Platelet to white blood cell ratio predicts 30-day postoperative infectious complications in patients undergoing radical nephrectomy for renal malignancy

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Abstract

Introduction: We sought to examine the relationship between preoperative platelet to white blood cell ratio (PLT/WBC), a hematologic marker of the systemic inflammatory response, and postoperative infectious complications following radical nephrectomy for localized renal cell carcinoma.

Methods: We performed a retrospective cohort study of patients treated with radical nephrectomy for localized kidney cancer between January 1, 2005 and December 31, 2014 (n=6235) using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database. Univariate and multivariate analyses were used to assess the association between PLT/WBC ratio and 30-day infectious complications, including surgical site infection, urinary tract infection, pneumonia, and sepsis. Secondarily, we examined major complications and bleeding requiring transfusion.

Results: A lower PLT/WBC ratio was associated with an increased risk of sepsis, pneumonia, and UTI rates ($p<0.05$ for all). Furthermore, there was a significant trend of decreasing rates of sepsis and pneumonia with increasing PLT/WBC ratio, across quintiles ($p<0.05$ for all). On multivariate analysis, patients with the lowest PLT/WBC ratios (quintile 1) had a two-fold risk of having a postoperative infectious complication compared to patients in the highest quintile (odds ratio [OR] 2.01; 95% confidence interval [CI] 1.42–2.86; $p<0.0001$). Patients in quintile 5 had a higher risk of requiring blood transfusion than those in quintiles 2–4 ($p<0.05$ for all).

Conclusions: The PLT/WBC ratio represents a widely available and novel index to predict risk of infectious and bleeding complications in patients undergoing radical nephrectomy. External validation is required and the biological underpinning of this phenomenon requires further study.

Introduction

Renal cell carcinoma is the ninth most common cancer in the United States and its incidence has been increasing in developed countries.[1 2] The vast majority of patients present with localized disease.[1 2] Surgical extirpation, by radical or partial nephrectomy, remains the standard of care for these patients.[3] Post-operative complications and re-admission rates following radical nephrectomy have been reported to be as high as 30%.[4 5] We previously identified bleeding (requiring transfusion) and infectious complications to be the most common post-operative complications.[6] While patient comorbidities are known to predict post-operative complications,[7 8] the risk is difficult to quantify depending on number and type. A simple test that could quickly assess perioperative risk in the clinic would be useful in counseling patients.

The systemic inflammatory response may be involved in kidney cancer progression and kidney tumor cell biology, and may have utility as a prognostic biomarker.[9 10] These scoring systems are calculated using hematologic tests which are routinely collected pre-operatively.[1] While their usefulness in predicting prognosis in localized renal cell carcinoma has recently been demonstrated,[11] the small number and heterogeneity of studies as well as the lack of large multi-institutional data, limits wider adoption.[1] The platelet to white blood cell count (PLT/WBC) has demonstrated prognostic ability for mortality and long-term outcomes following myocardial infarction,[12 13] but its association with perioperative outcomes has not been fully assessed.[14] The PLT/WBC ratio would be an ideal marker for perioperative outcomes as it is easily calculated and routinely collected prior to major surgery.

We hypothesized that there may be a relationship between the systemic inflammatory response and post-operative infections. We sought to evaluate the association between preoperative PLT/WBC ratio and post-operative infectious complications among patients undergoing radical nephrectomy for localized kidney cancer. Secondarily, we examined the relationship between the preoperative PLT/WBC ratio and post-operative bleeding complications. In order to do so, we utilized the National Surgical Quality Improvement Program (NSQIP), a multi-institutional registry developed by the American College of Surgeons (ACS).[15] Studies have found NSQIP to more accurately identify 30-day post-operative patient outcomes compared to single center or administrative data sources.[16-18]

