed. Long-term survival was analyzed based on hospital follow-up visit records and the national database.

Post-discharge mortality

All patients were followed up in the outpatient clinic. Annual as well as 5-year mortality are presented as a percent of patients. All deceased cases were easily identified since we had limited

access (confined only to the treated patients) to the National Health Care System.

Additionally, any association between the level of post-procedural response was estimated, expressed by means of NLR at 48th h after TAVI and 1-, 2- and 5-year probability of survival. For the purposes of this analysis, all patients irrespective of post-procedural kidney function, were split into three subgroups with different values of NLR:

- subgroup NLR1 — included subjects with lower than the 25th percentile (or 1st quartile; Q1) of NLR value;

- subgroup NLR2 — patients with NLR between 25th and 75th;
- subgroup NLR3 — TAVI individuals with the most prominent inflammatory response (exceeding 75th percentile).

Eventually, a comparison of survival probability was done for the two extreme groups (NLR1 vs. NLR3).

Statistical analysis

Continuous variables were checked for normality by means of the Shapiro-Wilk W test. These satisfying criteria of normal distribution were presented as mean and standard deviation (SD) and were compared using the unpaired t test (i.e., differences between AKI and non-AKI subgroups) or by repeated measures ANOVA (calculations of time-dependent morphological parameters, within groups applying one-way or between them [AKI vs. non-AKI] — two-way analysis, respectively). If continuous data were not normally distributed, they were expressed as median with interquartile range (IQR: 1st to 3rd quartile) and compared with the use of the nonparametric Mann-Whitney U test. Time-related changes of NLR, since its values in a few sampling points had not satisfied a normal distribution, were analyzed by means of ANOVA Friedmann and followed by the Dunn multiple comparisons of ranks. Survival probability was stratified with the use of Kaplan-Meier curves, then they were compared (for NLR1 vs. NLR3) by means of the log-rank test. Categorical variables were reported as numbers (n) and percentages (%), and were then compared with the use of the Fisher exact test. All tests were two-sided. P values less than 0.05 were considered statistically significant. Statistical analysis was performed using JASP statistical software.

Results

Prevalence of post-procedural renal injury

After TAVI procedures, 74 patients out of 203 (36.5%) developed AKI as diagnosed according to VARC-3 criteria. Twenty-three (11.3%) of them required temporary kidney replacement therapy. A simple comparison of pre-procedural characteristics between the non-AKI and AKI group revealed markedly higher risk stratified by mean of EuroSCORE II calculator and significantly lower eGFR. More details are outlined in Table 1.

Changes in laboratory parameters

Baseline morphological parameters did not differ between patients with and without post-procedural AKI. Those reflecting inflammatory response such as WBC and NEU increased significantly following TAVI procedures in both subgroups reaching peak values either at the 24th hour (non-AKI group) or at the 48th hour after interventions (AKI group), but this rise was more pronounced in AKI patients ($p < 0.001$ in the two-way repeated measures ANOVA) and the differences remained significant until discharge (Figs. 1A, B). Additionally, at the 72nd hour after procedures, there were no differences compared to baseline WBC and NEU counts whereas in AKI individuals, they were still higher. LYMPH count dropped in the consecutive blood tests, and similarly, the decrease was more prominent in the AKI subgroup during the first post-operative days. In a consequence, calculations of NLR revealed a significant difference between subgroups and this blood parameter-derived marker of inflammation was markedly higher ($p = 0.001$) in AKI subset of TAVI subjects (Fig. 2). Selected blood morphological parameters are summarized in Table 2.

Serum creatinine concentration remained stable in non-AKI patients throughout the post-procedural period while increasing significantly, particularly on days 2nd and 3rd in the AKI group. Of note, baseline value was also higher compared to non-AKI TAVI individuals. Detailed concentrations are presented graphically on Figure 3.

Post-procedural outcomes

In-hospital stay was markedly longer in the AKI group than in the others (median [IQR] 7 [6–8] vs. 10 [7–14] days, in group non-AKI vs. AKI, respectively; $p < 0.001$). The post-procedural hospitalization was complicated with stroke in 4 (2.0%) patients, bleeding complications in 58 (28.6%) patients, including nine with life-threatening bleeding, and vascular adverse events defined according to VARC-3 criteria in 25 (12.3%) patients. Thirty-five (17.2%) patients required pacemaker implantation due to serious conduction disturbances.

A comparison of Kaplan-Meier curves for two subgroups with completely unlike inflammatory response (NLR1 vs. NLR3) revealed a significant difference in the log-rank test ($p = 0.049$) (Fig. 4). Estimated probability of 1-, 2- and 5-year survival of TAVI patients were 100% vs. 79%, 94% vs. 77% and 75% vs. 46%, respectively in subgroup NLR1 and NLR3.

