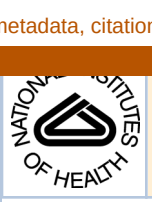

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Postoperative hyperphosphatemia significantly associates with adverse survival in colorectal cancer patients

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Abstract

Background—Hyperphosphatemia has been implicated in the development and treatment of various cancers. However, whether it can be used as a direct prognostic marker of colorectal cancer (CRC) has remained unexplored. Given new insights into the importance of hyperphosphatemia in CRC, we sought to evaluate the association of hyperphosphatemia with the clinical outcomes of this disease.

Methods—In a retrospective analysis of a well-characterized clinic-based cohort with 1,241 CRC patients, we assessed the association of postoperative hyperphosphatemia with patient overall survival.

Results—Postoperative hyperphosphatemia measured within the first month after surgery was significantly associated with CRC survival. Compared to patients with a normal phosphate level, those with hyperphosphatemia exhibited a significant unfavorable overall survival with a hazard ratio (HR) of 1.84 (95% confidence interval [CI] 1.49–2.29, $P=2.6\times10^{-8}$, (log-rank $P=1.2\times10^{-7}$). Stratified analyses indicated the association was more pronounced in patients with colon (HR=2.00, 95% CI 1.57–2.56, $P=3.17\times10^{-8}$) but not rectal cancer (HR=0.96, 95% CI 0.58–1.59, $P=0.889$) (P interaction=0.023), as well as in those not receiving chemotherapy (HR=2.15, 95% CI 1.59–2.90, $P=6.2\times10^{-7}$) but not in those receiving chemotherapy (HR=1.30, 95% CI 0.92–1.82, $P=0.136$) (P interaction=0.012). Flexible parametric survival model demonstrated that the increased risk for death conferred by postoperative hyperphosphatemia persisted over 150 months after surgery.

Conclusion—Our data indicated that postoperative hyperphosphatemia might be used as a prognostic marker of CRC patients after surgery. Since phosphate level is routinely tested in clinics, it may be incorporated into clinical models to predict CRC survival.

Keywords

phosphate; hyperphosphatemia; CRC; survival

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INTRODUCTION

Worldwide, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females [1]. According to the American Cancer Society, the year of 2012 will witness approximately 143,460 new cases and 51,690 deaths of CRC in the United States [2, 3]. Despite the recent reduction in CRC mortality, our understanding of its treatment and prognosis remains limited [4]. To further develop prognostic markers has important clinical value in the management of this devastating disease.

Phosphate, the most abundant mineral in the body, plays a fundamental role in several basic cellular functions such as energy metabolism, intracellular signaling, and bone and tooth mineralization [5, 6]. However, hyperphosphatemia, defined as having an excessive phosphate level (≥4.5 mg/dL), has emerged as a risk factor for diseases such as chronic kidney disease (CKD) and cardiovascular diseases [7–13]. Moreover, increasing evidence in case reports and systemic reviews has focused attention on hyperphosphatemia in the development and treatment of various solid tumors including CRC [14–21]. A cases report showed patient deterioration and death by acute renal failure in metastatic CRC with hyperphosphatemia [18]. Rapid elevation of phosphate levels may instigate sudden cardiac arrest and acute renal failure associated with metastatic CRC [19]. During cancer development and treatment, hyperphosphatemia may appear in rare events when tumor cells release metabolic contents into the bloodstream, either spontaneously or in response to therapy [22, 23]. The metabolic disturbance may progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, and death due to multi-organ failure [23, 24]. In a study that used the serum phosphate level of 110 patients to predict survival time in multiple myeloma, Umeda et al. found that hyperphosphatemia conferred a shorter survival time and was a negative prognostic factor [25]. Nonetheless, to date, few studies have followed postoperative serum phosphate levels in CRC patients. To the best of our knowledge, no large clinical cohort study has been reported to assess hyperphosphatemia as a biomarker to directly predict the survival in CRC patients. In this study, we sought to evaluate the association between postoperative phosphate level and overall survival in a clinic-based cohort of 1,241 CRC patients.

