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Prognostic factors for long-term survival following complete resection by lobectomy in stage I non-small cell lung cancer

Christian Galata[1] | Antje Messerschmidt[2] | Marko Kostic[3] | Ioannis Karampinis[1] | Eric Roessner[1] | Hazem El Beyrouti[4] | Thomas Schneider[2] | Davor Stamenovic[1,2]

[1]Department of Thoracic Surgery, University Center for Thoracic Diseases, University Medical Center Mainz, Johannes Gutenberg University Mainz, Mainz, Germany

[2]Department of Thoracic Surgery, ViDia Kliniken Karlsruhe, Karlsruhe, Germany

[3]Clinic for Thoracic Surgery, Clinical Center Belgrade, Serbia

[4]Department for Cardiac and Vascular Surgery, University Medical Center Mainz, Johannes Gutenberg University Mainz, Mainz, Germany

Correspondence
Davor Stamenovic, Department of Thoracic Surgery, University Center for Thoracic Diseases, University Medical Center Mainz, Johannes-Gutenberg University Mainz, Langenbeckstrasse 1, 55131 Mainz, Germany.
Email: davor.stamenovic@unimedizin-mainz.de

Abstract

Background: The aim of this study was to evaluate predictors for long-term overall survival (OS) in patients with stage I non-small cell lung cancer (NSCLC).

Methods: All patients undergoing complete resection by lobectomy for stage I NSCLC between October 2012 and December 2015 at a single center were included. Univariable and multivariable Cox regression analyses were performed to identify prognostic factors.

Results: A total of 92 patients were included. Univariable and multivariable Cox regression analyses revealed preoperative neutrophil to lymphocyte ratio (NLR, $p = 0.005$), preoperative diffusion capacity of the lungs for carbon monoxide (DLCO, $p = 0.010$) and forced expiratory volume in 1 second (FEV1, $p = 0.041$) as well as male gender ($p = 0.026$) as independent prognostic factors for OS. Combining the calculated cutoff values for FEV1 (<73.0%) and NLR (>3.49) into one parameter resulted in a highly significant difference in survival times when stratified by this variable.

Conclusions: Recently, much emphasis has been put on the prognostic importance of blood biomarkers in NSCLC. In our study, NLR was an independent factor for OS, as were baseline characteristics such as DLCO, FEV1, and gender. Further studies on the association of biomarkers for systemic inflammation and lung function parameters with respect to patient survival are warranted.

KEYWORDS
lobectomy, lung cancer, NSCLC, prognostic factors, survival

INTRODUCTION

Inflammation is a key factor in cancer progression and contributes to angiogenesis, invasion and metastatic spread.[1,2] In non-small cell lung cancer (NSCLC), systemic inflammation and immune microenvironment are of particular importance, as is clinically demonstrated by the widespread and effective use of targeted immunotherapy in both late-stage disease and, increasingly, in treatment with curative intent.[3,4] Therefore, several studies have investigated the importance of inflammatory parameters for overall survival (OS) in NSCLC. Here, clinical researchers have focused on markers like the neutrophil-lymphocyte ratio (NLR) or platelet to lymphocyte ratio (PLR). These can be easily calculated from blood values obtained as part of routine clinical practice and are therefore readily available. A recent systematic review and meta-analysis showed that high pretreatment NLR and PLR in NSCLC patients on immune checkpoint inhibitors were associated with low survival rates.[5] However, most studies on this topic have inhomogeneous patient populations (e.g., stage I–III) and include patients with advanced tumor stage (e.g. stage IV) or multimodal treatment or targeted immunotherapy.[6–12] Furthermore, many studies focus on biomarkers but neglect other clinically relevant variables, such as FEV1 and DLCO which are known to have significant prognostic relevance for patients with lung cancer.[13,14] This is also mostly true for the few studies that explicitly address stage I NSCLC.[15–17] Therefore, we aimed to evaluate prognostic factors for OS in a homogeneous

