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Clinical Study

Neutrophil to lymphocyte ratio and mortality in spinal epidural abscess

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Abstract

BACKGROUND CONTEXT: Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio have been previously identified as markers for overall survival in oncology but remain heretofore unexplored in spinal epidural abscess (SEA).

PURPOSE: The purpose of this study was to determine the impact of these routinely collected assessments on 90-day mortality in SEA.

STUDY DESIGN/SETTING: Retrospective, case-control study.

PATIENT SAMPLE: Patients 18 years or older diagnosed with SEA at 2 academic medical centers and 3 community hospitals.

OUTCOME MEASURES: Ninety-day postdischarge and in-hospital mortality.

METHODS: Complete blood count with differential obtained on the day immediately preceding or on the day of admission was used to calculate platelet to lymphocyte and neutrophil to lymphocyte ratios. Multivariate analyses were used to determine if these ratios were independent risk factors for 90-day mortality.

RESULTS: For 1,053 SEA patients included in the study, the rate of 90-day mortality was 134 (12.7%). The rate of 90-day mortality with neutrophil to lymphocyte ratio (≥8) was (20.5%) compared to (8.1%) with neutrophil to lymphocyte ratio <8. Neutrophil to lymphocyte ratio was positively associated with bacteremia, elevated erythrocyte sedimentation rate, and concurrent systemic infections (endocarditis, meningitis) and negatively associated with duration of symptoms prior to presentation. On multivariate analysis, elevated neutrophil to lymphocyte remained an independent risk factor for 90-day mortality (odds ratio=2.62, 95% confidence interval=1.66−4.17, p<.001). Platelet to lymphocyte ratio was not associated with 90-day mortality.

CONCLUSIONS: Absolute neutrophil to lymphocyte ratio is a routinely collected but overlooked biomarker in patients with spinal epidural abscess that is a novel independent risk factor for 90-day mortality. © 2019 Elsevier Inc. All rights reserved.

Keywords: Neutrophil to lymphocyte ratio; Platelet to lymphocyte ratio; Prognosis; Spinal epidural abscess; Systemic inflammation; Spine surgery; Survival

Background

Spinal epidural abscess (SEA) is a rare but devastating condition with an incidence of 2−3 per 10,000 hospital admissions [1−5]. Previous studies have identified several risk factors for poor outcomes in this pathology, including age, malignancy, pretreatment motor deficit, concurrent infection such as endocarditis, and diabetes mellitus, among

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Ethics Statement: This retrospective study was approved by our institutional review board.

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others [6–12]. Virtually all patients with suspected SEA are evaluated with a complete blood count (CBC). Nonetheless, the prognostic value of all components of the CBC in SEA has yet to be established.

Specifically, neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) have been linked to systemic inflammation and identified as prognostic factors for mortality and morbidity in multiple disease states [13–19]. Wang et al. studied 695 lung cancer patients and found that patients with low NLR (<6.0) had higher overall survival (819 days) than patients with high NLR (≥6.0) (629 days), p=.041 [20]. Tamhane et al. studied 2,833 patients admitted with a diagnosis of acute coronary syndrome (ACS) and found that NLR on admission predicted in-hospital and 6-month mortality in these patients [16]. Similarly, Yao et al. studied 303 patients admitted for acute exacerbation of chronic obstructive pulmonary disease and found that NLR and PLR were significantly elevated in patients who suffered in-hospital mortality [21].

Though these previous studies have established NLR and PLR as markers for disease severity and mortality, a similar investigation remains to be undertaken in SEA. As such, the purpose of this study was to determine the value of NLR and PLR in SEA. Based on the findings of these prior studies, we hypothesized that elevated PLR and NLR would be associated with increased risk of 90-day mortality.

Methods

Guidelines

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines [22,23].

