Venous Thromboembolism Risk in Head and Neck Cancer: Significance of the Preoperative Platelet-to-Lymphocyte Ratio

Tristan Tham, MD1, Lauren Rahman, MHA1, Christina Persaud, RN1, Caitlin Olson, MD1, and Peter Costantino, MD1

No sponsorships or competing interests have been disclosed for this article.

Abstract

Objective. We aimed to investigate the association between the preoperative platelet-to-lymphocyte ratio (PLR) and venous thromboembolism (VTE) in patients with head and neck cancer (HNC) undergoing major surgery.

Study Design. Retrospective cohort study.


Subjects and Methods. Patients with confirmed HNC undergoing major surgery were included in this study. The preoperative PLR was recorded for all patients. Known VTE risk factors, including Caprini score, age, sex, smoking, body mass index, prior VTE, and anticoagulation, were also recorded. Risk factors were screened in univariate analysis using Wilcoxon’s rank sum test and \( \chi^2 \) test (Bonferroni corrected). Significant covariates were included in a multivariate regression model. Bootstrap techniques were used to obtain credible confidence intervals (CIs).

Results. There were 306 patients enrolled with 7 cases of VTE (6 deep vein thromboses and 1 pulmonary embolism). On univariate analysis, length of stay (\( P = .0026 \)), length of surgery (\( P = .0029 \)), and PLR (\( P = .0002 \)) were found to have significant associations with VTE. A receiver operator characteristic (ROC) curve was constructed that yielded an area under the ROC of 0.905 (95% CI, 0.82-0.98). Using an optimized cutoff, the multivariate model showed that length of surgery (\( \beta \) 95% CI, 0.0001-0.0006; \( P = .0056 \)) and PLR (\( \beta \) 95% CI, 5.3256-5.3868; \( P < .0001 \)) were significant independent predictors of VTE.

Conclusion. This exploratory pilot study has shown that PLR offers a potentially accurate risk stratification measure as an adjunct to current tools in VTE risk prediction, without additional cost to health systems.

Keywords
platelet-to-lymphocyte ratio, venous thromboembolism, deep vein thrombosis, pulmonary embolism, head and neck cancer

Received August 25, 2017; revised December 22, 2017; accepted January 12, 2018.

Venous thromboembolism (VTE) is a potentially life-threatening complication in patients with head and neck cancer (HNC) undergoing surgical resection. VTE includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Although the incidence of VTE in the general otolaryngology population is low,\(^1\)–\(^5\) this is reported to be higher in patients with cancer at 1.4% to 5.8%.\(^5\),\(^6\) This higher incidence rate of VTE in patients with HNC is likely due to associated risk factors.\(^7\) Most VTEs are only diagnosed after the patient exhibits clinical symptoms—termed symptomatic VTE. A recent prospective study has shown that the actual true incidence of VTEs, including nonsymptomatic VTEs in the head and neck cancer surgical setting, is much higher than previously thought, at up to 13%.\(^8\) Therefore, there is a need to develop better VTE risk assessment tools that would assist head and neck surgeons in better stratifying their high-risk patients.

Within the cardiovascular/thrombosis research literature, there has been growing interest in using the platelet-to-lymphocyte ratio (PLR) to predict thrombosis and mortality.\(^9\),\(^12\) In 2 recent studies, the PLR biomarker has been demonstrated to predict VTE risk in patients with cancer.\(^11\),\(^12\) These studies were performed in heterogeneous populations with different tumor types and treatments. They were also performed in the ambulatory setting, which could arguably be a lower risk setting than in the inpatient

\(^1\)Department of Otolaryngology, New York Head and Neck Institute, Zucker School of Medicine at Hofstra/Northwell, New York, New York, USA

This article was presented at the 2017 AAO-HNSF Annual Meeting and OTO Experience; September 10-13, 2017; Chicago, Illinois.

