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Zimeng Huang Date

The Impact of Body Mass Index (BMI) on the Safety and Outcomes of Small Molecule Inhibitors (SMI) in Gastrointestinal Cancer, Lung Cancer, and Renal Cell Carcinoma.

By

Zimeng Huang

Master of Science in Public Health

Biostatistics and Bioinformatics

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B.S.

Tianjin University

2018

Thesis Committee Chair: Zhengjia (Nelson) Chen, PhD

Reader: Michael J Haber, PhD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Public Health,
in Biostatistics and Bioinformatics
2020

Abstract

The Impact of Body Mass Index (BMI) on the Safety and Outcomes of Small Molecule Inhibitors (SMI) in Gastrointestinal Cancer, Lung Cancer, and Renal Cell Carcinoma.

By Zimeng Huang

Nowadays more and more people are facing the health issue “obesity”. Usually, people would consider obesity as a risk factor to health. However, scientists found that obesity improved the survival of patients with cancer, which is called “obesity paradox”. This is a mutrual component in cardio-metabolic literature, but less in oncology. To identify the association between BMI and the treatment effect of Small Molecule Inhibitors (SMI) in gastrointestinal cancer, lung cancer, and renal cell carcinoma. We conducted a single center, retrospective study at Winship Center. We found that overall survival of patients are worse for low-weight patients compared with patients with high BMI during later period of these diseases, gastrointestinal cancer, lung cancer, and renal cell carcinoma. Overall survival of patients had adverse events were significantly shorter than patients had no adverse events.

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1. INTRODUCTION

It is widely known that obesity is a risk factor for malignancies such as colon cancer, renal cell carcinoma and breast cancer. Obesity increases the incidence and mortality of these diseases. Calle and colleagues conducted prospective analysis identifying the association between increased body weight and increased mortality rate for cancers.[1] This association could be explained by the increased release of free fatty acids and tumor necrosis factor-α within patients with increased body weight, resulting in insulin resistance and increased insulin levels. This phenomenon is also related to the reduced release of adiponectin. Overall, cellular proliferation can be promoted, and apoptosis can be inhibited within overweight patients, contributing to the development and maintenance of tumorigenesis.[2] These studies suggest that the efficacy of the treatment for a cancer patient can be affected by a patient's body weight.

Although the correlation of increased BMI and reduced cancer survival has been widely studied, some researchers have come to a different conclusion that overweight and early obese states can actually contribute to improved survival in cancer patients.[3-8] This phenomenon is called the"obesity paradox". The obesity paradox is a well-recognized component of cardio-metabolic literature, but less studied in oncology.[9] The use of immunotherapy and small molecule inhibitors (SMI) in malignancies is also affected by obesity paradox.[10, 11] McQuade and colleagues conducted a retrospective analysis of the association of body-mass index (BMI) and the outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy. This analysis illustrated that male patients with metastatic melanoma and obesity had longer progression free survival (PFS) and overall survival (OS)

compared with metastatic melanoma patients and normal BMI.[10] Martini and colleagues conducted a retrospective analysis to evaluate the impact of BMI on toxicities and clinical outcomes in metastatic renal cell carcinoma patients treated with cabozantinib. This analysis evidence that the adverse event rate shows no difference between high body weight and low body weight. Additionally, increased baseline BMI indicated a trend towards longer OS.[11]

According to the obesity paradox and the retrospective analysis mentioned above, we expect that BMI has an impact on PFS, OS, and adverse events of patents receiving SMI for treatment of gastrointestinal cancer, lung cancer, and renal cell carcinoma. Studies examining the obesity paradox have not focused on the three diseases with treatment of receiving SMI. Thus, we conducted a retrospective analysis to assess the possible correlations between BMI and outcomes of patients treated with SMI for gastrointestinal cancers, thoracic cancer, and renal cell carcinoma to test the hypothesis that patients with high BMI tend to have improved outcomes.

2. METHODS

2.1 STUDY DESIGN

A single-center, retrospective chart review project was conducted at Winship Cancer Institute. The target population of interest was patients who were prescribed SMI for gastrointestinal, lung, and renal malignancies at Winship Cancer Institute and followed through any visits to hospitals within the Emory Healthcare System.

