

Prostate Exams as Indicators of Tumor Penetration of the Prostatic Capsule

Andrew Bates

December 11, 2018

Executive Summary

In this paper we investigate various prostate exam results and their relationship with tumor penetration of the prostatic capsule. A logistic regression model is constructed based on a subset of data collected by the Ohio State University Comprehensive Cancer Center in order to quantify the relationship. The components of the model are the results of a digital rectal exam, total Gleason score, and prostate specific antigen value. The most significant factor is whether a nodule was detected in a digital rectal exam. Presence of a nodule is associated with up to a 4.7 times increase in odds of tumor penetration compared to absence of a nodule. A one unit increase in Gleason score is associated with a 2.7 times increase in odds of tumor penetration. Prostate specific antigen value is related to tumor penetration via a 3% increase in odds of penetration for each additional mg/ml increase. We also assess the potential of using the model as an overall diagnostic tool that combines the results of a digital rectal exam, prostate specific antigen value and Gleason score into a single measure of risk, rather than considering each measure individually.

1 Introduction

Prostate cancer is one of the most common cancers among males, second only to skin cancer (American Cancer Society 2016). The American Cancer Society estimates 164,000 new cases will occur in 2018 with approximately 29,000 deaths from prostate cancer (American Cancer Society 2016). Early detection is crucial because if the cancer is found prior to penetration of the prostatic capsule a successful treatment plan can often be implemented. In this paper we investigate the relationship between the results of various prostate related exams and whether tumor penetration of the prostatic capsule has occurred. The primary purpose of this analysis is to determine if there are any factors that have a particularly influential relationship with prostate capsule penetration. All patients have abnormal tumors with some having cancer and some not. A secondary aim is to develop a method to use the model resulting from the primary analysis as a diagnostic aid that merges the results of several exams into a single risk measure instead of considering each result independently.

The prostate related exams considered here include a digital rectal exam, prostate specific antigen value, and total Gleason score. In a digital rectal exam, doctors insert a finger and feel for any abnormalities in the prostate such as lumps (WebMD 2018). The PSA test measures the level of prostate specific antigen, a protein produced in the prostate gland, in the patients blood. It is produced by both normal and malignant cells with higher levels associated with prostate cancer (National Cancer Institute 2017). Gleason score is a measure of the abnormality of tumor cells. It is comprised of two scores with higher scores indicating more abnormality. The first score is assigned based on the composition of the majority of cells and the second assigned to the remaining cells. These scores are then added together to get a total Gleason score (American Cancer Society 2017).

2 Methods

In this analysis we examine a subset of data collected by the Ohio State University Comprehensive Cancer Center as part of a study to determine the potential of standard exam results to predict whether a tumor will penetrate the prostatic capsule. Out of 380 patients, 153 have experienced capsule penetration and 227 have not. The data set contains six explanatory variables: the patients age and race, results of a digital rectal exam (DRE), whether capsular involvement was detected, prostate specific antigen (PSA) value, and total Gleason score. Also included in the data set is an identification code which is not used in the analysis as it simply identifies the patient. For a detailed description of each variable see Table 1. There are two numeric variables, PSA and age. The remaining variables are categorical. Observe that race is recorded as only Black or White. This may be related to why three observations contain missing values for race. Perhaps three of the patients were neither Black nor White. Without access to the details of the study though, we can only speculate. Instead of attempting some sort of imputation method, we favor the simpler method of removing these observations before conducting our analysis. The data set used for analysis then, consists of 377 observations. Of these, 151 patients have experienced tumor penetration of the prostatic capsule, and 226 have not.

Table 1: Detailed description of variables included in the data set (except id). The two continuous variables are age and prostate specific antigen value. The remaining variables are categorical; their levels are indicated in the Details column.

| Name | Description | Details |
|-----------|---|---|
| penetrate | Tumor penetration of prostatic capsule? | Yes, no |
| age | Patient age | Years |
| race | Patient race | Black, White |
| dre | Results of digital rectal exam | No nodule, unilobar left, unilobar right, bilobar |
| caps | Detection of capsular involvement? | Yes, no |
| psa | Prostate specific antigen value | mg/ml |
| gleason | Total Gleason score | 0 - 10 |

To investigate the relationship between the covariates and tumor penetration status, we use a logistic regression model for its interpretability. In addition to the explanatory variables included in the data set, all two-way interaction terms are considered. Using this as a starting point, the model is chosen via a stepwise procedure using Akaike Information Criteria (AIC) as the model selection criterion. In the model constructed with this procedure age and race are not significant at the 0.05 level so they are subsequently removed along with any associated interaction terms.