Corresponding Author:
Tristan Tham, MD, Department of Otolaryngology, New York Head and Neck Institute, Hofstra Northwell School of Medicine, 130 East 77th St, Black Hall Building, New York City, NY 10075, USA.
Email: ttham@northwell.edu
postoperative setting because of the patient’s mobility status. To our knowledge, no studies have investigated the effect of the PLR in predicting VTE in HNC or in the surgical setting. In this context, we performed this exploratory pilot study with the aim of investigating the predictive association of the preoperative PLR for VTE in a high-risk cohort: patients with HNC undergoing surgical resection.

Methods

Subjects

This retrospective cohort study included patients with HNC treated at the New York Head & Neck Institute (NYHNI) from January 1, 2011, to June 30, 2017. This study was approved by the Institutional Review Board of the Northwell Health System (IRB 17-0068-LHH). This study was designed to specifically include patients who were at minimum “high risk” as determined by VTE scoring systems. Inclusion criteria were as follows: (a) histologically confirmed HNC (excluding thyroid) and (b) undergoing major surgery. These patients are classified as “high risk” for VTE regardless of other factors such as comorbidities, immobilization, and age. Exclusion criteria were the following: (a) lymphoproliferative malignancies; (b) metastatic disease or palliative procedures; (c) minor procedures lasting <1 hour, including but not limited to biopsies and tracheostomies; (d) incomplete medical records, including absence of preoperative complete blood count (CBC) differential; and (e) CBC that was taken more than 2 weeks preoperatively. Patients were screened using predefined International Classification of Diseases, Ninth and Tenth Revisions (ICD-9/10) codes (Supplemental Material, available in the online version of the article). All patients were treated according to the NYHNI postoperative protocol that included sequential compression devices and early mobilization. Postoperative VTE prophylaxis was not mandated for all patients and was administered according to the surgeon’s clinical judgment.

Variable Selection

The literature was reviewed for important VTE risk factors in HNC that could be used to build univariate and multivariate models. Established risk factors for VTE were included in the data collection process: age, sex, smoking status, body mass index (BMI), length of stay, length of surgery, prior VTE, postoperative heparin, and postoperative aspirin. We also retrospectively evaluated all patients with the Caprini Risk Assessment to compare our results with a validated risk stratification tool.

Data Collection

The electronic health care records of patients were reviewed and stored in a REDCAP database. Clinical information was retrieved from the patient’s scanned notes. Imaging reports for all patients were examined to confirm the presence of VTE/PE. Preoperative laboratory results were retrieved to obtain the CBC parameters. The PLR was calculated as platelet count (10^3/μL) divided by the lymphocyte count (10^3/μL), both taken from the same blood sample, within 2 weeks of surgery. For additional descriptive data, pathology reports were examined to determine the tumor site and histopathology, and operative reports were examined to determine if free flap reconstructive surgery was performed.

End Point

The primary end point of this study was VTE, defined as any DVT or PE. VTE was confirmed by diagnostic imaging, with either Doppler ultrasonography for DVT or with spiral CT for PE. VTEs that occurred within 30 days postoperatively were included.

Statistical Analysis

Because of the expected sparse data set, we did not impose the assumption of a Gaussian distribution and therefore used nonparametric statistical tests wherever possible. Continuous variables were compared using Wilcoxon’s rank sum test. Categorical variables were compared using the χ² test. Correlation testing was performed using Spearman’s rank correlation. Bonferroni correction was applied to α level to compensate for multiplicity (P = .0036). For all other analyses, a P < .05 was considered significant. To further investigate the PLR, we also constructed a boxplot to visualize the differences in both groups. Cutoff limits for the outliers in the boxplot were set at >1.5 interquartile range (IQR) because it corresponds to approximately ±2.7σ, ensuring good coverage of normally distributed data. The cutoff between a “high” or “low” PLR has not yet been unified in the literature. Therefore, we used a simple linear discriminant analysis (LDA) classifier between PLR and VTE to generate a receiver operator characteristic (ROC) curve. This ROC curve was used to obtain an optimal cutoff point for the PLR to maximize sensitivity and specificity. A dichotomized PLR variable based on this cutoff was used to separate patients and compared with a χ² test. The multiple logistic regression model was performed using the ROC cutoff and other significant variables discovered in univariate analysis. In the inference stage, we used Firth’s penalized method for deriving the maximum likelihood estimators to avoid serious bias due to the sparse events data. Firth’s method uses the Jeffreys’ prior and is used in many related applications.