2.2. DATA COLLECTION

Data were retrieved from the Data Warehouse and Emory electronic Medical Record (EeMR). The EeMR is reviewed for patients who are identified to have received a SMI from Winship Cancer Institute for the treatment of gastrointestinal cancer, lung cancer, or renal cell carcinoma. This primary identification will occur through data that is collected through Data Warehouse. Variables outlined below was collected after the review of each patient's EeMR. The data was collected in a secure Excel database with a coding mechanism that was defined in the header. After statistical analysis the de-identified data was permanently removed from the medical center servers.

Variable collected: Age, Race, Gender, Drug (Including 7 kinds of drug used for treating patients), ADR (Indicating adverse event happened or not), Diagnosis (Liver related cancer or colon cancer)

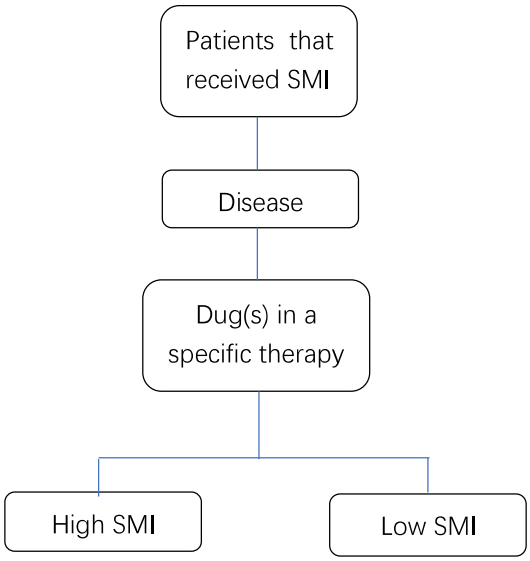
2.3. PARTICIPANT SELECTION

Patients to be evaluated for inclusion in study were identified via a drug query for the SMI listed in the inclusion criteria in Data Warehouse. Among adult patients with lung cancer, gastrointestinal cancer, and renal cell carcinoma, patients received at least one cycle of SMI between January 1, 2010 and June 1, 2019 will be included in this project.

Patients in this study all received one of the following Small Molecule Inhibitors (SMI), Sunitinib, Sorafenib, Lenvatinib, Cabozantinib, Regorafenib, Pazopanib,

Axitinib, Osimertinib, Erlotinib, Crizotinib, Certinib, Alectinib, Everolimus. Patients in pregnancy, lactation or prison were excluded.

2.4. GENERALIZED STRATIFICATION MECHANISM



2.5. OUTCOME OF INTEREST

The primary objective is to identify the impact of BMI on PFS. PFS is defined as the time from date of treatment initiation until disease progression or death or last contact whichever comes first. Another primary objective is to identify the impact of BMI on OS. OS is defined as time from date of treatment initiation until death.

The secondary objective is to identify the impact of BMI on the rate of adverse events.

2.6. STATISTICAL ANALYSIS

Summary statistics was estimated for all variables collected. Categorical variables was summarized with frequencies and percentages.

For progression free survival (PFS), disease progression or death from any cause was defined as the event. Time of PFS was calculated as the time from date of treatment initiation to disease progression date, death date, or last contact whichever coms first. Disease progression is deined as tumor size grow at least 20 percent compared with the baseline. For overall survival (OS), death from any cause was defined as the event. Time of OS was calculated as the time from study enrollment to death or last contact. For both PFS and OS, patients were censored at time of last follow-up. PFS and OS rates were estimated with the Kaplan-Meier method and compared between two patient groups (BMI >= 25 vs BMI<25) using the log-rank test. Cox proportional hazards models were further used in the multivariable analyses to assess adjusted effects of BMI on the patients' OS and PFS after adjusting for other factors. The proportional hazards assumption was evaluated graphically and analytically with regression diagnostics.

For the secondary objectives, overall response and incidence of adverse events will estimate as frequency and percentage, and then compared between the two groups using Chi-Square test. Logistic regression and General linear model (GLM) will be further used in the multivariable analysis to estimate the impact of BMI on overall response and adverse events after adjusting for other factors, respectively. All data management and statistical analysis were conducted using SAS Version 9.4.

