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BMI AND PROSTATE CANCER SEVERITY: DO OBESE MEN HARBOR MORE AGGRESSIVE DISEASE ON PROSTATE BIOPSY?

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Abstract

OBJECTIVES—We sought to examine the association of obesity with pre-biopsy PSA, Gleason score, clinical stage, and D'Amico tumor risk in two independent cohorts of men with prostate cancer.

METHODS—We retrospectively reviewed the medical records of men with biopsy-proven prostate cancer from California's IMPACT program and from a random sample of men treated at the University of Michigan. We performed multivariate analyses to examine the relationship of body mass index (BMI) with pre-biopsy PSA, Gleason score, clinical stage, and D'Amico tumor risk while controlling for demographics.

RESULTS—The mean age was 61.5 years and median pre-biopsy PSA 6.7 ng/ml. Greater than 70% of men were at least overweight. On univariate analysis, BMI was not associated with pre-biopsy PSA, Gleason score, or D'Amico tumor risk. On multivariate analysis, we found no association between BMI and log-transformed PSA, Gleason score, clinical T-stage, or D'Amico risk. Advancing age was associated with a higher risk of a higher pre-biopsy PSA, Gleason score, and D'Amico tumor risk.

CONCLUSIONS—Obese men with prostate cancer were no more likely to have a higher pre-biopsy PSA, Gleason score, clinical T-stage, or D'Amico risk than those who of normal weight. While we do not know whether BMI impacted pre-biopsy PSA values in those without a diagnosis of prostate cancer, our findings suggest that BMI does not affect the interpretation of pre-biopsy PSA levels in those with cancer.

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Keywords

Prostate Cancer; Obesity; Body Mass Index; PSA; Tumor Risk

INTRODUCTION

Obesity is a major public health problem in the United States. Currently 70% of adults older than 40 years old are overweight, and 30% of the entire population are obese.[1,2] The risk of cardiovascular-related mortality among those who are obese is significant with 112,159 excess deaths in 2004.[3] Most of these excess deaths were attributed to coronary artery disease, diabetes, and kidney disease. Notwithstanding an awareness of obesity as a public health concern and recent reports of plateauing,[4] there is no clear indication that obesity prevalence is reverting back to healthier levels. Obesity is second only to tobacco use as a risk factor for cancer, and accounted for approximately one-third of the 577,190 cancer-related deaths in 2012.[5] Obesity is associated with increased mortality for all cancers combined, including prostate.[6] Modifiable reasons for higher cancer-related deaths are obesity-mediated 1) delay of diagnosis due to the insufficiencies of our testing and 2) underestimation of severity of disease.

Our current understanding of obesity-mediated delay in diagnosis hinges on the relative association of obesity and lower levels of detected PSA. [1,7–14] Possible mechanisms for this inverse association include hemodilution with increased blood volume, and lower testosterone levels in obese patients. [15] Moreover, numerous studies suggest that obesity constitutes an obstacle to cancer screening in general.[2,16,17] Thus, obese patients harbor occult locally-advanced disease all the while PSA remains relatively low—stage for stage. [18,19] In a study involving a free prostate screening program in North Carolina, Price *et al.* controlled for multiple clinical characteristics and found an inverse relationship between PSA and body mass index (BMI).[14] Since then, however, multiple publications have yielded mixed results. Some found no association, [20–22] while the majority suggests an inverse relationship between BMI and PSA.[1,7–14]

With regard to BMI and tumor risk, MacInnis *et al.* conducted a meta-analysis and systematic review of the literature involving 31 cohort and 25 case-control studies.[23] They surmised that BMI was a weak but statistically significant predictor of tumor risk (RR 1.05 per 5 kg/m^2 increment; 95% CI 1.01–1.08).

While the debate over PSA and obesity will linger on, the more pressing issue is what to do with those diagnosed with cancer. Overutilization of surgery and irradiation among obese men with indolent cancer (clinically) may result in unnecessary morbidity from treatment, especially in a cohort that may be at higher risk of complications. In a cohort of 5041 men with clinically localized prostate cancer, Davies *et al.* found that not only are overweight, obese, and very obese men undergoing aggressive treatment just as often, but possibly even more than normal weight individuals (80% vs 71%, $p<0.01$).[24] Treatment type varied by degree of obesity—very obese were more likely to be treated with brachytherapy or external beam radiotherapy while overweight and obese men were just as likely to be treated surgically.