Diagnostics of the resulting model are performed via explanatory variable patterns and a Hosmer-Lemeshow goodness-of-fit test. The strength of the relationship between the covariates and tumor penetration of the prostatic capsule is measured by the odds ratio. The predictive power of the model is evaluated by the area under the receiver operating characteristic curve. A method based on predictions from the model is proposed as a tumor penetration diagnostic tool to assist physicians in determining if further investigation of a given patient is warranted. The analysis is conducted using the statistical software R and the report is written using R Markdown and the bookdown package. The R code is available in the appendix. All other materials used in this analysis are available online at <https://github.com/asbates/stat696/tree/master/reports/prostate-cancer>.

3 Analysis

3.1 Exploratory Analysis

We begin by inspecting tables of the categorical variables against whether tumor penetration has occurred. Rather than examining contingency tables of counts, we find it more informative to view tables marginalized by the covariates. This provides more context by allowing us to see, for example, the proportion of Black patients who had tumor penetration and the proportion who did not. Table 2 displays the proportion of patients who did and did not experience tumor penetration of the prostatic capsule grouped by the results of a digital rectal exam. It shows that the majority of patients who do not have a nodule have not experienced tumor penetration. For those patients who did have a nodule, the rate of tumor penetration is reversed. The most pronounced difference is for patients who had a bilobar nodule with 65% experiencing tumor penetration.

Table 2: Results of digital rectal exam vs. whether tumor penetration of prostatic capsule occurred, marginalized by the digital rectal exam results.

| | DRE Result | | | |
|-----------------------|------------|---------------|----------------|---------|
| | no nodule | unilobar left | unilobar right | bilobar |
| No Penetration | 80.8 | 63.4 | 47.4 | 34.6 |
| Penetration | 19.2 | 36.6 | 52.6 | 65.4 |

The relationship for the remaining categorical variables can be found in Tables 5 to 7 in the appendix. For Gleason score we find a similar story as DRE results. As Gleason score increases from zero to nine, the tumor penetration rate increases from zero to 92%. Where we do not see a significant change in the rate of tumor penetration is with race. Both Black and White patients have a tumor penetration rate of approximately 40%. This is in contrast with some research as the American Cancer Society asserts that prostate cancer is more common among African-American men (American Cancer Society 2016). This discrepancy may be related to the population considered in this data set. Perhaps a future analysis can investigate the disagreement.

For the numeric variables, we examine summary statistics and plots of age and PSA grouped by whether prostate capsule penetration has occurred. Summary statistics and a box plot for age can be found in Table 8 and Figure 3 in the appendix. There is virtually no difference in the age distribution of patients who have experience tumor penetration and those who have not. On the other hand, PSA value displays a noticeable difference. Figure 1 is a histogram of PSA value where color indicates tumor penetration of the prostatic capsule. The distribution has a similar shape for low PSA values however, for PSA values above 67 mg/ml there are no cases where tumor penetration has occurred.

3.2 Modeling

To model the relationship between tumor penetration and the predictor variables, we use a logistic regression model. As most of the covariates are tests covering different aspects of the prostate, it is not hard to imagine that some of them are connected in their relationship with tumor penetration. As such, the initial model is fit using all first-order interaction terms. This serves as the starting point for model selection which is done via stepwise regression with AIC as the selection criteria.

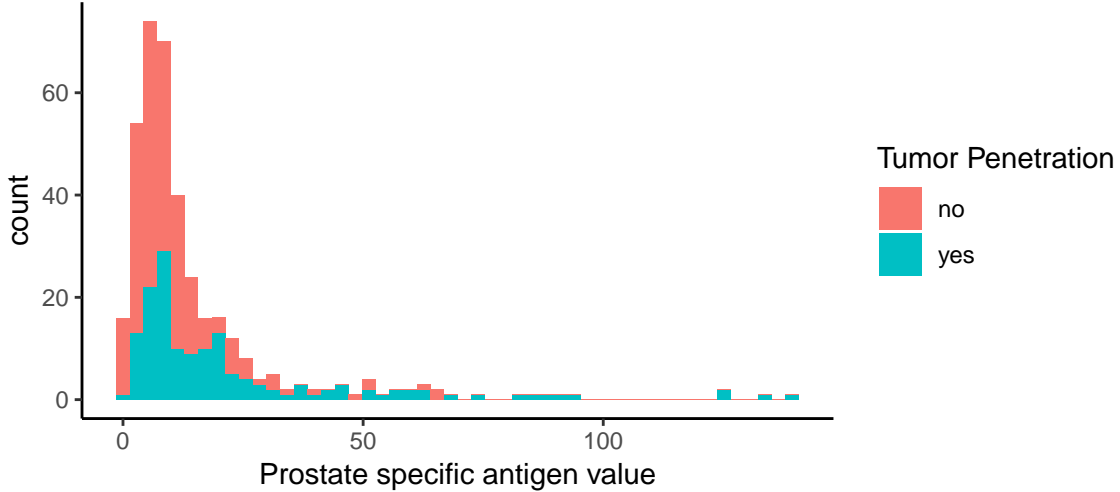


Figure 1: Histogram of prostate specific antigen value colored by whether tumor penetration of prostatic capsule occurred.