We also used the “bootstrap method” to obtain a credible confidence intervals (CIs), which is indicated for uncertain parameter distribution in small samples. Regression coefficients (β) and their 95% CIs are presented. All statistical analyses were conducted using the R software, v3.3.3 (R Development Team, Vienna, Austria).

Results

Descriptive Characteristics

A total of 306 patients were included in this study between January 2011 and June 2017. There were 7 cases of VTE (6
DVTs, 1 PE) and 299 patients without VTE. This incidence rate of ~2.3% is in agreement with previous reports.6,25,26 All of the VTEs occurred in the inpatient setting. The average age was 61.8 ± 14.4 years, and most were male (66.8%). The most common histological type was squamous cell carcinoma (66.7%). The subsites were the lip and oral cavity (23.5%), tonsil/oropharynx (14.0%), larynx (14.3%), salivary gland (13.7%), nasal cavity and paranasal sinuses (9.1%), cervical lymph node and unknown primary (9.8%), skull base (7.2%), nasopharynx (2.0%), hypopharynx (0.7%), cutaneous head and neck (4.6%), and other sites (1.3%). The mean platelet count, white blood cell (WBC) count, lymphocyte count, and PLR were 232.46 ± 71.71 × 10^3/μL, 7.02 ± 2.23 × 10^3/μL, 1.68 ± 0.73 × 10^3/μL, and 160.90 ± 83.33 × 10^3/μL, respectively. Four patients had a history of VTE, but none developed postoperative VTE, and thus the “prior VTE” variable was discarded from further analysis. Baseline clinical characteristics and laboratory parameters between the 2 groups are presented in Table 1.

Patients with free flap reconstruction may be at added risk of VTE because of prolonged immobilization, prolonged length of stay, and typically longer operative times. Of 307 patients, 34 patients had free flap microvascular reconstruction in our cohort. Of 34 patients, 2 had VTEs. Therefore, 2 of the 7 patients with VTE had free flap reconstruction. There was no association between free flap reconstruction and VTE (P = .1356). Since our study was not designed to look at free flap patients specifically, our study is perhaps underpowered to detect the association between free flap reconstruction and VTE.

A Caprini risk assessment was also retrospectively performed for all patients. The mean scores were 6.89 ± 1.50 for the entire cohort, 6.86 ± 1.45 for controls, and 8.00 ± 3.00 for patients with VTE. There was no difference in the Caprini scores between both groups (P = .3608; Figure 1). There was also no significant correlation between the Caprini scores and PLR (P = .6428; Figure 2).