3. RESULTS

TABLE 1 DESCRIPTIVE STATISTICS

Variable	Level	N (%) = 282
BMI	Low	120 (42.6)
	High	162 (57.4)
Adverse Event Indicator (ADR)	Yes	112 (39.7)
	No	170 (60.3)
DRUG	1	12 (4.3)
	3	97 (34.4)
	4	107 (37.9)
	5	66 (23.4)
AGE	<65	161 (57.1)
	>=65	121 (42.9)
GENDER	Male	186 (66.0)
	Female	96 (34.0)
DIAGNOSIS	Gastrointinal	123 (43.6)
	Lung	127 (45.0)
	Renal	32 (11.3)
RACE	Caucasian	148 (52.5)
	African-American	104 (36.9)
	Others/Unknown	30 (10.6)

TABLE 2 UNIVARIATE ASSOCIATION WITH BMI

			BMI		
Covariate	**Statistics**	**Level**	**Low N=120**	**High N=162**	**Parametric P-value***
AGE	N (Col %)	<65	69 (57.5)	92 (56.79)	0.905
	N (Col %)	>=65	51 (42.5)	70 (43.21)	
RACE	N (Col %)	Caucasian	60 (50)	88 (54.32)	**0.017**
	N (Col %)	African-American	40 (33.33)	64 (39.51)	
	N (Col %)	Others/Unknown	20 (16.67)	10 (6.17)	
GENDER	N (Col %)	Male	87 (72.5)	99 (61.11)	**0.046**
	N (Col %)	Female	33 (27.5)	63 (38.89)	
DIAGNOSIS	N (Col %)	Gastrointinal	46 (38.33)	77 (47.53)	0.277
	N (Col %)	Lung	58 (48.33)	69 (42.59)	
	N (Col %)	Renal	16 (13.33)	16 (9.88)	
DRUG	N (Col %)	1	6 (5)	6 (3.7)	0.556
	N (Col %)	3	45 (37.5)	52 (32.1)	
	N (Col %)	4	40 (33.33)	67 (41.36)	
	N (Col %)	5	29 (24.17)	37 (22.84)	
ADR	N (Col %)	Yes	32 (26.67)	80 (49.38)	**<.001**
	N (Col %)	No	88 (73.33)	82 (50.62)	

* The parametric p-value is calculated by chi-square test.

At 0.05 significant level, BMI was significantly different in different RACE, GENDER, and ADR groups.

TABLE 3 UNIVARIATE ASSOCIATION WITH PFS

			PFS		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
BMI	Low	120	1.21 (0.96-1.54)	0.110	0.107
	High	162	-	-	
AGE	<65	161	0.85 (0.67-1.08)	0.184	0.181
	>=65	121	-	-	
RACE	Caucasian	148	1.21 (0.81-1.79)	0.348	0.416
	African-American	104	1.31 (0.87-1.98)	0.193	
	Others/Unknown	30	-	-	
GENDER	Male	186	1.20 (0.94-1.54)	0.145	0.142
	Female	96	-	-	
DIAGNOSIS	Gastrointinal	123	0.85 (0.57-1.26)	0.425	0.131
	Lung	127	1.10 (0.75-1.62)	0.626	
	Renal	32	-	-	
DRUG	1	12	1.12 (0.60-2.07)	0.723	**0.048**
	3	97	0.89 (0.65-1.22)	0.469	
	4	107	0.68 (0.49-0.93)	**0.015**	
	5	66	-	-	
ADR	Yes	112	1.03 (0.81-1.30)	0.831	0.830
	No	170	-	-	

Progression Free Survival was significantly different among different drug groups at 0.05 significant level. Compared with High BMI group, the hazard ratio of Low BMI group is 1.21, and the association between Progress Free Survival was not significant. Compared with Renal Cancer, the hazard ratio of Gastrointinal Cancer is 0.85 and the hazard ratio of Lung Cancer is 1.10.

