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ORIGINAL ARTICLE

Validation of the neutrophil-to-lymphocyte ratio as a prognostic factor in a cohort of European prostate cancer patients

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Abstract
Purpose Recent studies have expanded the concept that the systemic inflammatory response has an important role in the progression of several solid tumors. The neutrophil-to-lymphocyte ratio (NLR), an easily determinable marker of systemic inflammation, has been associated with clinical outcome in various cancer entities. In the present study, we validated the prognostic relevance of an elevated NLR in a cohort of European prostate cancer patients.
Methods Data from 415 consecutive prostate cancer patients treated with 3D conformal radiotherapy at a single tertiary academic center from 1999 to 2007 were included in this retrospective study. Clinical progression-free survival (PFS), distant metastases-free survival (DMFS), and overall survival (OS) were assessed using the Kaplan–Meier method. To evaluate the prognostic relevance, univariate and multivariate Cox regression models were performed for each end point.
Results Based on previously published studies, an NLR ≥ 5 was selected as cutoff value for external validation. Multivariate analysis identified an increased NLR as an independent prognostic factor for clinical PFS [hazard ratio (HR) 3.09, 95 % CI 1.64–5.82, $p < 0.001$], DMFS (HR 3.51, 95 % CI 1.80–6.85, $p < 0.001$), and OS (HR 2.16, 95 % CI 1.17–3.99, $p = 0.013$).
Conclusion The NLR seems to represent an independent prognostic marker and should be considered for future individual risk assessment in patients with prostate cancer.

Keywords Prostate cancer · Prognosis · Inflammation · Neutrophil-to-lymphocyte ratio

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Introduction

In recent years, many efforts have been undertaken to identify novel immunological and histological prognostic markers in order to improve the prediction of the risk of prostate cancer recurrence. Although several potential molecular and cellular prognostic biomarkers have been detected, their widespread routine application has not yet been established due to lack of standardization and regional availability [1, 2].

Tumor progression and metastasization comprise a cascade of steps that involve the interaction between the tumor and the host-derived stromal microenvironment, which includes factors that support angiogenesis and inflammation [3, 4]. Recent studies have shown that the systemic inflammatory response which is usually measured by surrogate blood-based parameters, such as C-reactive protein or circulating inflammatory blood cells, has an important role in the progression of several solid tumors [4–7]. Of these inflammatory parameters, an increased

neutrophil-to-lymphocyte ratio (NLR) has been proposed as an easily accessible and reliable marker to predict cancer patients' survival [8–11].

Cumulating evidence suggests that a high NLR might represent an independent adverse prognostic factor in docetaxel-treated [12–14], abiraterone-treated [15], as well as in ketoconazole-treated [16] patients with metastatic castration-resistant prostate cancer (mCRPC).

In addition, the results of the Glasgow Inflammation Outcome Study demonstrated that an increased NLR had prognostic value in different types of cancer including localized prostate cancer [8, 17]. However, the study included a rather heterogeneous population of prostate cancer patients, and external validation of the NLR as a prognostic risk assessment tool in an independent cohort of prostate cancer patients has not yet been performed.

Therefore, the aim of the present study was to assess the prognostic significance of the pre-treatment NLR in a large cohort of European prostate cancer patients.

Methods

This retrospective study included data from 415 consecutive patients with histologically confirmed adenocarcinoma of the prostate treated at the Comprehensive Cancer Center Graz, Department of Therapeutic Radiology and Oncology, between 1999 and 2007. Eligible for inclusion in the present analysis were male patients with histologically confirmed prostate cancers who had neutrophil and lymphocyte counts recorded for any reason and underwent radiation therapy for prostate cancer.

Data on clinical characteristics including prostate specific antigen (PSA) at the time of diagnosis, tumor node metastasis (TNM) stage, histological grade, age at diagnosis, and family history were retrieved from electronic patient records of our institution. Prostate cancer patients were stratified into low-, intermediate-, and high-risk groups on the basis of pre-treatment PSA level, Gleason score (GS), and American Joint Commission on Cancer T stage. The patients were classified as high risk if they met any of the following criteria: T3–4, GS 8–10, or PSA > 20 ng/ml. The intermediate-risk group included stages T2b-2c, GS 7, or PSA 10–20 ng/ml; the low-risk group contained stages T1–T2a, GS $\leq$ 6, and PSA < 10 ng/ml.