The model chosen via the stepwise procedure includes race, age, DRE results, PSA value, and Gleason score as well as age interacted with DRE result and race interacted with PSA value. A detailed summary can be found in Table 10 (appendix). We note here that the AIC is 391 and the p-values for age and race are quite high at 0.11 and 0.99, respectively.

Since the p-values for age and race are so high we remove them, along with associated interaction terms, and refit our model. Note that for this model, removing the relevant interaction terms actually means removing all interaction terms. Once this is done, we are left with a model that relates tumor penetration to just three variables: DRE results, PSA value, and Gleason score. The AIC for this model is 393. This is essentially the same as the AIC of the model with interaction terms included and we favor this model because of its simplicity. With this simpler model in hand, we now proceed to diagnostics to assess the fit.

3.3 Diagnostics

To assess the model we use diagnostic tools on explanatory variable patterns¹ (EVP). We collapse the original data into groups where each group shares the same covariate values. Recall that one of the variables, PSA, is continuous so we first break the values into non overlapping bins. Then we fit the model to the EVPs using the number of original observations in each EVP as weights. Standardized Pearson residuals, Cook's distance, and leverage from the EVP model are what we use to perform our diagnostics. A plot of the residuals vs. fitted probabilities is shown in Figure 2. The dotted horizontal lines indicate the standard cut off values of -3, -2, 2, and 3. There are no discernible patterns in the residuals and they are scattered roughly equally about zero. For larger fitted probabilities there is a bit more variability in the residuals but nothing too concerning. One EVP (lower right hand corner of plot) is slightly smaller than the lowest cut off bound, having a value of -3.4. This is only a minor violation and the cut off values are simply rules-of-thumb so we consider this EVP satisfactory.

¹Also called covariate patterns.

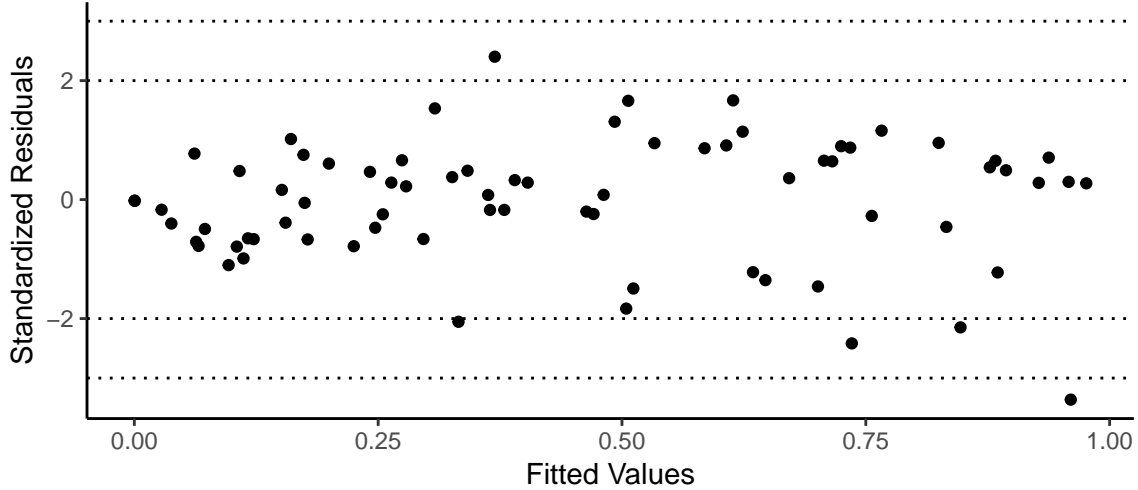


Figure 2: Standardized Pearson residuals vs. fitted values via Explanatory Variable Patterns. The horizontal reference lines indicate the usual residual cutoffs of ± 2 and ± 3 .

Further diagnostic plots can be found in Figure 4 in the appendix. Only one other EVP is of any concern as its Cook's distance and leverage values are both outside the standard cut off values. However, 22 of the original observations are contained in this EVP and given that the deviations are only slight, we proceed with this model instead of removing so many data points.

As a final diagnostic measure we perform a Hosmer-Lemeshow goodness-of-fit test using the model fit to the EVPs. The EVP data is separated into bins according to quantiles of the fitted values. Then observed and expected counts are computed for each bin and a χ^2 test is performed to assess the overall fit. The obtained test statistic is 3.9 with a corresponding p-value of 0.42. The p-value may seem unfruitful at first as we are typically looking for small values. However in the situation at hand this is not the case. The null hypothesis in this test is that the model fits the data well so we do *not* want to reject the null in our situation. So based on this test our model seems to fit the data well and we can move on to inferences.