TABLE 4 MULTIVARIABLE SURVIVAL ANALYSIS OF PROGRESSION FREE SURVIVAL

			PFS		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Type3 P-value**
BMI	Low	120	1.15 (0.90-1.46)	0.262	0.262
	High	162	-	-	
DRUG	1	12	1.04 (0.56-1.95)	0.892	**0.041**
	3	97	0.88 (0.64-1.21)	0.430	
	4	107	0.66 (0.48-0.90)	**0.010**	
	5	66	-	-	
AGE	<65	161	0.85 (0.67-1.09)	0.199	0.199
	>=65	121	-	-	
GENDER	Male	186	1.22 (0.94-1.57)	0.130	0.130
	Female	96	-	-	

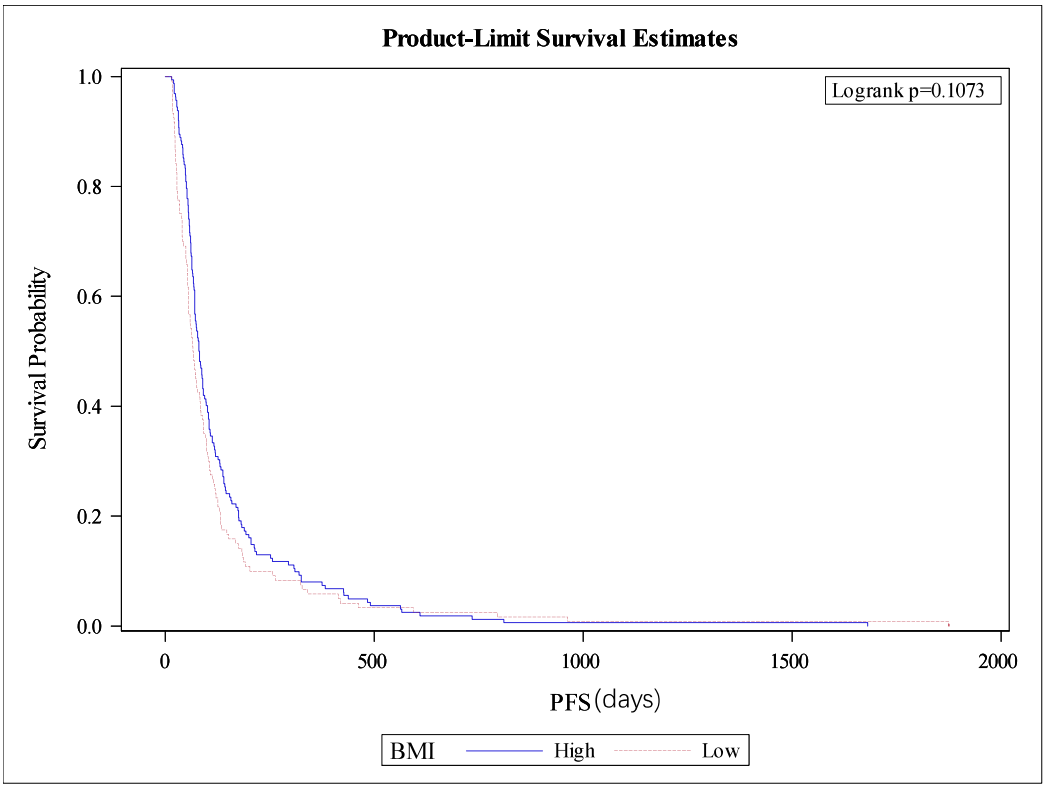
Covariate	Level	N	PFS		
			Hazard Ratio (95% CI)	HR P-value	Type3 P-value

* Number of observations in the original data set = 282. Number of observations used = 282.

** Backward selection with an alpha level of removal of .2 was used. Forcing BMI into the model. The following variables were removed from the model: ADR, DRUG, DIAGNOSIS, and RACE.

At 0.05 significant level, Progress Free Survival of subjects was significantly associated with drug groups, holding other variables fixed, which meant that using different drug would affect the Progress Free Survival.

FIGURE 1 PROGRESS FREE SURVIVAL (PFS) CURVES BY BMI



BMI	No. of Subject	Event	Censored	Median Survival (95% CI)
High	162	162 (100%)	0 (0%)	81 (70, 91)
Low	120	120 (100%)	0 (0%)	66.5 (56, 83)

Figure above showed that PFS Curves of High BMI group and Low BMI group are close, although median survival rate of High BMI (81 days) is a bit higher than Low BMI (66.5 days).