Data source and patients

The initial population of patients was obtained by retrospectively screening electronic health records from 1993 to 2016 at 2 tertiary care centers and 3 community hospitals for patients with an International Classification of Diseases (ICD), ninth and/or 10th edition codes for intraspinal abscess or granuloma (ICD-9=324.1 or ICD-10=G06.1) or Current Procedural Terminology (CPT) codes (63275–63278) for intraspinal, extradural laminectomy for lesion other than neoplasm. The following inclusion and exclusion criteria was applied to this initial population. Inclusion criteria: (1) age greater than or equal to 18 years (2) diagnosis of SEA confirmed by admission note of the admitting clinician, operative notes, radiographic reports, or pathology report. Exclusion criteria: (1) patients who began treatment for SEA at another institution before admission to our healthcare center (2) patients who may have met the CPT screening criteria of laminectomy for intraspinal lesions, such as synovial cysts or epidural hematoma, but without a diagnosis of SEA. Retrospective review of medical charts was approved by our institutional review board.

Outcome

The primary endpoint was 90-day mortality, defined as death of patient while in the hospital or within 90 days after discharge from the medical center. Mortality was ascertained through the Social Security death index and chart review.

Covariates

Covariates were assessed on the basis of previous studies: demographic factors (age, sex, and body mass index), comorbidities (diabetes, dialysis, and human immunodeficiency virus [HIV] status), habits (smoking status, intravenous drug use, and alcohol use), prior spinal intervention, presence of spinal instrumentation, and symptoms at presentation (fever, back pain, motor deficit, and nonmotor neurologic deficits). The American Spinal Injury Association (ASIA) Impairment Scale was used to ascertain status of motor function. Other explanatory factors were location of the abscess, causative micro-organism, and presence of concurrent spinal and non-spinal infections. The following laboratory markers were included on the basis of prior studies: white blood cell count (WBC) ($\times 10^3/\mu$L), hemoglobin (Hgb) (g/dL), c-reactive protein (CRP) (mg/dL), and erythrocyte sedimentation rate (ESR) (mm/hr). NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. PLR was calculated by dividing the platelet count by the absolute lymphocyte count. All laboratory values were collected on the date of admission or the day immediately preceding admission. Multiple imputation was used to impute variables with less than 30% missing data.

Statistics

Descriptive statistics were generated for the baseline study population. Lopez-Raton's optimal cutpoint technique with the area under the receiver operating curve metric for continuous biomarkers was used to determine the threshold for NLR and PLR [24]. Bivariate statistics were generated for NLR and PLR with 90-day mortality and the baseline patient characteristics with bivariate logistic regression. Multivariable logistic regression with hundred-fold bootstrapped backward stepwise elimination was undertaken to determine association of systemic inflammatory markers with 90-day mortality. Sensitivity analyses were undertaken by repeating the multivariable analysis by using cut-offs for NLR previous proposed by others and by including NLR as a continuous marker.

Results

Descriptive statistics

Our study included 1,053 SEA patients, of which 660 (62.7%) were under 65 years of age and 408 (38.7%) were female (Table 1). The rate of 90-day mortality in the cohort