PATIENTS AND METHODS

Study population

The subjects in this study were selected from an existing and ongoing clinic-based cohort with histologically confirmed CRC patients who visited the Thomas Jefferson University Hospital (TJUH) since 1990. This study included 1,241 patients who: (1) had a definitive diagnosis of pathologically confirmed adenocarcinoma of CRC between January 1999 and January 2012; (2) had a definitive initial diagnostic date; (3) underwent surgery with a definitive surgery date; and (4) had a phosphate level measurement within the first month after surgery date (Table 1). Diagnosis dates of the patients ranged from August 1998 to January 2011. This study was approved by the Institutional Review Board of Thomas Jefferson University.

Collection of demographic and clinical data

Demographic and clinical data were obtained through medical chart review. Demographic variables analyzed in this study included age, gender, ethnicity, smoking status, and drinking status. Clinicopathologic variables included primary tumor site, tumor stage, tumor grade, and treatment (surgery, chemotherapy, and radiation therapy). Phosphate level was measured through routine clinical laboratory tests and the values were obtained from chart

review. The average, maximum, and first time measurements of phosphate level during the first month after surgery were analyzed in this study.

Statistical analysis

The clinical endpoint analyzed in this study was overall survival which was defined as the time from initial surgery to death from any cause. Determination of hyperphosphatemia was based on a clinical cut-off of 4.5 mg/dL as previously defined [26]. In addition, analyses based on the median, tertile, or quartile cut-off was also conducted. The associations between the average, maximum, or first time measured phosphate level and patient survival were estimated using hazard ratio (HR) and 95% confidence interval (95% CI) calculated by multivariate Cox proportional hazards model adjusting for age, gender, ethnicity, smoking status, drinking status, primary tumor site, tumor stage, tumor grade, chemotherapy, and radiation therapy, where appropriate. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Interaction analysis was performed by adding an interaction term into the Cox model. Time-dependent effects of phosphate level on CRC outcomes were analyzed using a flexible parametric survival model with a restricted cubic spline function. SAS (Version 9.3, SAS Institute, Cary, NC) and STATA (Version 11.0, STATA Corp., College station, TX) software packages were used for these analyses. All P values were 2-sided, with $P \leq 0.05$ considered the threshold of statistical significance.

RESULTS

Characteristics of the study population

The distributions of patient demographics and clinicopathologic variables are listed in Table 1. A total of 1,241 CRC patients with an average age of 65.9 (Standard deviation, 13.3) were included in the analysis of this study. There were 539 (43.4%) patients identified as being dead and 702 (56.6%) alive during a median follow-up duration of 39.7 months. Other data included the distributions of females and males (49.8% vs. 50.2%), ever smokers and never smokers (47.8% vs. 47.0%), and ever drinkers and never drinkers (47.3% vs. 45.1%). Most patients were Caucasian (76.9%), with the primary tumor site in the colon (72.6%), moderately differentiated tumor grade (838, 67.5%), and early stage disease (stages 0, 1, and 2, 57.6%). Less than half of the patients had received chemotherapy (40.3%) and only 16.8% of patients received radiation therapy.

The association of postoperative phosphate level and CRC survival

The associations of postoperative phosphate level by the average, maximum, or first time measured concentration during the first month following surgical procedure (excluding the day of surgery) and CRC survival were analyzed using multivariate Cox proportional hazard model and the results were displayed in Table 2. Compared to patients with a normal phosphate concentration range (<4.5mg/dL) by the maximum phosphate concentration during the first month after surgery, those with hyperphosphatemia (defined as phosphate concentrations ≥4.5mg/dL) exhibited a significant unfavorable overall survival (HR=1.84, 95%CI 1.49–2.29, $P=2.6\times10^{-8}$) (Table 2). Comparison of major demographical and clinical characteristics between patients with normal and elevated phosphate levels did not reveal significantly different distributions (Supplementary Table 1). When the analysis was conducted further adjusting the level of creatinine, an important indicator of renal dysfunction, the results remained highly significant (HR=1.58, 95% CI 1.25–1.99, $P=9.4\times10^{-5}$) (Supplementary Table 2). Similar results were obtained when the analyses were conducted by the average (HR=2.86, 95%CI 1.90–4.31, $P=5.0\times10^{-7}$), or the first time measured phosphate concentration (HR=1.60, 95%CI 1.18–2.16, $P=0.0023$) (data not shown). Consistently, Kaplan-Meier curves indicated patients with hyperphosphatemia (median survival time, 93.6 months) showed a significantly unfavorable survival (log-rank

P=1.2×10^{-7}) compared to those with normal phosphate levels (median survival time, 55.5 months (Fig. 1 and Table 2). We further conducted similar analyses using the median, tertile, and quartile cut-off values of postoperative phosphate level and the results indicated that the association between high phosphate and poor CRC survival were dose-dependent (Supplementary Table 3).