According to the table 2 and table 3, none of the variables is the confounder of PFS and BMI. BMI is significantly different in different RACE, GENDER and ADR groups. Drug is significantly associated with PFS. Backward selection was used to fit the multivariate regression model for PFS. ADR, DRUG, DIAGNOSIS, and RACE were removed with an alpha level of removal of 0.2. Based on the model, we found that BMI was not significantly associated with PFS, but DRUG was significantly associated with PFS. We can also tell from figure 1 that survival curves for high BMI and low BMI are close.

TABLE 5 UNIVARIATE OS ANALYSIS

			OS		
Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
BMI	Low	120	1.65 (1.05-2.58)	**0.030**	**0.028**
	High	162	-	-	
AGE	<65	161	0.82 (0.52-1.29)	0.390	0.389
	>=65	121	-	-	

			OS		

Covariate	**Level**	**N**	**Hazard Ratio (95% CI)**	**HR P-value**	**Log-rank P-value**
RACE	Caucasian	148	1.30 (0.58-2.91)	0.527	0.534
	African-American	104	1.55 (0.68-3.52)	0.300	
	Others/Unknown	30	-	-	
GENDER	Male	186	1.43 (0.88-2.32)	0.151	0.148
	Female	96	-	-	
DIAGNOSIS	Gastrointinal	123	1.01 (0.44-2.29)	0.987	0.333
	Lung	127	1.41 (0.63-3.18)	0.401	
	Renal	32	-	-	
DRUG	1	12	1.69 (0.56-5.06)	0.351	0.410
	3	97	1.01 (0.54-1.87)	0.986	
	4	107	0.76 (0.41-1.41)	0.378	
	5	66	-	-	
ADR	Yes	112	0.41 (0.23-0.73)	**0.002**	**0.002**
	No	170	-	-	

BMI and ADR were significantly associated with OS. According to results in Table 2 and Table 5, we found that ADR is the confounder of OS and BMI, thus we forced ADR in the following model.

TABLE 6 MULTIVARIATE ASSOCIATION OVERALL SURVIVAL[14] ANALYSIS

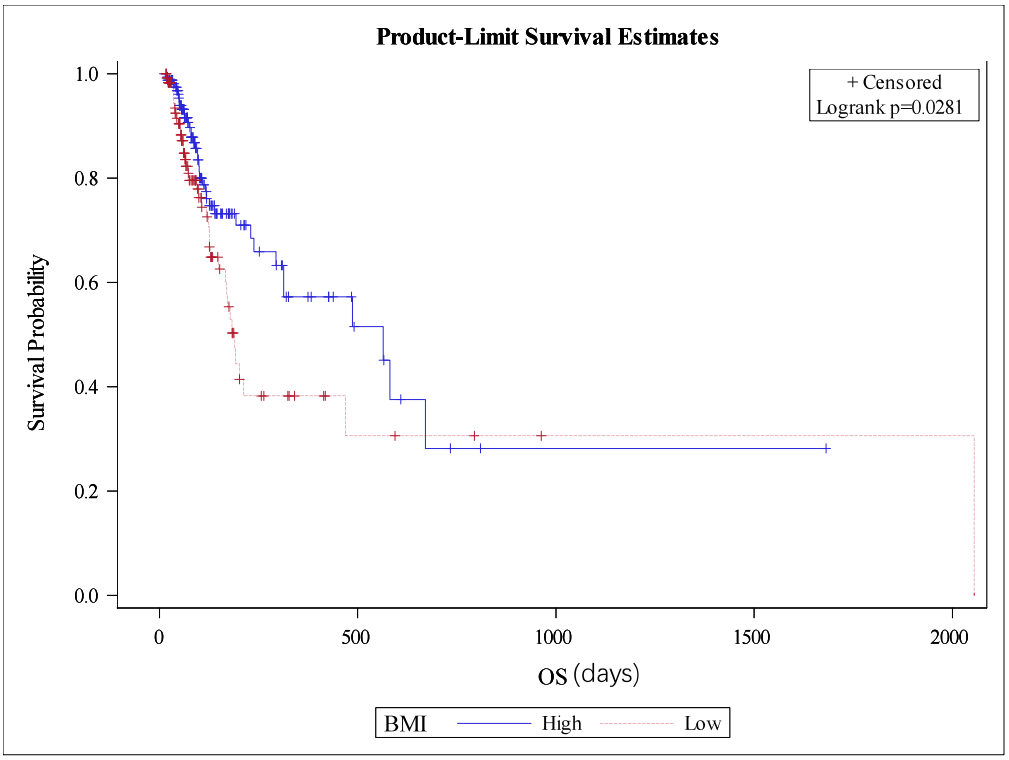
Covariate	Level	N	OS		
			Hazard Ratio (95% CI)	**HR P-value**	**Type3 P-value**
BMI	Low	120	1.45 (0.92-2.29)	0.110	0.110
	High	162	-	-	
ADR	Yes	112	0.44 (0.24-0.79)	**0.006**	**0.006**
	No	170	-	-	

