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Body mass index does not improve the ability to predict biochemical recurrence after radical prostatectomy

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ABSTRACT

Purpose: To test whether body mass index (BMI) improves pre- or post-operative biochemical recurrence (BCR) predictions after radical prostatectomy.
Materials and methods: Pre- and post-operative data were available in 2416 and 2499 men, respectively. Cox regression models addressed the association between BMI and the rate of BCR after adjusting for pre- and post-operative predictors. Predictive accuracy was quantified using Harrell's concordance index, with and without BMI and subjected to 200 bootstraps to reduce overfit bias. Differences in predictive accuracy were compared using the Mantel–Haenszel test.
Results: After adjusting for either pre- or post-operative variables, increasing BMI was a statistically independent risk factor of BCR in both models (both $p \leqslant 0.003$). Its addition to pre- and post-operative variables respectively increased predictive accuracy measures from 69.6 to 70.2% (+0.6%, $p = 0.7$) and from 78.1 to 78.4% (+0.3%, $p = 0.8$).
Conclusion: Our data emphasise that despite its significance, inclusion of BMI into models, to predict BCR, does not improve their accuracy.

1. Introduction

Up to 30% of the United States population is estimated to suffer from obesity.[1] The increase in prevalence of obesity has been paralleled by an increase in prevalence of prostate cancer (PCa). Obesity has been linked to chronic diseases such as coronary artery disease, hypertension and diabetes,[2–4] as well as to several types of cancer.[5] Furthermore, obesity,[6] defined as a body mass index (BMI) in excess of 30 kg/m^2, has been associated with an increased risk of PCa death indicating more aggressive disease among obese men.

However, controversy surrounds the association between obesity and PCa risk and biochemical recurrence (BCR) after radical prostatectomy (RP).[7–10] Despite obesity's value as an independent risk factor regarding prognostic outcome after RP which has been recently demonstrated,[7,8] its informative potential to increase predictive accuracy of BCR predictions has been questioned.[10]

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We addressed this controversy in a large dataset of RP patients with available pre- and post-operative data. Subsequently, we applied analytical methods that were more stringent than those used in the previous reports.[7,8] Besides testing BMI's multivariable independent status, these methods quantified the increment in predictive accuracy related to its inclusion to established pre- and post-operative predictors in RP BCR models.[11,12]

2. Materials and methods

2.1. Patient population

Between January 1995 and August 2004, 3310 PCa patients were treated with RP for clinically localised disease at a single tertiary care, referral centre. Patients with unavailable pre- ($n = 894$) or post-operative data ($n = 811$) such as pre-treatment PSA, clinical stage or biopsy Gleason score, organ confinement (OC), extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node invasion (LNI), positive surgical margin status (+SM), pathologic Gleason score, or lack of follow-up information were excluded from the study. This resulted in respectively 2416 and 2499 evaluable PCa patients for the pre- and post-operative BCR model.

2.2. Pathological and clinical evaluation

Clinical stage was assigned by the attending urologist according to the 2002 TNM system. Between six and 24 systematic needle biopsy cores were obtained under transrectal- ultrasound (TRUS) guidance. Pre-treatment PSA (Abbott Axym PSA assay, Abbott Park, IL, USA) was measured before digital rectal examination (DRE) and TRUS. Primary and secondary biopsy Gleason scores were assigned by a single pathologist (A.E.). All prostatectomy specimens were surface inked and processed according to the Stanford protocol.[13] Pathological stage was defined according to the 2002 AJCC staging classification.[14] Histological tumour grading was performed according to the Gleason grading system.[15] A positive surgical margin was defined as cancer cells in contact with the inked specimen surface. Body mass index (BMI) was recorded before the diagnosis of PCa by dividing the weight (kg) by the square of the height (m^2).[16] For Kaplan–Meier survival analysis, patients were stratified into the following BMI categories according to the World Health Organisation (WHO) classification:[6] Category 1, defined as acceptable, is represented by a BMI of <25 kg/m^2; Category 2, defined as overweight, is represented by a BMI between $\geqslant$25 and <30 kg/m^2; Category 3, defined as obese, is represented by a BMI between $\geqslant$30 and <40 kg/m^2; Category 4, defined as morbidly obese, is represented by a BMI of $\geqslant$40 kg/m^2. In all patients, PSA values were measured quarterly in the first year, followed by biannual measurements in the second and annual measurements in the third year after RP. BCR was defined as a postoperative PSA of 0.1 ng/ml and rising after an initial undetectable PSA. The first PSA value above or equal to 0.1 ng/ml was used to define the time to BCR. Patients without evidence of BCR were censored at last follow-up.