### Table 1. Patient Characteristics and Exploratory Univariate Analysis.a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>204</td>
<td>4</td>
<td>200</td>
<td>1.51 (0.22-9.13)</td>
<td>.6897</td>
</tr>
<tr>
<td>Female</td>
<td>102</td>
<td>3</td>
<td>99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>180</td>
<td>2</td>
<td>138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quit or active</td>
<td>126</td>
<td>5</td>
<td>161</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative heparin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>130</td>
<td>2</td>
<td>128</td>
<td>1.87 (0.30-19.91)</td>
<td>.7029</td>
</tr>
<tr>
<td>Yes</td>
<td>176</td>
<td>5</td>
<td>171</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>261</td>
<td>5</td>
<td>256</td>
<td></td>
<td>.2746</td>
</tr>
<tr>
<td>Yes</td>
<td>45</td>
<td>2</td>
<td>43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>61.82 ± 14.44</td>
<td>67.71 ± 8.28</td>
<td>61.69 ± 14.53</td>
<td></td>
<td>.2537</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>7.87 ± 8.95</td>
<td>14.57 ± 5.41</td>
<td>7.71 ± 8.96</td>
<td></td>
<td>.0026b</td>
</tr>
<tr>
<td>Platelet count, 10^3/μL</td>
<td>232.46 ± 71.71</td>
<td>265.43 ± 108.34</td>
<td>231.69 ± 70.72</td>
<td></td>
<td>.4252</td>
</tr>
<tr>
<td>WBC, 10^3/μL</td>
<td>7.02 ± 2.23</td>
<td>8.60 ± 2.47</td>
<td>6.98 ± 2.21</td>
<td></td>
<td>.0659</td>
</tr>
<tr>
<td>Lymphocyte count, 10^3/μL</td>
<td>1.68 ± 0.73</td>
<td>0.90 ± 0.51</td>
<td>1.70 ± 0.72</td>
<td></td>
<td>.0041</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.39 ± 5.62</td>
<td>27.41 ± 9.02</td>
<td>26.37 ± 5.54</td>
<td></td>
<td>.7689</td>
</tr>
<tr>
<td>Surgery length, min</td>
<td>352.95 ± 213.24</td>
<td>585.00 ± 131.83</td>
<td>347.52 ± 211.88</td>
<td></td>
<td>.0029b</td>
</tr>
<tr>
<td>Caprini score</td>
<td>6.89 ± 1.50</td>
<td>8.00 ± 3.00</td>
<td>6.86 ± 1.45</td>
<td></td>
<td>.3608</td>
</tr>
<tr>
<td>PLR (continuous)</td>
<td>160.90 ± 83.33</td>
<td>340.73 ± 130.11</td>
<td>156.69 ± 77.39</td>
<td></td>
<td>.0002b</td>
</tr>
<tr>
<td>PLR &gt;320 (ROC)</td>
<td>95.95 (13.20-1134.48)</td>
<td>294</td>
<td>292</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operator characteristic; WBC, white blood cell count.

aValues are presented as numbers or mean ± SD.
bAfter Bonferroni correction, P values <.0036 are considered significant.

Univariate and Multivariate Analysis

The variables length of stay (P = .0026), surgery length (P = .0029), and PLR (P = .0002) were found to be significant in the univariate analysis (Table 1). To further investigate the PLR, we constructed a boxplot to visualize the difference between cases and controls (Figure 3). On visual inspection of the boxplot, there was a difference between these 2 distributions, as suggested by previous literature.11,12 To obtain the PLR cutoff, an ROC curve was generated for VTE detection using the PLR (Figure 4). Using the bootstrap method,
the area under the curve (AUC) of the ROC model was approximately 0.91 (95% CI, 0.82-0.98), which is an indication of excellent discriminatory ability. We then used the ROC curve to obtain the optimum cutoff point of 320, which had a sensitivity of 97.66% and specificity of 71.43%. Once the PLR was dichotomized to this cutoff level, a $\chi^2$ test was performed, which showed significance ($P < .0001$; Table 1). Multiple logistic regression with 1000 bootstrap iterations was performed for the significant variables discovered in the univariate analysis: PLR (ROC cutoff), length of surgery, and length of stay. In the multivariate model, surgery length ($P = .0056$) and PLR ($P < .0001$) were found to be significant independent predictors of VTE (Table 2). Of note, the regression coefficient ($\beta$) for PLR (95% CI, 5.3256-5.3868) was shown to be much larger than length of surgery (95% CI, 0.0001-0.0006).

### Discussion

In this study, we retrospectively analyzed the clinical and laboratory data in patients with HNC undergoing major surgery, comparing patients with and without VTE. These results demonstrated that PLR was significantly higher in patients with VTE.