In this context, we turned to two different cohorts: 1) an underserved, multi-ethnic California population and 2) a well-educated, Caucasian Michigan population to validate these findings. Our objective was to examine the relative association between BMI and pre-biopsy PSA, Gleason score, clinical T-stage, and tumor risk among men with biopsy proven prostate cancer after adjusting for ethnic, socioeconomic and regional differences. We hypothesized that after controlling for clinical characteristics, we would find 1) an inverse

association between pre-biopsy PSA level and BMI, and 2) a weak but significant direct relationship between clinical stage, Gleason score, D'Amico tumor risk and BMI.

MATERIAL AND METHODS

Study Design and Patient Population

After Institutional Review Board approval from the University of Michigan and University of California, Los Angeles, we conducted a multi-center, retrospective review of the medical records of patients who had a prostate biopsy as part of the Improving Access, Counseling and Treatment for Californians with Prostate Cancer (IMPACT) program and a prostate cancer cohort study in Michigan. The California cohort included all eligible men enrolled in IMPACT, who are without health insurance or at <200% Federal Poverty Level with biopsy-proven prostate cancer between 2001 and 2008 (n=300). The Michigan cohort consisted of a simple random sample of 300 men from the University of Michigan diagnosed with prostate cancer in 2005–2008. Since profoundly elevated pre-biopsy PSA levels (>100) were indicative of advanced and metastatic disease, we assumed BMI would no longer be a major driver of pre-biopsy PSA in these patients. Thus, we excluded patients with a pre-biopsy PSA>100 (n=27) to arrive at our final study cohort of 573. We reviewed the medical records to collect patient (age, race, language, educational status, weight, height, and comorbid conditions) and tumor (pre-biopsy PSA, clinical stage, biopsy Gleason score, and D'Amico tumor risk) information.

Statistical Analysis

We categorized patient age (<60, 60–64.9, ≥65), race/ethnicity (White, Hispanic, Black, other), preferred language (English, not English), education (less than high school, high school graduate or greater), BMI, coexisting diabetes mellitus (yes, no), pre-biopsy PSA (<4.0, 4.0– 10.0, >10.0 ng/ml), biopsy Gleason score (<7, 7, >7), clinical stage (cT1, cT2, cT3/cT4), and D'Amico tumor risk (low, intermediate, high).[25]

Subjects were categorized into four categories based on BMI (kg/m^2): normal weight (BMI <25), overweight (BMI 25 to <30), mildly obese (BMI 30 to <35), and moderately to severely obese (BMI ≥35). We compared patient characteristics between the Michigan and California cohorts, as well as across the BMI categories using Chi-square, Fisher's exact, and Student's *t*-tests as appropriate.

To quantify a potential association between BMI and pre-biopsy PSA, we employed two strategies for multivariate analyses comparing BMI and pre-biopsy PSA. The first replicated the Price *et al.* model, whereby each patient per BMI category was assigned the imputed median for that corresponding BMI category, and then a linear regression was performed.[14] The second included a categorical BMI variable based on the four categories above. Pre-biopsy PSA was not normally distributed, so a log-transformation was employed. Because only 41 subjects were moderately-severely obese with a BMI ≥35, we collapsed that category with subjects with a BMI ≥30. In both models, we adjusted for previously determined patient characteristics, including age at study enrollment (continuous), race (White vs not White), site of care (California vs Michigan), and Gleason score (<7 vs ≥7). For both models, we also performed sensitivity analysis by excluding patients with pre-biopsy PSA >20, in an effort to parallel the Price *et al.* study.[14]

To analyze the association between BMI and disease severity, we performed four logistic regressions (using multinomial logistic regression as appropriate for the outcomes with more than two categories), controlling for age, race, and site of care. The estimates are either represented as odds ratios (OR) or relative risk ratios (RRR). The models tested the association of BMI as a predictor for pre-biopsy PSA (<4 as referent), Gleason score (<7 as

referent), clinical T-stage (T1 as referent, combining cT2 and cT3 patients due to small sample size, and excluding two T4 patients), or D'Amico risk (low risk as referent).