Laboratory data, including neutrophil and lymphocyte counts, were obtained as part of routine clinical evaluation using standard clinical testing methodology.

Patients were treated with three-dimensional conformal radiation therapy using high-energy photons (18 MV) to a total dose of 70 Gy delivered in 1.8–2.0 Gy per fraction. A total of 277 patients (66.7 %) received additional neo-adjuvant and/or adjuvant androgen deprivation therapy (ADT).

Follow-up examinations included PSA measurements and digital rectal examinations (3-month interval in years 1–3, 6-month interval in years 4–5, and 12-month interval in years 6–15 after diagnosis). Patients with PSA relapse, defined as a rise by $\geq$2 ng/ml above the nadir PSA, were regularly checked through diagnostic tests, comprising isotope bone scan, chest X-ray, and abdominal and pelvic computed tomography as well as magnetic resonance imaging studies to detect local recurrences and/or distant metastases.

Statistical analyses

The primary end point of the study was clinical progression-free survival (PFS) which was defined as the time from prostate cancer diagnosis to the occurrence of local recurrence and/or distant metastases. The secondary end points included distant metastases-free survival (DMFS) defined as the time between diagnosis and the occurrence of distant metastases and overall survival (OS) calculated from time of diagnoses to the date of death of any cause. The NLR was calculated as the absolute neutrophil count measured in G/l divided by the absolute lymphocyte count measured in G/l. According to previously published studies, an NLR $\geq$ 5 was selected as cutoff value for external validation [8, 17]. The NLR was correlated with the clinicopathological features by nonparametric tests. To analyze the association between the clinicopathological features and the NLR with clinical PFS, DMFS, and OS, we generated Kaplan–Meier curves and compared them by the log-rank test. Furthermore, the association of individual variables with clinical PFS, DMFS, and OS was assessed using Cox proportional hazards models. To determine the independent effect of the NLR on the study end points, multivariate Cox proportional hazards models including age at diagnosis, androgen deprivation therapy, and risk group were used. Hazard ratios (HRs) estimated from the Cox analysis were reported as relative risks with corresponding 95 % confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). A two-sided $p \leq 0.05$ was considered statistically significant.

Results

Baseline patient and tumor characteristics are shown in Table 1. The median age at time of diagnosis was 68.2 years (mean 69.9 $\pm$ 7.2 years). The median follow-up time was 87 months (95 % CI 82–92 months). None of the

Table 1 Baseline patient characteristics and univariate Cox proportional hazards analysis of the association between clinical parameters and clinical progression-free survival, distant metastases-free survival, and overall survival

n	415	Progression-free survival		Distant metastases-free survival		Overall survival	
		HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age at diagnosis, years (mean ± SD)	66.9 ± 7.2	0.96 (0.92–0.99)	0.011	0.95 (0.92–0.99)	0.009	1.00 (0.97–1.04)	0.821
PSA at first diagnosis (ng/ml)							
0–10	209 (50.4 %)	1		1		1	
10–20	102 (24.6 %)	0.49 (0.19–1.31)	0.158	0.49 (0.17–1.47)	0.205	1.69 (0.91–3.12)	0.097
>20	84 (20.2 %)	3.11 (1.74–5.56)	<0.001	3.66 (1.96–6.81)	<0.001	1.59 (0.83–3.05)	0.162
Missing data	20 (4.8 %)						
Tumor stage							
T1/2	215 (51.8 %)	1		1		1	
T3/4	174 (41.4 %)	3.29 (1.70–6.38)	<0.001	3.03 (1.51–6.10)	0.002	0.99 (0.57–1.74)	0.988
Missing data	26 (6.3 %)						
Gleason score							
Gleason < 7	258 (62.2 %)	1		1		1	
Gleason ≥ 7	156 (37.6 %)	3.22 (1.87–5.56)	<0.001	3.93 (2.17–7.11)	<0.001	1.46 (0.87–2.44)	0.148
Missing data	1 (0.2 %)						
Risk group							
Low risk	87 (21 %)	1		1		1	
Intermediate risk	105 (25.3 %)	1.81 (0.45–7.24)	0.402	1.46 (0.35–6.09)	0.607	2.64 (1.05–6.65)	0.04
High risk	223 (53.7 %)	6.68 (2.08–21.4)	0.001	5.86 (1.82–18.9)	0.003	2.24 (0.94–5.33)	0.067
Neo–adjuvant/adjuvant androgen deprivation							
No	112 (27 %)	1		1		1	
Yes	277 (66.7 %)	0.56 (0.31–1.00)	0.05	0.53 (0.28–0.99)	0.047	1.77 (0.91–3.44)	0.092
Missing data	26 (6.3 %)						
Neutrophil-to-lymphocyte ratio							
<5	350 (84.3 %)	1		1		1	
≥5	65 (15.7 %)	2.01 (1.10–3.67)	0.023	2.13 (1.14–4.00)	0.018	2.10 (1.17–3.78)	0.013