2.3. Statistical methods

Biochemical recurrence-free probability after RP was calculated using the Kaplan–Meier method, and the log-rank test to compare BMI strata. Due to few individuals with a BMI of $\geqslant$40 kg/m^2 in either the clinical or the pathological datasets ($n = 3$ and $n = 4$), these men were included within category 3 (BMI between $\geqslant$30 and <40 kg/m^2).

Pre-operative variables consisted of PSA, clinical stage and biopsy Gleason sum. Post-operative variables consisted of PSA, OC, ECE, SVI, LNI, +SM and pathologic Gleason sum. These pre- and post-operative base predictors were used in univariable and multivariable Cox regression models addressing the association between continuously coded BMI and the rate of BCR after RP. Predictive accuracy of BCR predictions was quantified using Harrell's concordance index, in models with and without BMI. This method was selected with the intent of quantifying the increment in predictive accuracy, associated with the addition of BMI to all base predictor variables. Two hundred bootstrap resamples were used for internal validation of all accuracy estimates and to reduce overfit bias. Differences in predictive accuracy were tested for statistical significance using the Mantel–Haenszel test. All statistical tests were performed using S-PLUS Professional, version 1 (MathSoft Inc., Seattle, Washington). Moreover, all tests were two-sided with a significance level at 0.05.

3. Results

Patient characteristics according to pre- and post-operative model are shown in Table 1. In the pre-operative model, 475 (19.7%) versus 487 (19.5%) in the post-operative model demonstrated BCR during follow-up, which ranged for both models from 0.1 to 112 months (mean 30.6; median 25.9 months). Pre-treatment PSA ranged from 0.1–49.0 ng/ml (mean 9.0, median 7.0) for the pre-operative model versus 0.1–49.8 ng/ml (mean 8.9, median 6.9) for the post-operative model. BMI for both models was identical ranging from 15.7 to 43.3 kg/m^2 (mean 26.2, median 25.9).

The 2 and 5 year biochemical recurrence-free probabilities for the WHO-derived BMI categories are shown in Table 2. Interestingly, in both models, BMI of 25–30 was associated with statistically significantly lower rates of BCR versus BMI $\leqslant$25 ($p = 0.009$ and $p = 0.11$). Figs. 1A and 2A graphically display the overall biochemical recurrence-free probability for both models. Figs. 1B and 2B show the effect of WHO–BMI categories on BCR rates after RP for the pre-operative and the post-operative model.

Table 3 shows the univariable and multivariable Cox regression models predicting BCR using pre-operative and post-operative predictors. In both univariable models, all variables including BMI were highly statistically significant predictors of BCR after RP (all $p \leqslant 0.001$). In the pre-operative model, univariable predictive accuracy values for biopsy Gleason sum, PSA and clinical stage were 66.0, 62.9 and 59.3%. BMI demonstrated 54.6% accuracy, where 50% is equal to a flip of a coin and 100% equals perfect prediction. In the post-operative model, univariable predictive accuracy estimates for OC, RP Gleason sum, SVI, PSA, +SM, LNI, and ECE were respectively

Table 1 – Descriptive characteristics of, respectively, 2416 and 2499 men treated with radical prostatectomy according to available clinical and pathological variables which were respectively used in the pre-operative and post-operative biochemical recurrence model