Stratified analysis of the effect of postoperative phosphate level on CRC survival

In stratified analysis, the association between hyperphosphatemia and CRC survival remained significant in both strata of most variables, including age, gender, ethnicity, smoking status, drinking status, primary tumor site, tumor stage, tumor grade, and radiation therapy (Table 3). However, the association was only significant in patients with colon (HR=2.00, 95% CI 1.57–2.56, P=3.17×10^{-8}) but not rectal cancer (HR=0.96, 95% CI 0.58–1.59, P=0.889) (P interaction=0.023), and in those not receiving chemotherapy (HR=2.15, 95% CI 1.59–2.90, P=6.2×10^{-7}) but not in those receiving chemotherapy (HR=1.30, 95% CI 0.92–1.82, P=0.136) (P interaction=0.012). A significant interaction between hyperphosphatemia and gender was also observed (P interaction=0.027) (Table 3).

Time-dependent effects of postoperative phosphate level on CRC survival

We analyzed the time-dependent effect of postoperative phosphate level on CRC survival using a flexible parametric modeling framework adjusting all major host variables (Fig. 2). We found that the increased risk of death by phosphate level persisted over 150 months and the risk keeps increasing over time after an initial U shape decrease at 7.5 month after surgery (Fig. 2).

DISCUSSION

A few previous case reports and small-scale clinical studies have implicated hyperphosphatemia as a complication in the management of several solid tumors including CRC [14–21]. To the best of our knowledge, the current study is the first that comprehensively evaluated postoperative phosphate level using a large and well-characterized clinical CRC patient cohort. We substantiated the prognostic value of phosphate level using an epidemiological approach and reported interaction effects between phosphate and clinical variables such as primary tumor site and chemotherapy use. Moreover, we demonstrated that the association between postoperative hyperphosphatemia and patient survival might persist for long time after surgery.

The unfavorable prognosis conferred by elevated phosphate level could be explained by many factors such as the development of metabolic disturbances, use of prophylactic agents, treatment-related complications like infections or organ failures, or the development of cardiovascular complications [21, 27, 28]. Hyperphosphatemia may develop spontaneously [20] or associated with tumor lysis syndrome (TLS), a rare event that is sometimes observed in rapidly proliferating tumors or triggered by systemic cytotoxic treatments [14, 29–32]. However, these complications associated with elevated phosphate level in CRC management are relatively rare and mostly documented in case reports or small-scale clinical studies. Therefore, their contributions to the explanation of the effect on CRC survival by elevated phosphate level observed in the present study remain elusive. Since phosphate and its derivatives also play an essential role in a wide spectrum of molecular and cellular functions, especially protein kinase-mediated signaling pathways, whether the unfavorable prognosis conferred by high phosphate level may be potentially related to disturbed signaling transductions during treatment remains an interesting topic for future investigations. In stratified analysis, we observed a significant interaction effect between phosphate and primary tumor site on CRC survival. The association between high phosphate

level and poor survival was only evident in colon but not rectal cancer patients. Similar interaction effect was noticed between phosphate and the use of chemotherapy as the effect was much more pronounced in patients without chemotherapy compared to those receiving chemotherapy. The mechanisms of these observations are unknown. Although colon and rectal cancers generally have similar path of oncogenic development and receive similar treatment modalities, there are minor differences in their treatment plans on surgery and cytotoxic therapies, due to the differences in tumor locations and other factors, according to the treatment guidelines of the National Comprehensive Cancer Network [33]. It may be possible that some complications associated with high phosphate level are more prevalent in colon cancer patients or mitigated by the use of chemotherapy. Also, we cannot rule out the possibility of false positive findings due to small sample size in the stratified analysis, since the significant interactions disappeared after correction for multiple comparisons (data not shown). Larger and more homogeneous patient populations are needed to further test these results.