CI confidence interval, *HR* hazard ratio

clinicopathological features were associated with the NLR (data not shown).

In our study cohort, we found a significant association of age, PSA level at initial diagnosis, tumor stage, Gleason score, risk group, and (neo-) adjuvant ADT with clinical PFS, and DMFS; furthermore, a significant association between intermediate-risk situation and OS was observed (Table 1). Since risk group derives from tumor stage, Gleason score, and PSA level at time of diagnosis, only risk group, age at diagnosis, and additional androgen deprivation treatment were included in further multivariate models.

Based on previous studies, an NLR cutoff value of 5 was applied to differentiate between a low (<5) and high (≥5) NLR. Overall, there were 350 patients (84.3 %) with a low NLR and 65 patients (15.7 %) with a high NLR. A high NLR ≥ 5 significantly correlated with high neutrophil counts ($p < 0.001$) as well as with low lymphocyte counts ($p < 0.001$).

Of the 415 prostate cancer patients, 64 (15.4 %) developed local and/or distant tumor recurrence, 53 patients (12.8 %) developed distant metastases, and 60 (14.5 %) died within the follow-up period. Kaplan–Meier analyses show a significant association between an NLR ≥ 5 and decreased clinical PFS ($p = 0.020$, log-rank test; Fig. 1), DMFS ($p = 0.015$, log-rank test; Fig. 2), and OS ($p = 0.011$, log-rank test; Fig. 3).

In univariate analysis, the elevated NLR was significantly associated with decreased clinical PFS (HR 2.01, 95 % CI 1.10–3.67, $p = 0.023$; Table 1) that remained significant in the multivariate analysis (HR 3.09, 95 % CI 1.64–5.82, $p < 0.001$; Table 2). In a total of 212 patients (51.1 %), information on C-reactive protein (CRP) levels was available. After inclusion of CRP levels in our multivariate analysis in this subgroup of patients, the NLR ≥ 5 remained a significant predictor of clinical PFS (HR 2.86, 95 % CI 1.20–6.82, $p = 0.018$). Furthermore, we evaluated

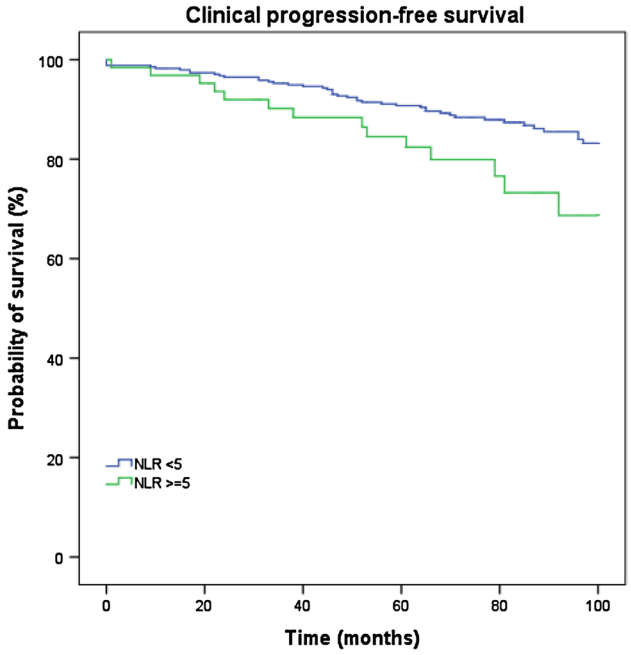

Fig. 1 Kaplan–Meier curves for clinical progression-free survival of prostate cancer patients categorized by the neutrophil-to-lymphocyte ratio (NLR; $p = 0.020$, log-rank test)