Type of model	Variables	
Clinical variables:	Total number of patients (%)	2416 (100.0%)
Pre-operative model	PSA (ng/ml)	
	Mean (median)	9.0 (7.0)
	Range	0.12-49.0
	Clinical stage	
	T1c	1563 (64.7%)
	T2	817 (33.8%)
	T3	36 (1.5%)
	Biopsy Gleason sum	
	2–5	239 (9.9%)
	6	1364 (56.5%)
	7	727 (30.1%)
	8–10	86 (3.6%)
	BMI (kg/m^2)	
	Mean (median)	26.2 (25.9)
	Range	15.7–43.3
	BMI (quartiles, kg/m^2)	
	15.7–24.2	595 (24.6%)
	>24.2–25.9	620 (25.7%)
	>25.9–27.8	610 (25.2%)
	>27.8–43.3	591 (24.5%)
	Events of BCR	475 (19.7%)
	Follow-up (months)	
	Mean (median)	30.6 (25.9)
	Range	0.1–112.0
Pathologic variables:	Total number of patients (%)	2499 (100.0%)
Post-operative model	PSA (ng/ml)	
	Mean (median)	8.9 (6.9)
	Range	0.12–49.8
	Organ confinement status	1693 (67.7%)
	Extracapsular extension	499 (20.0%)
	Seminal vesicle invasion	294 (11.8%)
	Lymph node invasion	86 (3.4%)
	Positive surgical margins	528 (21.1%)
	RP Gleason sum	
	2–5	281 (11.2%)
	6	863 (34.5%)
	7	1313 (52.5%)
	8–10	42 (1.7%)
	BMI (kg/m^2)	
	Mean (median)	26.2 (25.9)
	Range	15.7–43.3
	BMI (quartiles, kg/m^2)	
	15.7–24.2	622 (24.9%)
	>24.2–25.9	640 (25.6%)
	>25.9–27.8	626 (25.1%)
	>27.8–43.3	611 (24.4%)
	Events of BCR	487 (19.5%)
	Follow-up (months)	
	Mean (median)	30.6 (25.9)
	Range	0.1–112.0

PSA - prostate specific antigen; RP - radical prostatectomy; BMI - body mass index; BCR - biochemical recurrence.

Table 2 – Recurrence free survival (RFS) at 2 and 5 years after radical prostatectomy of the pre-operative and post-operative model stratified according to WHO–BMI categories

	BMI (kg/m^2)^{ref}	Number of patients (%)	RFS @ 2 years (95% CI) *[No. pts. at risk]*	RFS @ 5 years (95% CI) *[No. pts. at risk]*
Pre-operative model	<25	909	86.7% (84.3–89.2) [500]	76.0% (72.2–79.9) [136]
	⩾25–<30	1254	82.3% (80.0–84.7) [660]	67.3% (63.7–71.2) [157]
	⩾30–<40	250	84.4% (79.5–89.6) [130]	67.7% (59.5–77.0) [30]
Post-operative model	<25	945	86.7% (84.4–89.2) [514]	76.1% (72.4–79.9) [142]
	⩾25–<30	1292	82.5% (80.2–84.9) [683]	68.0% (64.4–71.8) [163]
	⩾30–<40	258	83.8% (79.0–89.0) [131]	68.9% (61.1–77.7) [32]