Table 1
Baseline characteristics of study population, n=1053

Variable	n (%) Median (IQR)
Age (years)	
<65	660 (62.7)
≥65	393 (37.3)
Sex	
Female	408 (38.7)
Male	645 (61.3)
BMI (kg/m^2)	
Median (IQR)	27.4 (24.0–32.2)
Not recorded	647 (61.4)
Smoking status	286 (27.2)
Current	208 (19.8)
Quit >1 year	
Intravenous drug use	191 (18.1)
Alcohol use	183 (17.4)
Diabetes mellitus	241 (22.9)
Active malignancy	79 (7.5)
Hemodialysis	44 (4.2)
HIV positive	21 (2.0)
Spinal instrumentation in place	70 (6.6)
Spinal procedure in past year	207 (19.7)
Pathologic or compression fracture in past 5 years	56 (5.3)
Fever at presentation	283 (26.9)
Back pain at presentation	1014 (96.3)
ASIA	
Normal (E)	656 (62.3)
Incomplete injury (B–D)	331 (31.4)
Complete (A)	31 (2.9)
Sedated/existing deficit	33 (3.1)
Missing	2 (0.2)
Sensory changes	250 (23.7)
Urinary incontinence or retention	113 (10.7)
Fecal incontinence or retention	41 (3.9)
Symptom duration prior to presentation	
<72h	209 (19.8)
72h–2w	497 (47.2)
>2w	345 (32.8)
Unknown	2 (0.2)
WBC ($\times 10^3$/uL)	
<15	754 (71.6)
≥15	299 (28.4)
Platelet ($\times 10^3$/uL)	
<150	148 (14.1)
150–450	725 (68.9)
>450	151 (14.3)
Unknown	29 (2.8)
Hemoglobin (g/dL)	
<11	639 (60.7)
≥11	389 (36.9)
Unknown	25 (2.4)
ESR (mm/hr)	
<100	519 (49.3)
≥100	259 (24.6)
Unknown	275 (26.1)
CRP (mg/dL)	
<130	315 (29.9)
≥130	255 (24.2)
Unknown	483 (45.9)
Platelet to lymphocyte ratio	
<262	501 (47.6)
≥262	366 (34.8)
Unknown	186 (17.7)
Neutrophil to lymphocyte ratio	
<8	520 (49.4)
≥8	351 (33.3)
Unknown	182 (17.3)
Number of affected levels	
One or two	465 (44.2)
Three or more	587 (55.8)
Region of spine	
Cervical	132 (12.5)
Cervicothoracic	58 (5.5)
Thoracic	223 (21.2)
Thoracolumbar	70 (6.6)
Lumbar	306 (29.1)
Lumbosacral	195 (18.5)
Location of abscess relative to thecal sac	
Circumferential	80 (7.6)
Dorsal	264 (25.2)
Multiple locations	120 (11.5)
Ventral	583 (55.7)
Organism	
No growth	176 (16.7)
Methicillin-sensitive S. *aureus*	421 (40.0)
Methicillin-resistant S. *aureus*	151 (14.3)
Streptococcus	104 (9.9)
Coagulase-negative staphylococcal species	68 (6.5)
Escherichia coli	27 (2.6)
Other	106 (10.1)
Bacteremia	
Local spinal infections	614 (58.3)
Spondylodiscitis	483 (45.9)
Psoas/paraspinal abscesses	476 (45.2)
Vertebral osteomyelitis	120 (11.4)
Prevertebral abscess/retropharyngeal abscess	88 (8.4)
Discitis	51 (4.8)
Wound infection	67 (6.4)
Local nonspinal infections	
Endocarditis	64 (6.1)
Nonspinal abscess cellulitis	55 (5.2)
Septic arthritis	56 (5.3)
Pneumonia/empyema	57 (5.4)
Meningitis	20 (1.9)
Nonvertebral osteomyelitis	14 (1.3)
Initial treatment modality	28 (2.7)
Operative	581 (55.2)
Nonoperative	472 (44.8)
Death in hospital or within 90 days of discharge	134 (12.7)

ASIA: American Spinal Injury Association Impairment Scale; BMI: body mass index; CRP: c-reactive protein; ESR: erythrocyte sediment rate; (g/dL): grams per deciliter; h: hours; (IQR): interquartile range; (kg/m^2): kilogram per meter squared; (mg/dL): milligrams per deciliter; WBC: white blood cell; uL: microliter

was 12.7% (134 patients). The thresholds for PLR and NLR, determined by the optimal cutpoint method with the area under the receiver operating curve metric, were PLR≥262, and NLR≥8. Ninety-day mortality in patients with elevated NLR (≥8) was 20.5% whereas 90-day mortality in patients with NLR<8 was 8.1%. Ninety-day mortality in patients with PLR (≥262) was 13.9%, whereas 90-day mortality in patients with PLR<262 was 12.6%.