Figure 1. Time-related changes in white blood cells (leucocytes) (WBC) and neutrophil (NEU) counts following transcatheter aortic valve implantation procedures. An increase in WBC (**A**) and NEU (**B**) counts was less pronounced and earlier in non-acute kidney injury (AKI) vs. AKI groups. At 72nd hour after procedures, there were no differences compared to baseline WBC and NEU counts whereas in AKI individuals, they were still higher; *refers to the post-hoc multiple comparisons between groups (AKI vs. non-AKI) in the subsequent sampling points; bs — baseline; disch — discharge; SD — standard deviation.

Interestingly, there were no significant differences in long-term survival between AKI and non-AKI patients.

Discussion

The current study confirmed the importance of inflammatory response and AKI after TAVI. It was found that NLR is associated with the devel-

Figure 2. Neutrophil-to-lymphocyte ratio (NLR) value variation in both subgroups. NLR values are presented as the medians (Q2) with interquartile range (IQR; Q1–Q3) since they are not satisfied criteria of normal distribution; *is a result of multiple comparisons of ranks (differences between groups in the consecutive sampling points); AKI — acute kidney injury; bs — baseline; disch — discharge.

opment of AKI and worse prognosis regarding post-discharge survival probability. Though there are some literature data regarding assessment of NLR in TAVI patients [11] but so far, no studies have been published that estimated its significance for the long-term outcome, particularly in patients who developed AKI soon after the procedures.

Besides pre-existing kidney disease, older age, and co-morbidities (diabetes, hypertension, COPD), several peri-operative conditions were proposed as potential risk factors for AKI after TAVI, including short periods of hypotension during balloon valvuloplasty and prosthesis deployment or manipulation with the wire and catheter in the atherosclerotic aorta [1].

The present study underlines the role of the inflammatory response in aggravating kidney injury. A significant difference was found in post-operative levels of inflammatory markers between patients who developed AKI and those without that complication. A significant increase in leucocyte and neutrophil counts and decrease in lymphocyte count accompanied AKI development and persisted for at least 72 hours. In our opinion the occurrence and degree of inflammatory response may result from renal ischemia-reperfusion injury during the procedure, particularly during balloon valvuloplasty, prosthesis deployment and prosthesis post-dilatation.

Table 2. Time-related changes of the selected laboratory parameters.

Parameters*	Whole group (n = 203)	AKI group (n = 74)	Non-AKI group (n = 129)	P#
Lymphocytes				
Baseline	1.5 ± 0.6	1.4 ± 0.6	1.5 ± 0.6	0.167
8 hours	1.0 ± 0.6	1.0 ± 0.5	1.1 ± 0.7	0.372
24 hours	0.9 ± 0.5	0.8 ± 0.5	0.9 ± 0.5	0.005
48 hours	1.2 ± 0.9	1.1 ± 0.5	1.2 ± 1.0	0.091
72 hours	1.1 ± 0.4	0.9 ± 0.4	1.1 ± 0.4	0.002
Discharge	1.3 ± 0.5	1.3 ± 0.7	1.3 ± 0.4	0.242
Red blood cells				
Baseline	4.3 ± 0.5	4.2 ± 0.6	4.3 ± 0.5	0.222
8 hours	3.8 ± 0.5	3.8 ± 0.5	3.9 ± 0.4	0.145
24 hours	3.8 ± 0.4	3.8 ± 0.5	3.9 ± 0.4	0.601
48 hours	3.7 ± 0.4	3.6 ± 0.5	3.7 ± 0.4	0.268
72 hours	3.6 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	0.686
Discharge	3.8 ± 0.5	3.7 ± 0.5	3.8 ± 0.4	0.199
Platelets				
Baseline	204.9 ± 71.6	214.0 ± 81.5	199.6 ± 65.0	0.349
8 hours	163.5 ± 62.4	169.7 ± 71.8	159.9 ± 56.1	0.598
24 hours	148.7 ± 58.4	152.5 ± 69.6	146.4 ± 51.1	0.702
48 hours	128.7 ± 53.0	129.7 ± 64.3	128.1 ± 45.5	0.201
72 hours	127.5 ± 54.5	127.8 ± 66.1	127.2 ± 45.6	0.233
Discharge	189.5 ± 85.1	204.6 ± 104.3	180.3 ± 69.8	0.178

*Continuous variables are expressed as the means with standard deviations (SD) (normally distributed). #Refers to the comparison between acute kidney injury (AKI) and non-AKI subgroups.

Figure 3. Serum creatinine concentration (CREA) in both subgroups. Significant differences in CREA were noted between non-acute kidney injury (AKI) and AKI patients, including also its baseline value; *refers to the difference between AKI and non-AKI patients in each sampling points; bs — baseline; disch — discharge; SD — standard deviation.