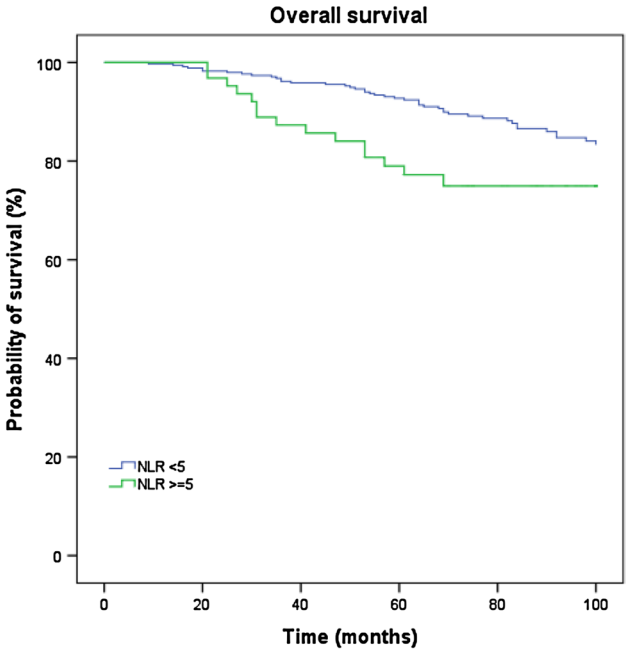

Fig. 3 Kaplan–Meier curves for overall survival of prostate cancer patients categorized by the neutrophil-to-lymphocyte ratio (NLR; $p = 0.011$, log-rank test)

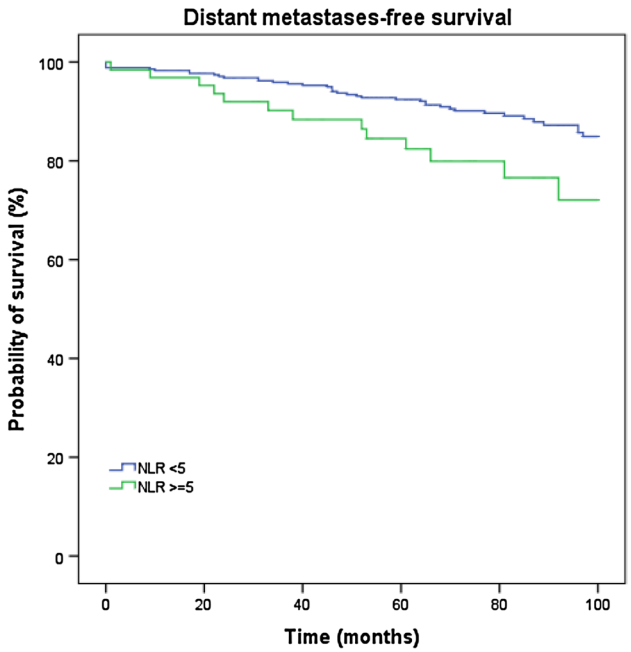

Fig. 2 Kaplan–Meier curves for distant metastases-free survival of prostate cancer patients categorized by the neutrophil-to-lymphocyte ratio (NLR; $p = 0.015$, log-rank test)

the combined effect of the NLR and GS on clinical PFS. For this analysis, patients were stratified into 4 groups on the basis of the NLR and GS as follows: GS < 7 and NLR < 5, GS < 7 and NLR ≥ 5, GS ≥ 7 and NLR < 5, and GS ≥ 7 and NLR ≥ 5. Patients with GS ≥ 7 and NLR ≥ 5 had a significantly shorter clinical PFS when compared to patients with GS < 7 and NLR < 5 ($p < 0.001$), GS < 7 and NLR ≥ 5 ($p = 0.002$), and GS ≥ 7 and NLR < 5 ($p = 0.004$, log-rank test; Fig. 4).