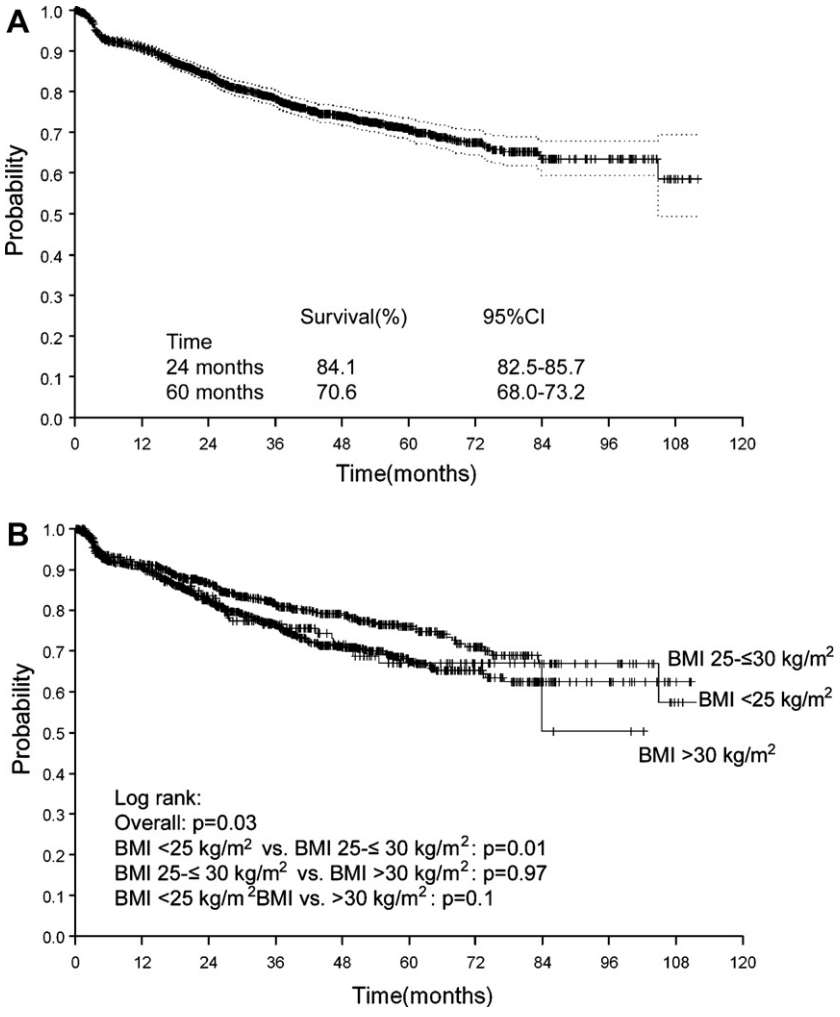

Fig. 1 – Pre-operative model: Overall biochemical recurrence-free probability after RP and biochemical recurrence-free probability stratified according to the WHO body mass index categories. (A) Overall biochemical recurrence-free probability after RP: Pre-operative model; (B) Biochemical recurrence-free probability stratified according to the WHO body mass index categories: Pre-operative model.

69.6, 68.4, 63.7, 63.0, 60.3, 56.0, and 54.8%. BMI demonstrated 55.1% accuracy. In multivariable BCR models, we fitted two models. The first model tested the association between BMI and BCR after adjusting for the pre-operative variables. In the second model, the adjustment was performed for post-operative variables. In both models, all variables represented highly statistically significant predictors (all $p \leqslant 0.008$) of BCR after RP, except for ECE ($p \geqslant 0.5$) and SVI ($p \geqslant 0.4$) in the post-operative model. The combined multivariable predictive accuracy of both the pre- and post-operative models exceeded respectively any single univariable predictor. The addition of BMI failed to improve bootstrap-adjusted multivariable predictive accuracy of the pre-operative model, where a non-significant (Mantel–Haenszel test: $p = 0.7$) predictive accuracy increase from 69.6 to 70.2% (0.6% gain) was recorded. Absence of a significant gain (Mantel–Haenszel test: $p = 0.8$) was also