Table 2
Bivariate analyses for neutrophil to lymphocyte ratio with baseline characteristics

Variable	Odds ratio	95% CI	p value
Age (years)			
<65	*Ref.*	–	–
≥65	1.39	1.08−1.79	.01
Sex			
Female	*Ref.*	–	–
Male	1.04	0.81−1.34	.76
Smoking status			
Never	*Ref.*	–	–
Current	0.97	0.72−1.30	.85
Quit >1 year	1.27	0.92−1.74	.15
Intravenous drug use	0.95	0.58−1.30	.73
Alcohol use	1.25	0.90−1.72	.18
Diabetes mellitus	1.26	0.94−1.68	.12
Active malignancy	1.47	0.93−2.34	.10
Hemodialysis	1.09	0.58−2.00	.78
HIV positive	0.61	0.22−1.52	.31
Immunocompromised	1.30	0.91−1.85	.14
Spinal instrumentation in place	0.55	0.32−0.94	.03
Spinal procedure in past year	0.65	0.47−0.90	.01
Pathologic or compression fracture in past 5 years	1.71	0.99−2.94	.05
Fever at presentation	1.81	1.37−2.38	<.001
Back pain at presentation	0.67	0.35−1.28	.22
Motor deficit	1.85	1.43−2.40	<.001
Sensory changes	0.97	0.73−1.30	.85
Urinary incontinence or retention	1.80	1.22−2.67	.003
Fecal incontinence or retention	0.99	0.51−1.86	.97
Symptom duration prior to presentation			
<72h	*Ref.*	–	–
72h−2w	0.87	0.62−1.21	.41
>2w	0.48	0.63−1.21	<.001
Hemoglobin <13 (g/dL)	1.51	1.18−1.94	.001
WBC ≥15 ($\times 10^3$/uL)	4.96	3.65−6.74	<.001
ESR ≥100 (mm/hr)	1.65	1.28−2.13	<.001
Platelet ($\times 10^3$/uL)			
150−450	*Ref.*	–	–
<150	1.74	1.22−2.49	.002
>450	0.93	0.66−1.31	.68
Number of affected levels			
One or two	*Ref.*	–	–
Three or more	1.84	1.44 −2.36	<.001
Region of spine			
Cervical	1.31	0.96−1.80	.09
Thoracic	1.56	1.21−2.01	<.001
Lumbar	0.82	0.64−1.06	.13
Location of abscess relative to thecal sac			
Dorsal	1.22	0.95−1.57	.11
Ventral	1.02	0.77−1.36	.87
Circumferential	0.73	0.44−1.17	.2
Organism			
No growth	0.26	0.17−0.39	<.001
Methicillin-sensitive Staph aureus	1.71	1.33−2.20	<.001
Methicillin-resistant Staph aureus	2.04	1.44−2.89	<.001
Streptococcus	1.18	0.76−1.83	.45
Coagulase-negative staphylococcal species	0.54	0.29−0.99	.04
Escherichia coli	1.24	0.53−2.91	.62
Bacteremia	4.24	3.22−5.64	<.001
Local spinal infections			
Spondylodiscitis	0.63	0.49−0.80	<.001
Psoas/paraspinal abscesses	1.03	0.80−1.32	.81
Vertebral osteomyelitis	0.78	0.53−1.14	.19
Prevertebral abscess/retropharyngeal abscess	1.19	0.76−1.85	.44
Discitis	1.28	0.72−2.26	.39
Wound infection	0.69	0.40−1.16	.17
Local nonspinal infections			
Endocarditis	2.94	1.75−5.06	<.001
Nonspinal abscess cellulitis	2.07	1.20−3.62	.009
Septic arthritis	1.99	1.16−3.44	.01
Pneumonia/empyema	1.42	0.83−2.42	.20
Meningitis	3.69	1.47−10.5	.008
Initial treatment modality			
Nonoperative	*Ref.*	–	–
Operative	2.27	1.76−2.94	<.001
Death within 90 days of discharge	3.35	2.30−4.93	<.001