Methods

Study design and population

We performed a retrospective cohort study of patients aged 18 years and older who underwent a radical nephrectomy for kidney cancer between January 1, 2005 and December 31, 2014 using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database. NSQIP employs surgical clinical reviewers who collect validated preoperative and perioperative data until 30 days after surgery on patients at participating hospitals.[15] Its registry includes over 700 hospitals and is focused on reporting and improving perioperative outcomes.[19]

We identified patients undergoing radical nephrectomy using Common Procedural Terminology (CPT) codes (CPT 50220, 50225, 50230, 50545 and 50546) who had complete data for pre-operative platelet and white blood cell count. We subsequently restricted our cohort to

patients with a post-operative diagnosis of kidney cancer (ICD-9 codes 189 or 189.0). Patients with a cancer diagnosis were chosen as previous studies have linked the systemic inflammatory response to cancer prognosis.[9 20] Patients younger than 18 years (n=2) and those missing data on weight (n=47), height (n=99), length of stay (n=3) or American Society of Anesthesiology (ASA) class (n=16) were excluded.[6] Finally, patients with disseminated cancer (n=588), missing hematocrit (n=4) or gender (n=3) were excluded from our final analysis.

Exposure and covariates

Our exposure of interest was pre-operative platelet (PLT, 10^3/microliter) to white blood cell (WBC, number of WBC/microliter) ratio (PLT/WBC), categorized as quintiles. We abstracted data on *a priori* selected covariates based on a literature review to identify pre-operative patient factors that may affect post-operative outcomes and may thus confound the relationship between PLT/WBC ratio and perioperative complications. These covariates included age, gender, race, American Society of Anesthesiologists (ASA) score, body mass index (BMI kg/m^2), smoking status (active smoker within one year of surgery), history of cardiac disease, history of diabetes (requiring oral medication or insulin therapy), history of neurologic disease, history of chronic obstructive pulmonary disease (COPD), requirement for hemodialysis, functional status (dependent, partially dependent, independent and unknown), chronic steroid use, surgical technique (laparoscopic vs. open) and preoperative anemia (hematocrit <39%).

Outcome

Our primary outcome was infectious complications (surgical site infections, pneumonia, urinary tract infection or sepsis) within 30 days after surgery. Secondary outcomes included bleeding requiring transfusion and major complications within 30 days. Major complications included mortality, reoperation, neurological event (stroke or coma) and/or cardiac event (myocardial infarction or cardiac arrest). These outcome were chosen as they are major contributors to patient mortality, morbidity and increased healthcare costs.[21]

Statistical analysis

Baseline demographic variables were assessed using frequencies and proportions for categorical variables, means and standard deviations for normally-distributed continuous variables, and medians and interquartile ranges for non-normal continuous variables. We compared differences between PLT/WBC ratio quintiles using the Pearson chi-squared test for categorical variables and one-way analysis of variances (ANOVA) for continuous variables. For variables with ordinal structure, we assessed trends across the quintiles using the Cochran-Armitage test for trend.

We compared the proportion of cases resulting in a complication between each of our quintiles. We assessed for differences between the quintiles using the Pearson chi-squared test and examined trends across quintiles using the Cochran-Armitage test. Multivariable logistic regression modeling was used to assess the association between PLT/WBC ratio and each outcome while adjusting for age, gender, race, BMI category, ASA class, history of cardiac disease, diabetes, COPD, neurologic disease, on dialysis, chronic use of steroids, functional status, anemia and smoking status.

Statistical significance was set at p-value equal to 0.05. All tests were two tailed and all statistical analyses were performed using SPSS v24 (IBM Corp., Armonk, NY, USA).

Results

We identified 6,235 eligible patients who underwent radical nephrectomy for localized kidney cancer during the study period. We found that both lower pre-operative WBC as well as higher pre-operative PLT counts were responsible for the observed variation in PLT/WBC ratio (Table 1). Patients in the lowest quintile were older, more likely to be male, have medical comorbidities, to have undergone laparoscopic surgery and be of non-African descent than patients in higher quintiles (Table 1).