TABLE 1 Preoperative baseline characteristics

Variable	n/median	%/IQR
Female	41	44.6
Age (years)	67.5	60–75
BMI (kg/m^2)	25.0	22.0–29.1
Smoker (current)	23	25.0
FEV1 (%)	82.2	63.9–95.0
DLCO (%)	69.2	56.5–85.8
ACCI		
≥ 5	43	46.7
< 5	49	53.3
Preoperative laboratory data		
Thrombocytes (150–360 /nl)	279	231–338
Leukocytes (3.5–10.0 /nl)	7.5	6.5–8.7
Neutrophils (1.7–7.2 /nl)	5.0	4.1–6.1
Lymphocytes (1.0–2.8 /nl)	1.7	1.4–2.2
CRP (mg/l)	0.5	0.3–1.0
PLR	169	117–224
NLR	2.9	2.2–4.0

Abbreviations: ACCI, age-adjusted Charlson comorbidity index; BMI, body mass index; CRP, c-reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory pressure in 1 second; IQR, interquartile range; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

TABLE 2 Data on surgery

Variable	n/median	%/IQR
Type of surgery		
VATS	67	72.8
Thoracotomy	25	27.2
Type of lobectomy		
RUL	33	35.9
ML	7	7.6
RLL	17	18.5
LUL	24	26.1
LLL	11	12.0
Surgical outcomes		
Harvested lymph nodes	18	14–26
Complications	25	27.2
Mortality	0	0
Total blood loss (ml)	808	510–1199
Length of surgery (min)	177	139–208
Chest tube duration (days)	4	3–7
Length of stay (days)	9	6–14
Follow up (months)	67	50–91
UICC stage		
IA1	6	6.5
IA2	23	25.0
IA3	21	22.8
IB	42	45.7

Abbreviations: IQR, interquartile range; LLL, left lower lobe; LUL, left upper lobe; ML, middle lobe; RLL, right lower lobe; RUL, right upper lobe; UICC, Union for International Cancer Control; VATS, video-assisted thoracoscopic surgery.

single-center cohort of stage I NCSLC patients who underwent complete resection by lobectomy, including NLR and PLR.

METHODS

Study design

This was a single-center retrospective cohort study.

Patients

All consecutive patients undergoing lobectomy for stage I non-small cell lung cancer (NSCLC) between September 2012 and December 2015 in the department of thoracic surgery, ViDia Kliniken Karlsruhe, Karlsruhe, Germany, were identified. Medical records were reviewed and clinical data that might influence OS were extracted. Preoperative blood tests, spirometry and DLCO were routinely performed within 4 weeks prior to surgery. Follow-up (FU) data were collected during routine clinical follow-up based on medical records and/or direct contact with the patients or with their treating physicians. OS was defined as the interval from surgery to death by any cause or the latest point in time the patient was known to be alive. The eighth edition of the Union for International Cancer Control (UICC) staging system for NSCLC was used to assess tumor stage in all cases, restaging patients retrospectively if required. The amount of total blood loss was calculated using Mercuriali's formula.[18]

Statistical analysis

The median together with the interquartile range (IQR) is presented for quantitative variables. Qualitative variables are quoted as absolute numbers and relative frequencies. Univariable and multivariable Cox regression analyses were performed to identify prognostic factors for OS. A significance level of $\alpha = 0.10$ in the univariable Cox regression analyses was chosen to select covariates for the multivariable Cox regression analysis. In the multiple analysis, the backward stepwise selection based on the probability of the Wald statistic was used, and a significance level of $\alpha = 0.05$ was chosen to identify variables that might influence OS. Hazard ratios are presented together with their 95% confidence intervals (CI). The Kaplan–Meier method was used to estimate survival curves. The log-rank test was used to compare survival times. A receiver operating characteristic (ROC) analysis was done to determine cutoff values with joint maximum sensitivity and specificity for the variables "diffusing capacity for carbon monoxide (DLCO)", "forced expiratory volume in 1 second (FEV1)" and "neutrophil to lymphocyte ratio (NLR)" regarding the occurrence of death during follow-up. All statistical tests were two-sided. Analyses were performed using IBM SPSS Statistics (version 26, IBM Corp.).

