Impact of Biopsy Gleason Upgrading On Biochemical Recurrence and Prediction for Prostate Cancer Aggressiveness among Obese and African American Men

By

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Overview: Background and Context

Prostate cancer (PCa) is the one of the most commonly diagnosed cancers and the leading cause of cancer deaths in American men. Currently, diagnosing PCa requires decision-making tools such as the biopsy Gleason grade (BGR), prostate specific antigens (PSA) and clinical tumor staging. Among these three tools, BGR is considered the most important staging tool for PCa diagnosis, risk classification and treatment decision in initial evaluation of PCa. However, BGR can be misclassified after radical prostatectomy (RP), leading to PCa patients being upgraded to more aggressive Gleason grades. This upgrading has been suggested to be associated with adverse outcomes, including cancer recurrence (biochemical recurrence) or PCa mortality. Additionally, prostate cancer disproportionately burdens certain groups, such as those who are obese, men aged 60 and older, and African American men. However, there is very limited research that has looked at the effect of Gleason upgrading on biochemical recurrence among these risk factor groups. In this research, we used PCa data from the Study of Clinical Outcomes, Risk and Ethnicity (SCORE) to examine the effect of Gleason upgrading on biochemical recurrence and to develop better prediction models for Gleason grades after surgery. In project 1, we examined the rate of Gleason biopsy upgrading after radical prostatectomy, and evaluated if this upgrading is associated with biochemical reoccurrence, and if this association varies by obesity, race and advanced age. In project 2, we compared accuracy PSA vs. PSA mass for predicting Gleason path aggressiveness. Further univariate and stepwise selections were used to define the best models for prediction of Gleason pathology aggressiveness. We examined the risk factors associated with race and obesity status, to determine whether preoperative prostate-specific antigen mass (PSA mass) is a better predictor for prostate cancer aggressiveness compared to PSA. Also, whether the prediction accuracy varies by obesity and race.

Project 1

Abstract

Introduction: Biopsy Gleason grade (BGR) upgrading in radical prostatectomy (RP) specimens is associated with a higher risk of biochemical reoccurrence (BCR). However, research to examine this association in high-risk groups for prostate cancer, such as obese, African-American (AA) and advanced age men is limited.

Objectives: To examine whether BGR upgrading is associated with increased risk of biochemical recurrence among obese, AA and older men.

Methods: Retrospective analyses of a cohort of 1028 men with low and medium risk of prostate cancer (PCa) (BGR groups 1&2) who underwent RP between 1995- 2012 at the University of Pennsylvania Health System (UPHS, Philadelphia, PA). Association of BGR upgrading and BCR after RP among obese, AA and older men were examined using log rank test and Cox proportional hazards models.

Results: In this cohort, there were 251 obese men and 200 AA men. Upgrading from BGR 1 and 2 (low and middle risk PCa, respectively) to RPG≥ 3 (high risk PCa) significantly increased BCR; the log rank test p value for upgraded compared to concordant in both groups was 0.0037 and <0.0001respectively.

In low risk PCa group, the log rank P values showed no difference between BGR upgrading and concordance group among obese 0.14, AA 0.07 and older men 0.12. BGR upgrading from both low and middle risk to high risk PCa showed significant difference in BCR compared to concordant group, and was independent of obesity, race and age.

The log rank test p values comparing upgrading versus concordant groups among obese, AA and older men were 0.0005, 0.001 and <0.0001 respectively.

Conclusions: This study confirmed that BGR upgrading from low and middle risk PCa groups to high risk PCa group increases BCR. Additionally, obesity, AA race and older age are independent risk factors for BCR in low risk PCa group regardless of upgrading. Further studies are warranted to confirm these associations in larger and diverse populations.

Introduction

Prostate cancer (PCa) is the most common malignant cancer and the second leading cause of cancer death of men in the USA(1). Widespread use of prostate-specific antigen (PSA) for initial PCa screening has led to an overwhelming increase in diagnosis of early stages of PCa. Consequently, this has resulted in many aggressive treatments, including radical prostatectomy (RP) (2). Low and middle risk groups with indolent PCa treated for radical prostatectomy or radiation therapy showed substantial risk of long-term post-surgery consequences such as bowel dysfunction and urinary complications, as well as high morbidity (3, 4). Thus, over diagnosis and aggressive choice of treatment for this low-middle risk group can cause adverse side effects that impact the quality of life and longevity.

Currently, clinically diagnosing prostate cancer (PCa) involves decision-making tools such as the biopsy Gleason grade (BGR), prostate specific antigens (PSA) measurements, and clinical tumor staging. Since most patients are diagnosed with non-metastatic disease, among these three tools, BGR is considered the most important tool for PCa risk classification and treatment decisions in the initial evaluation of patients with PCa (5-7).

In 2014, a new PCa prognostic grading system, known as Gleason groups (GGs 1-5), was adopted by the International Society of Urological Pathology (ISUP) in order to provide more accurate stratification of tumors (8).

The new Grading System is divided into the following groups according to PCa aggressiveness: Grade Group 1 (Gleason score ≤6); Grade Group 2 (Gleason score 3+4=7); Grade Group 3 (Gleason score 4+3=7); Grade Group 4 (Gleason score 8); Grade Group 5 (Gleason scores 9-10). Previous research has reported that there was still a 20%-40% discrepancy in the agreement between BGR and radical prostatectomy Gleason grade (RPGG) in pathology specimens,

resulting in postsurgical Gleason grade upgrading (9-16). Furthermore, results from recent studies suggested that upgrading of biopsy Gleason grade after RP is associated with a higher risk of biochemical reoccurrence (BCR) and other postsurgical adverse outcomes (14-16). Interestingly, there are some potential risk factors that have been associated with PCa and BCR risk, such as obesity, advanced age, and being of African American race (7, 13, 17, 18). However, to our knowledge, research on the risks of BGR upgrading and BCR among these groups remains limited and inconclusive. Therefore, the primary objective of this study is to measure the rate of Gleason upgrade in pathology specimens after radical prostatectomy in men with low and middle risk PCa at biopsy, and to determine whether upgrading is associated with increased risk of biochemical recurrence in obese, African-American, and older men.

Methods

Patient Population

A retrospective secondary analysis of data was conducted using the Study of Clinical Outcomes, Risk and Ethnicity (SCORE). The SCORE is a retrospective cohort of 2,166 men with prostate cancer, recruited by the University of Pennsylvania Health System (UPHS; Philadelphia, PA) who had a Radical Prostatectomy (RP) between 1995 and 2012 (19, 20). The study was approved by the Institutional Review Board of the University of Pennsylvania, and informed consent was obtained from all patients who participated in the study. Patients were evaluated to have prostate cancer at time of diagnosis and were given a detailed history examination, a physical examination (which included a digital rectal examination (DRE)), and prostate-specific antigen (PSA) serum measurements. A needle biopsy to determine Gleason stage and grade was performed and reviewed by trained pathologists at the UPHS. The 1992 American Joint Committee on Cancer staging system was used as a clinical standard for Gleason staging of all patients (10).

Data Collection

Data was collected for the SCORE study from patients' pre-surgery data, biopsy data, and post-surgery data. Pre-surgery data included information on sociodemographic characteristics, such as age, height, weight, and race, as well as clinical information on preoperative PSA levels. Biopsy data included clinical Gleason score on diagnostic biopsy and clinical T-stage. Post-surgery data included pathologic information on RP Gleason pathological score stage, tumor grade, presence of adverse pathological features (surgical margin status, extraprostatic extension, seminal vesicle invasion, and lymph node involvement), follow-up PSA levels, and follow-up months.

Exclusions Criteria

In this secondary analysis of the SCORE study data, patients were excluded from this analysis if: not African American or Caucasian race (N = 39); missing information on preoperative PSA; missing information required on weight and height to calculate BMI and PSA Mass (N = 259); or missing clinical Gleason grade (N=457) and/or clinical T-stage. Furthermore, patients were excluded if missing information to calculate survival time (N = 213), leaving a final sample of 1,028 patients available for this study.

Follow-up and Biochemical Recurrence

After the radical prostatectomy, patients were followed up and PSA levels were measured 1 month postoperatively and then at 3 month intervals for 1 year, every 6 months for 5 years, and then annually. At each follow up visit, a complete evaluation, including DRE and serial PSA values, were determined and recorded. PSA failure (prostate cancer recurrence) after initial radical treatment was defined as single PSA≥0.2 ng/ml or two consecutive PSA values of 0.2 ng/ml (obtained following an undetectable PSA value). During the post-operative follow-up, date of surgery was defined as time zero. If PSA levels were never undetectable during the follow-up period after surgery, then PSA was assigned a PSA failure at time zero.

Study Outcomes

The primary outcome was pathological upgrading from biopsy Gleason group 1 (BGG 1) to radical prostatectomy Gleason group ≥2 (RPGG ≥ BGG2) specimen. The secondary outcome was pathological upgrading from biopsy Gleason group 2 (BGG 2) to radical prostatectomy Gleason group ≥3 (RPGG ≥ BGG3) specimen.

Statistical Analysis

Patients' preoperative and postoperative variables such as age, serum PSA level, preoperative serum PSA mass level (μg), BMI, kg/m^2, surgery year, and follow up month were analyzed and presented as median (IQR). The Categorical variables, such as age categories (<60 vs. ≥60 year) and BMI were classified (normal weight <25, overweight ≥ 25 and obese ≥ 30 kg/m^2); Biopsy Gleason Group (BGG1-5), Gleason biopsy tumor stage (CT1 and CT2) and Radical Prostatectomy Gleason Group (RPGG1-5) were analyzed and presented as numbers and percentage N(%). Time from biopsy to prostatectomy was calculated in subset of patients using completed information on biopsy abstraction date and radical prostatectomy date. In order to account for PSA in body volume and eliminate the effect of hemodilution on PSA value, PSA mass has been proposed as an alternate marker for PSA, accounting for the absolute amount of PSA protein that is secreted in circulation. Therefore, we compared PSA mass vs. PSA and BMI throughout this analysis to determine the more accurate predictor. PSA mass was calculated from PSA as: PSA mass [μg] = (weight [kg])0.425 × (height [cm])0.72 × 0.007184 × 1.670 × PSA concentration [ng/ml].

Univariate and multivariate Logistic regressions were performed to identify the preoperative risk factors (age, age category, race, BMI, BMI categories, PSA, PSA mass, CT categories) that may predict biopsy Gleason upgrading after RP. In the multivariable models with stepwise selection, we included all variables in the models due to their clinical significance and known risk factors for PCa. We compared two models, one with PSA and BMI included, and the other with the PSA mass without BMI. PSA, PSA mass and BMI were not normally distributed. Therefore, those variables were log transformed in the univariate and multivariate models (Supplementary figure. 1a. 1b and 1c). Time to biochemical recurrence was compared between concordant and upgraded groups of biopsy Gleason grade after RP using Kaplan-Meier plots and the log rank test. To examine the

effects of upgrading, Cox-proportional hazard methods were used to calculate the hazard ratio (HR) and 95% confidence interval (CI). In each case, the survival time was measured in follow-up months to the outcome. A “fail” event corresponds to biochemical recurrence. No recurrence at follow-up is designated a survival event. Subgroup analysis was performed for age group, race, and BMI category. All analyses were performed with R statistical software version 3.6.3 (R Foundation for Statistical Computing).

Results

In this prospective analysis, we identified 1,028 prostate cancer (PCa) patients who underwent radical prostatectomy between 1995-2012. The pre-and post-operative characteristic (clinical and demographic) information of the men was included in this analysis (Table 1). The median age at diagnosis was 59 years with interquartile range (IQR) of (54,64); 49.7% of participants were older than 60 years old. Median for PSA is 5.4 ng/ml with IQR (4.2,7.4). Median BMI was 26.6 IQR (25.1,29.9), with the majority (77.8%) being overweight and obese. Most of the study participants were Caucasian (80.5%); the remainder were African American (19.5%). The majority of the patients (73.7%) had biopsy Gleason Group =1 (BGG1), also referred to as low risk PCa (Gleason score ≤6). Time from biopsy to prostatectomy was approximately 3.5 months on average, and ranged from 1 to 36 months (Supplementary figure. 2s). Only four cases had longer time from biopsy to RP, ranging between 61-123 months. This reflects that only a few men were in active surveillance before undergoing RP as treatment option.

The number and percentage (%) of RPGG in pathology specimens were stratified by BGR (Table 2). The number of GG1 reported unchanged (concordant) for the radical prostatectomy Gleason group 1 (RPGG1) was 461 (60.8%). The number for GG1 patients upgraded to RPGG2 was 238 (31.4%). For the middle risk PCa group (GG2=3+4), 101 (62.7%) results remained unchanged. In BGG2, 29 patients (18.1%) were upgraded to RPGG ≥3 and 31 (19.3%) were downgraded to RPGG1. Biopsy GG3 and GG4 were the least upgraded in terms of RPGG3/4 with 13 (25.5%) and 7 (14.6%) unchanged, respectively. Of 1,028 patients overall, 587 (57.1%) BGR remained unchanged and 348 (33.9%) were upgraded; of these, 276 (79%) were upgraded by one group and 72 (21%) upgraded by two groups. Only 93 (9%) of the entire patient population were downgraded (Table 3). In summary, the most frequent upgrading occurred in men with GG1 on

biopsy, who were upgraded in 85.3% of cases, mainly into RPGG2. Downgrading was more commonly seen in men with BGG3 and BGG4, with downgrading in 19.3% and 51%, respectively, in these two groups. BGG3 and BGG4 were the most misclassified in the RPG group with only 13 (25.5%) and 7 (14.6%) unchanged, respectively (Table 2 and 3).

Subgroup analysis by race (African-American vs. Caucasian), BMI (normal, overweight, obese) and age (<60, ≥60) categories were conducted to look for agreements between BGG and RPG (Figure 1, 2, and 3). In African-American men (AA) group, there was a 50% upgrade from BGG1 to ≥ RPGG2, compared to 37% upgrade for Caucasian men (CA). For the same race category, upgrading from BGG2 to ≥ RPGG3 was 19% for AA, compared to 21% for CA. Downgrading from BGG2 to RPGG1was 31% for AA, compared to 14% for CA (Figure 1).

In the BMI category, obese men upgrading from BGG1 to RPGG2 is slightly higher (45%), compared to normal weight (40%), and overweight men (36%) (Figure 2). Similarly, obese men upgrading from BGG2 to ≥ RPGG3 have higher upgrade (22%) compared to overweight (16%) and normal men (16%). Conversely, in downgrading from RPGG2 to BGG1, obese men were the lowest to be downgraded (12%) compared to normal (15%) and overweight men (24) (Figure 2). For men aged 60 years and older, upgrading from BGG1 to RPGG2 was higher (43%) than for men younger than 60 years (36%). Upgrading to RPGG3 for men aged ≥ 60 was higher (16%) than for men aged < 60 (7%) (Figure 3).