Figure 4. Comparison between Kaplan-Meier survival curves in NLR 1 and NLR 3 subgroups; NLR 1 — subgroup with neutrophil-to-lymphocyte ratio results 48 hours after transcatheter aortic valve implantation — lower than the 25th percentile; NLR 3 — subgroup with neutrophil-to-lymphocyte ratio results 48 hours after transcatheter aortic valve implantation — higher than the 75th percentile.

It must be stressed that NLR is a simple parameter calculated from complete blood count by dividing the number of neutrophils by the lymphocytes number. Both cell types are important for inflammation. Many subpopulations of leukocytes have been implicated in AKI, including neutrophils and lymphocytes, macrophages and dendritic cells [12]. The inflammatory response plays an essential role in pathogenesis of atherosclerosis, coronary artery disease and heart failure [13]. Increased NLR was linked to worse prognosis and higher pulmonary vascular resistance in patients with congestive heart failure [14]. Its predictive value was shown for unfavorable outcomes after acute myocardial infarction, cardiac surgical procedures, sepsis and operations on the gastrointestinal tract [15–17].

Ischemia-reperfusion injury occurs even after short periods of blood supply impairment. Ischemia results in tissue hypoxia and the release of reactive oxygen species (ROS). ROS increase intracellular calcium, change tissue pH as well as deplete ATP and nitric oxide which leads to further cell injury and necrosis [18]. The increase in adhesion molecules act as chemoattractant for neutrophils recruitment. Resident macrophages, dendritic cells and damaged endothelial cells release cytokines which promote pro-inflammatory recruiting and activation of neutrophils [18].

A subpopulation of neutrophils increases in the kidney following AKI and accumulates particularly in the peritubular capillary network shortly after ischemia-reperfusion episodes [19]. According to histological studies [20] transmigration into interstitium and an increase in vascular permeability is the strongest factor for kidney dysfunction. Neutrophils secrete several inflammatory mediators including proteases, elastase, myeloperoxidase, cytokines and produce a large quantity of ROS [13, 14, 18, 21–23]. Elastase mediates degradation of basement membrane constituents and endothelial damage [21]. Degranulation of neutrophils aggravate injury. Adhesion of neutrophils to endothelial cells together with platelets and red blood cells may cause capillary plugging and congestion which in turn impairs oxygen and nutrition delivery [19, 20]. Lymphocytes regulate the inflammatory response [13] and may have an inhibitory effect on atherosclerosis. Low lymphocyte count is a marker of physiologic stress and systemic collapse secondary to myocardial injury [13]. Recently, studies supporting the clinical importance of lymphocytes B and T were published [12, 24]. B cells serve as cytokine and chemokine producers and can both augment and inhibit inflammation, e.g., may release CCL7

— a monocyte and neutrophils chemokine, and interleukin-10 which have been shown to attenuate AKI severity [24]. Inaba et al. [24] observed a 4-fold increase in circulating leucocytes within an hour of AKI development and one third was recognized as B cells. A simultaneous increase was found in kidney parenchyma. At a later point of 15 hours an increase in kidney T cells and monocytes was observed. Based on these observations a conclusion should be drawn that kidney injury mobilizes neutrophils, monocytes and B cells in the early phase.

Based on these considerations, it may be supposed that every effort to diminish or even inhibit inflammatory response, most importantly by modifying the neutrophils recruitment and infiltration, would change the risk of AKI development.

The problem of inflammatory response occurred to be even more important after evaluation of short- and long-term outcomes after TAVI. It was found herein, that higher values of NLR after TAVI are related to higher 1- and 5-year mortality. Dividing the study group into three subgroups with respect to NLR levels' percentiles showed a significant difference between patients with declined and markedly increased inflammatory response.

Similarly, inflammation was a predictor of clinical outcomes after lower extremity angioplasty [25], coronary angioplasty [26], coronary artery bypass grafting [17] and carotid artery stenting [27]. Wasser et al. [27] showed that majority of in-stent restenosis occurs within the first year after carotid artery stenting and periprocedural inflammation during carotid artery stenting plays a pivotal role in its development.

Limitations of the study

The main limitation of the present study is a moderate heterogeneity of the study group in terms of operative access, anesthesia or prosthesis manufacturer. However, the numbers of patients did not differ statistically between both groups. Moreover, the goal was to present the results of treatment in a real-life population of TAVI patients.

Conclusions

Inflammatory response, reflected by increased counts of leukocytes, neutrophils and value of NLR after TAVI is more pronounced in patients with post-procedural AKI. Moreover, higher NLR is associated with lower probability of long-term survival after TAVI.

Conflict of interest: None declared

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