Lastly, we conducted sensitivity analyses that included 1) stratifying the analyses by site of care (California vs Michigan, to counter the argument that averaging of the two sites would negate any trends), 2) excluding an additional 66 patients with pre-biopsy PSA values in the 20– 100 range (to replicate the Price et al. patient population), 3) utilizing BMI as a continuous variable, and 4) adding clinical T-stage as a covariate. We compared these results to the original findings to determine if the associations were affected. $P<0.05$ was defined as statistically significant. All statistical analyses were performed using SAS 9.3 (SAS Institute, Carey, North Carolina).

RESULTS

The mean (SD) age of enrollment was 61.5 (8.2) years with a range of 40–89 years (Table 1). The median pre-biopsy PSA was 6.7 ng/ml. Over 70% of all patients had a BMI that was abnormally high—44% were overweight, 20% were mildly obese, and 7% were moderately to severely obese. When the cohort was stratified on site of care (California vs Michigan), age at enrollment, race/ethnicity, preferred language, education, BMI, pre-biopsy PSA, biopsy Gleason score, and clinical T-stage were all significantly different (Table 1). The plurality of patients from the Michigan series was White (91%), English-speaking (100%), had a high school degree or greater (96%), and had a median pre-biopsy PSA of 5.80 ng/ml. In contrast, the California cohort was comprised of predominantly Hispanics (53%), only 57% spoke English, and 54% finished high school. This cohort also had a significantly higher median pre-biopsy PSA (8.2 ng/ml). Prevalence of diabetes or D'Amico risk was not significantly different between cohorts.

When stratified by BMI categories, we discovered statistically significant differences in age at enrollment, race/ethnicity, preferred language, education, and clinical T-stage (Table 2). With increasing BMI, the proportion of patients <60 ($p=0.04$), Blacks and Hispanics ($p<0.01$), high school graduates or greater ($p<0.01$), non-English speakers ($p<0.01$), and cT1 disease ($p=0.04$) also increased. There were no significant differences in diabetes status ($p=0.38$), pre-biopsy PSA ($p=0.57$), biopsy Gleason score ($p=0.27$), or D'Amico risk ($p=0.90$) across BMI categories.

After adjusting for age at enrollment, race/ethnicity, site of care, and Gleason score, we found no statistically significant association between BMI and pre-biopsy PSA (Table 3). The multivariate analyses with categorical BMI and log-transformed PSA did not demonstrate any significant association ($p=0.46$ for overweight and $p=0.47$ for obese). Similarly, we found no significant association when we imputed the median BMI per category for each patient (Price *et al.* model) and log-transformed PSA ($p=0.40$). In both models, age at enrollment (advancing age) and Gleason score (higher Gleason score) were significantly associated with higher pre-biopsy PSA. There was a trend towards significance whereby the Michigan cohort had lower pre-biopsy PSA values than those in California ($p=0.06$ and 0.07).

In assessing the association between BMI and disease severity, we found no significance between BMI (as a continuous variable) and pre-biopsy PSA, Gleason score, or D'Amico risk (Table 4). The sensitivity analyses included stratifying the data by site of care, excluding an additional 66 patients with pre-biopsy PSA values in the 20–100 range, utilizing BMI as a continuous variable, and adding clinical T-stage as a covariate. All of these sensitivity analyses (alone or in combination) produced minor changes in the

estimates, but did not yield any changes in statistical significance. Results are not reported here.

DISCUSSION

We found no statistically significant relationship between BMI and pre-biopsy PSA in patients with biopsy proven prostate cancer. We also found that BMI was not associated with higher-risk disease based on Gleason score, clinical T-stage, or D'Amico risk. This suggests that obese patients were no more likely to harbor more advanced disease and hence, may not benefit from more aggressive treatment options.

Prior positive literature on BMI and PSA focused on screening populations, whereas our patient population had biopsy-proven prostate cancer. In particular, Price *et al.* evaluated an ethnically diverse population in North Carolina undergoing free prostate cancer screening including patients with and without disease.[14] In contrast, our patients all had biopsy-proven prostate cancer. Although there were some negative studies in screening populations,[20,21,26] most found an association.[7,9–13] There is very limited literature on the association of BMI and PSA in patients with proven prostate cancer. Freedland *et al.* studied the association of BMI as a predictor of PSA and severity of prostate disease in patients undergoing radical prostatectomy.[22] Like our study, they found no association between BMI, PSA and clinical T-stage. While biopsy Gleason sum was significant across BMI categories, pathologic Gleason sum was not. Furthermore, their study only found an association between obesity and prostate size in a subset of men younger than 63 years of age. Irrespective, these results did not demonstrate a strong, consistent relationship between obesity and lower PSA levels or more advanced disease in those with biopsy proven prostate cancer.