In the univariate analysis, among patients who were BGG =1 and upgraded to RPGG=2 (minor upgrade), predictors PSA mass odds ratio (OR) 1.01 and, 95% confident interval (CI) (1.00-1.02) and age at diagnosis OR 1.04, 95% CI (1.02-1.06)) were associated with slightly higher risk of GG upgrading. (Table 4). Patients older than 60 (OR 1.49, 95% CI (1.04-2.04)) were at higher risk for upgrade. Overweight men (OR 1.4, 95% CI (0.93-2.07)) were more likely to upgrade,

and obese men (OR 1.67, 95% CI (1.01-2.50)) had higher significant risk for upgrade. Caucasian men had significantly lower risk for upgrading compared to African American men (OR 0.56, 95% CI (0.37-0.85)). The univariate analysis for the BGG =1 upgrade to RPGG ≥3, or BGG ≤2 upgrade to RPGG ≥ 3 (major upgrade for both BGG1 and BGG2), the effect of the demographic predictors (age, BMI, and race) on upgrading is diminished. The only statistically significant clinical predictors were PSA and PSA Mass. Clinical staging (CT) showed a non-significant increase risk for upgrade (OR 1.59, 95% CI (0.96-2.98)) (Table 4).

Time-to-biochemical recurrence (BCR) was calculated for BGG =1 upgrade to RPGG=2 (minor upgrade), BGG =1 upgrade to RPGG ≥3 (major upgrade in BGG1), or BGG ≤2 upgrade to RPGG ≥ 3 (major upgrade for both BGG1 and BGG2), and survival curves for the three groups are presented in Figure 4-11. Figure 4. (a, b, and c) shows Kaplan-Meier curves for BCR stratified by upgrade vs. concordant groups. For the minor upgrade group (BGG =1 upgraded to RPGG =2), the ten-years BCR probability is 50% compared to the 70% BCR for the concordant group. The log rank p=0.0037 and (HR 1. 97 95% CI (1.23, 3.14)) indicated that an upgraded patient is approximately two times more likely to have experienced BCR than a concordant patient (Figure 4a). Furthermore, for both major upgrade groups 2 (BGG =1 upgrade to RPGG ≥ 3) and 3 (BGG1=1& 2 upgrade to RPGG ≥ 3), the seven-years BCR probability for Group 2 is 30% for upgrading, compared to the 85% BCR for concordant: log rank p<0.0001 (HR 5.81 95% CI (3.35,10.1)). For Group 3, the seven-years BCR probability was 35%, compared to the 80% BCR for the concordant group: log rank p<0.0001 and (HR 4.1 95% CI (2.75,6.12)), respectively.

Furthermore, we explored the effects of risk factors (BMI, race, and age) on time to biochemical recurrence in the upgrade group. In the BMI category, normal men in the minor upgrade who

were upgraded showed significant difference in BCR after 10 years: 70% compared to 85% for those who remained concordant. For overweight men who upgraded, 70% experienced BCR after 8 years, compared to 75% for those who remained concordant. Conversely, for obese men in the same group, there was a shorter time of 4 years for BCR after follow-up. Moreover, there was no difference between those who upgraded and those who remained concordant (Figures 5a, 5b, and 5c). For the major upgrade group (RPGG1 $\geq$ 3), there was significant difference between upgraded and concordant in terms of obesity status (normal, overweight, and obese); the 10-year survival rate fell between 75% and 30% for the upgrade group (Figures 6,7a, 7b and 7c).

In the race category, African-American men in the minor upgrade group showed an insignificant difference in BCR after 10 years for the upgrade group (50%), compared to the concordant group (60%). However, Caucasian men in the same group showed a significant difference in BCR after 10 years for the upgrade group (70%), compared to the concordant group (85%). Major upgrading showed a significantly shorter BCR survival rate (30% vs. 75%) for Caucasians who upgraded, while African American showed a significantly shorter BCR survival rate (50%) for one of the major upgraded groups (5 years vs. 8-10), but have the same long term failure rates as Caucasians. In the age category, those with minor upgrade showed a significant difference between younger men who were concordant (80% survival after 10 years) and those who upgraded (50% survival after 10 years). Older men showed no significant difference in 10-year BCR between those who were concordant and those who upgraded (50% survival after 10 years). For the major upgrades, BCR was shorter with a significant difference between upgraded and concordant for both younger and older men. The younger cohort had 40% survival after 8 years, while the older cohort had a <10% rate after 10 years. Concordant older men also dropped to 50% survival after 10 years.

Discussion

Our findings indicate a misclassification between the biopsy Gleason grade (BGR) and radical prostatectomy pathology specimens, with disagreement of more than 57% overall. Our results agree with several studies that reported upgrading from biopsy GG1 to RPGG2 or higher (9-11, 21, 22). Such inaccuracies highlight the need to include specific risk factors in initial clinical evaluation, in order to provide the best treatment options.

The results for biopsy Gleason group 1 and 2 had the most upgrading from all the biopsy Gleason groups. Interestingly, most upgrading occurred in Group 1 to 2, indicating the importance of considering treatments other than RP for low risk GG1 PCa patients (23).

When we looked at the risk factor subgroups, we found higher counts of upgrading of African American (AA), obese, and advanced age men, compared to other groups. AA men in the BGG1 were the most misclassified: about 40% were upgraded to RPGG2 compared to Caucasian men, about 30%, compared to 25% downgraded from RPGG2 to GG1. To our knowledge, only two studies so far have explored the upgrading and reclassification among AA men. Our results also match the study of a large sample size (256 AA men), which found BGG reclassification among AA with favorable risk PCa (18). On the other hand, a recent study with a small sample of 89 men found no difference between BGG and RPGG specimens (24). There is a lack of extensive research on the incorporation of African American race in the low risk PCA group, which is more likely to be upgraded; our findings support the need for more research among this group.

Similar to the disagreement in AA men, we found the number of obese men upgrading from GG1 to RPGG2 is slightly higher compared to normal weight and overweight men. No studies by far have looked at the BGG discordant with RPGG in obese men. A

comprehensive analysis of a large number of clinical and pathological variables in a larger sample found obesity an independent predictor of upgrading of low risk patient biopsies with risk of 1.90 (25). In our analysis, we found that in men 60 years and older, upgrading from GG1 to RPGG2 was higher compared to men younger than 60 years (Figure 3). Although age at PCa diagnosis has shown to be a strong risk factor for progression and mortality of PCa, only one study measured the risk rate of biopsy group reclassification of BGG2 to RPGG ≥3 (major upgrade) but not for BGG1 to RPGG2(26), and their findings were similar to ours for BGG2 upgrading to RPGG3 or greater in men age < 60 years compared to men ≥ 60 years (Figure 3).

Univariate and multivariate analysis showed prediction factors for upgrading. For the biopsy Gleason group 1 to RPGG2 minor upgrade, the predictors were age, BMI, and race. Those predictors remained in the multivariate models. For upgrading from BGG≤ 2 to RPGG 3 and up (major upgrade), age, BMI, and race were not significant predictors for all univariate models. It seems that demographic factors play an important role for minor upgrade (RPGG2). Therefore, we should consider patient demographic information with biopsy Gleason for more accurate classification. However, higher PSA and PSA mass were significant predictors for upgrading to PRGG3. For the higher group RPGG3, we found that PSA and PSA mass were significant predictors for upgrading to RPGG3. Several studies have investigated predictors of BGR upgrading in the literature with conflicting results; previous studies have pointed to potential predictors, such as higher BMI, older age, higher PSA, and clinical stage T2. In our findings, obesity has no effect and race plays an inconsistent role, shortening failure times for African Americans but not for Caucasians. Therefore, race has a detectable effect on minor upgrade but no effect on major upgrades.

Our data did not support the predictive power of preoperative PSA level in BGR upgrading. For Gleason upgrade to both RPGG2 and RPGG ≥3 (minor and major upgrade) groups (RPGG2), upgrading was a significant predictor of higher risk for biochemical recurrence (BCR), and these findings are supported by the literature (14-16). In the subgroup analysis, we found that for obese, AA, and older men, BCR was shorter in only the minor upgrade, and was the same risk factor predicting for upgrading among this subgroup. Our findings demonstrate that upgrading increases BCR among patients in the low risk PCa group. This research supports the idea that population risk factors are important parameters to focus efforts on improving accuracy of Gleason grading in the evaluation of PCa patients. This will lead to better treatment options to improve patient longevity and quality of life outcomes, particularly among obese, African American, and advanced age men.

Strengths and Limitations

A major strength of this study is the fact that it represents a diverse population, which gave us the opportunity to study disease disparity among obese and African American men. These results also provide strong evidence that future research to explore the role of risk factors on PCa progression among disadvantaged populations is highly warranted. Despite these strengths, our study has some limitations. Firstly, the median follow-up for the study cohort was relatively short, which restricted our ability to evaluate prostate cancer death as a primary outcome. Another study limitation included relying only on biochemical recurrence as a surrogate biomarker for PCa outcomes and mortality However, biochemical recurrence is still considered clinically relevant as a decision point for treating high-risk patients and is used as intermediate end point for PCa poor outcomes and mortality. Another potential limitation is the fact that the study did not collect information on obesity measurements

beyond BMI, such as waist-to-hip ratio and lean body fat percentage .Including all these obesity measurements could give a more accurate prediction of effect of obesity on PCA. Nevertheless, BMI remains an important clinical measure for obesity that can be easily calculated in the clinic and widely used to evaluate PCA risk and adverse outcomes. Moreover, because blood biosamples were not obtained during time of surgery, biologic factors that may contribute effects of elevated BMI on disease aggressiveness and treatment outcomes were unavailable. Additionally, the biopsy and surgical grading were performed by different pathologists from the same institution, which could cause inter-observer variability in diagnosis and grading. However, all the Gleason grading and surgery procedures conform to the 1992 American Joint Committee on Cancer staging system clinical standard, which are performed by well-trained pathologists. Of note, not all men with high body weight or African American race patients developed adverse outcomes after radical prostatectomy, such as biochemical recurrence.

Summary

In summary, our study confirms the current literature findings that biopsy Gleason upgrading in the radical prostatectomy (RP) specimen is associated with increased risk of biochemical recurrence after RP. Upgrading from Biopsy Gleason group 1(low risk PCa group) to group 3 or up (high risk PCa group) after radical prostatectomy increased biochemical recurrence of prostate cancer independently of obesity status, African-American race and older age. Therefore, this study suggests it may be important to include in active surveillance low risk PCa patients who are obese and/or African American race and provide more extensive treatment. This will allow such groups to benefit from early intervention, prevention of disease progression and reduced mortality risk.

Table 1. Pre-and Post-operative Characteristics and Pathological Outcomes of Patients Overall Undergoing Radical Prostatectomy at University of Pennsylvania Between 1990 -2015

PREOPERATIVE		POSTOPERATIVE	
VARIABLES	**VALUE**	**VARIABLES**	**VALUE**
PCa Patients	1028	Surgery Year	2004 (2000, 2008)
Age at diagnosis, years	59.0 (54.0, 64.0)	Follow Up, Months	26 (12, 58)
PSA Categories		**Radical Prostatectomy Group (RPGG)**	
PSA, ng/mL	5.4 (4.2, 7.4)	RPGG1 (<=6)	500 (48.6)
PSA mass (µg)	18.4 (14.1, 25.7)	RPGG2 (3+4)	371 (36.1)
		RPGG3 (4+3)	92 (8.9)
Age Categories		RPGG4 (8)	35 (3.4)
<60	517 (50.3)	RPGG5 (>=9)	30 (2.9)
≥60	511 (49.7)		
		Biochemical Reoccurrence	
BMI Categories		Y	841 (81.8)
BMI, kg/m ^{2}	26.6 (25.1, 29.9)	No	187 (18.2)
Normal	228 (22.2)	**Tumor Margin**	
Overweight	549 (53.4)	Y	189 (18.4)
Obese	251 (24.4)	N	838 (81.5)
Race Categories		**Nodal Status**	
African American/Black	200 (19.5)	N0	1019 (99.1)
Caucasian	828 (80.5)	N1	9 (0.9)
Biopsy Gleason Group (BGG)		**Extracapsular Extension**	
BGG1 (<=6)	758 (73.7)	Y1	266 (25.9)
BGG2 (3+4)	161 (15.7)	N	762 (74.1)
BGG3 (4+3)	51 (5.0)	**Seminal Vesicle Invasion**	
BGG4 (8)	48 (4.7)	N	964 (93.8)
BGG5 (>=9)	10 (1.0)	Y	64 (6.2)
Clinical Stage			
T1	724 (70.4)		
T2	304 (29.6)		

Continuous variables presented as median (IQR) and categorical variables presented as n (%)
PSA = prostate-specific antigens. IQR = interquartile range.

Table 2. Gleason Groups of Biopsy and Radical Prostatectomy (RP) in Pathology Specimens of Patients Undergoing RP at University of Pennsylvania

Biopsy Gleason Groups	RP Gleason Groups, N (%)*					
	1 (<=6)	**2 (3+4)**	**3 (4+3)**	**4 (8)**	**5 (9 & 10)**	**Total**
1(<=6)	**461 (60.8)**	238 (31.4)	42 (5.5)	7 (0.9)	10 (1.3)	758 (100.0)
2(3+4)	31 (19.3)	**101 (62.7)**	18 (11.2)	8 (5)	3 (1.9)	161 (100.0)
3(4+3)	6 (11.8)	20 (39.2)	**13 (25.5)**	10 (19.6)	2 (3.9)	51 (100.0)
4(8)	2 (4.2)	12 (25)	17 (35.4)	**7 (14.6)**	10 (20.8)	48 (100.0)
5(>=9)	0 (0)	0 (0)	2 (20)	3 (30)	**5 (50)**	10 (100.0)
Total	500 (48.6)	371 (36.1)	92 (8.9)	35 (3.4)	30 (2.9)	1028 (100.0)

*Numbers and Percentage
Bold numbers indicate values with no change of GG after RP (concordant)

Table 3. Prostate Biopsy and Radical Prostatectomy (RP) in Pathology Specimens; GG Concordance, N (X, Y%) in Patients Undergoing RP at University of Pennsylvania

Biopsy Gleason Group	RP Gleason Groups, N (% Row, % Column)					
	Downgraded	**Concordant**	**Upgraded by any group**	**Total**	**Upgraded by 1 group**	**Upgraded by ≥ 2 groups**
1(<=6)	0 (0,0)	461 (60.8,78.5)	297 (39.2,85.3)	758 (100,73.7)	238 (86.2)	59 (81.9)
2(3+4)	31 (19.3,33.3)	101 (62.7,17.2)	29 (18,8.3)	161 (100,15.7)	18 (6.5)	11 (15.3)
3(4+3)	26 (51,28)	13 (25.5,2.2)	12 (23.5,3.4)	51 (100,5)	10 (3.6)	2 (2.8)
4(8)	31 (64.6,33.3)	7 (14.6,1.2)	10 (20.8,2.9)	48 (100,4.7)	10 (3.6)	0 (0)
5(>=9)	5 (50,5.4)	5 (50,0.9)	0 (0,0)	10 (100,1)	0 (0)	0 (0)
Total	93 (9,100)	587 (57.1,100)	348 (33.9,100)	1028 (100,100)	276 (100)	72 (100)