TABLE 3 Prognostic factors in univariable and multivariable Cox regression analyses

Parameter	Univariable p-value	Multivariable p-value	Hazard ratio (95% CI)
NLR	0.026*	0.005*	1.287 (1.080–1.533)
DLCO	0.002*	0.010*	0.036 (0.003–0.444)
FEV1	0.001*	0.041*	0.107 (0.013–0.914)
Gender	0.029*	0.026*	2.976 (1.139–7.780)
Length of surgery	0.019*	0.456	—
Lymphocytes	0.026*	0.462	—
PLR	0.056	0.497	—
Site of surgery (left vs. right)	0.089	0.486	—
Type of surgery (VATS vs. open)	0.159	—	—
Age	0.131	—	—
BMI	0.958	—	—
ACCI	0.755	—	—
Complications	0.237	—	—
Chest tube duration	0.785	—	—
Length of stay	0.151	—	—
Smoking status	0.200	—	—
Harvested lymph nodes	0.593	—	—
Total blood loss	0.645	—	—
Thrombocytes	0.638	—	—
Neutrophils	0.709	—	—
Leukocytes	0.218	—	—
CRP	0.916	—	—

Note: Asterisks (*) indicate statistical significance.
Abbreviations: ACCI, age-adjusted Charlson comorbidity index; BMI, body mass index; CI, confidence interval; CRP, c-reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory pressure in 1 second; IQR, interquartile range; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; VATS, video-assisted thoracoscopic surgery.

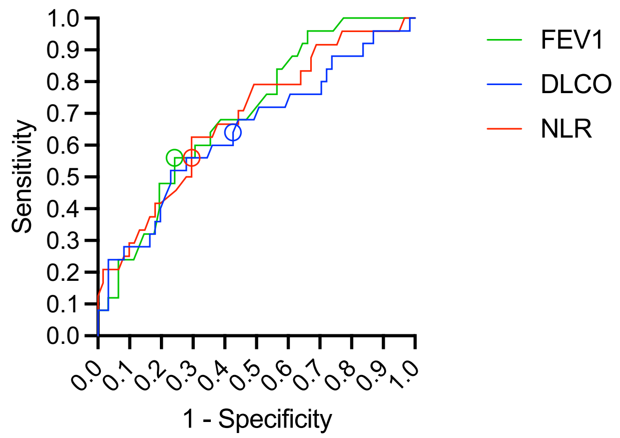

FIGURE 1 ROC curves for the determination of cutoff values for independent predictors of OS. Circles indicate sensitivity and specificity at the highest Youden's J observed for each parameter (FEV1: Sensitivity 56.0%, specificity 75.8%, AUC 0.698; DLCO sensitivity 62.5%, specificity 70.5%, AUC 0.688; NLR: Sensitivity 52.00%, specificity 77.0%, AUC 0.646). AUC: Area under the curve; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory pressure in 1 second; NLR, neutrophil to lymphocyte ratio; OS, overall survival; ROC, receiver operating characteristic

RESULTS

Patients and procedures

During the study period, a total of 92 patients with stage I NSCLC underwent complete resection by lobectomy. The preoperative baseline characteristics of these patients are shown in Table 1. A majority of the patients were male with a median age of 67.5 years. About half of the patients (46.7%) had scores ≥5 on the age-adjusted Charlson comorbidity index (ACCI).[19] Twenty-five percent of the patients were active smokers at the time of surgery. Preoperative median values for DLCO and FEV1 were respectively 69.2 and 82.2% of the individual's predicted value. Data on the surgery are presented in Table 2. A video-assisted thoracoscopic approach was performed in 72.8% of the cases, the most common resection was right upper lobectomy (35.9%). The median lengths of chest tube duration and hospital stay were 4 and 9 days, respectively. Postoperative complications occurred in 27.2% of the patients, and no case of in-hospital mortality was observed. The median length of FU was 67 months.

Prognostic factors for OS in patients with stage I NSCLC

Univariable and multivariable Cox regression analyses were performed to identify factors that could influence OS in patients after complete resection of stage I NSCLC (Table 3). In the univariable analysis, higher preoperative NLR ($p = 0.026$), lower preoperative DLCO ($p = 0.002$) and FEV1 ($p = 0.001$), male gender ($p = 0.029$), longer operating time ($p = 0.019$) and lower preoperative lymphocyte concentrations ($p = 0.026$) were significantly associated with worse OS. In the multivariable analysis, only NLR ($p = 0.005$), DLCO ($p = 0.010$), FEV1 (0.041) and male gender (0.026) remained as independent risk factors for decreased OS after lobectomy for stage I NSCLC.