In DMFS analysis, we detected a significant correlation of an elevated NLR with decreased DMFS in univariate (HR 2.13, 95 % CI 1.14–4.00, $p = 0.018$; Table 1) and in multivariate analysis (HR 3.51, 95 % CI 1.80–6.85, $p < 0.001$; Table 2). In addition, the elevated NLR was significantly associated with decreased OS in univariate analysis (HR 2.10, 95 % CI 1.17–3.78, $p = 0.013$; Table 1) and multivariate analysis (HR 2.16, 95 % CI 1.17–3.99, $p = 0.013$, Table 2).

Subgroup analysis revealed a significant association between an elevated NLR and clinical PFS in intermediate-risk patients (HR 7.91, 95 % CI 1.57–39.7, $p = 0.012$) and high-risk patients (HR 2.61, 95 % CI 1.25–5.42, $p = 0.010$) after adjustment for age at diagnosis and additional androgen deprivation therapy.

Discussion

The present study was performed to validate the prognostic role of the NLR in patients with prostate cancer and demonstrated a significant association between an elevated

Table 2 Multivariate Cox proportional hazards analysis of clinical parameters for the prediction of clinical progression-free survival, distant metastases-free survival, and overall survival in prostate cancer patients

Parameter	Progression-free survival		Distant metastases-free survival		Overall survival	
	HR (95 % CI)	*p* value*	HR (95 % CI)	*p* value*	HR (95 % CI)	*p* value*
Age at diagnosis (years)	0.98 (0.94–1.02)	0.304	0.97 (0.93–1.02)	0.232	0.99 (0.95–1.03)	0.716
Risk group						
Low risk	1		1		1	
Intermediate risk	1.92 (0.48–7.68)	0.359	1.54 (0.37–6.48)	0.553	2.70 (1.07–6.82)	0.035
High risk	4.92 (1.50–16.1)	0.008	4.10 (1.24–13.5)	0.021	2.16 (0.89–5.21)	0.088
Neo-adjuvant/adjuvant androgen deprivation therapy						
No	1		1		1	
Yes	0.63 (0.34–1.16)	0.136	0.60 (0.31–1.15)	0.122	1.75 (0.89–3.48)	0.107
Neutrophil-to-lymphocyte ratio						
<5	1		1		1	
≥5	3.09 (1.64–5.82)	<0.001	3.51 (1.80–6.85)	<0.001	2.16 (1.17–3.99)	0.013

CI confidence interval, *HR* hazard ratio

* Adjustment for all factors listed in the Table

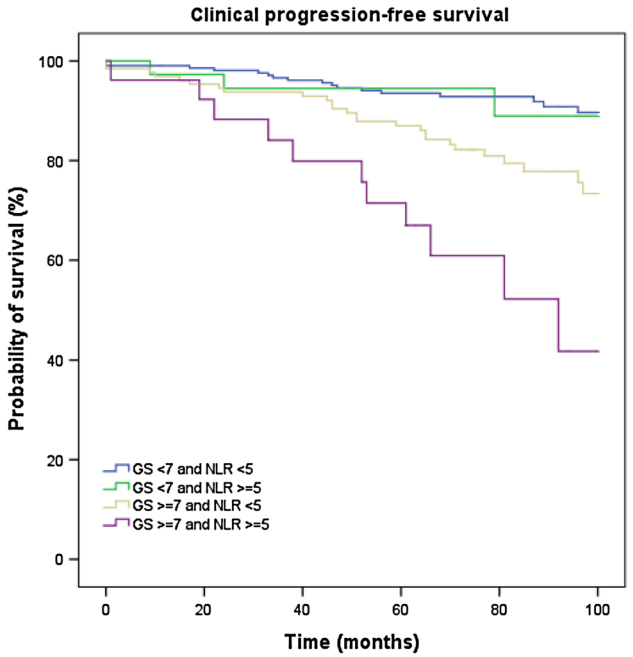

Fig. 4 Kaplan–Meier curves for clinical progression-free survival of prostate cancer patients categorized by the Gleason score (GS) and the neutrophil-to-lymphocyte ratio (NLR)

NLR and poor clinical PFS, DMFS, and OS. The association with poor clinical outcome was independent of patient age, additional androgen deprivation therapy, and risk group that is based on tumor stage, Gleason score, and PSA level at diagnosis.