Table 4. Univariate and Multivariate Models for Preoperative Factors Predicting Radical Prostatectomy (RP) Gleason Group Upgrading in Patients Undergoing RP at University of Pennsylvania

Group 1. All patients in Biopsy Gleason Group =1 (≤6) who Upgrade after Surgery to RP Specimens Gleason Group = 2 (3+4), N= 699									
	Univariate analysis			Best PSA Model			Best PSA Mass Model		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
PSA level (ng/mL)	1.04	0.99-1.08	0.07	1.03	0.99 1.08	0.116	--	--	--
PSA mass (µg)	1.01	1.00-1.02	**0.003**	--	--	--	1.01	1.03 1.06	0.060
Age	1.04	1.02-1.06	**<0.001**	1.04	1.02 1.07	**0.001**	1.04	0.98 1.07	0.**002**
BMI	1.05	0.99-1.08	0.06	1.04	1.00 1.08	**0.05**	-	--	--
Age Categories									
Age <60	Reference	--	--	--	--	--	--	--	--
Age ≥60	1.49	1.09-2.04	**0.01**	1.51	1.10 2.08	**0.012**	1.47	1.07 2.02	0.**02**
BMI Categories									
Normal Weight	Reference	--	--	--	--	--	--	--	--
Overweight	1.40	0.93-2.07	0.10	1.38	0.92 2.08	0.120	--	--	--
Obese	1.67	1.01-2.50	**0.05**	1.65	1.02 2.66	**0.04**	--	--	--
Race Categories									
AF	Reference	--	**--**	--	--	--	--	--	--
CA	0.56	0.37-0.85	**0.01**	0.57	0.38 0.88	**0.01**	0.55	0.36 0.83	**0.004**
Clinical Stages									
CT1	Reference			--	--	--	--	--	--
CT2	1.11	0.781-1.58	0.55	--	--	--	--	--	--

Group 2. All patients in Biopsy Gleason Group =1 (≤6) who Upgrade after Surgery to RP Specimens Gleason Group ≥ 3 (≥4+3), Major Upgrade, N =520									
	Univariate analysis			Best PSA Model			Best PSA Mass Model		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
PSA level (ng/mL)	1.12	1.10-1.22	**<0.001**	1.16	1.10 1.22	**<0.001**	--	--	--
PSA mass (µg)	1.05	1.03-1.06	**<0.001**	--	--	--	1.05	1.03 1.06	**<0.001**
Age	1.02	0.98-1.05	0.33	1.02	0.98 1.06	0.322	1.02	0.98 1.07	0.246
BMI	1.04	0.97-1.11	0.28	--	--	--	--	--	--
Age Categories									
Age <60	Reference	--	--	--	--	--	--	--	--
Age ≥60	1.32	0.77-2.28	0.31	--	--	--	1.42	0.80 2.53	0.234
BMI Categories									
Normal Weight	Reference	--	--	--	--	--	--	--	--
Overweight	0.85	0.43-1.70	0.62	--	--	--	--	--	--
Obese	1.50	0.70-3.04	0.32	--	--	--	--	--	--
Race Categories									
AF	Reference	--	--	--	--	--	--	--	--
CA	0.83	0.39-1.77	0.63	--	--	--	--	--	--
Clinical Stages									
CT1	Reference	--	--	--	--	--	--	--	--
CT2	1.67	0.96-2.98	0.07	--	--	--	--	--	--

Group 3. All patients in Biopsy Gleason Group =1 (≤6)and Group=2 (3+4) who Upgrade after Surgery to RP Specimens to Gleason Group ≥ 3 (≥4+3), Major Upgrade, N =888

	Univariate analysis			Best PSA Model			Best PSA Mass Model		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
PSA level (ng/mL)	1.13	1.08-1.17	**<0.002**	1.12	1.08 1.17	**<0.001**	--	--	--
PSA mass (µg)	1.04	1.02-1.05	**<0.01**	--	--	--	1.03	1.02 1.05	**<0.001**
Age	1.03	0.99-1.06	0.11	1.02	0.99 1.06	0.16	1.03	0.99 1.06	0.12
BMI	1.03	0.98-1.09	0.26	--	--	--	--	--	--
Age Categories									
Age <60	Reference	--	--	--	--	--	--	--	--
Age ≥60	1.38	0.88-2.15	0.16	--	--	--	1.42	0.90 2.26	0.13
BMI Categories									
Normal Weight	Reference	--	--	--	--	--	--	--	--
Overweight	0.84	0.48-1.46	0.54	--	--	--	--	--	--
Obese	1.30	0.71- 2.38	0.40	--	--	--	--	--	--
Race Categories									
AF	Reference	--	--	--	--	--	--	--	--
CA	1.03	0.58-1.86	0.92		--	--	--	--	--
Clinical Stages									
CT1	Reference	--	--	--	--	--	--	--	--
CT2	1.60	1.00-2.49	0.06		--	--	--	--	--

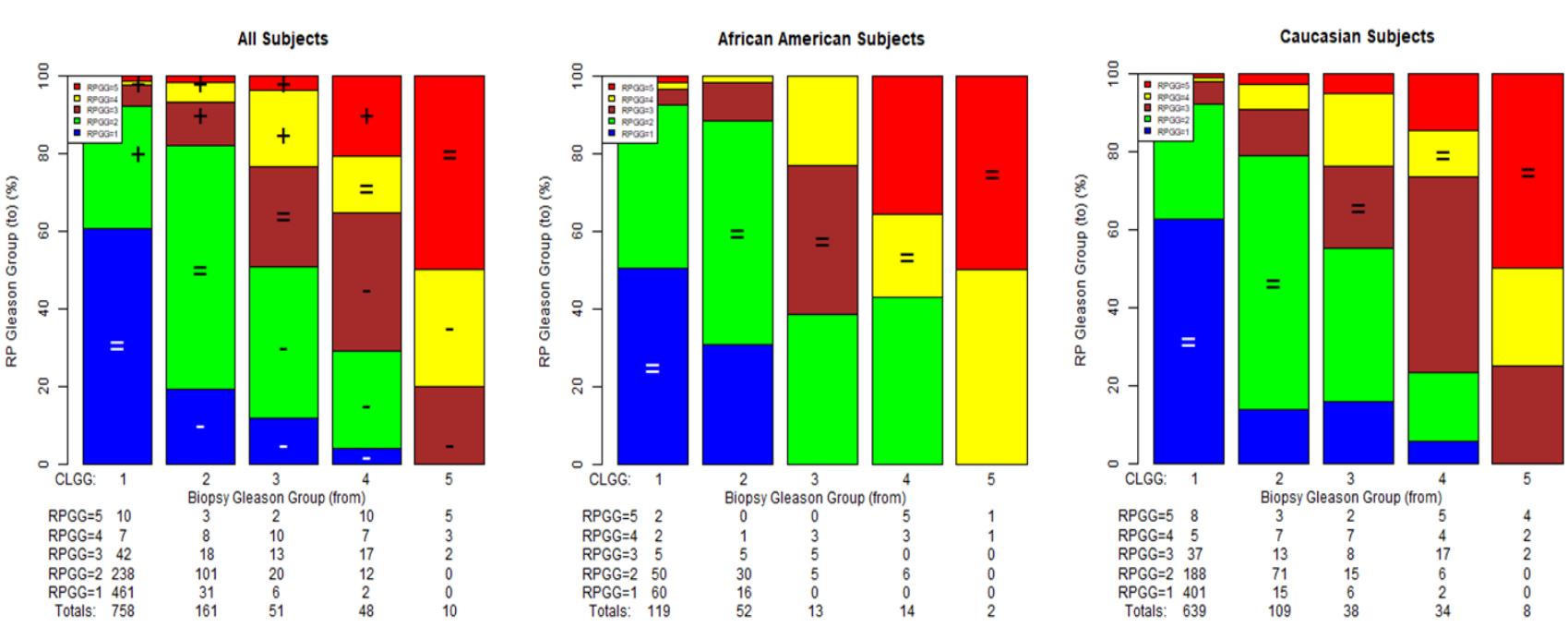

Figure 1. Rate of Biopsy Gleason groups (GG) Upgrade to Radical Prostatectomy Gleason Group (RPGG) Specimens for Patients Undergoing RP at University of Pennsylvania (All subjects, African-American and Caucasian men)

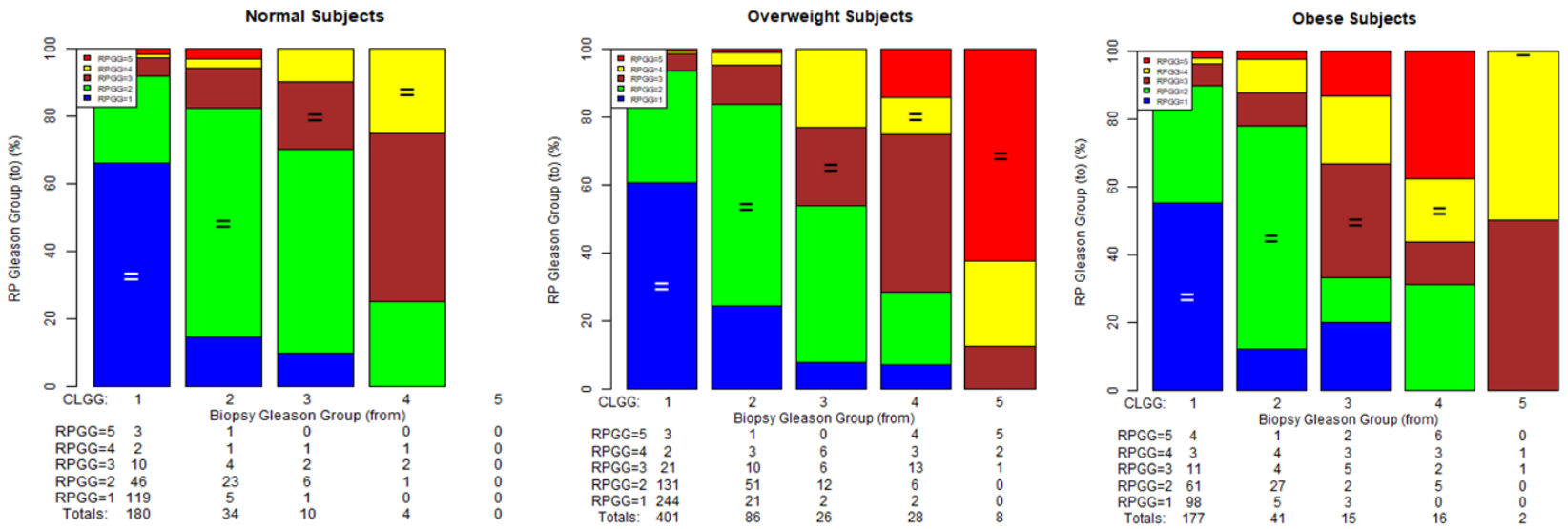

Figure 2. Rate of Gleason Groups of Biopsy Upgrades to Radical Prostatectomy (RP) Specimens of Patients Undergoing RP at University of Pennsylvania (Normal, Overweight And Obese Men)

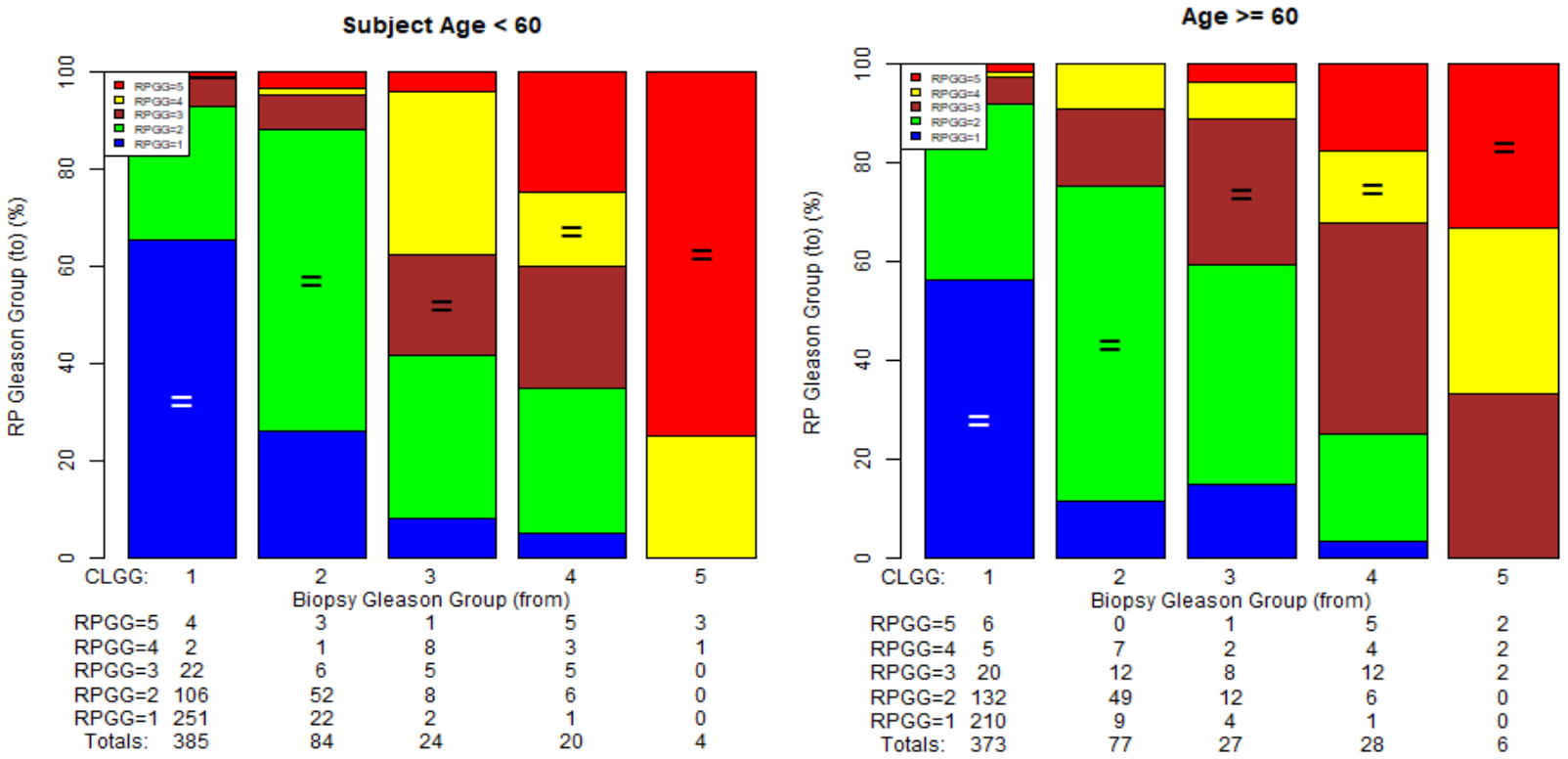

Figure 3. Rate of Gleason Groups of Biopsy Upgrades to Radical Prostatectomy (RP) Specimens of Patients Undergoing RP at University of Pennsylvania (Men < 60 Years, And Men ≥ 60 Old)