* Number of observations in the original data set = 282. Number of observations used = 282.

** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: AGE, DRUG, DIAGNOSIS, GENDER and RACE.

ADR were significantly associated with OS. Patients with adverse event during the treatment had better overall survival. The hazard ratio of patients with adverse event relative to those without adverse event is 0.44 (p-value = 0.006).

FIGURE 2 OVERALL SURVIVAL CURVES BY BMI



BMI	No. of Subject	Event	Censored	Median Survival (95% CI)
High	162	38 (23%)	124 (77%)	564 (313, NA)
Low	120	39 (33%)	81 (68%)	190 (150, 469)

As we can see in Figure 2, overall survival curve of Low BMI is much lower than the curve of High BMI in later cancer period, which is consistent with Figure 1. The median survival rate of High BMI group is 564 days, and the median survival rate of Low BMI group is 190 days, indicating that the High BMI group might have longer overall survival. However, Table 6 showed that BMI and OS doesn't have significant association.

So far, we found that during the whole process BMI doesn't significantly

associate with progress free survival and the relationship between BMI and overall survival may vary by periods of cancer.

TABLE 7 MULTIVARIABLE LOGISTIC REGRESSION WITH OUTCOME = ADR

			ADR=Yes		
Covariate	**Level**	**N**	**Odds Ratio (95% CI)**	**OR P-value**	**Type3 P-value**
BMI	High	282	2.66 (1.58-4.47)	<.001	**<.001**
	Low	282	-	-	
DIAGNOSIS	Gastrointinal	282	1.38 (0.57-3.33)	0.473	0.109
	Lung	282	2.16 (0.90-5.16)	0.084	
	Renal	282	-	-	
GENDER	Female	282	1.59 (0.95-2.68)	0.079	0.079
	Male	282	-	-	

* Number of observations in the original data set = 282. Number of observations used = 282.

** Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: AGE, DRUG, and RACE.

BMI was significantly associated with ADR. Subjects who are heavier have higher probability of having adverse events than subjects who are thinner.

4. CONCLUSION

According to the univariate association results between BMI and other covariates (Table 2), we found that at 0.05 significant level, RACE, GENDER and ADR were significantly associated with BMI. In other words, BMI were different among Caucasian people, African-American people and other people. Also, BMI were different between male and female. Patients with adverse events had higher BMI compared with patients without adcerse events during the study. Based on the univariate association results between Progression Free Survival and all variables. We found that only DRUG was significantly associated with Progression Free Survival, at 0.05 significant level. Durg 1 had highest hazard, and Durg 4 had lowest hazard. Compared with Durg 5, Drug 4 had the hazard rate that was 32% lower. Forcing BMI into the model of Progression Free Survival, backward selection with an alpha level of removal of .2 was used. ADR, DRUG, DIAGNOSIS, and RACE were dropped. After accounting for other variables (Table 4), the hazard ratio relative for Low BMI relative to High BMI was 1.15 (95% CI [0.09,1.46]), which means that patients who were thinner might have cancer progression earlier than patients who were heavier. However, this conclusion (P-value = 0.262) was not significant at 0.05 significant level. We can tell from Figure 1 that although Progress Free Suvival Curve of Low BMI was generally lower than High BMI, these two curves were close. We also conducted univariate association analysis between Overall Survival and each covariate (Table 5). Based on the result of the analysis, we know that the hazard ratio for Low BMI relative to High