Cutoff values for independent predictors of survival

For the independent predictors of survival in multivariable Cox regression analysis NLR, DLCO and FEV1, ROC analyses were performed to determine joint maximum sensitivity and specificity of cutoff values to stratify patients at high risk of death. The corresponding ROC curves are shown in Figure 1. For NLR, the highest Youden's J was observed for

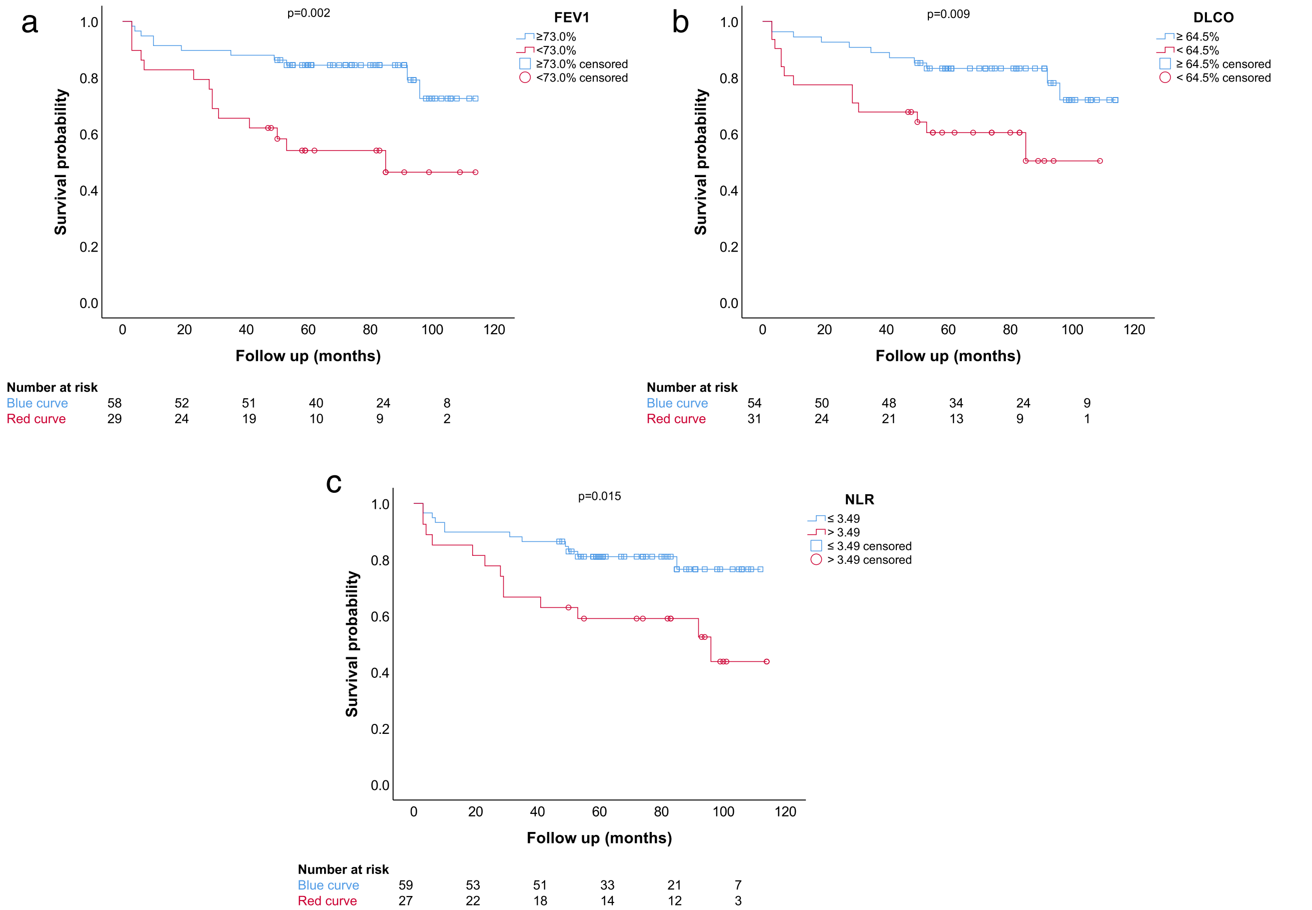

FIGURE 2 Kaplan Meier survival curves with stratification according to cutoff values determined by ROC analysis. Five-year OS rates were significantly different for (a) FEV1 (84.4% vs. 54.0%), (b) DLCO (83.2% vs. 60.4%) and (c) NLR (81.1% vs. 59.0%). DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory pressure in 1 second; NLR, neutrophil to lymphocyte ratio; OS, overall survival