A PLR value of >320 was found to have an independent and strong association with the occurrence of VTE ($\beta$ 95% CI, 5.3256-5.3868; $P < .0001$). In addition to PLR, length of surgery was also found to have an independent association with VTE ($\beta$ 95% CI, 0.0001-0.0006; $P = .0056$). The results of our analysis are consistent with published reports in other cancers in the ambulatory setting by Yang and Liu and Ferroni et al. These authors showed that pre-treatment PLR was associated with VTE in the ambulatory chemotherapy setting. In this article, we have shown that this association is present in our cohort of patients with HNC undergoing major surgery.

In our study, the Caprini risk assessment was performed retrospectively for all patients. The Caprini risk assessment tool scores various VTE risk factors from 1 to 5 points. Scores from individual risk factors are added to give a total score. Using this total score, the VTE risk is stratified into low, moderate, high, and highest risk. There are several important considerations to take into account when considering the Caprini score. For every increment in the Caprini score, there are different VTE rates among different surgical subspecialties. A recent study by Cramer et al. found that across different surgical subspecialties, there were different VTE rates for each respective Caprini score. In addition, different Caprini score thresholds are used in different settings to guide thromboprophylaxis. A caveat to using the Caprini score as a prophylactic guide is that surgeons must also weigh the intrinsic risks and benefits associated with anticoagulation that are specific to their patient population. The mean score for our cohort was 6.89, which is
classified as the “highest” risk in the Caprini system. In our cohort, we found that Caprini scores were not significantly different between the control and VTE groups. Similar findings had previously been reported by others.6,8 It might be possible that our study was not sufficiently powered to detect differences in Caprini scores between the 2 groups, as larger studies had shown different VTE rates across increasing Caprini scores.28

Although the results of our analysis are positive, the exact underlying mechanisms behind the observed association of PLR and thrombosis are speculative.9-12 In the past few years, there has been increasing interest in the tumor microenvironment and its effect on systematic inflammation.30 This has led to the study of other biomarkers in addition to PLR, such as the neutrophil-to-lymphocyte ratio (NLR)31,32 and the lymphocyte-to-monocyte ratio (LMR).33 The “seed and soil” hypothesis postulates that the tumor extracellular matrix interacts with and is in turn affected by the inflammatory cells and mediators.34,35 Others had previously demonstrated that there is altered lymphocyte homeostasis in squamous cell carcinoma (SCC) of the head and neck, resulting in reductions in all T-cell subsets.36 Since malignancies have been known to be associated with thrombotic events,37,38 the lymphocyte count might thus be acting as a nonspecific surrogate for magnitude of the tumor’s systemic interaction and, by extension, its thrombotic potential.11,12

On the other hand, the link between platelets and cancer-associated thrombosis has been well documented.39,41 By combining the platelet and lymphocytes counts into the PLR, a crude “summary effect” between the tumor-induced prothrombotic (platelet) and inflammatory states (lymphocyte) is encapsulated. The superiority of the PLR over platelet count or WBC count alone was demonstrated in our study, in agreement with other authors.11,12 Ferroni and colleagues11 speculated that increased levels of platelets in itself could be related to underlying inflammation. In this context, our results were also in agreement, showing a small but highly significant relationship between the platelet count and lymphocyte count ($R^2 = 0.05$, $P < .0001$), as well as platelet count and WBC ($R^2 = 0.08$, $P < .0001$).

In our study, ROC curve analysis showed that the optimal PLR cutoff value was 320. However, other published studies investigating this effect had used different cutoffs.11,12 In the study by Yang and Liu,12 they had used the cutoffs previously published by Ferroni et al.11 In the article by Ferroni et al,11 ROC curves were used to generate a cohort-specific cutoff value of 260. It is plausible that a different population-specific PLR cutoff exists for each patient population. But if a unified PLR cutoff exists, it should be discovered using a much larger data set.

Consistent with other studies, our results also showed that length of surgery was also an independent predictor of VTE.42 The association of length of surgery, although highly significant, was not shown to be as strong as PLR, demonstrated by the marginal $\beta$ coefficient. Our results did not show postoperative heparin or aspirin to be associated with VTE. This could be due to the high amounts of
patients already receiving postoperative VTE chemoprophylaxis in this high-risk cohort, which would therefore require a much larger sample size to detect a significant difference.