CI: confidence interval; ESR: erythrocyte sediment rate; h: hours; (mm/hr): millimeters per hour; NLR: neutrophil to lymphocyte ratio; (w): weeks; WBC: white blood cell; (uL): microliter

Bivariate and multivariate analyses

Elevated PLR was not associated with 90-day mortality (Odds Ratio [OR] = 1.2, 95% Confidence Interval [CI] = 0.83−1.72, p=.34) whereas elevated NLR conferred an increased risk for 90-day mortality (OR = 3.35, 95% CI = 2.30−4.93, p<.001) on bivariate analysis. On Kaplan Meier curve analysis, NLR (≥8) increased risk for mortality at all-time points up to 90-days postdischarge. On bivariate analysis, elevated NLR was associated with bacteremia (OR=4.24, 95% CI=3.22−5.64, p<.001) and elevated ESR levels (OR=1.65, 95% CI=1.28−2.13, p<.001) (Table 2). Elevated NLR was negatively associated with abscesses characterized by growth of no organisms (OR=0.26, 95% CI=0.17−0.39, p<.001) and positively associated with methicillin-sensitive *Staphylococcus aureus* (OR=1.71, 95% CI=1.33−2.20, p<.001) and methicillin-resistant S. *aureus* (OR=2.04, 95% CI=1.44−2.89, p<.001).

On multivariable analysis, elevated NLR remained an independent prognostic factor for 90-day mortality (OR= 2.62, 95% CI=1.66−4.17, p<.001) (Table 3). The full multivariable model included age ≥65 years (OR=3.56, 95% CI=2.35−5.47, p<.001), hemodialysis (OR=3.84, 95% CI=1.84−7.87, p<.001), diabetes (OR=2.30, 95% CI=1.49−3.52, p<.001), active malignancy (OR=4.08, 95% CI=2.27−7.22, p<.001), endocarditis (OR=2.02, 95% CI=0.98−4.01, p=.05), pretreatment motor deficit (OR=1.68, 95% CI=1.10−2.55, p=.002), symptom duration 72 hours−2 weeks (OR=0.53, 95% CI=0.33−0.87, p=.01), symptom duration ≥2 weeks (OR=0.41, 95% CI=0.23−0.71, p=.001), WBC ≥ $15 \times 10^3/\mu$L (OR=1.08, 95% CI=0.68−1.72, p=.73), and

Table 3
Multivariate analysis for 90-day mortality

Variable	Odds ratio	95% CI	p value
Age ≥65 years	3.56	2.35–5.47	<.001
Hemodialysis	3.84	1.84–7.87	<.001
Diabetes	2.30	1.49–3.52	<.001
Active malignancy	4.08	2.27–7.22	<.001
Endocarditis	2.02	0.98–4.01	.05
Pretreatment motor deficit	1.68	1.10–2.55	.002
NLR ≥8	2.62	1.66–4.17	<.001
Symptom duration prior to presentation			
<72h	*Ref.*	–	–
72h–2w	0.53	0.33–0.87	.01
>2w	0.41	0.23–0.71	.001
WBC ($\times 10^3$/uL) ≥15	1.08	0.68–1.72	.73
ESR (mm/hr) ≥100	1.40	0.92–2.12	.12

CI: confidence interval; ESR: erythrocyte sediment rate; h: hours; (mm/hr): millimeters per hour; NLR: neutrophil to lymphocyte ratio; (w): weeks; WBC: white blood cell; (uL): microliter

ESR ≥100 mm/hr (OR=1.40, 95% CI=0.92–2.12, p=.12). With repeated multivariable sensitivity analyses with NLR as a continuous variable (OR=1.02, 95% CI=1.01–1.04, p=.005) (Supplementary Table 1) and with NLR at a threshold of ≥5 (OR=1.85, 95% CI=1.06–3.22, p=.03) (Supplementary Table 2), NLR remained associated with 90-day mortality.