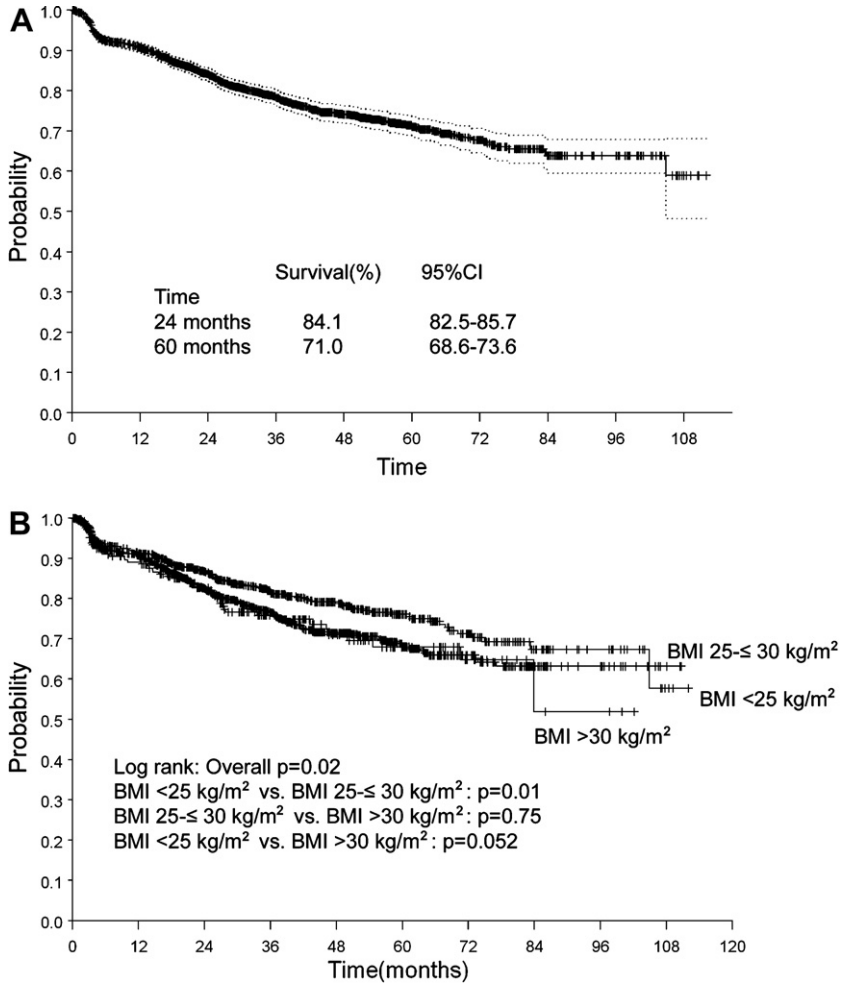

Fig. 2 – Post-operative model: Overall biochemical recurrence-free probability after RP and biochemical recurrence-free probability stratified according to the WHO body mass index categories. (A) Overall biochemical recurrence-free probability after RP: Post-operative model; (B) Biochemical recurrence-free probability stratified according to the WHO body mass index categories: Post-operative model.

noted in the post-operative model, where predictive accuracy increased from 78.1 to 78.4% (0.3%), when BMI was added.

4. Discussion

Accurate prediction of pathological stage and BCR following definitive treatment for localised PCa is important for patient counselling and treatment planning.[11,12] Recently, prognostic tools incorporating various clinical and histopathological features, have been used to predict relapse in clinically localised PCa after RP.[11,12] However, no tool predicts perfectly and incorporation of novel markers may potentially increase overall model predictive accuracy.[17]

Recently, obesity has been investigated as a potential novel marker for PCa. Increasing BMI has been shown to increase the risk of PCa mortality. However, there is no consensus about the effect of obesity on the rate of BCR after RP.[5,7–10] Based on the potential value prognostic value of BMI, we hypothesised that the extent of obesity, quantified as BMI, may add to our ability to predict BCR after RP. We tested this hypothesis in the largest so far BMI dataset in the context of RP. Moreover, we used stringent statistical analyses, where besides demonstrating the multivariable independent predictor status, a novel marker should enhance the overall model predictive accuracy. We complemented the standard univariable and multivariable tests of the parameter defining BMI with these predictive accuracy tests. Finally, we used the Mantel–Haenszel test to assess whether the change in predictive accuracy related to the inclusion of BMI to established pre-operative or post-operative predictors of BMI is statistically significant.

In Kaplan–Meier analyses, we demonstrated that the biochemical recurrence-free probabilities after RP decreased significantly with increasing BMI in the pre- ($p = 0.03$) as well as in the post-operative model ($p = 0.02$). Moreover, the multivariable pre- and post-operative Cox regression BCR models (Table 3) indicated that increasing BMI represents a highly statistically significant (both models, $p < 0.001$) and independent risk factor (both models, $p = 0.003$) of BCR after RP.