values >3.49 (sensitivity 52.0%, specificity 77.0%) with an area under the curve (AUC) of 0.646. For DLCO and FEV1, thresholds <64.5% (sensitivity 62.5%, specificity 70.5%, AUC 0.688) and <73.0% (sensitivity 56.0%, specificity 75.8%, AUC 0.698) were calculated.

Kaplan–Meier analysis of independent prognostic factors

The estimated 5-year OS rate of the entire study population was 74.5%. The estimated 5-year OS rate of female patients in this study was 87.2% compared to 64.5% in male patients; OS of females was significantly longer ($p = 0.022$).

Figure 2 shows the Kaplan–Meier survival curves stratified according to the calculated cut-off values for the independent prognostic factors identified in multiple Cox regression analysis. The OS rate in patients with a preoperative FEV1 ≥ 73.0% of the predicted value was significantly higher ($p = 0.002$) compared to patients with a preoperative FEV1 < 73.0% of the predicted value (5-year OS 84.4% vs. 59.0%). Similarly, significantly longer ($p = 0.009$) OS rates were observed in patients with a preoperative DLCO ≥64.5% of the predicted value (5-year OS 83.2% vs. 60.4%) and in patients with a NLR ≤3.49 ($p = 0.015$; 5-year OS 81.1% vs. 59.0%).

Patients with both FEV1 and DLCO below the determined cutoff values showed a significantly worse OS ($p = 0.002$, Figure 3a). The same is true if the patients are stratified according to the cutoff values for an FEV1 (below the cutoff value) and an NLR (above the cutoff value). Again, significant differences in OS utilizing the Kaplan–Meier analysis were observed compared to the rest of the cohort (Figure 3b).

DISCUSSION

In this study, we present data on prognostic factors for long-term survival after lobectomy for stage I NSCLC. The main finding of this study was the identification of four independent risk factors for worse OS in multivariable Cox regression analysis. We show that both classic prognostic markers such as DLCO, FEV1, and male gender, but also NLR as a

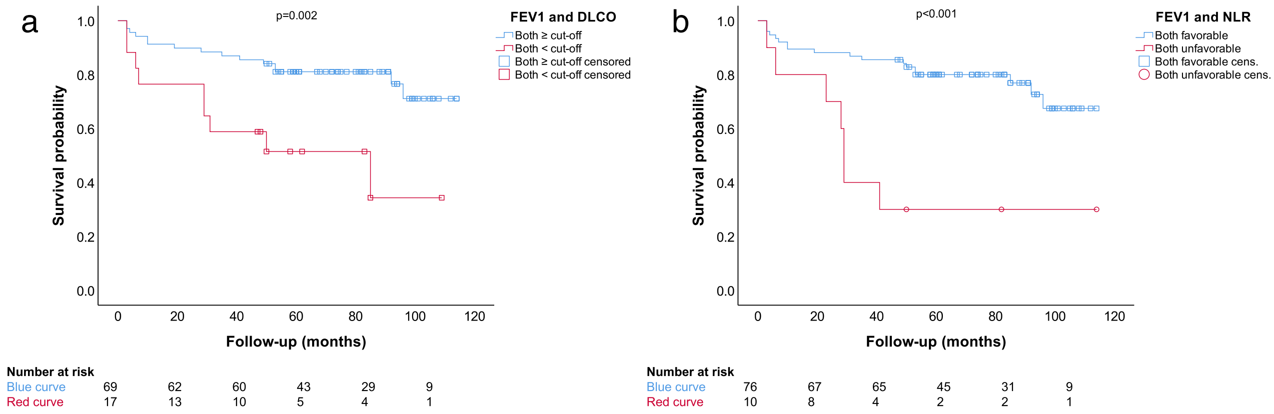

FIGURE 3 Kaplan Meier survival curves with stratification for combined parameters. (a) FEV1 and DLCO, (b) FEV1 and NLR. DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory pressure in 1 second; NLR, neutrophil to lymphocyte ratio