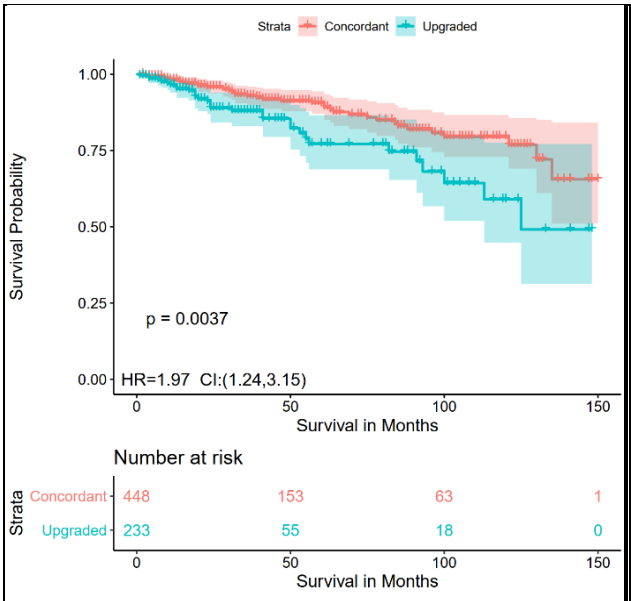

Figure 4a. All patients BGG =1 up upgrade to RPGG =2

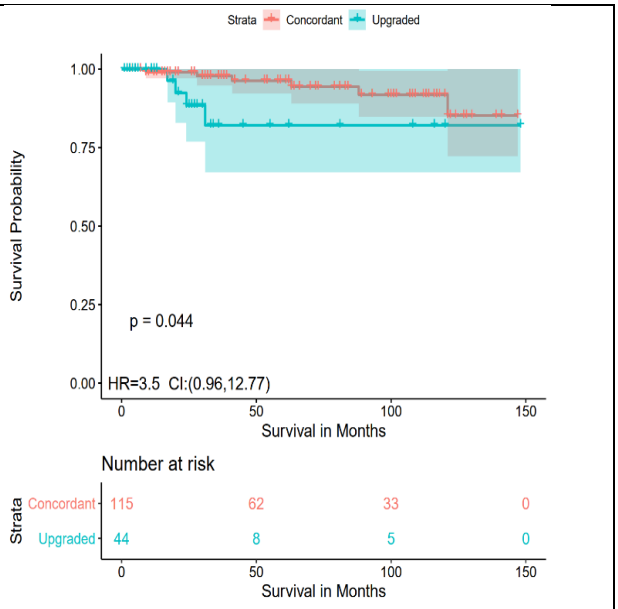

Figure 5a Normal weight patients BGG =1 up upgrade to RPGG =2

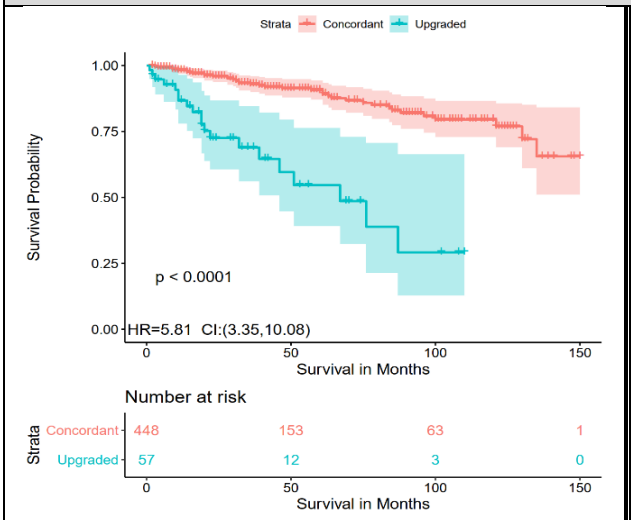

Figure 4b. All patients BGG1=1 upgrade to RPGG ≥3

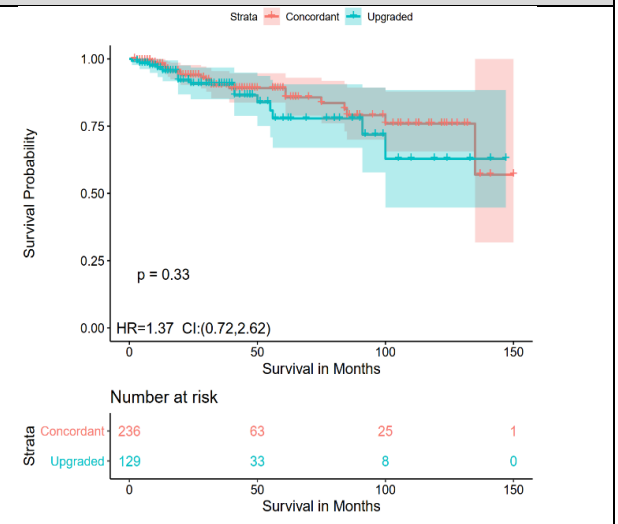

Figure 5b. Overweight patients BGG =1 up upgrade to RPGG =2

Figure 4. All patients by to one group or any upgrades

Figure 5. Patients with upgrade to RPGG=2 by BMI category

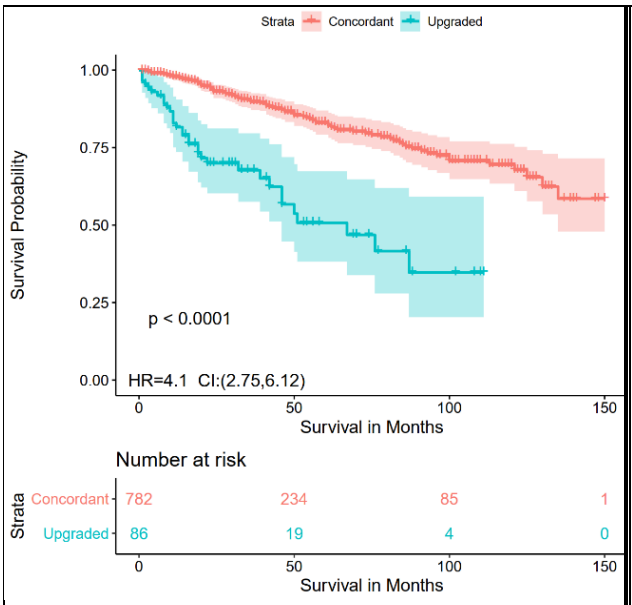

Figure 4c. All patients BGG1=1& 2 upgrade to RPGG ≥ 3

Figure 4. All patients by to one group or any upgrades

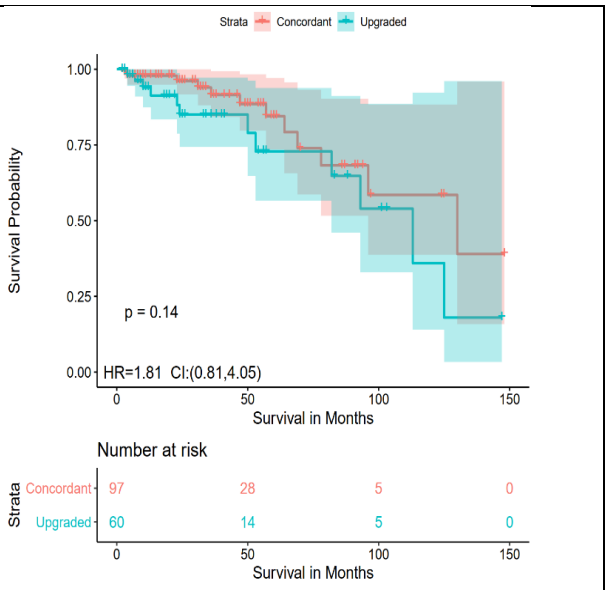

Figure 5c. Obese patients BGG =1 upgrade to RPGG =2

Figure 5. Patients with upgrade to RPGG=2 by BMI category

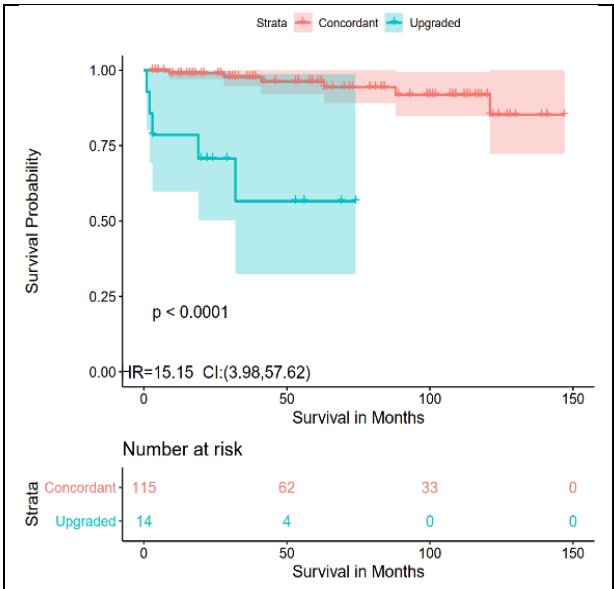

Figure 6a. Normal patients BGG =1 upgrade to RPGG ≥ 3

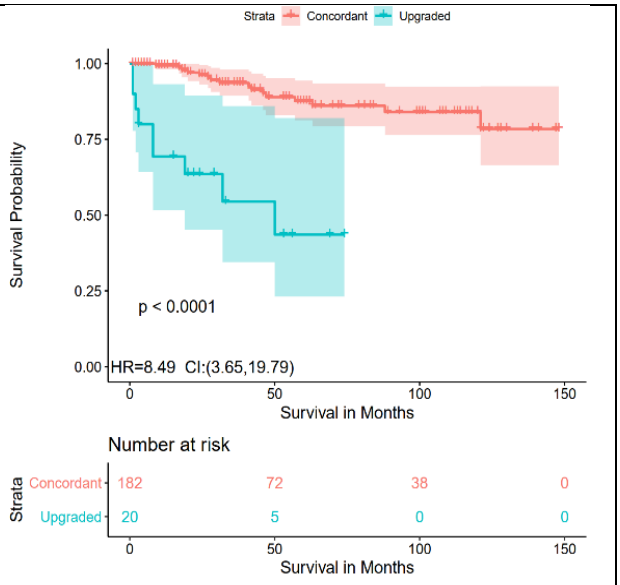

Figure 7a. Normal patients BGG =1 upgrade to RPGG ≥ 3

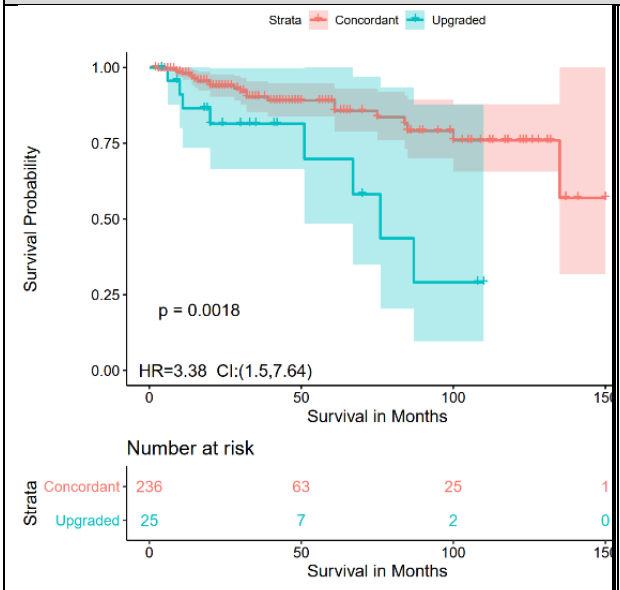

Figure 6b. Overweight patients BGG =1 upgrade to RPGG ≥ 3

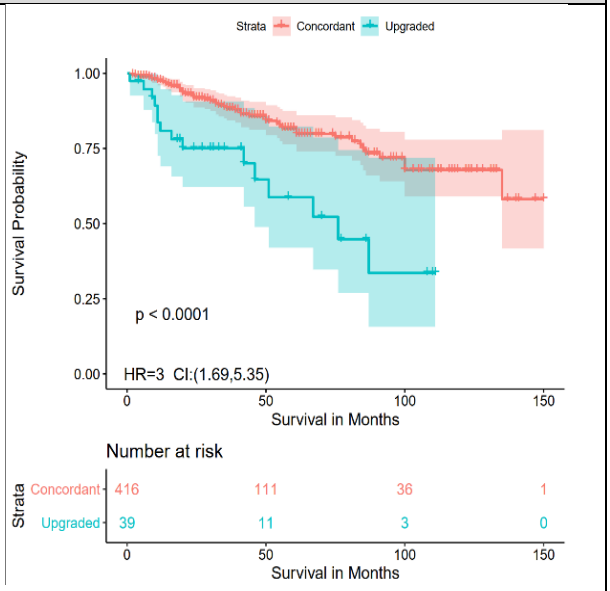

Figure 7b. Overweight Patients BGG =1 upgrade to RPGG ≥ 3

Figure 6. Patients with upgrade =1 to RPGG ≥ 3 by BMI category

Figure 7. Patients with upgrade =1 to RPGG ≥ 3 by BMI category

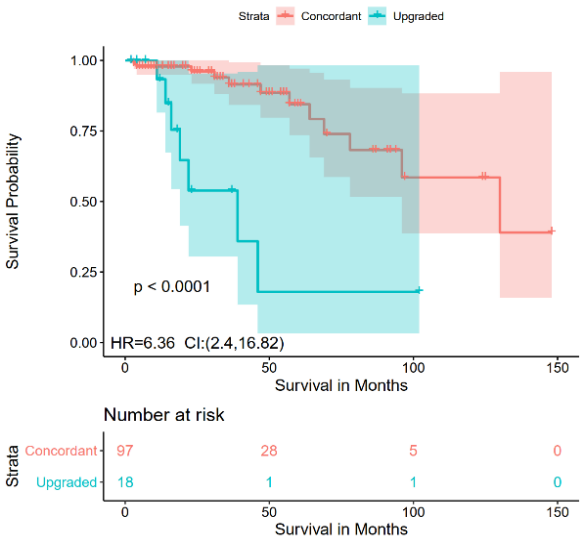

Figure 6c. Obese Patients BGG =1 upgrade to RPGG ≥ 3

Figure 6. Patients with upgrade =1 to RPGG ≥ 3 by BMI category

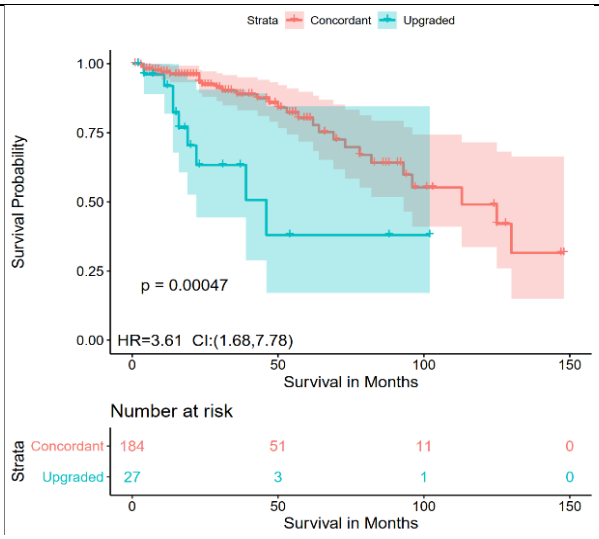

Figure 7c. Obese patients BGG =1 upgrade to RPGG ≥ 3

Figure 7. Patients with upgrade =1 to RPGG ≥ 3 by BMI category

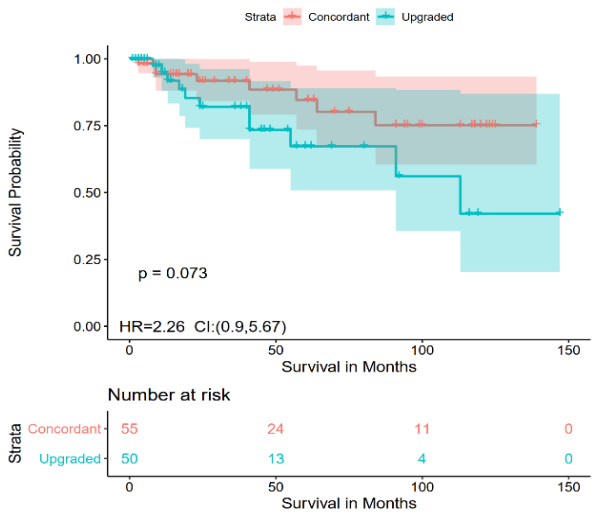

Figure 8a. BGG =1 upgrade to RPGG =2

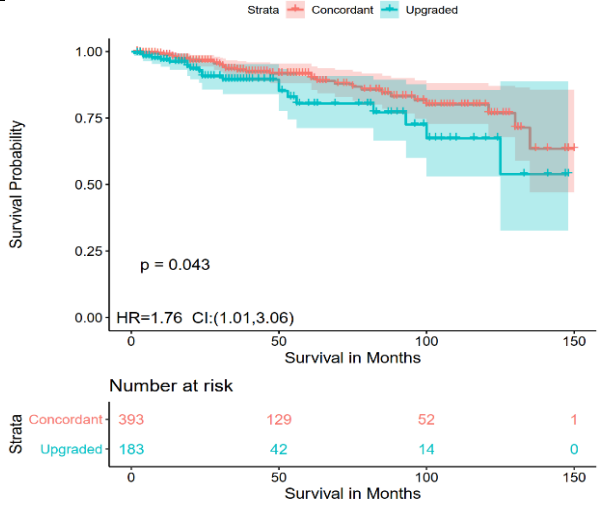

Figure 9a. BGG =1 upgrade to RPGG =2

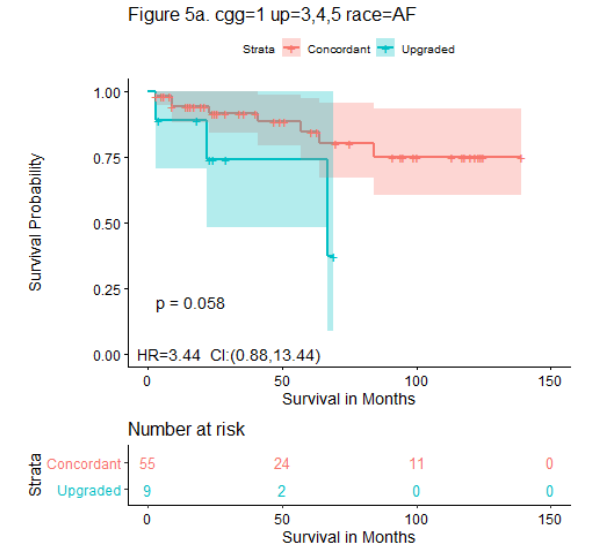

Figure 8b. BGG =1 upgrade to RPGG ≥ 3

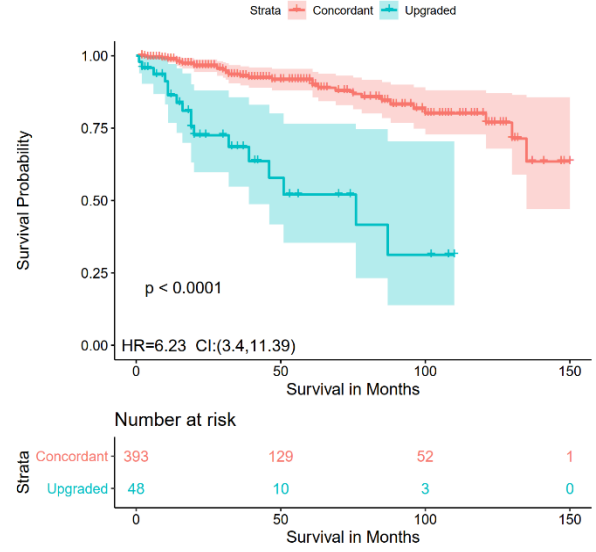

Figure 9b. BGG =1 upgrade to RPGG ≥ 3

Figure 8. African American patients by upgrade type

Figure 9. Caucasian patients by upgrade type

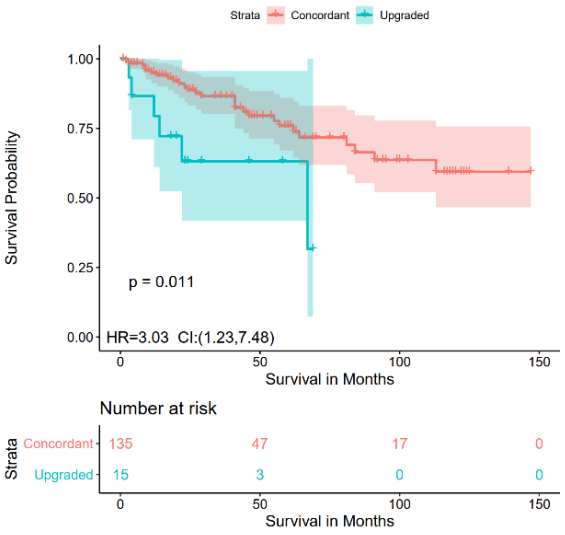

Figure 8c. BGG =1 upgrade to RPGG ≥ 3

Figure 8. African American patients by upgrade type

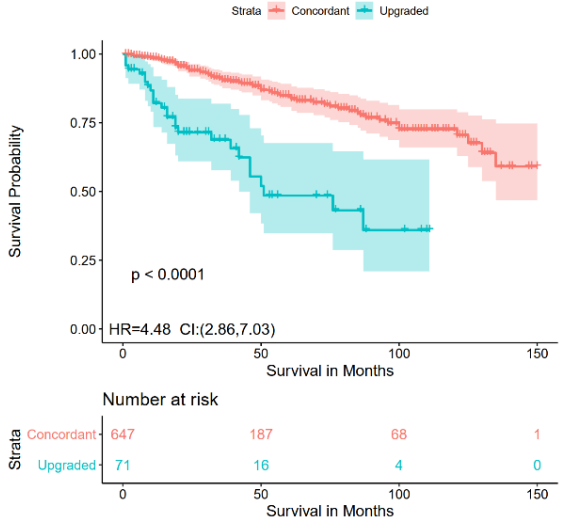

Figure 9c. BGG =1 upgrade to RPGG ≥ 3

Figure 9. Caucasian patients by upgrade type

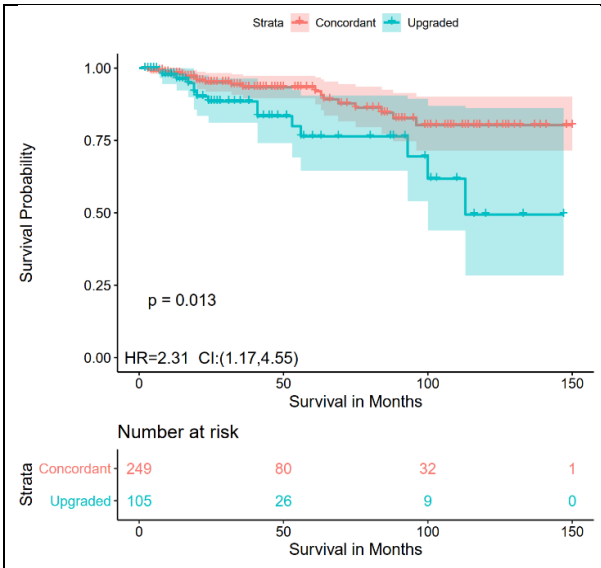

Figure 10a. BGG =1 upgrade to RPGG =2

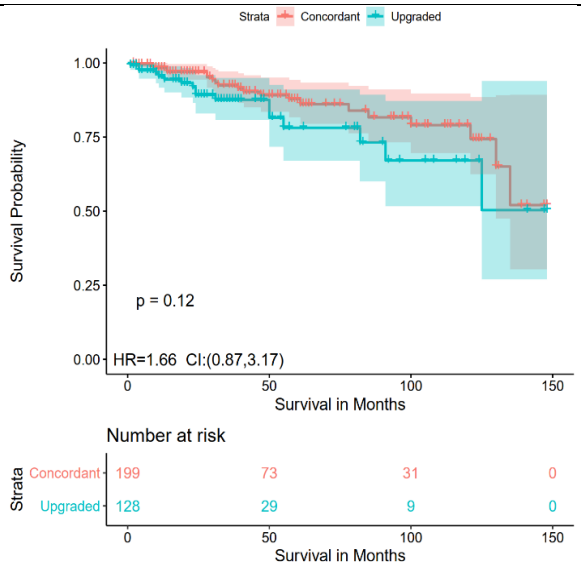

Figure 11a. BGG =1 upgrade to RPGG =2

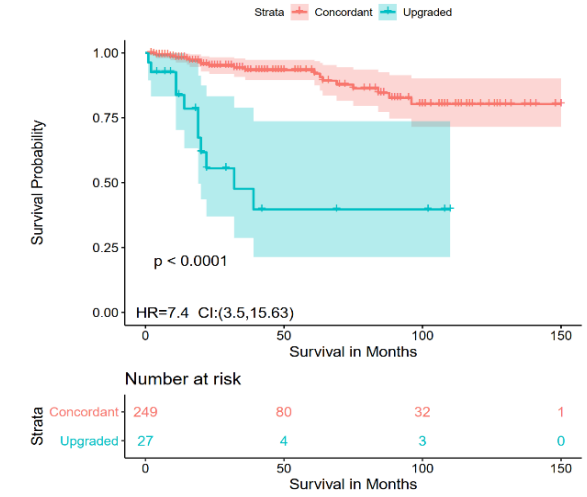

Figure 10b. BGG =1 upgrade to RPGG ≥ 3

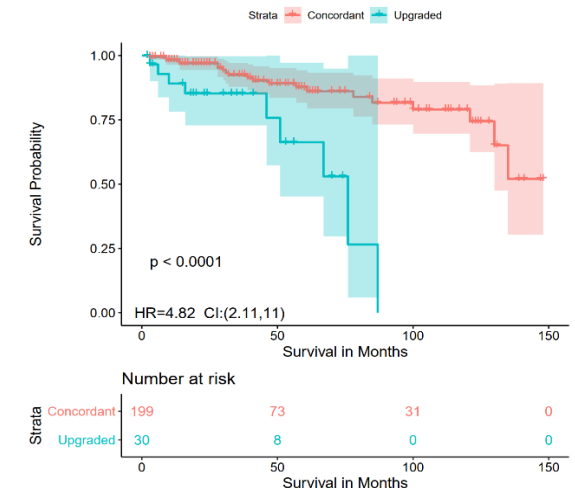

Figure 11b. BGG =1 upgrade to RPGG ≥ 3

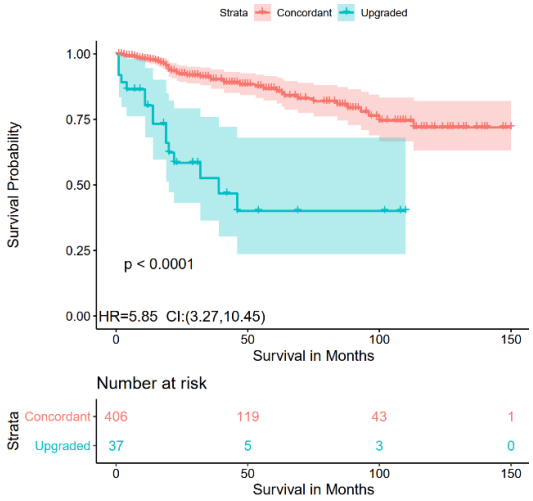

Figure 10c. BGG =1 upgrade to RPGG ≥ 3

Figure 10. Patient Age < 60

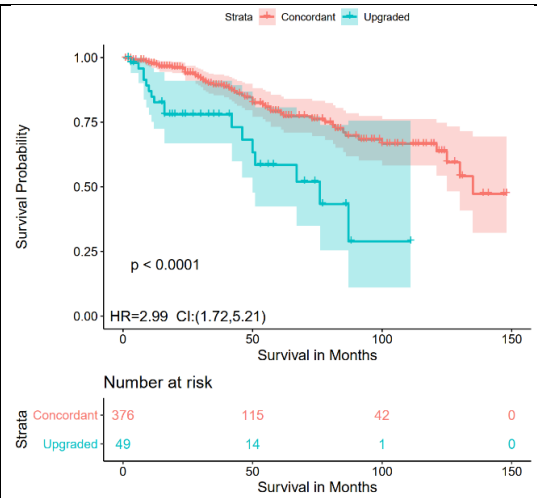

Figure 11c. BGG =1 upgrade to RPGG ≥ 3

Figure 11. Patient Age >= 60

Supplementary Figures

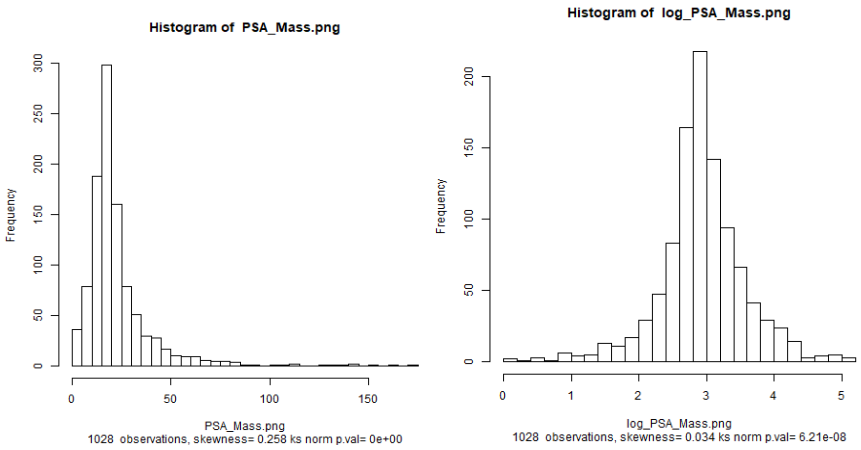

Figure 1s. A

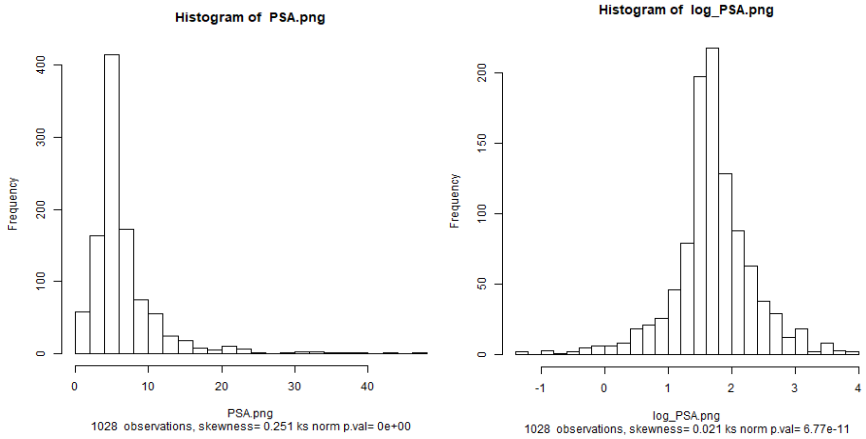

Figure 1s. B

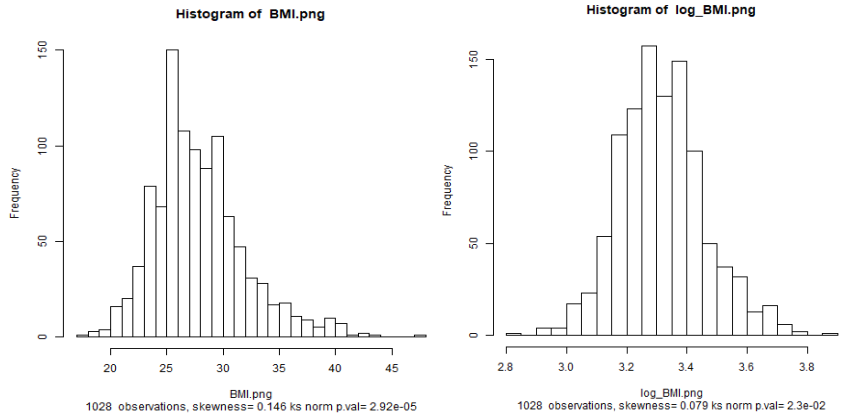

Figure 1s.C

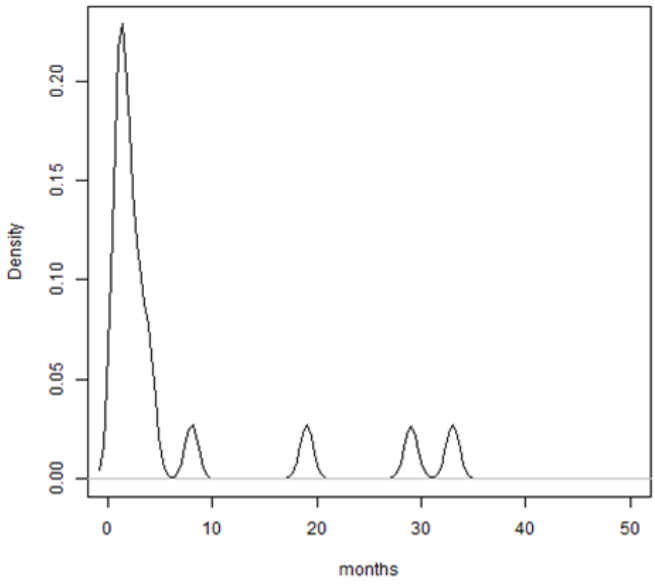

Figure 2s. Time from Biopsy to Prostatectomy

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Project 2

Abstract

Introduction: Biopsy Gleason grade (BGG) is used as a diagnostic tool to predict prostate cancer aggressiveness, in conjunction with radical prostatectomy Gleason grade group (RPGG). However, studies have shown that there is 20%- 40% discordance between these two measures, which can lead to adverse outcomes. Therefore, more accurate prediction models for prostate cancer aggressiveness are needed.

Objectives: The objective of this study is to determine whether preoperative prostate specific antigen mass (PSA mass) is a more accurate predictor for prostate cancer aggressiveness (RPGG ≤ 2 vs. RPGG ≥ 3) than prostate specific antigens (PSA). Additionally, whether prediction of PCa aggressiveness varies by obesity status (normal vs. overweight and obese), and race (African American vs. European Caucasian).

Methods: Multivariate logistic regression with stepwise selection, including PCa risk factors, age, BMI and race were used. The Receiver Operating Characteristic (ROC) curves and area under the curve (AUC) were calculated for biopsy Gleason, PSA and PSA mass models to predict prostate cancer aggressiveness.

Results: We found non-significant difference in the median PSA and PSA mass between obese and non-obese groups (5.4 vs. 5.2) ng/ml and (18.1 vs. 19.5) µg, respectively. However, the medians for PSA, PSA mass, and BMI were significantly higher among African men (AA), compared to Caucasian (CA) (5.6 vs. 5.4) ng/ml and (20.0 vs. 18.1) µg, respectively. Prediction for RPGG ≥ 3 for the whole population were similar to CA for both PSA and PSA mass models, with improvement of 10% for AA and obese men for both models, compared to BGR alone.