In univariate predictive accuracy tests, BMI's bootstrap-corrected predictive accuracy was 54.6% versus 55.1% in the post-operative model. Perfect predictions are represented by 100% predictive accuracy and 50% represents a flip of a coin. The multivariable, bootstrap-corrected predictive accuracy

Table 3 – Pre- and post-operative univariable and multivariable Cox regression models predicting biochemical recurrence according to inclusion/ exclusion of the body mass index

	Prediction of BCR: Pre-operative model			
Type of analyses	Univariable model		Multivariable model	
Predictors	Predictive accuracy (%)	RR; *p* value	Base model[a] RR; *p* value	Base model + BMI RR; *p* value
Clinical Stage		– ; <0.001	– ; 0.005	– ; 0.005
T2 versus T1c	59.3	1.97; <0.001	1.37; 0.001	1.37; 0.001
T3 versus T1c		4.80; <0.001	1.36; 0.22	1.39; 0.19
PSA	62.9	1.06; <0.001	1.06; <0.001	1.04; <0.001
Biopsy Gleason sum	66.0	– ; <0.001	– ; <0.001	– ; <0.001
6 versus 2–5		1.27; 0.32	1.26; 0.34	1.26; 0.33
7 versus 2–5		4.09; <0.001	3.37; <0.001	3.352; <0.001
8–10 versus 2–5		9.08; <0.001	6.16; <0.001	6.220; <0.001
BMI	54.6	1.05; <0.001		1.04; 0.003
Predictive accuracy (%)	–		69.6	70.2
[Mantel–Haenszel test]			+ 0.6 [$p = 0.7$]	
	Prediction of BCR: Post-operative model			
Type of analyses	Univariable model		Multivariable model	
Predictors	Predictive accuracy (%)	RR; *p* value	Base model[b] RR; *p* value	Base model + BMI RR; *p* value
PSA	63.0	1.06; <0.001	1.03; <0.0001	1.0; <0.001
OC: yes versus no	69.6	0.19; <0.001	0.39; 0.008	0.36; 0.005
ECE: yes versus no	54.8	1.76; <0.001	0.80; 0.53	0.75; 0.41
SVI: yes versus no	63.7	25.77; <0.001	1.46; 0.26	1.35; 0.38
LNI: yes versus no	56.0	7.04; <0.001	1.88; <0.001	1.86; <0.001
SM: positive versus negative	60.3	2.76; <0.001	1.70; <0.001	1.68; <0.001
RP Gleason sum	68.4	– ; <0.001	– ; <0.001	– ; <0.001
6 versus 2–5		0.74; 0.26	0.81; 0.44	0.83; 0.46
7 versus 2–5		4.60; <0.001	2.51; <0.001	2.54; <0.001
8–10 versus 2–5		16.73; <0.001	6.65; <0.001	7.07; <0.001
BMI	55.1	1.05; <0.001		1.04; 0.003
Predictive accuracy (%)	–		78.1	78.4
[Mantel–Haenszel test]			+ 0.3 [$p = 0.8$]	

PSA - prostate specific antigen.
BMI - body mass index.
OC - organ confinement.
ECE - extracapsular extension.
SVI - seminal vesicle invasion.
LNI - lymph node invasion.
SM - surgical margin status.
a Pre-operative base model: PSA, clinical stage, biopsy Gleason sum.
b Post-operative base model: PSA, OC, ECE, SVI, LNI, RP Gleason sum, SM.

of the established pre-operative predictors was 69.6% and 78.1% for the post-operative predictors. When BMI was added to the pre-operative model, bootstrap-corrected predictive increased from 69.6 to 70.2% (0.6% gain). A 0.3% gain was noted in the postoperative model, where predictive accuracy increased from 78.1 to 78.4%. Neither of the recorded gains demonstrated statistical significance.

Taken together these observations indicate a dichotomy, as BMI represents an independent predictor of BCR but at the same time it does not result in either a statistically significant or clinically meaningful increase in the ability to predict the rate of BCR after RP, in either pre-operative or post-operative models. These findings suggest that we have to reject our hypothesis and we have to conclude that BMI does not fulfill the characteristics of a novel and informative marker to improve BCR predictions.