Inconsistent results may in part be attributed to the imperfect use of BMI, which combines adipose and non-adipose body components, as a proxy for obesity. Some cohort studies attempted to obviate this obstacle by utilizing a validated estimate of lean body mass using an algorithm based on age, height and weight; however, their findings were largely inconclusive.[19,27,28] Using bioelectric impedance, MacInnis *et al.* discovered that risk of high-grade disease was increased for men with high adipose mass, but was not related to non-adipose mass.[29] While the amount of adiposity has been associated with prostate cancer risk, the diffusion of bioelectric impedance and subsequent variation in interpretation into routine practice for risk stratification is impractical. Moreover, the association of obesity with PSA and prostate cancer severity overlooks the big elephant in the room—cardiovascular health. In an analysis of 1,482 Veterans with varying degrees of prostate cancer severity (36% low risk, 33% intermediate risk, and 30% high risk) and mean follow-up of 6 years, only 3% died of prostate cancer.[30] The vast majority died of other causes. Nevertheless, as our population becomes more obese, improvements above and beyond BMI need to be made to better risk stratify patients not just for prostate cancer, but also for cardiovascular disease.

While our findings are significant, our study is not without its limitations. First, our study was retrospective in nature, and is therefore subject to omitted variable bias. This is particularly relevant, as we did not include pre-biopsy PSA values of men without prostate cancer. However, the concern is not so much that obese patients may harbor prostate cancer insomuch as having occult locally advanced or metastatic disease. In our analysis, we found that increasing BMI was not associated with a higher pre-biopsy PSA, clinical stage, Gleason score, or D'Amico risk. Second, our cohort consisted of ethnic, regional, and socioeconomic extreme patient populations; thus our combined sample may not adequately represent the US population as a whole. However, even when stratified, we found no statistically significant association with pre-biopsy PSA or prostate cancer severity. Third,

pre-biopsy PSA levels were measured at multiple facilities over the course of seven years, making our findings susceptible to laboratory heterogeneity. Nonetheless, this level of variation is within the expected error of the test, and would not fully explain the negative findings. Last, BMI may be an imperfect measure of obesity. We calculated BMI from self-reported height and weight, leading to potential deviations from the patients' true measurements. While additional markers for obesity such as body fat composition and waist circumference to height ratio may be preferred proxies for obesity, we used weight and subsequently BMI as a convenient alternative. Moreover, BMI is measured universally and its association with PSA has been thoroughly studied, making it a generalizable and convenient proxy for obesity.

With these limitations in mind, our results still have implications for the screening and detection of prostate cancer in obese patients. In this cohort of men with biopsy proven prostate cancer, we did not find a statistically significant association between BMI and disease severity— pre-biopsy PSA, clinical stage, Gleason score or D'Amico tumor risk. Increasing efforts should be made to measure the association between BMI and pre-biopsy PSA on a population-level with adequate representation of economically, regionally, and ethnically diverse US population.