Including PCa risk factors such as BMI and age to the PSA and PSA mass models improved the performance and accuracy.

Conclusions: The performance of prediction models were similar for PSA mass and PSA. Models performance for both AA and obese men were the highest. Specified Risk factors, gene profile and family history should be considered for incorporation into the models to get more accurate prediction of PCa aggressiveness.

Introduction

Biopsy Gleason grading is one of the most important predictors of prostate cancer (PCa) outcomes in men. However, there is a documented disagreement between the biopsy Gleason grade (BGR) and the radical prostatectomy Gleason group (RPGG). This disagreement has been associated with postsurgical biochemical recurrence (BCR) and short and long-term adverse outcomes such as urinary complications and increased risk of prognosis and PCa mortality (3, 4). Therefore, it is crucial to increase accuracy of Gleason biopsy grading when determining the Gleason pathology in order to provide better diagnosis and treatment to PCa patients. Researchers have proposed fully accounting for other risk factors associated with PCa and BCR, such as obesity and race, as tools for improving accuracy (16, 27-30).

Obesity is defined as an excess of adipose tissue in the body and has been associated with increased risk of cancers, including breast and prostate cancer (31). Obesity can impact the diagnosis and detection of cancer by interfering with imaging tests and assessment of soluble tumor markers in serum such as PSA (32). Moreover, obesity has been associated with increased risk of mortality and BCR after RP (33, 34). One explanation for these adverse outcomes among obese men may stem from either a biological mechanism, such as a hormone that impedes diagnosis, or a technical inability to accurately detect the tumor in obese men or define proper disease stage (35). Similarly, racial association, particularly African American (AA), has also been shown to be an established risk factor, presenting 1.7× greater likelihood of AA men being diagnosed with PCa than Caucasians (CA) and 2× greater likelihood to die [6, 7]. Additionally, African Americans have been disproportionally impacted by adverse risk after RP. Although active surveillance (AS) is a promising alternative to RP and other techniques, the lack of representation of African Americans under AS presents a challenge in diagnosis and prognosis

(29, 30). However, the implications for using active surveillance (AS) on certain high-risk groups remain uncertain. It has been hypothesized that AA men, who present a higher incidence of PCa and a higher risk of aggressive forms, may be the ideal target population to explore the genetic and environmental risk factors responsible for this disparity (29). Moreover, there is a lack of active surveillance of AA men, for whom the prevalence of obesity is high. Therefore, there is a pressing need for a better tool to accurately classify these risk populations by using their demographic and clinical information in order to offer enhanced treatment options beyond RP (10). This project aims to examine whether preoperative prostate-specific antigen mass (PSA mass) is a better predictor for prostate cancer aggressiveness compared to PSA and whether prediction of PCa aggressiveness varies by obesity status (normal vs. overweight and obese), and race (African American vs. European Caucasian).

Methods

The Study of Clinical Outcomes, Risk, and Ethnicity (SCORE) is a retrospective study conducted at the University of Pennsylvania Health System (UPHS, Philadelphia, PA). The study recruited 2,080 patients with PCa who underwent radical prostatectomy between 1995 and 2012. After patients were recruited, those who signed informed consent forms were included in the study under a provision of the Declaration of Helsinki protocol, which was approved by the Institutional Review Board at the University of Pennsylvania. A subset of 1,028 cases with complete information such as race, BMI, age, and PSA were used for this analysis. Patients missing information on Gleason clinical stage, primary and secondary on either Gleason grade biopsy or Gleason grade pathology were excluded (19, 20). BMI parameters based on the WHO classification were used to define obesity status. Those presenting a BMI between 25 kg/m2 and 30 kg/m2 were marked as overweight. Those presenting a BMI above 30 kg/m2 were classified as obese. Preliminary analysis showed no difference between normal and overweight men (data not shown here), therefore for this analysis, we categorized men from 18.5 to 25 kg/m2 as normal/overweight, and BMI above 30 kg/m2 were classified as obese. PSA mass, defined as the absolute amount of PSA protein, accounting for plasma volume, was calculated using the formulae: body surface (EBS)= (weight) 0.425 × (height) 0.72 × 0.007184, plasma volume [liters] (PV)= EBS × 1.670, and PSA mass [μg] = PV × PSA concentration.