The flexible parametric model network has been used in previous cancer prognosis studies and clinical trials [34–36]. In this study, we applied this model to test the association between phosphate level and the long-term survival of CRC patients. We observed a persistently higher chance of death in those patients with hyperphosphatemia over the entire follow-up period of up to 150 months in this study. Moreover, the risk appeared to keep increasing over time after an initial drop at 7.5 month after surgery (Fig. 2). Although the confidence interval of this analysis increasingly widened along with time due to the smaller number of patients with longer follow-up, its lower limit did not reached 1, indicating the observation remained statistically significant across the analyzed time period. These results were consistent with the main effects analysis and strongly corroborated the role of postoperative phosphate level in predicting CRC survival.

Our study has several strengths. We had a large population of 1,241 CRC patients from a single institute. The study was focused on the extensive analysis of a single variable and, thus, did not have the multiple comparison issue. The findings were highly statistically significant in both the Cox regression and the log-rank analyses. There are also limitations in our study. Because this study used archived clinical data obtained from chart review instead of data collected from questionnaire interview in prospective cohorts, missing values in some variables were noticed. Another limitation is the small number of hyperphosphatemic patients (N=206) included in the analysis. Although the results derived using these patients are highly significant, validation studies with larger populations of hyperphospatemic patients are warranted to further confirm our findings. Because we did not have complete information on relevant co-morbidities such as renal dysfunction or cardiovascular diseases that may be associated with CRC prognosis and confound our findings, we were not able to adjust the effects of these events in the multivariate survival analysis. Therefore, our data, although highly statistically significant, need to be further substantiated in more rigorous studies using large independent and prospective populations with a more comprehensive data collection.

Taken together, we presented one of the first epidemiologic studies elucidating the role of hyperphosphatemia in CRC prognosis. Our results suggest that postoperative blood phosphate level is significantly associated with CRC survival. Since phosphate level is routinely tested in clinics, if validated, it may be incorporated with other factors to develop clinical models for the prediction of CRC prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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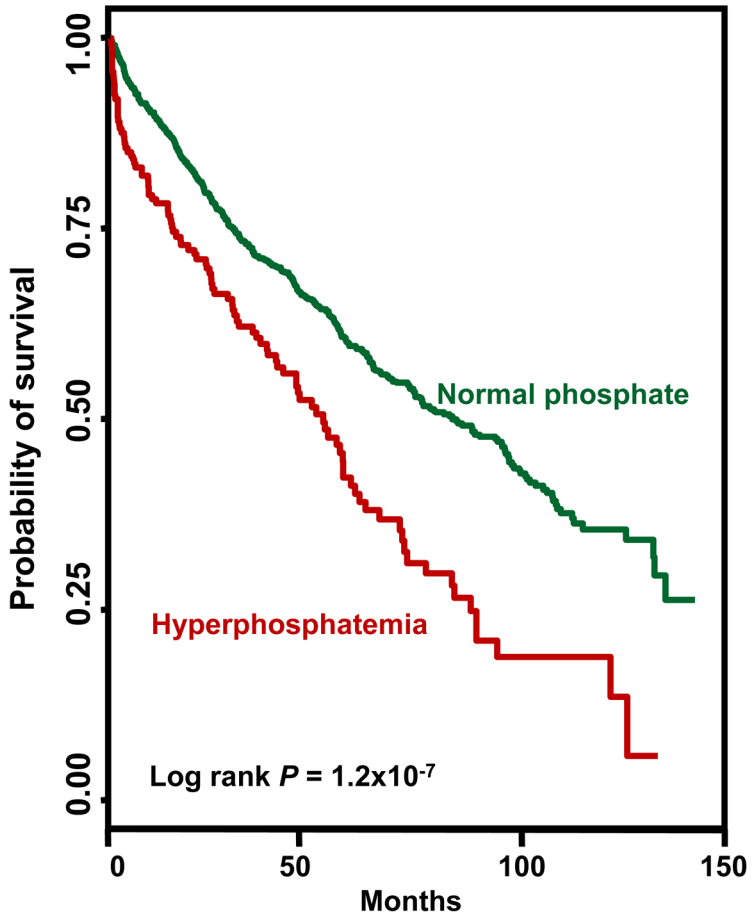

Figure 1.
Kaplan-Meier curve of the analyses between postoperative phosphate level and CRC survival, evaluated by the maximum values of phosphate level measured with one month after surgery.