BMI is 1.65 (95% CI [1.05, 2.58]), which means that patient with lower weight had larger hazard than with higher weight. This conclusion is significant (P-value = 0.03) at 0.05 significant level. Also, patients had adverse event (ADR = Yes) during the treatment period had significant lower hazard than patients didn't have adverse event (ADR = No). The hazard ratio for patients had adverse event relative to patients had no adverse event is 0.41. After conducting multivariate association analysis of Overall Survival, we had BMI and ADR left in the model. (Table 6) In this model, p-value for the coefficient of BMI is 0.110, which was greater than 0.05, and the p-value for the coefficient of ADR was 0.006. We conclude that compared with High BMI, patient with Low BMI had shorter oveall survival, but it was not a significant result. The hazard ratio for patients had adverse event relative to patients had no adverse event is 0.44 (95% CI [0.24, 0.79], p-value = 0.006). Overall survival of patients had adverse events were significantly shorter than patients had no adverse events. According to Figure 2, it is abvious that at the beginning, overall survival curves of High BMI and Low BMI were close. After around 100 days, curve of Low BMI became much lower than the curve of High BMI. Median survival for High BMI was 564 days (around 1.5 years), but median survival for Low BMI was 190 days (around half year). Intuitively, High BMI survive longer than Low BMI.

For our secondary objective, we conducted a multivariate association analysis of ADR. We found that BMI, DIAGNOSIS, and GENDER were included in the model. Patients with High BMI significantly had higher risk of getting adverse events than patients with Low BMI. Patients with renal cancer had lowest risk of having adverse

events, and patients with lung cancer had highest risk of having adverse events. Proportion of females having adverse events would be larger than males'.

To conlude, for gastrointinal cancer, lung cancer and renal cell cancer, BMI didn't significantly affect patients' progress free survival. BMI marginally affect patients' overall survival, and adverse event happened or not significantly affect patients' overall survival. People with High BMI tend to had longer survival in these three diseases. Also, patients overweight tend to have adverse events when have these malignancies.

5.DISCUSSION

We found that BMI was not a significant term in both regression model of progress free survival and overall survival. However, Figure 2 showed that overall survival curves for High BMI and Low BMI were apart. The reason why BMI was not significant might because of only two levels of BMI. In this study, we only divided BMI into two levels, which might make the differences between different levels BMI unclear. We are expected to do it with more levels in future. Another point is that, BMI might affect different period cancers differently. The beginning of overall survival curve and the beginning of overall survival curve are close, which is consistent with the trend of pregress free survival curve. However, after 100 days, curve of Low BMI dropped significantly, and curves for High BMI and Low BMI were far apart. In future, we could also do subgroup analysis for later cancer period patients to figure out how BMI affect those patients.

REFERENCES

1. Calle, E.E., et al., Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. 2003. 348(17): p. 1625-1638.

2. Calle, E.E. and R.J.N.R.C. Kaaks, Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. 2004. 4(8): p. 579-591.

3. Kruk, J. and H.Y.J.A.p.j.o.c.p. Aboul-Enein, Physical activity in the prevention of cancer. 2006. 7(1): p. 11.

4. Renehan, A.G., et al., Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. 2008. 371(9612): p. 569-578.

5. Schlesinger, S., et al., Postdiagnosis body mass index and risk of mortality in colorectal cancer survivors: a prospective study and meta-analysis. 2014. 25(10): p. 1407-1418.

6. Hakimi, A.A., et al., An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. 2013. 105(24): p. 1862-1870.

7. Amptoulach, S., G. Gross, and E.J.j.o.s.r. Kalaitzakis, Differential impact of obesity and diabetes mellitus on survival after liver resection for colorectal cancer metastases. 2015. 199(2): p. 378-385.

8. Tsang, N.M., et al., Overweight and obesity predict better overall survival rates in cancer patients with distant metastases. 2016. 5(4): p. 665-675.

9. Lennon, H., et al., The obesity paradox in cancer: a review. 2016. 18(9): p. 56.

10. McQuade, J.L., et al., Association of body-mass index and outcomes in patients with metastatic melanoma treated with targeted therapy, immunotherapy, or chemotherapy: a retrospective, multicohort analysis. 2018. 19(3): p. 310-322.

11. Martini, D.J., et al., Body mass index (BMI) and toxicities and association with clinical outcomes (CO) in metastatic renal cell carcinoma (mRCC) patients (pts) treated with cabozantinib (cabo). 2019, American Society of Clinical Oncology.