3.4 Inferences

Table 3 contains a summary of the final model used in this analysis. Included in the table are estimates for the coefficients with their associated standard errors and p-values. Also include are the odds ratio for each term and 95% confidence intervals for the odds ratio. The largest odds ratio corresponds to a digital rectal exam where a unilobar nodule is found on the patient's ride side. The odds of experiencing tumor penetration of the prostatic capsule for such patients is 4.73 times more than the odds for patients which did not have a nodule present. Interestingly, the odds of tumor penetration for patients with a unilobar nodule on the left are about half the odds for patients with either a nodule on the right or a bilobar nodule. The odds ratio for Gleason score indicates that each unit increase in score corresponds to increase in odds of 2.71 times. Since the odds ratio for PSA is smaller than two, it has a slightly different interpretation. One additional mg/ml of PSA is associated with a 3% increase in odds when the remaining variables are unchanged. Of course, all of these interpretations are made with the caveat that only the variable under question changes and the others are held fixed.

Table 3: Summary for final model fitting tumor penetration of prostatic capsule with covariates digital rectal exam result, prostate specific antigen value, and total Gleason score. Coefficient estimates with standard errors and p-values are provided along with odds ratios and 95% confidence intervals for odds ratios. AIC for the model is 393.

| Term | Estimate | SE | p-value | Odds ratio | OR 95% CI |
|---------------------------------|----------|------|---------|------------|------------------|
| Intercept | -8.14 | 1.06 | 0.000 | 0.00 | (0.00 , 0.00) |
| DRE: unilobar left | 0.77 | 0.36 | 0.030 | 2.17 | (1.09 , 4.43) |
| DRE: unilobar right | 1.55 | 0.37 | 0.000 | 4.73 | (2.32 , 10.00) |
| DRE: bilobar nodule | 1.43 | 0.45 | 0.001 | 4.18 | (1.75 , 10.25) |
| Prostate specific antigen value | 0.03 | 0.01 | 0.004 | 1.03 | (1.01 , 1.05) |
| Gleason score | 1.00 | 0.16 | 0.000 | 2.71 | (2.00 , 3.76) |

In addition to making inferences on the odds ratios of each of the variables in our model, we can assess the models potential predictive ability. This is not a prediction problem per se and so we did not follow the usual paradigm of splitting our data into a training and testing set. This means that the predictions we consider here are in-sample predictions and will no doubt have much better performance than what would actually be seen in practice. Nonetheless, we can still get some sense of how well the model performs at predicting tumor penetration. To that end, we plot a receiver operating characteristic (ROC) curve (Figure 5 in the appendix) and compute the area under the curve (AUC). The ROC curve indicates that our model performs significantly better than the default comparison of randomly assigning whether tumor penetration will occur. The AUC for our final model is 0.82 which is quite good. The ROC curve and AUC indicate that the model developed here has potential as an overall diagnostic tool that combines the results of a digital rectal exam, prostate specific antigen value, and Gleason score into a single measure of risk, rather than considering each measure individually.

We now discuss how our model can be used as the aforementioned diagnostic tool. Let us suppose that we have three patients who have had a digital rectal exam, have a PSA test done, and have received a Gleason score. Of course in reality we would have this information available but for the sake of demonstration we will use hypothetical values. Table 4 presents the supposed values as well as the probability of tumor penetration obtained from the model. Doctors would likely be satisfied with the first two patients whose predicted probability of tumor penetration are quite low. However, further investigation would probably be desired for the third patient who has a reasonably high chance (0.88) of tumor penetration.

But is this probability really that high? What if it was 0.85 instead of 0.88? How do we determine what is considered ‘high’ and what is considered ‘low’? One way to do this is by considering the false positive rate and the false negative rate. We start by setting a cutoff value, say 0.85, for which values above we say that tumor penetration has occurred and otherwise we say that it has not. Patients with scores above the cutoff would warrant a deeper investigation while patients below the cutoff would proceed with a regular prostate exam schedule. Both false positives and false negatives are inevitable so the game here is to find an appropriate balance between the two and determine which one is more important. For example, we may want to minimize the false negative rate because this means a patient walks away thinking they have not experienced tumor penetration when in reality they have. Ultimately, a team of physicians would need to weigh the costs and benefits of an incorrect prediction and an appropriate cutoff value can be determined from there.