more recent surrogate parameter for systemic inflammation, have a statistically significant, independent impact on long-term OS. Unlike most other studies, we demonstrate this in a homogeneous, single-center collective strictly focusing on stage I patients who had undergone complete resection by lobectomy.[6–11] The common practice to examine stages I to III together results in patient cohorts where pT1 pN0 patients are mixed with patients who have a pT4 tumor and/or a pN2 or pN3 stage. In our view, these are patient populations that may well differ in tumor biology and tumor-associated inflammation. However, some studies exist that have investigated the significance of NLR for oncological outcomes in stage I NSCLC, but these often focus on biomarkers and do not consider a number of other known prognostic factors. The study by Sarraf et al. identified increasing preoperative NLR as an independent predictor of survival after complete resection for primary lung cancer but did not report data on DLCO or FEV1.[15] Likewise, Mizuguchi et al. reported the prognostic value of the NLR in patients with completely resected stage I NSCLC.[16] In their study, the results of "pulmonary function tests" were prognostic factors only in univariable but not in multivariable analysis, but explicit values for DLCO and FEV1 were not presented. Furthermore, both parameters appear to have been recorded, which may make the analysis prone to error. Sulibhavi et al. report data on stage I and pT1 NSCLC and controlled for FEV1, but not for DLCO.[17] The studies by Łochowski et al. and Huang et al. show prognostic value for NLR; however, DLCO and FEV1 were not analyzed.[11,12] In our opinion, well-known risk factors for adverse outcomes should be included in the analysis when the prognostic significance of new biomarkers for patient survival is assessed.

The predictors identified in our study are consistent with data from the literature. First, this is true for the well-known prognostic factors FEV1, DLCO and gender.[13,14,20,21] Second, this is true for NLR, which is the best-studied and most frequently identified predictor among inflammatory parameters derived from routine blood tests. In the study by Huang et al. a cutoff value for the NLR of 3.18 was determined, a value that corresponds well with the value of 3.49 calculated by us.[11] However, a closer look at the calculated thresholds reveals that none of the identified parameters is clearly superior to the others in its prognostic significance. Sensitivities and specificities calculated in our study range between 56.0% and 75.8%, which is not excellent for a diagnostic test. The ROC curves published by other authors indicate similar results.[11,12,15] This is surprising in a disease like NSCLC, where the importance of inflammation and tumor immunology has been demonstrated so early and as well as in hardly any other solid tumor. One reason might be that as clinicians, we do not focus our research on the best potential biomarkers, but instead select parameters such as NLR, PLR and others, because these can be easily derived from results of routine blood sampling and thus are widely available. Although these biomarkers are independent prognostic factors, they do not appear to be superior to known predictors such as lung function parameters. Nevertheless, the significant difference in survival for patients identified by combining the cutoff values for FEV1 and NLR indicates that joint consideration of lung function parameters on the one hand and inflammatory markers on the other hand, could prove to be valuable in preoperative risk stratification regarding long-term survival. The results of this study are limited by the relatively small patient cohort and the retrospective analysis. This is especially true for the small number of patients "at risk" in specific groups when the combined parameters were evaluated, which makes the study susceptible to bias. Nevertheless, both biomarkers for systemic inflammation, lung function parameters and their interaction might be promising predictors and should be further investigated.

In conclusion, the NLR was an independent predictor of OS in stage I NSCLC patients who underwent curative resection by lobectomy in this study. However, in its prognostic significance, it does not appear to be superior to known risk factors for poor OS like DLCO and FEV1. The combination of lung function parameters and new biomarkers could contribute to risk stratification. Further studies on the relationship between parameters of systemic inflammation and pulmonary function are needed to clarify their prognostic relevance.

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CONFLICT OF INTEREST

The authors declare there are no conflict of interest.

ORCID

Christian Galata https://orcid.org/0000-0001-9898-7154
Davor Stamenovic https://orcid.org/0000-0003-3302-3471

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