An increasing PLT/WBC ratio was associated with a decreasing risk of 30-day post-operative infectious complications ($p<0.0001$, Table 2). Univariate analysis examining each site of infection demonstrated a significant difference between quintiles for sepsis, pneumonia and urinary tract infections with significant trend for decreasing complication rate with increasing PLT/WBC quintile for both sepsis and pneumonia (Table 2). While there appeared to be a decreasing trend for UTIs with increasing PLT/WBC quintiles, this was not significant ($p=0.14$). There was no significant difference in surgical site infection rates between quintiles ($p=0.38$). After multivariable regression, patients with low PLT/WBC ratio (Quintiles 1 and 2) had a significantly higher risk of infectious complication compared to patients in Quintile 5 (Table 3).

Among our secondary outcomes, there was a significant difference in transfusion rates, but not major complication rates between PLT/WBC quintiles (Table 2). Further, there was a significant trend for higher transfusion rates among patients in higher quintiles (Cochran Armitage test for trend, $p=0.0009$). On multivariable analysis, patients in Quintiles 2, 3 and 4 had significantly lower odds of requiring transfusion compared to Quintile 5 (Table 3). There was no significant difference in major complication rates between quintiles on either univariate or multivariable analyses (Tables 2 and 3).

Discussion

Using a large, prospectively-collected and validated multi-institutional registry, we identified platelet to white blood cell (PLT/WBC) ratio as a novel, independent predictor of infectious and bleeding complications following radical nephrectomy for kidney cancer. While PLT/WBC ratio was strongly related to baseline patient characteristics including age and comorbidity, a lower PLT/WBC ratio (Quintile 1) was independently associated with a 2-fold higher risk of infectious complications compared to patients in the highest PLT/WBC quintile (Quintile 5) after adjusting for these characteristics. Further, a higher PLT/WBC ratio was independently associated with higher risk of requiring blood transfusion compared to lower PLT/WBC ratios (Quintiles 2, 3 and 4). The major complication rate for the whole cohort was low, consistent with rates reported in the literature,[22] and not associated with the PLT/WBC ratio.

To the best of our knowledge, this is the first study to identify PLT/WBC ratio as a predictor of post-operative complications in surgical patients with localized cancer. Previous studies have used other hematologic markers as surrogates to the inflammatory response to predict prognosis in patients with metastatic and localized disease.[1 11 23] However, the use of such markers to predict short-term outcomes has not been previously studied. Furthermore, these

calculations usually require neutrophil and lymphocytes counts, data that is not uniformly collected in registry databases.

It is notable that PLT/WBC ratio was significantly associated with sepsis, pneumonia and urinary tract infection but not wound infections. Wound infections are much more likely to be influenced by technical considerations including skin preparation, shaving and wound closure,[24] in addition to patient factors, as compared to other sites of infection. Further, because radical nephrectomy incisions are considered clean, SSI are rare.[25]

The mechanistic relationship between PLT/WBC ratio and infection remains to be elucidated. One possibility is that the PLT/WBC ratio is a surrogate for a patient's baseline health status. Patients with low ratios were more likely to have more comorbidities (diabetes, COPD, dialysis dependence, use of chronic steroids) and to be current smokers, which are all known to alter the inflammatory response and are risk factors for post-operative infections.[26 27] Furthermore, other studies have found poor health status (high BMI, >5% weight loss, low albumin, lymphocyte count) of patients to result in worse post-operative outcomes in patients undergoing nephrectomy for renal cell carcinoma. [28 29] Notably, PLT/WBC ratio remained an important predictor of infectious complications after adjusting for these factors. Further, this ratio is likely also an indicator of metabolic syndrome, a constellation of physiologic and biochemical abnormalities, resulting in inappropriate activation of inflammatory pathways.[30] Metabolic syndrome is a well-known risk factor for post-operative complications, including infection.[27 31 32]