Discussion

Two routinely collected markers of systemic inflammation previously unexamined in spinal epidural abscess were studied in this analysis. Elevated NLR was associated with increased risk of 90-day mortality in patients with SEA on bivariate and multivariate analysis. Elevated PLR was not a marker for 90-day mortality.

Systemic inflammation is marked by neutrophilia and lymphocytopenia [25–28]. In homeostatic state, neutrophils have short circulatory half-lives and neutrophil levels are regulated by apoptosis [29]. In inflammatory conditions, apoptosis of neutrophils is delayed, increasing lifespan, and time in circulation [30]. In addition to increased circulating neutrophils, systemic inflammation decreases circulating lymphocytes. Systemic inflammation leads to increased apoptosis of lymphocytes and margination into the liver and lymphatic systems [28]. This combination of elevated neutrophils and decreased lymphocytes provides one mechanism for elevated NLR as a barometer for severity of systemic inflammation.

NLR has been previously used as a prognostic marker and barometer of systemic inflammation in multiple disease states [14–16,31]. In this study, the finding of no significant association between elevated PLR and 90-day mortality was unexpected given the above pathophysiology of decreased circulating lymphocytes in heightened inflammatory states. However, elevated PLR and NLR were both significantly associated with other markers of inflammation (WBC, ESR). In addition, whereas PLR was positively associated with symptom duration greater than 2 weeks prior to presentation, NLR and 90-day mortality were negatively associated with symptom duration greater than 2 weeks prior to presentation. This suggests that PLR may represent not only systemic inflammation but also the duration of the inflammatory process. In oncology, systemic inflammation occurs on a much longer time scale than that in hospitalization for SEA. Consequently, PLR's value for prognostication in oncology did not translate in the same manner to hospitalization for SEA in this study. Additionally, other studies in oncology have reported findings similar to the ones in this study; for example, Xie et al. studied 359 patients with osteosarcoma and found only NLR, and not PLR, as an independent predictor for progression-free survival and overall survival on multivariate analyses [32].

To our knowledge, there has been no previous study that focuses on evaluating the role of NLR in patients with SEA. However, other markers of systemic inflammation, such as WBC, CRP, and ESR have been studied in relationship to outcomes in SEA patients [6,7,11,33]. Additionally, we previously identified eight independent predictors (active malignancy, age greater than 65 years, hemodialysis, endocarditis, diabetes mellitus, pretreatment motor deficit, and WBC count $>15 \times 10^9$ cells/L, and symptom duration greater than 2 weeks prior to presentation) associated with 90-day mortality in patients with spinal epidural abscess [6]. In this study, after the inclusion of NLR on multivariate analysis, WBC, ESR, and endocarditis did not remain independent risk factors for 90-day mortality.

There are several limitations to this study. First, this was a retrospective study that requires prospective validation in independent patient populations. Furthermore, this was an analysis of SEA patients admitted to one health care system and external validation of the findings of this study remains to be undertaken. In addition, CRP was only collected in 54.1% of patients in this study while ESR was available in 778 (73.9%), WBC was available in all patients (1053), and NLR was available in 871 (82.7%). Despite these limitations, this study contributes a simple and novel prognostic marker to the existing literature on mortality in SEA. Future studies developing prognostic models for mortality in spinal epidural abscess should consider assessment of NLR. This marker was routinely collected in the majority of the study population on the day preceding admission or on the day of admission. NLR requires no changes to the existing pipeline of patient management in SEA and provides a reliable and potentially cost-effective option for prognostication in this population.

Conclusion

This study extended prior work on prognostic factors in SEA by identifying NLR as a novel independent risk factor for 90-day and in-hospital mortality among SEA patients evaluated at one healthcare system. Future studies should

consider updating existing prognostication models in SEA and validating the results presented here in independent external populations.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2019.02.005.

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