Baseline preoperative characteristics and postoperative characteristics were compared across the BMI categories using Chi-square test (category variables) and T-test (continuous variables). Gleason aggressiveness as an outcome was classified to Gleason group <2 (BGG1&2) versus ≥3 (BGG 3, 4, 5). For regression analysis, PSA mass, PSA and BMI were log transformed in the univariate and multivariate models.

To compare and assess PSA mass accuracy vs. PSA for predicting Gleason path aggressiveness, logistic regression and the receiver operator characteristics (ROC) curves were plotted as a false positive rate (1- specificity) versus sensitivity. Further univariate and stepwise selection were used to define the best models for prediction of Gleason pathology rate aggressiveness. Three models were performed:1) Clinical Gleason group only: RPGG ~ BBG(CGG); 2) PSA+BMI: RPGG ~ BBG(CGG) + log(PSA) + log(PSA mass) + log(BMI) + Age + Race + all pairwise interactions; and 3) PSA mass: RPGG ~ BBG(CGG) + log(PSA mass) + Age + Race + all pairwise interactions. All analyses were performed with R statistical software version 3.6. 3 (R Foundation for Statistical Computing).

Results

Of the 2,066 patients recruited in the SCORE study, 1,028 were used for this analysis. Table 1. summarizes baseline characteristics by PSA mass tertiles categories (N =335 vs 355 and 338). PSA and BMI were significantly higher in African American men in highest tertile of PSA mass were slightly higher (25%) vs. lowest tertile (18%). Table 2. summarizes the baseline characteristics by non-obese (777) and obese (251) patients. For the continuous variable, data was presented in median inter quartile range (IQR) and categorical variables were presented in numbers (%). There was no significant difference in the median PSA and PSA mass between the two groups; however, PSA mass was higher in the obese group versus the non-obese group at 16.6 vs. 19, respectively. Moreover, there was a significant age group difference: obese men were younger than normal and overweight groups with a median of 58 years versus 60 years. For race, there were 134 (17%) African Americans (AA) in the overweight group and 66 (26%) in the obese group. For BGR upgrading RP pathology specimens, there was a significantly higher number of patient upgrades among obese men 99 (39.4%) compared to overweight men 249 (32%).

Table 3. summarizes the baseline characteristics between AA versus CA men groups. The median for PSA, PSA mass, and BMI were significantly higher among AA men versus CA men. AA men were younger but not significantly so compared to those in the CA group. AA men (36.5%) showed a higher upgrade rate than the CA men (33.2%), but CA men showed a significantly higher number (58.9%) of men who remained concordant vs. the AA group (49.5%). Also, for downgrading, African Americans showed a significantly higher downgrading (14%) versus the CA group (7.9%). Biochemical recurrence or failure time was significantly higher among obese vs. non-obese men (23.1% vs. 16.6%) and AA vs. CA (25.0% vs. 16.5%).

For prediction models, three models were presented in each figure of the results. Logistical regression (stepwise selection) was used to predict radical prostatectomy Gleason group (RPGG=1) from biopsy Gleason group (BGG/CGG=0). Orange indicated prediction of RPGG from BGG using Gleason clinical biopsy; red indicated PSA mass with Gleason clinical and other baseline characteristics; blue indicated PSA + BMI with other clinical variables.

Optimal models were presented with the regression coefficients tables, including P values. For accuracy, positive predictive value (PPV) and the negative predictive value (NPV) were calculated as well as the relative accuracy.

Figure 1. and 2. showed ability of the models to discriminate between positive and negative biopsy findings of RPGG ≤ 2 Vs. RPGG ≥ 3. In the whole population, the PSA + BMI model is favored over the PSA mass model, with a slightly better performance. Receiver operating characteristic (ROC) showed area under the curve (AUC) 83% vs. 82%, compared to 72.4% for BGG alone. The accuracy was similar for both models (89%).

Figures 3, 4, 5, and 6 show the prediction of RPGG ≥ 3 by race (AA vs. CA). The PSA mass model was similar to the PSA + BMI in accuracy (89%). PSA+BMI models showed better performance compared to PSA Mass models, AA 84.4% vs 83.6%, compared to 76.7% for BGG alone. For CA, the PSA+BMI and PSA mass model performances were 81.6% and 81.3%, compared to 71% for BGG. The PSA + BMI models for AA showed interaction for PSA and BMI p value ≤ 0.02 (Figure 3 and 4); whereas the PSA + BMI models for CA included age in model, with no interaction found (Figure 5 and 6).