Table 4: Hypothetical values for DRE result, PSA value, and Gleason score along with predicted probability of tumor penetration of prostatic capsule obtained from the model.

| DRE result | PSA value | Gleason score | Probability of Tumor Penetration |
|----------------|-----------|---------------|----------------------------------|
| no nodule | 15.26 | 6 | 0.15 |
| unilobar right | 8.70 | 4 | 0.09 |
| no nodule | 80.42 | 8 | 0.88 |

4 Conclusion

In this analysis we developed a logistic regression model to aid in the understanding of how various factors relate to tumor penetration of the prostatic capsule. Along with this we compared the strength of the relationship by examining the odds ratio for each factor. The patient’s age and race were not included in the model from which we can infer that these have a weak relationship with tumor penetration, if any. The most significant factor was whether a nodule was detected in a digital rectal exam. Presence of a unilobar nodule on the right relates to a 4.7 times increase in odds than for patients with no nodule detected. An increase in Gleason score by one is associated with a 2.7 times increase in odds. For a one mg/ml increase in prostate specific antigen value, we can expect a 3% increase in odds. The predictive power of the model was assessed via AUC which was 0.82. This led us to believe the model has the potential to be used as a tool to help determine if a given patient has experienced tumor penetration. We also discussed how the model can be used in practice for this purpose.

We should note that the analysis performed here does have its limitations. The most obvious of these limitations is the population that the data represents. Although race and age were not included in the model, they do limit our inferences because they were quite limited in scope. Only Black and White patients were included in this data set and 75% of the patients were over 62 years of age. One needs to be careful not to extrapolate outside this population. Future investigations should include a broader population to widen the scope of the inferences.

Another aspect of this analysis that should be handled with care is using the model developed to predict tumor penetration. The predictive capability assessment of this analysis was done on data that was used to fit the model. These predictions will no doubt be an overestimate of the ability of predictions on previously unseen data. If it is desired to use this model as a primary method to determine if a patient has experienced tumor penetration, a different approach should be followed than was done in this analysis such as splitting the data into a training and testing set to estimate the out-of-sample predictive performance. One would likely also want to determine a cutoff point as this model outputs probabilities and not yes-no decisions. This has its own inherent difficulties. Experts would need to determine an acceptable level of false positives and false negatives and an appropriate balance between the two.

A Supplementary Tables and Figures

Table 5: Race vs. whether tumor penetration of prostatic capsule has occurred, marginalized by race.

| | Race | |
|-----------------------|-------|-------|
| | white | black |
| No Penetration | 59.8 | 61.1 |
| Penetration | 40.2 | 38.9 |

Table 6: Detection of capsular involvement vs. whether tumor penetration of prostatic capsule occurred, marginalized by capsular involvement.

| | Capsular Involvement | |
|--------------------------|----------------------|------|
| | no | yes |
| No Penetration | 64.1 | 25.0 |
| Tumor Penetration | 35.9 | 75.0 |

Table 7: Total Gleason score vs. whether tumor penetration of prostatic capsule occurred, marginalized by Gleason score.

| | Gleason Score | | | | | | |
|--------------------------|---------------|-------|------|------|------|------|------|
| | 0 | 4 | 5 | 6 | 7 | 8 | 9 |
| No Penetration | 100.0 | 100.0 | 91.0 | 72.5 | 43.3 | 20.7 | 7.7 |
| Tumor Penetration | 0.0 | 0.0 | 9.0 | 27.5 | 56.7 | 79.3 | 92.3 |

Table 8: Summary statistics of patient age grouped by whether tumor penetration of prostatic capsule occurred.

| | min | median | mean | max |
|--------------------------|------|--------|------|------|
| No Penetration | 50.0 | 67.0 | 66.3 | 79.0 |
| Tumor Penetration | 47.0 | 66.0 | 65.7 | 79.0 |

Table 9: Summary statistics for prostate specific antigen value grouped by whether tumor penetration of prostatic capsule occurred.

| | min | median | mean | max |
|--------------------------|-----|--------|------|-------|
| No Penetration | 0.3 | 7.5 | 10.0 | 66.7 |
| Tumor Penetration | 1.4 | 12.9 | 23.1 | 139.7 |