In addition to the association with infectious complications, PLT/WBC ratio was significantly associated with rates of bleeding requiring transfusion. Patients in the lowest quintile were overall in poorer general health compared to patients in higher quintiles and were more likely to have undergone laparoscopic surgery compared to patients in Quintile 5. These higher transfusion rates may be explained by the fact that a greater proportion of patients underwent open surgery in Quintile 5. Many studies have found higher transfusion rates with open compared to laparoscopic nephrectomy[33 34]. Indeed, in our model, open surgical technique was a strong predictor of increased transfusion risk (data not shown). Furthermore, it is unknown if patients undergoing open surgery had increased tumour complexity (data is not captured), which could increase risk of transfusion. Another explanation is that there are a higher proportion of female patients in Quintile 5 (49.7%) compared to Quintile 1 (27.3%). Biologically, females have lower hemoglobin levels compared to males.[35] As these patients were treated at many different hospitals, it is unknown what parameters were used for initiating transfusion and how these may have differed between institutions.

We excluded patients with disseminated cancer at time of surgery, as studies have found these patients to be at increased risk of complications compared to patients with localized disease.[6 36] Further, we excluded patients for whom the post-operative diagnosis was not explicitly recorded as kidney cancer. Thus, these results may not directly be extrapolated to patients with metastatic disease nor those undergoing nephrectomy for benign indications.

Despite the strengths of the NSQIP database, there are limitations to this analysis. As we used retrospective data, there are likely other confounders that were not included in our model that could be affecting complication rates. In addition, as NSQIP only captures complications within the first 30-days post-operation, the results may not apply to complications that occur

beyond this period. NSQUIP does not collect information on tumour staging and renal nephrometry scores. As a result, we cannot comment on stage migration over time. However, epidemiological data suggest that due to imaging studies being performed for other indications, RCC is commonly found incidentally.[37] This has led to a stage migration overall towards lower stage of disease at time of diagnosis.[38]

In order to provide clinically-meaningful interpretations of PLT/WBC ratio, we used quintiles. However, future research may identify more informative ways to operationalize this variable such as a dichotomous threshold. Currently, no such cutoff has been identified. As this study only examined PLT/WBC ratio in patients with RCC, its results may not be applicable to patients undergoing other procedures. Finally, we cannot assess whether neutrophil to lymphocyte ratio would perform similarly to PLT/WBC ratio.

It was our hypothesis that the PLT/WBC, a measure of the systemic inflammatory response, would reflect the overall health status of the patient, taking into account their medical comorbidities, cancer status and lifestyle. We found that the PLT/WBC ratio was associated with post-operative infections both in univariate analysis and independently in multivariable analyses accounting for these factors. Thus, this simple ratio may prove useful for busy clinicians, as it is easier to interpret this result than to integrate the risks of each predictive factor.

Conclusion

Our study is the first to examine usefulness of the PLT/WBC ratio in predicting short-term 30-day post-operative outcomes in patients undergoing surgery for renal malignancy. Patients who had low PLT/WBC ratios had significantly higher odds of infectious complications compared to patients with high PLT/WBC ratios. Further studies need to be performed to verify these findings in other populations.

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Tables

Table 1. Demographic characteristics of patients treated with radical nephrectomy for localized kidney cancer, according to quintiles of platelet to white blood cell count (PLT/WBC) ratio