The NLR represents a marker of host inflammation that can easily be derived from the differential blood count. An elevation of the NLR may reflect both an elevated neutrophil-dependent inflammatory reaction and a lower lymphocyte-mediated antitumor immune response.

Neutrophils have been shown to promote tumor growth and metastasis by remodeling the extracellular matrix and releasing reactive oxygen species (ROS), nitric oxide (NO), and arginase which suppress the cytolytic activity of immune cells and increase the rate of mutagenesis [18–20]. In prostate cancer, tumor-associated neutrophils have been shown to contribute to enhanced angiogenesis and tumor cell intravasation by releasing matrix metalloproteinase-9 [25]. Additionally, circulating neutrophils have been found to produce inflammatory mediators, such as tumor necrosis factor, interleukin (IL)-1, and IL-6, which promote cancer cell proliferation and survival and angiogenesis [21].

Lymphocytes play a major role in cancer immune surveillance, which inhibits tumor cell proliferation and metastasization [22]. The importance of lymphocytes has been demonstrated in several studies in which an increased infiltration of tumors with lymphocytes has been associated with better prognosis in cancer patients [23]. Additionally, elevated circulating lymphocyte counts have been linked with prolonged survival in different types of cancer, and normalization of an initial lymphocytopenia has been associated with an improved clinical outcome [24–26].

A combined index using neutrophil and lymphocyte counts likely reflects a more aggressive behavior of tumors and has already been shown to predict prognosis in several studies for different solid tumors [8–17, 27]. Keizman et al. [16] found that an NLR > 3 is associated with a worse response rate and shorter PFS interval in patients with mCRPC treated with ketoconazole. A high NLR has also been shown to represent an independent poor prognostic marker in patients with mCRPC undergoing docetaxel

therapy [12, 14]. Additionally, Leibowitz-Amit et al. [15] have demonstrated a significant role of an NLR > 5 in predicting response to abiraterone acetate and decreased OS in patients with mCRPC.

However, data on the role of the NLR in patients with non-metastatic prostate cancer are sparse. In the Glasgow Inflammation Outcome Study, 897 prostate cancer patients, who had a blood sample taken within a period of 2 years before or after prostate cancer diagnosis, were included and followed over a median time of 2.5 years [17]. Individuals that showed an elevated NLR of ≥5 measured within 2 years after initial diagnosis of prostate cancer had a higher risk of mortality. However, the study cohort comprised a rather heterogeneous patient population including localized and metastatic prostate cancer patients. Furthermore, information on treatment characteristics and other important prognostic factors such as disease stage and PSA level at diagnosis was not provided.

The present study was performed to externally validate the prognostic role of the pre-published NLR cutoff value of 5 and revealed a statistically significant association between NLR ≥ 5 and decreased PFS, DMFS, and OS in both univariate and multivariate analyses. Major strengths are the well-defined study cohort and the inclusion of information on treatment and important measures of prognosis such as tumor stage and PSA level.

Our study is not without limitations. Because of its retrospective design, we are unable to exclude the possibility of an unequal distribution of unidentified clinicopathologic parameters in our patient cohort that may have biased the observed results.

Furthermore, the present study included patients with NLR determined prior to the start of radiotherapy or neoadjuvant ADT that might have caused changes in NLR. As the analysis of the NLR before, during, and after therapy was originally beyond the scope of our analysis, we were unfortunately not able to provide data concerning the influence of treatment on the NLR.

In addition, neutrophil and lymphocyte counts may be influenced by concurrent infection and drugs, which we could not account for in this analysis. Concurrent inflammatory diseases may underlie the increased overall mortality we observed in our cohort of prostate cancer patients with an increased NLR; however, a major effect on clinical PFS and DMFS is unlikely suggesting that an elevated NLR may independently influence prostate cancer prognosis and may serve as a cost-effective, readily available marker in daily clinical practice to guide individualized treatment decisions in prostate cancer patients.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard The study was complied with the Declaration of Helsinki and has been approved by the local Ethical Committee (EK 27-032 ex 14/15). As this is a retrospective nonintervention study, the institutional review board waived the need for written informed consent from the participants.

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