There are limitations to our study that we acknowledge. First, our study was a retrospective cohort study and therefore was subject to retrospective bias. Since only patients with suspected VTEs had diagnostic ultrasounds, it is possible that there are patients in our cohort with undiagnosed VTEs. The prospective study by Clayburgh et al8 suggested that VTEs are being underdiagnosed in patients with HNC undergoing surgery. Similarly, since patients do not get ultrasound screenings on admission, some of the patients in the cohort might have developed their VTEs prior to admission. Second, our study had a small sample size with a small number of VTEs. This problem of small sample sizes is a similar problem faced by other authors investigating VTEs in HNC, with Thai et al6 and Clayburgh et al8 reporting 2 and 8 VTEs, respectively. Unlike other published studies of VTE in the HNC literature, we compensated for our small data set with statistical techniques using bootstrap22 and statistical penalization.19 Another limitation to our study is that it is very likely that many thrombotic risk factors may not be represented by the PLR value, such as venous stasis and thrombophilia. The relationship of additional thrombotic factors to the PLR value, as well as how the PLR value would fit into a screening or diagnostic framework, is outside the scope of this exploratory pilot study. We did not collect data on LMR or NLR because of the lack of published data supporting their association with thrombotic risk, as well as a lack of theoretical evidence behind that association. Last, the association between PLR and various clinicopathologic features (stage, grade) is a phenomenon reported by other authors.43 We did not explore the detailed clinicopathologic relationship in tumors and PLR values because that was outside the scope of this study.

The results reported here have shown that PLR has a significant and strong association with VTE. Current guidelines by the American Society of Clinical Oncology,15 already recommend VTE chemoprophylaxis for patients with malignant disease undergoing surgery. Clayburgh et al8 prospectively performed ultrasound scans for all postoperative patients and found that the incidence of VTE was much higher than reported in previous retrospective studies. Drawing from this result, they hypothesized that a significant proportion of asymptomatic or mildly symptomatic VTEs go undetected in patients with HNC.

It is possible that the future utility of the PLR may be to stratify within high-risk patients with HNC—to decrease the clinical threshold in which to perform diagnostic VTE tests in patients with elevated PLR. If PLR is validated to be a useful diagnostic adjunct, it would be able to supplement existing VTE screening tools such as D-dimer levels, possibly reducing the length of time needed to diagnose and subsequently treat patients who develop VTEs.

Conclusion
This exploratory pilot study has shown that PLR offers a potentially accurate risk stratification measure as an adjunct to current tools, without additional cost to health systems. Future large prospective studies are needed to fully delineate the characteristics of the relationship between the PLR and thrombotic risk.

Acknowledgments
We thank Yonatan Bardash (Hofstra-Northwell School of Medicine, New York) for assistance in building our REDCAP database. We also thank Julian Khaymovich for help with data collection and our statistical consultants, Lydia Hsu, PhD (Columbia University, Department of Statistics, New York), and Guillaume Stoffels, MS (Feinstein Institute of Medical Research, Department of Biostatistics, New York), for their assistance with the statistical analyses.

Author Contributions
Tristan Tham, conception, design of study, data collection, drafting manuscript; Lauren Rahman, design of study and data collection, drafting manuscript; Christina Persaud, design of study and data collection, drafting manuscript; Caitlin Olson, data collection and design of study, drafting manuscript; Peter Costantino, conception, design of study, data collection, drafting manuscript.

Disclosures
Competing interests: None.
Sponsorships: None.
Funding source: None.

Supplemental Material
Additional supporting information is available in the online version of the article.

References
7. Schunemann HJ, Cook D, Guyatt G. Methodology for antithrombotic and thrombolytic therapy guideline development: American College of Chest Physicians Evidence-based Clinical Practice Guidelines. Chest 2008;133(6(suppl)):113S-122S.