Figures 7 and 8 showed prediction of RPGG ≥ 3 by obesity status (obese, not obese). In the obese men group the PSA + BMI and PSA mass models showed the highest performance AUC

85.1% vs. 83.7%, compared to 72.9% for BGG alone. The PSA mass model AIC was slightly better than the PSA + BMI models, showing interaction for both PSA and BMI (p=0.1), as well as BMI and race (p= 0.03) (Figure 7, 8). In the non-obese group, the PSA + BMI model vs. PSA mass model performance was 82.2% vs. 81.3%, compared to 72.1% for BGG alone. The PSA mass model AIC is similar to the PSA + BMI model. PSA+BMI model showed interaction between age and BMI (p=0.6) (Figure 9, 10).

Discussion

In this project, we examined the accuracy of PSA vs. PSA mass, when including other PCa risk factors, such as age, obesity, and African-American (AA) race. We used a cohort of 1,028 patients who underwent radical prostatectomy as a primary outcome treatment for PCa. We found that obese and AA PCa patients had a younger median age, and also that AA race is proportionally higher among obese patients. Our findings are consistent with previous literature that indicated that AA men present a more aggressive form of PCa and worse prognosis during initial evaluation (1). Furthermore, prior research has also suggested that obese men are at high risk for PCa disease progression (2). Our results agree with previous studies, showing significantly higher failure rates for AA than for CA men. Similarly, significant failure rates were higher for obese compared to non-obese men. We were unsurprised that PSA and PA mass levels were higher among AA patients, but it was interesting to note that the level of PSA mass, but not PSA, were higher among obese men. It has been previously proposed that obese men tend to present lower PSA levels due to the hemodilation effect of obesity. This can cause detection bias and delay diagnosis, which ultimately contributes to delayed treatment and worsening prognosis (3, 4).

Our findings for radical prostatectomy Gleason group (RPGG) showed a better prediction with PSA and PSA mass models compared to biopsy Gleason grade (BGR) for the whole population. Also, the prediction of RPGG for CA showed improvement of 10% from the BGR model. However, for AA, there was only a 7% improvement in all models. This is probably due to other factors that incorporate into the models for better prediction, such as oncologic family history and genetic information. Recent research has indicated that there is a difference in the gene

profile between AA and CA men, and that the AA population gene profile is associated with a more aggressive form of PCa (5, 6).

Incorporation of BMI and age in the prediction models showed improvement by more than 10%. Furthermore, our findings indicated that the association between PSA and BMI is similar if it is used in a multiplicative method in the case of PSA mass, by calculating plasma volume using height and weight. Therefore, for simplicity, it may be better for the clinician to use PSA mass computation instead of relying only on PSA, especially for obese and AA men. Recently, other researchers have recommended using the machine learning approach to predict PCa aggressiveness. This tool shows promise in determining the accuracy of Gleason biopsy classification. However, some of these techniques require comprehensive demographic and clinical data collection from the patient (7, 8). Moreover, recent studies have suggested including MRI imaging along with the machine learning approach for better prediction of prostate cancer biopsy aggressiveness (9). Though such proposals are promising, in a community setting it may be more cost effective and practical to just use biopsy and demographic information for initial diagnostic evaluation and active surveillance.

Strengths and Limitations

A major strength of this study is that it represents a diverse population of African American and obese men, allowing the study to predict prostate cancer (PCa) aggressiveness among this high-risk group. The study also collected information on BMI, which highlights the importance of BMI, a clinically accepted measurement for obesity, when evaluating a patient with low risk PCa. Moreover, the study provides contribution to the current literature on improving prediction of PCa aggressiveness among African American and obese men in low-middle PCA group, who are at high risk for disease progression. It must be

acknowledged that this study cannot be generalized to all radical prostatectomy patients, nor to all obese and AA patients due to a) small sample size of low/medium risk group, b) the relatively short follow-up time for the study, c) unavailability of other obesity measurements, such as waist-to-hip ratio and body mass information. Generally, PSA testing is done for both screening and diagnosis for prostate cancer. However, in this study we were not able to distinguish whether PSA measurement was measured for since all done around same time. Furthermore, this study relies on secondary data analysis without complete information of some patient data and variables, such as digital rectal exam, which is an important clinical predictor for PCa aggressiveness.

Summary

This study, which represented a diverse population with good representation of African American and obese men, indicated that PSA and PSA mass were more accurate predictors for PCa aggressiveness in AA and obese men, compared to Caucasian and non-obese men. Therefore, these results provide a novel contribution to the literature of potential improvement in accuracy of the current Gleason Grading system. This research will be important in guiding personalized medicine and evidence-based decision-making regarding screening, proper timing of diagnosis, and treatment decisions.

Table 1. Pre-and Post-operative Characteristics and Pathological Outcomes of Patients by PSA Mass Categories

	Tertile 1	Tertile 2	Tertile 3	P Value
Number of Patients	335	355	338	
PSA, ng/mL	3.6 (2.5, 4.2)	5.4 (4.9, 5.8)	9.3 (7.5, 12.7)	<0.001
PSA_Mass	12.1 (8.7, 14.0)	18.3 (17.1, 20.0)	32.0 (5.9, 44.3)	<0.001
Age	59 (54, 63)	60 (55, 64)	60 (54, 65)	0.16
BMI	26.6 (24.4, 29.6)	27.3 (25.1, 29.8)	27.7 (25.6, 30.5)	0.001
Race (%)				0.005
CA	279 (83.3)	296 (83.4)	253 (74.9)	
AF	56 (17.7)	59 (16.6)	85 (25.1)	
Biopsy Gleason Group (BGG)				0.005
BGG1 (<=6)	270 (80.6)	260 (73.2)	228 (67.5)	
BGG2 (3+4)	46 (13.7)	54 (15.2)	61 (18.0)	
BGG3 (4+3)	10 (3.0)	22 (6.2)	19 (5.6)	
BGG4 (8)	8 (2.4)	16 (4.5)	24 (7.1)	
BGG5 (>=9)	1 (0.3)	3 (0.8)	6 (1.8)	
Radical Prostatectomy Group (RPGG)				<0.001
RPGG1 (<=6)	192 (57.3)	174 (49.0)	134 (39.6)	
RPGG2 (3+4)	121 (36.1)	128 (36.1)	122 (36.1)	
RPGG3 (4+3)	13 (3.9)	35 (9.9)	44 (13.0)	
RPGG4 (8)	6 (1.8)	11 (3.1)	18 (5.3)	
RPGG5 (>=9)	3 (0.9)	7 (2.0)	20 (5.9)	
Surgery Year	2005 (2002, 2009)	2003 (2000, 2008)	2002 (1996, 2007)	<0.001
Follow Up Months	25.0 (12.0, 48)	27 (12, 61)	27.5 (11.0, 61.0)	0.31
Fail				<0.001
Yes	21 (6.3)	56 (15.8)	110 (32.5)	
NO	314 (93.7)	299 (84.2)	228 (67.5)	

Continuous variables presented as median (IQR) and categorical variables presented as n (%)

Table 2. Pre-and Post-operative Characteristics and Pathological Outcomes of Patients by Obesity Status

	Normal& Overweight	Obese	P Value
Number of patients	777	251	
PSA, ng/mL	5.4 (4.2, 7.5)	5.2 (4.1, 7.4)	0.4
PSA mass (µg)	18.1 (14.0, 24.9)	19.5 (14.7, 27.3)	0.1
Age at diagnosis, (years)	60.0 (55.0, 64.0)	58.0 (53.0, 63.0)	0.002
BMI, kg/m 2	26.2 (24.4, 27.9)	32.5 (31.0, 35.2)	<0.001
Race			0.002
Caucasian (CA)	643 (82.8)	185 (73.7)	
African American (AA)	134 (17.2)	66 (26.3)	
Biopsy Gleason Group (BGG)			0.49
BGG1 (<=6)	581 (74.8)	177 (70.5)	
BGG2 (3+4)	120 (15.4)	41 (16.3)	
BGG3 (4+3)	36 (4.6)	15 (6.0)	
BGG4 (8)	32 (4.1)	16 (6.4)	
BGG5 (>=9)	8 (1.0)	2 (0.8)	
Radical Prostatectomy Group (RPGG)			0.01
RPGG1 (<=6)	394 (50.7)	106 (42.2)	
RPGG2 (3+4)	276 (35.5)	95 (37.8)	
RPGG3 (4+3)	69 (8.9)	23 (9.2)	
RPGG4 (8)	21 (2.7)	14 (5.6)	
RPGG5 (>=9)	17 (2.2)	13 (5.2)	
Age categories			0.01
Age ≤60	371 (47.7)	146 (58.2)	
Age ≥60	406 (52.3)	105 (41.8)	

Continuous variables presented as median (IQR) and categorical variables presented as n (%)

Table 3. Pre-and Postoperative Characteristics and Pathological Outcomes of Patients by Race

	African American	Caucasian	P Value
Number of Patients	200	828	
PSA, ng/mL	5.6 (4.2, 8.4)	5.4 (4.2, 7.2)	0.04
PSA mass (µg)	20.0 (15.1, 28.9)	18.1 (14.0, 24.6)	0.01
Age at diagnosis (in years)	58.5 (53.0, 64.0)	60.0 (55.0, 64.0)	0.08
BMI, kg/m 2	28.6 (25.8, 31.4)	27.1 (25.1, 29.7)	<0.001
Biopsy Gleason Group (BGG)			
BGG1 (<=6)	119 (59.5)	639 (77.2)	
BGG2 (3+4)	52 (26.0)	109 (13.2)	
BGG3 (4+3)	13 (6.5)	38 (4.6)	
BGG4 (8)	14 (7.0)	34 (4.1)	
BGG5 (>=9)	2 (1.0)	8 (1.0)	0.004
Radical Prostatectomy Group (RPGG)			
RPGG1 (<=6)	76 (38.0)	424 (51.2)	
RPGG2 (3+4)	91 (45.5)	280 (33.8)	
RPGG3 (4+3)	15 (7.5)	77 (9.3)	
RPGG4 (8)	10 (5.0)	25 (3.0)	
RPGG(>=9)	8 (4.0)	22 (2.7)	
Patient categories			0.21
Age ≤60			
Age ≥60	91 (45.5)	420 (50.7)	
BMI categories			0.002
Normal/overweight			
Obese Men	66 (33.0)	185 (22.3)	
Biochemical recurrence	50 (25.0)	137 (16.5)	0.01

Continuous variables presented as median (IQR) and categorical variables presented as n (%)

Gleason Pathology Prediction Models

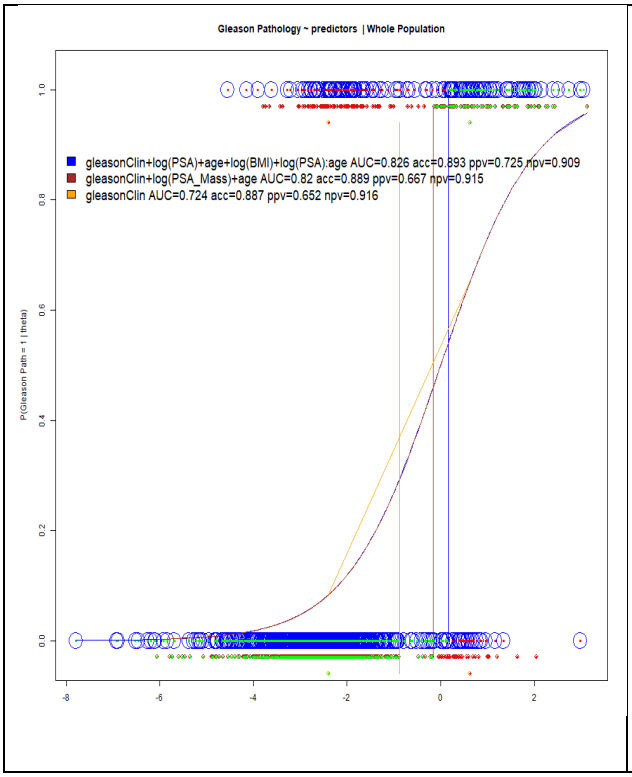
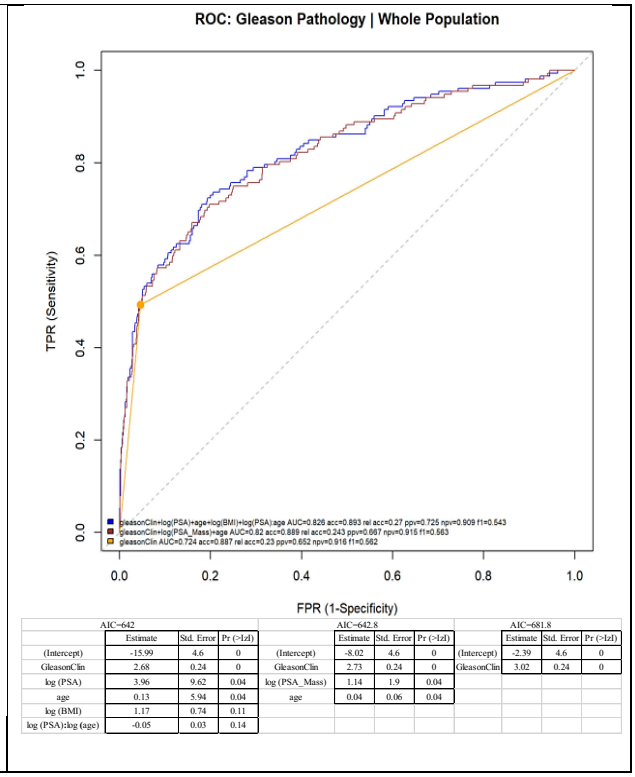


Figure 1. Gleason Pathology Whole Population



AIC=642

	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-15.99	4.6	0
GleasonClin	2.68	0.24	0
log (PSA)	3.96	9.62	0.04
age	0.13	5.94	0.04
log (BMI)	1.17	0.74	0.11
log (PSA):log (age)	-0.05	0.03	0.14

AIC=642.8

	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-8.02	4.6	0
GleasonClin	2.73	0.24	0
log (PSA_Mass)	1.14	1.9	0.04
age	0.04	0.06	0.04

AIC=681.8

	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-2.39	4.6	0
GleasonClin	3.02	0.24	0

Figure 2. ROC Gleason Pathology Whole Population

Gleason Pathology Data Analysis of Race
(Caucasian = CA, African American AA)