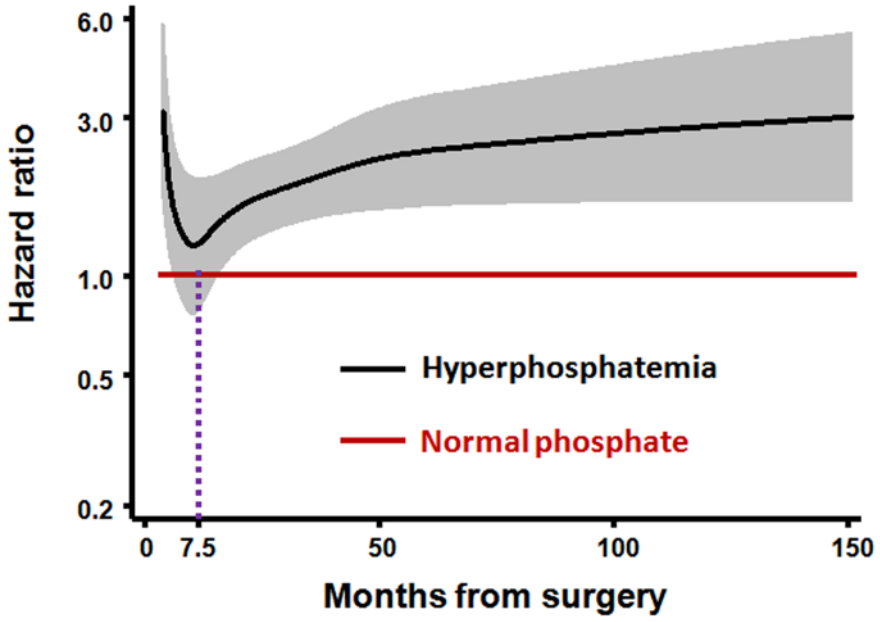

Figure 2.

Time-dependent effect of postoperative phosphate level on CRC survival. The analysis was adjusted for age, gender, ethnicity, tumor stage, tumor grade, chemotherapy, radiation therapy and surgery. Solid lines indicated hazard ratios and shaded areas showed the 95% confidence intervals. Dash lines represented the references.

Table 1

Characteristics of CRC patients included in this study

Variables	Number of patients N=1241, (%)
Age (mean ± SD *)	65.9 ± 13.3
Gender	
Female	618 (49.8)
Male	623 (50.2)
Ethnicity	
Black	223 (18.0)
Caucasian	954 (76.8)
Others	64 (5.2)
Smoking status	
Ever smokers	593 (47.8)
Never smokers	583 (47.0)
Unknown	65 (5.2)
Drinking status	
Ever drinking	587 (47.3)
Never drinking	560 (45.1)
Unknown	94 (7.6)
Primary tumor sites	
Colon cancer	901 (72.6)
Rectum cancer	340 (27.4)
Tumor grades	
Well differentiated	119 (9.6)
Moderately differentiated	838 (67.5)
Poorly differentiated	169 (13.6)
Cell type not determined	115 (9.3)
Tumor stages	
Stage 0	40 (3.2)
Stage 1	306 (24.7)
Stage 2	369 (29.7)
Stage 3	298 (24.0)
Stage 4	171 (13.8)
Unknown	57 (4.6)
Radiation therapy	
No	1025 (82.6)
Yes	209 (16.8)
Unknown	7 (0.6)
Chemotherapy	
No	684 (55.1)
Yes	500 (40.3)
Unknown	57 (4.6)

Variables	Number of patients N=1241, (%)
Vital status	
Alive	702 (56.6)
Dead	539 (43.4)

* SD, standard deviation.

Table 2

The association between the maximum phosphate measurement within one month after surgery and CRC survival

Phosphate*	Dead	Alive	Adjusted HR† (95%CI)	Cox *P*†	MST	Log Rank *P*
Normal	430	605	1.00		93.6	**1.2×10^{-7}**
Elevated	109	97	**1.84 (1.49–2.29)**	**2.6×10^{-8}**	55.5	

Significant *P* Values (<0.05) were in bold fonts

*4.5 mg/dL was used as the cut-off to separate patients with normal phosphate level and hyperphosphatemia

†Adjusted for age, gender, ethnicity, smoking status, drinking status, primary tumor sites, tumor state, tumor grades, chemotherapy, and radiation therapy.