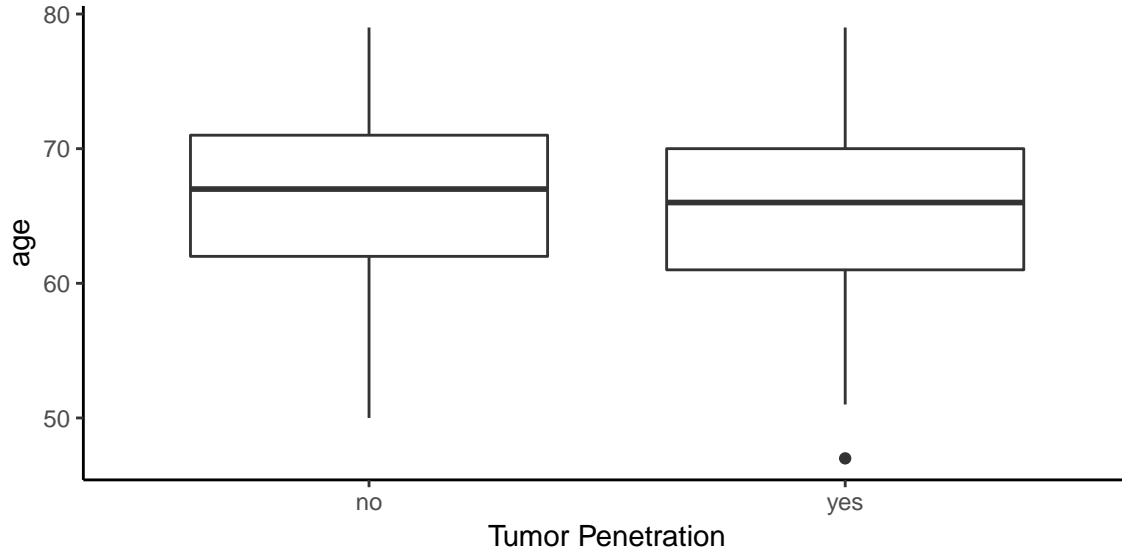


Figure 3: Boxplot of age vs. whether tumor penetration of prostatic capsule occurred.

Table 10: Summary of best stepwise fit of tumor penetration of prostatic capsule against age, race, digital rectal exam result, prostate specific antigen value, total Gleason score and the interaction terms age * dre results and race * psa. AIC is 391.

| Term | Estimate | SE | p-value |
|-----------------------|----------|-------|---------|
| (Intercept) | -28.15 | 12.36 | 0.023 |
| age | 0.29 | 0.18 | 0.107 |
| raceblack | -0.01 | 0.66 | 0.988 |
| dreunilobar left | 7.30 | 4.01 | 0.069 |
| dreunilobar right | -0.29 | 4.20 | 0.944 |
| drebilobar | 2.67 | 5.29 | 0.614 |
| psa | 0.04 | 0.01 | 0.001 |
| gleason | 3.94 | 1.84 | 0.032 |
| age:dreunilobar left | -0.10 | 0.06 | 0.095 |
| age:dreunilobar right | 0.03 | 0.06 | 0.646 |
| age:drebilobar | -0.02 | 0.08 | 0.821 |
| age:gleason | -0.04 | 0.03 | 0.110 |
| raceblack:psa | -0.03 | 0.02 | 0.134 |

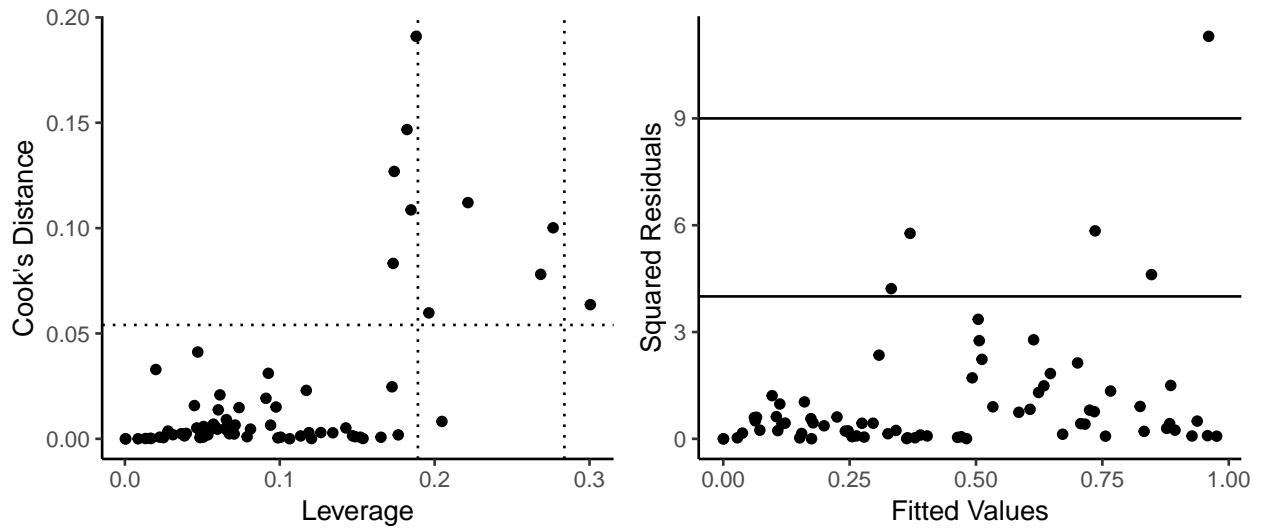


Figure 4: Diagnostic plots for the model fit on explanatory variable patterns. Left: Cook's distance vs. leverage. Right: squared Pearson standardized residuals vs. fitted probabilities