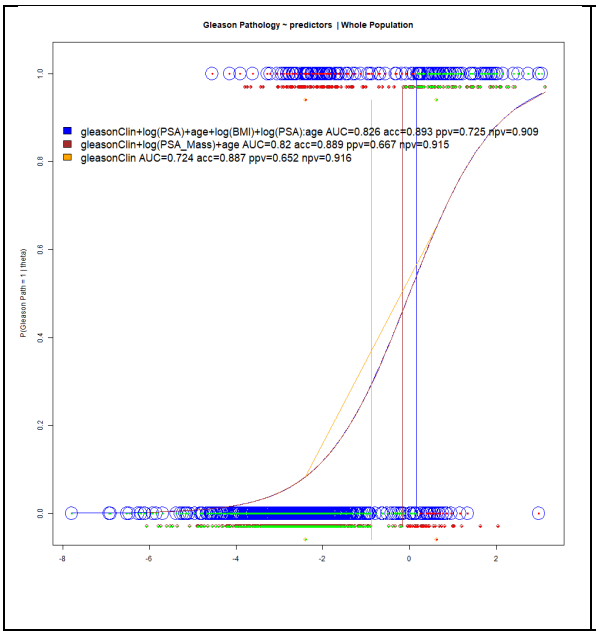
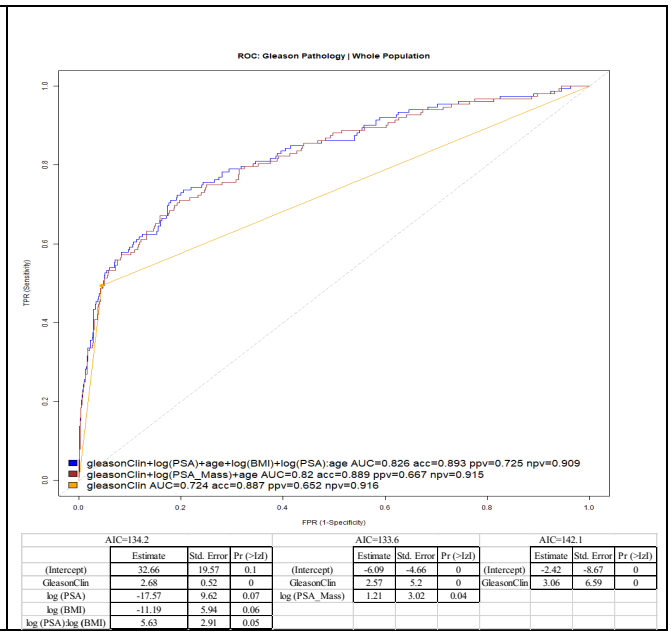


Figure 3. Gleason Pathology Race = AA



AIC=134.2	Estimate	Std. Error	Pr (>|z|)
(Intercept)	32.66	19.57	0.1
GleasonClin	2.68	0.52	0
log (PSA)	-17.57	9.62	0.07
log (BMI)	-11.19	5.94	0.06
log (PSA):log (BMI)	5.63	2.91	0.05

AIC=133.6	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-6.09	-4.66	0
GleasonClin	2.57	5.2	0
log (PSA_Mass)	1.21	3.02	0.04

AIC=142.1	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-2.42	-8.67	0
GleasonClin	3.06	6.59	0

Figure 4. ROC Gleason Pathology Race = AA

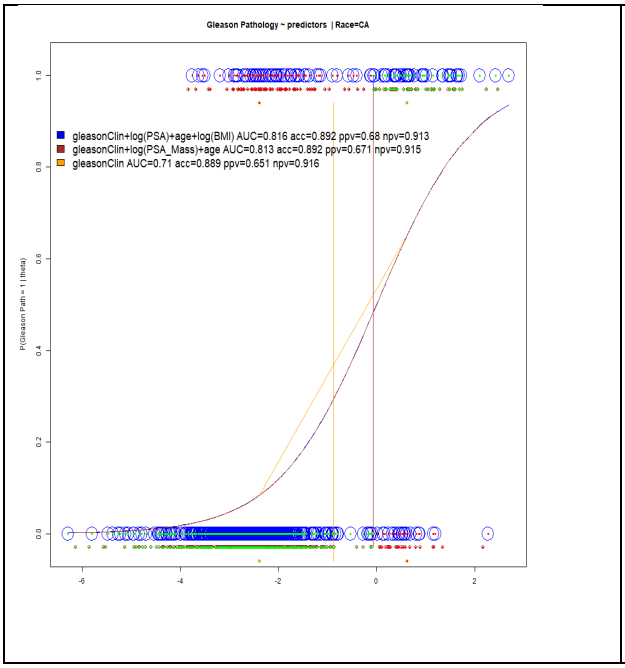
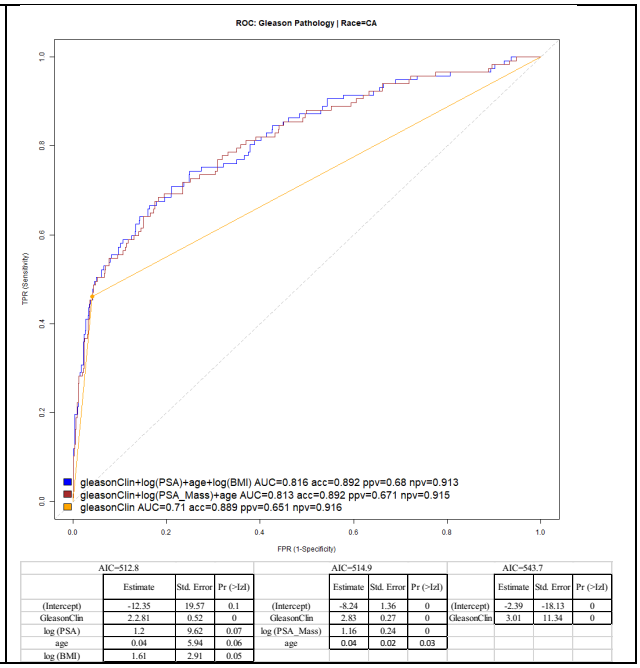


Figure 5. Gleason Pathology Race = CA



AIC=512.8	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-12.35	19.57	0.1
GleasonClin	2.2.81	0.52	0
log (PSA)	1.2	9.62	0.07
age	0.04	5.94	0.06
log (BMI)	1.61	2.91	0.05

AIC=514.9	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-8.24	1.36	0
GleasonClin	2.83	0.27	0
log (PSA_Mass)	1.16	0.24	0
age	0.04	0.02	0.03

AIC=543.7	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-2.39	-18.13	0
GleasonClin	3.01	11.34	0

Figure 6. ROC Gleason Pathology Race = CA

Gleason Pathology Prediction by Obesity

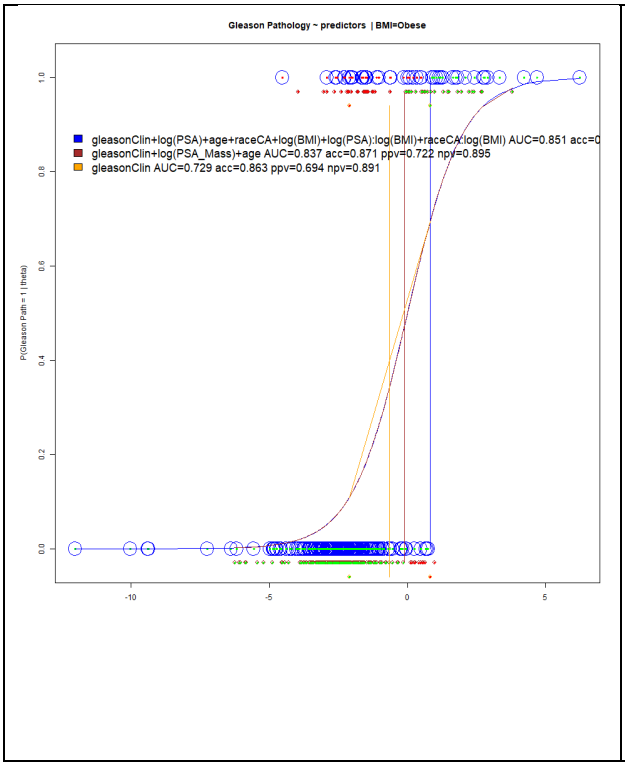
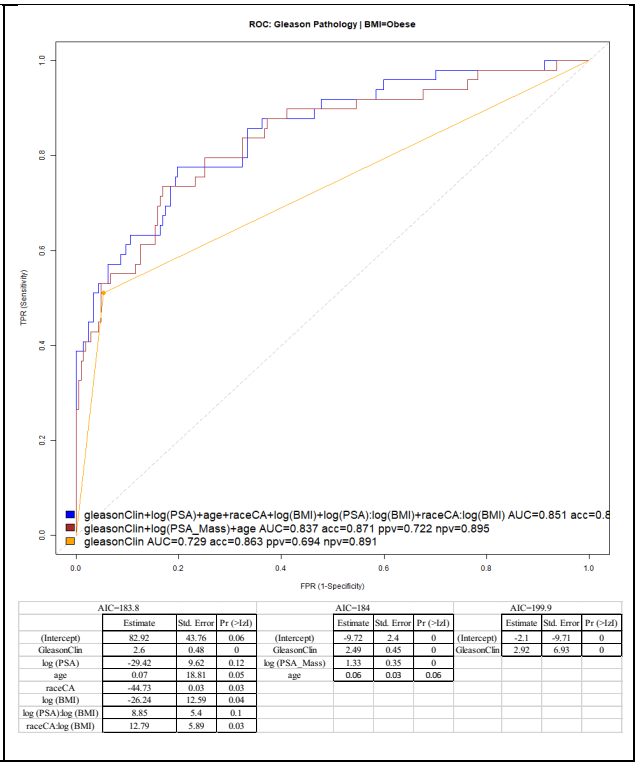


Figure 7. Gleason Pathology BMI=Obese



AIC=183.8	Estimate	Std. Error	Pr (>|z|)
(Intercept)	82.92	43.76	0.06
GleasonClin	2.6	0.48	0
log (PSA)	-29.42	9.62	0.12
age	0.07	18.81	0.05
raceCA	-44.73	0.03	0.03
log (BMI)	-26.24	12.59	0.04
log (PSA):log (BMI)	8.85	5.4	0.1
raceCA:log (BMI)	12.79	5.89	0.03

AIC=184	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-9.72	2.4	0
GleasonClin	2.49	0.45	0
log (PSA_Mass)	1.33	0.35	0
age	0.06	0.03	0.06

AIC=199.9	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-2.1	-9.71	0
GleasonClin	2.92	6.93	0

Figure 8. ROC Gleason Pathology BMI=Obese

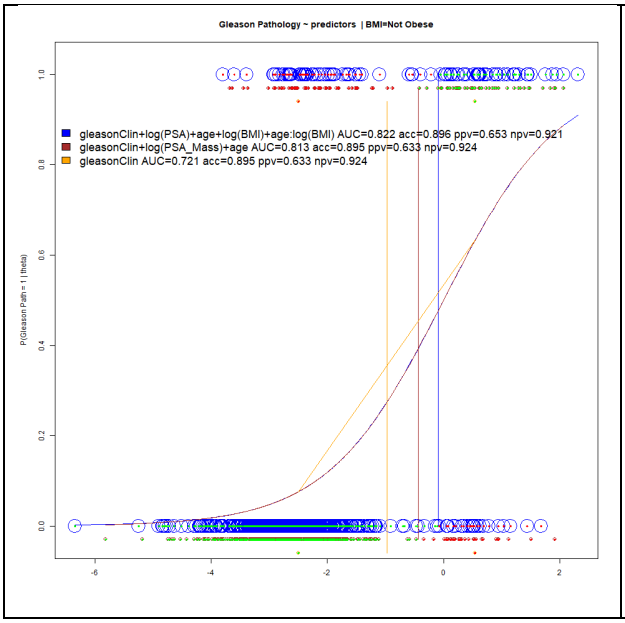
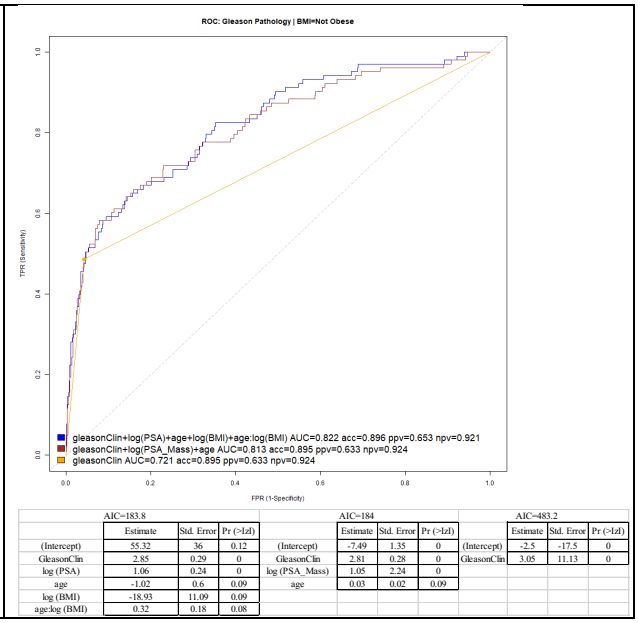


Figure 9. Gleason Pathology BMI= Not Obese



AIC=183.8	Estimate	Std. Error	Pr (>|z|)
(Intercept)	55.32	36	0.12
GleasonClin	2.85	0.29	0
log (PSA)	1.06	0.24	0
age	-1.02	0.6	0.09
log (BMI)	-18.93	11.09	0.09
age:log (BMI)	0.32	0.18	0.08

AIC=184	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-7.49	1.35	0
GleasonClin	2.81	0.28	0
log (PSA_Mass)	1.05	2.24	0
age	0.03	0.02	0.09

AIC=483.2	Estimate	Std. Error	Pr (>|z|)
(Intercept)	-2.5	-17.5	0
GleasonClin	3.05	11.13	0

Figure 10. ROC Gleason Pathology BMI= Not Obese

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Summary of Project 1 and Project 2 Conclusions

Project 1 Conclusion

Prostate cancer has a higher burden on obese and African American men, with both groups having a higher rate of biopsy Gleason upgrading (BGR) after surgery. Moreover, BGR upgrading was associated with higher risk for biochemical recurrence. This recurrence is more pronounced in obese, African American and advanced age men.

Project 2 Conclusion

Radical prostatectomy Gleason group (RPGG) showed a better prediction in PSA and PSA mass models, compared to biopsy Gleason grade (BGR) for the whole population and Caucasian race. However, for African American men, the model performers were not as accurate as the other risk groups. African American men normally present with a more aggressive form of the PCa, suggesting that gene profile and family history should be included when building prediction models for such groups.

Discussions and Perspectives

Strengths, Limitation and Future Directions

Strengths

The findings from this research provide a novel contribution to the current literature and also to the potential improvement in accuracy of the current Gleason Grading system and better treatment options. Our research also highlights the importance of BMI, a clinically accepted measurement for obesity, when evaluating a patient with low risk prostate cancer.

This study represents a diverse population that gave us the opportunity to study disease disparity among African American men. These results also provide strong evidence that future research to explore the role of risk factors on PCa progression among disadvantaged populations is highly warranted.

Limitations

Though this study used a large cohort, it is important to emphasize that the results cannot be generalized for mass risk group population. The study used only one measurement of obesity (BMI), and there are other important measurements such as waist-to-hip ration and body mass. The study cohort had a relatively short follow up and was based on secondary data analysis with missing information on some variables such as digital rectal exam, which would have been helpful in model prediction.

Future Directions

Research direction includes:

- Model validation, internally using test train approach, and externally using the Health Professional Study cohort.
- Incorporate genetic information, as well as other risk factors associated with prostate cancer to develop even more accurate markers, using a machine learning approach.