MST: median survival time

Table 3

The associations between postoperative phosphate level and CRC survival stratified by host characteristics

Variables	Stratum	Dead	Alive	Adjusted HR* (95%CI)	Cox *P**	MST	Log Rank *P*	*P* for interaction
Age at diagnosis								0.968
≤ 67 years	Normal	169	370	1.00		140.6	**0.0008**	
	High	46	66	1.48(1.04–2.10)	**0.031**	66.1		
> 67 years	Normal	261	235	1.00		63.7	**8.52×10^{-6}**	
	High	63	31	1.76(1.32–2.36)	**0.0001**	32.7		
Gender								**0.027**
Female	Normal	210	293	1.00		93.7	**0.0001**	
	High	60	55	2.08(1.54–2.80)	**1.87×10^{-6}**	58.6		
Male	Normal	220	312	1.00		93.6	**0.0003**	
	High	49	42	1.73(1.26–2.39)	**0.0008**	49		
Ethnicity								0.742
Caucasian	Normal	340	464	1.00		91.1	**1.94×10^{-6}**	
	High	82	68	1.9(1.48–2.43)	**4.35×10^{-7}**	53.3		
Black	Normal	72	107	1.00		87.8	0.109	
	High	21	23	1.74(1.05–2.88)	**0.033**	75		
Smoking status								0.315
Never smokers	Normal	206	293	1.00		100.3	**4.20×10^{-6}**	
	High	48	36	2.09(1.50–2.91)	**1.19×10^{-5}**	48.1		
Ever smokers	Normal	198	284	1.00		91.1	**0.0008**	
	High	56	55	1.91(1.40–2.60)	**4.57×10^{-5}**	60.2		
Drinking status								0.888
Never drinkers	Normal	200	262	1.00		80.2	**1.77×10^{-6}**	
	High	61	37	2.15(1.59–2.88)	**4.63×10^{-7}**	48.1		
Ever drinkers	Normal	197	299	1.00		103.2	**0.002**	
	High	42	49	1.84(1.29–2.62)	**0.0007**	60.3		
Primary tumor sites								**0.023**
Rectum cancer	Normal	112	175	1.00		93.7	0.933	
	High	20	33	0.96(0.58–1.59)	0.889	94.8		

Variables	Stratum	Dead	Alive	Adjusted HR* (95%CI)	Cox *P**	MST	Log Rank *P*	*P* for interaction
Colon cancer	Normal	318	430	1.00		93.6	**4.97×10^{-10}**	
	High	89	64	2.00(1.57–2.56)	**3.17×10^{-8}**	43.1		
Tumor stages								0.575
Early stages	Normal	193	411	1.00		114.4	**1.03×10^{-5}**	
	High	53	58	2.20(1.61–3.01)	**7.05×10^{-7}**	69.7		
Late stages	Normal	218	163	1.00		47	**0.008**	
	High	53	35	1.67(1.22–2.28)	**0.001**	26.9		
Tumor grades								0.409
Lower grades	Normal	316	486	1.00		101.4	**3.89×10^{-6}**	
	High	79	76	1.94(1.51–2.49)	**2.66×10^{-7}**	58.6		
Higher grades	Normal	75	63	1.00		46.2	0.269	
	High	17	14	2.20(1.19–4.07)	**0.012**	49		
Chemotherapy								**0.012**
Yes	Normal	177	224	1.00		76.9	0.240	
	High	46	53	1.30(0.92–1.82)	0.136	66.1		
No	Normal	232	352	1.00		102.1	**1.63×10^{-10}**	
	High	60	40	2.15(1.59–2.90)	**6.20×10^{-7}**	40.8		
Radiation therapy								0.113
Yes	Normal	72	95	1.00		93.7	0.879	
	High	15	27	0.98(0.54–1.76)	0.936	93.3		
No	Normal	354	509	1.00		93.7	**5.52×10^{-10}**	
	High	93	69	1.89(1.48–2.40)	**2.05E-07**	44.7		

Significant *P* Values (<0.05) were in bold fonts.

*Adjusted for age, gender, ethnicity, smoking status, drinking status, primary tumor sites, tumor state, tumor grades, chemotherapy, and radiation therapy, where appropriate.