	PLT/WBC ratio quintiles						
Variable	**Quintile 1 <24.42**	**Quintile 2 24.43 - 30.22**	**Quintile 3 30.23 - 36.20**	**Quintile 4 36.21- 44.55**	**Quintile 5 >44.55**	**p value**	**p value (trend)***
N	1265	1272	1257	1245	1196		
Age (Median, IQR)	64 (56-73)	64(55-72)	65 (55-72)	63 (54-71)	62 (54-71)	<0.0001[S]	n/a
WBC (Mean, SD)	9.96 (4.0)	8.1 (2.0)	7.4 (1.9)	6.9 (1.8)	6.2 (1.9)	<0.0001[S]	n/a
PLT count (Mean, SD)	187.4 (60.4)	221.2 (55.7)	244.8 (63.2)	274.2 (72.6)	341.6 (119.0)	<0.0001[S]	
Gender						<0.0001	<0.001
Male	920 (72.7%)	873 (68.6%)	811 (64.6%)	710 (57.1%)	602 (50.3%)		
Female	345 (27.3%)	399 (31.4%)	445 (35.4%)	533 (42.9%)	594 (49.7%)		
Preoperative Diabetes						<0.0001	<0.0001
Yes	339 (26.8%)	281 (22.1%)	268 (21.3%)	239 (19.2%)	203 (17.0%)		
Smoker within 1 year						<0.0001	<0.0001
Yes	313 (24.7%)	274 (21.5%)	237 (18.9%)	184 (14.7%)	182 (15.2%)		
Preoperative COPD						<0.0001	<0.0001
Yes	115 (9.1%)	86 (6.8%)	66 (5.3%)	46 (3.7%)	46 (3.8%)		
Preoperative MI, CHF or angina						0.002	<0.0001

Yes	68 (5.4%)	63 (5.0%)	54 (4.3%)	43 (3.5%)	30 (2.5%)		
ASA Classification						<0.0001	n/a
1	12 (1.1%)	10 (0.8%)	24 (1.9%)	24 (1.9%)	26 (2.2%)		
2	307 (24.3%)	409 (32.2%)	445 (35.4%)	460 (36.9%)	455 (38.0%)		
3	787 (62.2%)	737 (57.9%)	695 (55.3%)	692 (55.6%)	653 (54.6%)		
4	157 (12.4%)	116 (9.1%)	93 (7.4%)	69 (5.5%)	62 (5.2%)		
Preoperative Stroke or Neurological History						0.271	0.473
Yes	24 (1.9%)	23 (1.6%)	27 (2.1%)	29 (2.3%)	14 (1.2%)		
Preoperative BMI						<0.0001	n/a
<18.5	14 (1.1%)	7 (0.6%)	9 (0.7%)	13 (1.0%)	25 (2.1%)		
18.5-24.9	181 (14.3%)	191 (15.0%)	213 (16.9%)	262 (21.0%)	326 (27.3%)		
25-29.9	399 (31.5%)	419 (32.9%)	452 (36.0%)	429 (34.5%)	416 (34.8%)		
30+	671 (53.0%)	655 (51.5%)	583 (46.4%)	541 (43.5%)	429 (35.9%)		
Functional Status						0.073	n/a
Independent	1217 (96.2%)	1245 (97.9%)	1220 (97.1%)	1218 (97.8%)	1170 (97.8%)		
Partially dependent	40 (3.2%)	21 (1.7%)	29 (2.3%)	21 (1.7%)	19 (1.6%)		
Totally Dependent	2 (0.2%)	0	0	3 (0.2%)	3 (0.3%)		
Not reported	6 (0.5%)	6 (0.5%)	8 (0.6%)	3 (0.2%)	4 (0.3%)		
Race						<0.0001	n/a
African	76 (6.0%)	98 (7.7%)	98 (7.8%)	122 (9.8%)	149 (12.5%)		
Caucasian	1046	1017	1032	972	859		

	(82.7%)	(80.0%)	(82.1%)	(78.1%)	(71.8%)		
Other	143 (11.3%)	157 (12.3%)	127 (10.1%)	151 (12.1%)	188 (15.7%)		
Dialysis dependent						<0.0001	<0.0001
Yes	78 (6.2%)	61 (4.8%)	55 (4.4%)	45 (3.6%)	36 (3.0%)		
Chronic Steroid use						<0.0001	<0.0001
Yes	81 (6.4%)	53 (4.2%)	43 (3.4%)	41 (3.3%)	38 (3.2%)		
Anemia						<0.0001	<0.001
Yes	486 (38.4%)	430 (33.8%)	486 (38.7%)	596 (47.9%)	736 (61.6%)		