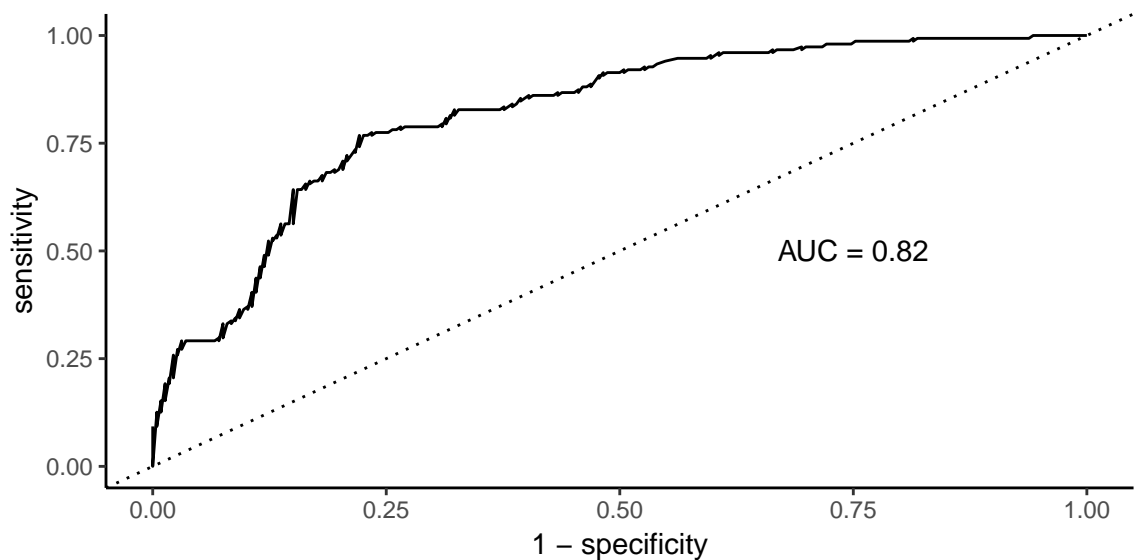


Figure 5: Receiver Operating Characteristic curve for final model fitting tumor penetration of prostatic capsule with covariates digital rectal exam result, prostate specific antigen value, and total Gleason score. The dotted line is a reference line indicating what the curve would be if we randomly decided whether tumor penetration occurred.

B R Code

```
library(here) # handles directories
library(readr) # read in data
library(MASS) # stepwise regression
library(dplyr) # manipulate data
library(forcats) # handle factors
library(ggplot2) # plotting
library(broom) # tidy model output
library(pROC) # assess predictions

# these packages were used for formatting tables and figures
# in the report but are not necessary to perform the analysis
library(knitr) # table formatting
library(kableExtra) # table formatting
library(gridExtra) # matrix of ggplot's

prostate_raw <- read_tsv(here("data", "prostate.txt"))

# =====
# ===== SETUP/CLEANING =====
# =====

dim(prostate)
names(prostate)
str(prostate)

# remove id, rename
prostate <- prostate_raw %>%
  select(-id)

prostate <- prostate %>%
  rename(
    penetrate = capsule,
    dre = dpros,
    caps = dcaps
  )

# re-encode variables
prostate <- prostate %>%
  mutate(
    penetrate = as.factor(penetrate),
    race = as.factor(race),
    dre = as.factor(dre),
    caps = as.factor(caps)
  ) %>%
  mutate(
```

```

penetrate = fct_recode(penetrate, yes = "1", no = "0"),
race = fct_recode(race, white = "1", black = "2"),
caps = fct_recode(caps, no = "1", yes = "2"),
dre = fct_recode(dre,
  "no nodule" = "1",
  "unilobar left" = "2",
  "unilobar right" = "3",
  "bilobar" = "4")
)

str(prostate)

# how many have experience capsule penetration?
prostate %>%
  group_by(penetrate) %>%
  summarise(n = n())

# any missing values?
apply(prostate, 2, function(x) sum(is.na(x)) )

# race has 3 missing values
summary(prostate)

prostate %>%
  filter(is.na(race))

# remove missing observations
prostate <- prostate %>%
  filter(!is.na(race))

dim(prostate)
prostate %>%
  group_by(penetrate) %>%
  summarise(n = n())

# =====
# ===== EDA =====
# =====

# ----- categorical predictors -----
race_tab <- table(`Capsule Penetration` = prostate$penetrate,
  Race = prostate$race)
dre_tab <- table(`Capsule Penetration` = prostate$penetrate,
  `DRE Result` = prostate$dre)
caps_tab <- table(`Capsule Penetration` = prostate$penetrate,
  `Capsular Involvement` = prostate$caps)
gleason_tab <- table(`Capsule Penetration` = prostate$penetrate,