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Table 1

Clinical and demographic features by study sample

	Total (*N*=573)		California (*N*=276)		Michigan (*N*=297)		*P*
Age at Enrollment							**<0.01**[a]
<60	210	36.6%	106	38.4%	104	35.0%	
60 to <65	212	37.0%	129	46.7%	83	27.9%	
≥65	151	26.4%	41	14.9%	110	37.0%	
Mean ± SD	62.36 ± 8.22		61.06 ± 6.81		63.38 ± 9.20		**<0.01**
Range	40–89		40–88		41–89		
Race/Ethnicity							**<0.01**
White	315	55.0%	45	16.3%	270	90.9%	
Black	73	12.7%	55	19.9%	18	6.1%	
Hispanic	148	25.8%	147	53.3%	1	0.3%	
Other	37	6.5%	29	10.5%	8	2.7%	
Preferred Language							**<0.01**
English	454	79.2%	157	56.9%	297	100.0%	
Not English	119	20.8%	119	43.1%	0	0.0%	
Education							**<0.01**
< High School	104	18.2%	92	45.8%	12	4.0%	
≥High School	394	68.8%	109	54.2%	285	96.0%	
BMI (kg/m2)							**0.04**
Normal Weight (<25)	164	28.6%	74	26.8%	90	30.3%	
Overweight (25.0–29.9)	253	44.2%	129	46.7%	124	41.8%	
Mildly Obese (30.0–34.9)	115	20.1%	61	22.1%	54	18.2%	
Moderately to Severely Obese (≥35)	41	7.2%	12	4.3%	29	9.8%	
Diabetes							0.07
Yes	57	9.9%	34	12.3%	23	7.7%	
No	516	90.1%	242	87.7%	274	92.3%	

	Total (*N*=573)		California (*N*=276)		Michigan (*N*=297)		*P*
PSA (ng/ml)							**<0.01**[a]
<4	84	14.7%	32	11.6%	52	17.5%	
4 to 10	339	59.2%	146	52.9%	193	65.0%	
>10	150	26.2%	98	35.5%	52	17.5%	
Median	6.7		8.2		5.8		
Biopsy Gleason Score							**<0.01**
6	263	46.3%	145	53.5%	118	39.7%	
7	189	33.3%	75	27.7%	114	38.4%	
8–10	116	20.4%	51	18.8%	65	21.9%	
Clinical T-Stage[b]							**<0.01**[c]
cT1	357	63.2%	141	52.6%	216	72.7%	
cT2	174	30.8%	97	36.2%	77	25.9%	
cT3/cT4	34	6.1%	30	11.3%	4	1.4%	
D'Amico Risk							0.31
Low Risk	202	35.4%	95	34.8%	107	36.0%	
Intermediate Risk	209	36.7%	94	34.4%	115	38.7%	
High Risk	159	35.4%	84	30.8%	75	25.3%	

Chi-square except where otherwise noted;

[a] *t*-test *p*-value;

[b] 8 missing subjects;

[c] Fisher's exact p-value;

[d] 3 missing subjects

Table 2

Clinical features stratified by body mass index

	Normal Weight (*N*=164) (<25 kg/m^2)		Overweight (*N*=253) (25.0–29.9 kg/m^2)		Mildly Obese (*N*=115) (30.0–34.9 kg/m^2)		Moderately to Severely Obese (*N*=41) (≥ 35 kg/m^2)		*P*
Age at Enrollment									**0.04**[a]
<60	49	29.9%	91	36.0%	51	44.4%	19	46.3%	
60 to <65	60	36.6%	97	38.3%	44	38.3%	11	26.8%	
≥65	55	33.5%	65	25.7%	20	17.4%	11	26.8%	
Race/Ethnicity									**<0.01**
White	100	61.0%	136	53.8%	51	44.3%	28	68.3%	
Black	17	10.4%	29	11.5%	19	16.5%	8	19.5%	
Hispanic	28	17.1%	75	29.6%	40	34.8%	5	12.2%	
Other	19	11.6%	13	5.1%	5	4.3%	0	0.0%	
Preferred Language									**<0.01**
English	139	84.8%	197	77.9%	79	68.7%	39	95.1%	
Not English	25	15.2%	56	22.1%	36	31.3%	2	4.9%	
Education									**<0.01**
<High School	139	84.8%	197	77.9%	79	68.7%	39	95.1%	
≥ High School	25	15.2%	56	22.1%	36	31.3%	2	4.9%	
Diabetes									0.38
Yes	14	8.6%	22	8.7%	15	13.0%	6	14.6%	
No	150	91.5%	231	91.3%	100	87.0%	35	86.4%	
PSA (ng/mL)									0.57[a]
<4	27	16.5%	35	13.8%	17	14.8%	5	12.2%	
4 to 10	88	53.7%	152	60.1%	70	60.9%	29	70.7%	
>10	49	29.9%	66	26.1%	28	24.4%	7	17.1%	
Biopsy Gleason Score									0.27
6	78	48.4%	116	46.2%	54	47.0%	15	36.6%	