Our BMI findings within the pre-operative model are in part corroborated by Mallah et al.[10], who investigated 2210 men with respect to the association between the continuously coded reciprocal of BMI and BCR. Unlike our analyses, the adjustment was exclusively made for pre-operative variables. In this analysis, the continuously coded reciprocal of BMI represented a statistical significant predictor of BCR in univariable analyses ($p = 0.04$), as well as an independent predictor of BCR in multivariable model ($p = 0.04$). In their North American cohort, Mallah et al. were the first to demonstrate that the added value related to the addition of reciprocal, continuously coded BMI to pre-operative variables was negligible (79.4 versus 79.8%; gain of 0.4%). When they repeated their analyses and used continuously coded BMI, as we did here, this variable failed to achieve an independent predictor status in BCR models ($p = 0.07$).

Our findings that BMI represents an independent risk factor of BCR corroborate a report by Freedland et al.[7] who indicated that either categorically coded BMI in excess of 35 kg/m^2 ($p = 0.02$) or continuously coded BMI ($p = 0.05$) represent independent, multivariable predictors of BCR after RP. In another report, Freedland et al.[8] restricted their analyses to pathologically organ confined disease with negative surgical margins. Again, they demonstrated that BMI in excess of 35 kg/m^2 represents an independent predictor of BCR after RP. Models integrating post-operative variables were not fitted or described in that report.

Taken together, our findings, indicating that continuously coded BMI represents an independent risk factor of BCR, corroborate reports of the Johns Hopkins group[7,8] where BMI in excess of 35 kg/m^2 was associated with increased risk of an adverse biochemical outcome after RP.

As postulated by Kattan[18], statistical significance is not synonymous with predictive ability. Instead, Kattan recommends that a novel marker should not only be judged according to its multivariable statistical significance, but should increase the combined predictive accuracy of base predictors, in addition to confirming the independent, multivariable predictor status of this marker. We followed this recommendation[18] and tested the accuracy of a pre- and post-operative base multivariable BCR model where BMI was omitted, with 200 bootstraps resamples to reduce overfit bias Thus, besides demonstrating BMI's multivariable independent predictor status, BMI should enhance the overall model ability to predict BCR. If this is demonstrated in a statistically and clinically meaningful fashion, then the marker may be qualified as clinically important.[19]

Unfortunately, predictive accuracy has not been assessed in any of the aforementioned studies.[7,8] We circumvented this limitation of previous studies, by complementing multivariable analyses with quantification of the added value related to inclusion of BMI to both the pre-operative model or to the post-operative model. Our findings, based on over 2400 patients, demonstrate that despite its independent predictor status, BMI does not represent an informative predictor of BCR. This was evidenced by dismal and statistically insignificant increases in predictive accuracy, in both the preoperative model (gain 0.6; $p = 0.7$) and the post-operative model (gain 0.3; $p = 0.8$). Thus, this final analytic step failed to demonstrate any benefit related to consideration of BMI for neither pre- nor post-operative BCR prediction.

Several limitations may apply to our findings. First, our patient cohort is limited to men undergoing surgical treatment for localised prostate cancer. Surgical patients tend not to exceed a certain BMI, which is reflected in our patient cohort, where respectively 1.1 and 1.2% had moderate to severe obesity. Therefore, our BMI range is limited and does not reflect the general population. Second, our median follow-up was short (median 25.9 months). Therefore, the rates of observed BCR might be lower than in a longer follow-up cohort. Moreover, BCR as an outcome after RP can be disputed. However, D'Amico et al.[20] showed that patients with evidence of BCR are at increased risk to die of PCa. Third, other measures of obesity such as waist-to-hip-ratio, the reciprocal of BMI or percentage of lean body fat were not available and may need to be taken into account in future studies.

5. Conclusion

Using the most stringent methodology, BMI was identified as a statistically independent yet uninformative variable that is not capable of increasing the predictive accuracy of multivariable BCR models.

Conflict of interest statement

None declared.

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