[S]statistical test performed using analysis of variance (ANOVA) with Dunnett's C post-hoc testing; *Cochrane Armitage test for trend

Table 2. Univariate analysis of 30-day post-operative complications in patients undergoing radical nephrectomy for localized kidney cancer (n= 6235)

	PLT/WBC ratio quintiles						
	Quintile 1	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	**Pearson chi-square p value**	**Cochrane Armitage test for trend**
Infectious complications						<0.0001	<0.0001
No	1155 (91.3%)	1186 (93.2%)	1196 (95.1%)	1195 (96.0%)	1138 (95.2%)		
Yes	110 (8.7%)	86 (6.8%)	61 (4.9%)	50 (4.0%)	58 (4.8%)		
Sepsis						<0.0001	<0.0001
No	1210 (95.7%)	1248 (98.1%)	1238 (98.5%)	1225 (98.4%)	1180 (98.7%)		
Yes	55 (4.3%)	24 (1.9%)	19 (1.5%)	20 (1.6%)	16 (1.3%)		
Surgical Site Infections						0.383	Not performed
No	1237 (97.6%)	1241 (98.2%)	1234 (98.4%)	1225 (98.4%)	1178 (98.5%)		

Yes	28 (2.2%)	31 (2.4%)	23 (1.8%)	20 (1.6%)	18 (1.5%)		
Pneumonia							
No	1239 (97.9%)	1247 (98.0%)	1240 (98.6%)	1236 (99.3%)	1182 (98.8%)	0.028	0.005
Yes	26 (2.1%)	25 (2.0%)	17 (1.4%)	9 (0.7%)	14 (1.2%)		
Urinary Tract Infection							
No	1239 (97.9%)	1251 (98.3%)	1243 (98.9%)	1236 (99.3%)	1175 (98.2%)	0.042	0.144
Yes	26 (2.1%)	21 (1.7%)	14 (1.1%)	9 (0.7%)	21 (1.8%)		
Major complications						0.655	Not performed
No	1215 (96.0%)	1231 (96.8%)	1219 (97.0%)	1206 (96.9%)	1160 (97.0%)		
Yes	50 (4.0%)	41 (3.2%)	38 (3.0%)	39 (3.1%)	36 (3.0%)		
Bleeding requiring transfusion						<0.0001	0.0009
No	1078 (85.2%)	1133 (89.1%)	1109 (88.2%)	1095 (88.0%)	962 (80.4%)		
Yes	187 (14.8%)	139 (10.9%)	148 (11.8%)	150 (12.0%)	234 (19.6%)		

Table 3. Multivariate analysis assessing the association between PLT/WBC ratio and major, bleeding and infectious complications 30-days post-operation in patients who underwent radical nephrectomy for kidney cancer (n=6235)				
Variable	**Odds Ratio***	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Infectious Complications				
Quintile 1	1.88	1.33	2.66	<0.0001
Quintile 2	1.58	1.10	2.25	0.013
Quintile 3	1.11	0.76	1.62	0.60
Quintile 4	0.87	0.59	1.29	0.48
Quintile 5	REFERENCE			
Major Complications				
Quintile 1	1.04	0.66	1.65	0.87
Quintile 2	0.94	0.58	1.50	0.78
Quintile 3	0.89	0.55	1.43	0.63
Quintile 4	0.98	0.61	1.56	0.91
Quintile 5	REFERENCE			
Bleeding Requiring Transfusion				
Quintile 1	0.83	0.66	1.05	0.114
Quintile 2	0.65	0.51	0.83	0.001
Quintile 3	0.67	0.53	0.85	0.001
Quintile 4	0.62	0.49	0.79	<0.0001
Quintile 5	REFERENCE			

*Adjusted for the effect of age, diabetes history, smoking history, COPD history, cardiac history, ASA classification, neurological history, body mass index (BMI), gender, mobility, race, undergoing dialysis, chronic steroid use and anemia history.