	Normal Weight (*N*=164) (<25 kg/m^2)		Overweight (*N*=253) (25.0–29.9 kg/m^2)		Mildly Obese (*N*=115) (30.0–34.9 kg/m^2)		Moderately to Severely Obese (*N*=41) (≥ 35 kg/m^2)		*P*
7	49	30.4%	90	35.9%	36	31.3%	14	34.2%	
8–10	34	12.1%	45	17.9%	25	21.7%	12	29.3%	
Clinical T Stage[b]									**0.04**
cT1	95	59.0%	157	62.6%	76	67.3%	29	72.5%	
cT2	55	34.2%	72	28.7%	36	31.9%	11	27.5%	
cT3/cT4	11	6.8%	22	8.8%	1	0.9%	0	0.0%	
D'Amico Risk[c]									0.90
Low risk	57	35.0%	89	35.5%	42	36.5%	14	34.2%	
Intermediate risk	55	33.7%	96	38.3%	44	38.3%	14	34.2%	
High risk	51	31.3%	66	26.3%	29	25.2%	13	31.7%	

Chi-square except where otherwise noted;

[a] T-test *p*-value;

[b] 8 missing subjects;

[c] 3 missing subjects

Table 3

Multivariate linear regressions of log-transformed PSA with BMI as the main predictor

BMI as a Categorical Variable				**BMI as an Imputed Median**			
	Estimate	**SE**	**p-value**		**Estimate**	**SE**	**p-value**
BMI Category	---	---	---	BMI, continuous	−0.01	0.01	0.40
Normal		Referent			---	---	---
Overweight	0.07	0.10	0.46		---	---	---
Obese	−0.08	0.11	0.47		---	---	---
Age at Enrollment	0.01	0.01	**0.01**	Age at Enrollment	0.01	0.01	**0.01**
Race/Ethnicity				Race/Ethnicity			
White		Referent		White		Referent	
Non-White	0.06	0.13	0.64	Non-White	0.06	0.13	0.64
Site of Care				Site of Care			
CA		Referent		CA		Referent	
Michigan	−0.22	0.13	0.07	Michigan	−0.24	0.13	0.06
Gleason Score				Gleason Score			
6		Referent		6		Referent	
7–10	0.48	0.08	**<0.01**	7–10	0.48	0.08	**<0.01**

Table 4

BMI predictors of disease severity based on multinomial logistic regression (RRR or OR (95% CI)).

	PSA Referent: <4 ng/mL		Gleason Score Referent: Gleason 6		T-stage Referent: cT1	D'Amico Risk Referent: Low	
	>10 ng/ml	**4–10 ng/ml**	**8–10**	**7**	**T2–T4**	**High**	**Intermediate**
BMI							
Normal	1.00 (referent)		1.00 (referent)		1.00 (referent)	1.00 (referent)	
Overweight	1.06(0.56–2.03)	1.37(0.77–2.42)	1.00(0.58–1.73)	1.33(0.84–2.10)	1.22(0.80–1.86)	0.89(0.54–1.47)	1.16(0.72–1.86)
Obese	1.05(0.50–2.20)	1.47(0.77–2.79)	1.54(0.85–2.79)	1.28(0.76–2.16)	1.45(0.89–2.36)	1.03(0.58–1.83)	1.17(0.69–1.98)
Age (continuous)	1.08(1.04–1.11)[a]	1.03(1.00–1.07)[d]	1.05(1.02–1.04)[a]	1.01(0.99–1.04)	0.98(0.96–1.00)[a]	1.06(1.03–1.09)[a]	1.02(1.00–1.05)
Race/Ethnicity							
White	1.00 (referent)		1.00 (referent)		1.00 (referent)	1.00 (referent)	
Non-White	1.19(0.52–2.71)	1.21(0.58–2.52)	0.81(0.41–1.61)	0.64(0.36–1.13)	1.05(0.62–1.78)	0.76(0.40–1.44)	0.83(0.46–1.50)
Site							
CA	1.00 (referent)		1.00 (referent)		1.00 (referent)	1.00 (referent)	
Michigan	0.30(0.13–0.69)[a]	0.89(0.43–1.82)	1.16(0.58–2.31)	1.32(0.75–2.34)	2.64(1.55–4.51)[a]	0.55(0.29–1.05)	0.91(0.50–1.64)

[a]Denotes p<0.05