```

```

`Gleason Score` = prostate$gleason)

race_tab
dre_tab
caps_tab
gleason_tab

# proportion tables marginalized by covariate
prop.table(race_tab, margin = 2) * 100
prop.table(dre_tab, margin = 2) * 100
prop.table(caps_tab, margin = 2) * 100
prop.table(gleason_tab, margin = 2) * 100

# ----- numeric predictors -----

# ---- age ----

# summarize age by prostate
age_sum <- prostate %>%
  group_by(penetrate) %>%
  summarise(
    min = min(age),
    median = median(age),
    mean = mean(age),
    max = max(age)
  )

# bar chart of age
ggplot(prostate, aes(x = age)) +
  geom_bar()

# penetrate vs. age bar plot
ggplot(prostate, aes(x = age, fill = penetrate)) +
  geom_bar(position = "dodge") +
  labs(fill = "Capsule Penetration")

# boxplot - age vs. penetrate
ggplot(prostate, aes(x = penetrate, y = age)) +
  geom_boxplot()

# ----- psa ----
# summary stats for psa by prostate
prostate %>%
  group_by(penetrate) %>%
  summarise(
    min = min(psa),
    median = median(psa),

```

```

    mean = mean(psa),
    max = max(psa)
  )

# histogram of psa
ggplot(prostate, aes(x = psa)) +
  geom_histogram(bins = 50)

# histogram of psa vs. penetrate
ggplot(prostate, aes(x = psa, fill = penetrate)) +
  geom_histogram(bins = 50)

# boxplot - psa vs. penetrate
ggplot(prostate, aes(x = penetrate, y = psa)) +
  geom_boxplot()

# =====
# ===== MODELING =====
# =====

# fit a 'full' model with all first-order interactions
full_fit <- glm(penetrates ~.*,
               data = prostate,
               family = binomial(link = "logit"))

# 'best' fit by stepwise regression
best_step <- stepAIC(full_fit, data = prostate)

best_step
summary(best_step)

# or via the broom package
tidy(best_step)

# if we remove variables from best_step according to p-value
# we are left with penetrates ~ dre + psa + gleason

# =====
# ===== DIAGNOSTICS =====
# =====

# functions used for residual analysis
one_fourth_root=function(x){
  x^(0.25)
}
source(here("reports", "prostate-cancer","code","examine.logistic.reg.R"))

```

```

# note: we're using the 'raw' data here with the default encoding
pros_diag <- prostate_raw %>%
  rename(
    penetrate = capsule,
    dre = dpros,
    caps = dcaps
  )

# Create EVPs by binning continuous covariates
g <- 5 # number of categories
psa_interval = cut(pros_diag$psa,
  quantile(pros_diag$psa, 0:g/g), include.lowest = TRUE)

w <- aggregate(penetrate ~ psa_interval + gleason + dre,
  data = pros_diag,
  FUN = sum)
n <- aggregate(penetrate ~ psa_interval + gleason + dre,
  data = pros_diag,
  FUN = length)
wn <- data.frame(
  w,
  trials = n$penetrate,
  prop = round(w$penetrate / n$penetrate, 2)
)

dim(wn) # 74 EVPs

diag_fit <- glm(penetrate/trials ~ psa_interval + gleason + dre,
  data = wn,
  family = binomial(link = "logit"),
  weights = trials)

# with identify.points = TRUE we can click points
# and see their location in the data frame
# In residuals vs. fitted, we see EVP 73 has a small residual (< 3)
# In Cook's distance vs. leverage, we find EVP 25 with large Cook's
# distance and large leverage
# In delta X^2 (squared residuals) vs. fitted (size prop. to trials)
# we find EVP 73 with high delta X^2 (>9)
# In delta X^2 vs. fitted (size prop. to Cook's distance)
# we find EVP 73 with high delta x^2 (>9)
# there are a few other EVPs that are outside some cutoffs
# but these two are the worst
examine <- examine.logistic.reg(diag_fit,
  identify.points = FALSE,
  scale.n = one_fourth_root,
  scale.cookd = sqrt)

```

```

wn_diag <- data.frame(
  wn,
  pi_hat = round(examine$pi.hat, 2),
  std_res = round(examine$stand.resid, 2),
  cooks_d = round(examine$cookd, 2),
  h = round(examine$h, 2)
)

p <- length(diag_fit$coefficients)

# locate points of interest
which_look_at <-
  abs(wn_diag$std_res) > 2 |
  wn_diag$cooks_d > 4 / nrow(wn) |
  wn_diag$h > 3*p / nrow(wn)
look_at <- wn_diag[which_look_at, ]

# look at points of interest
look_at

dim(look_at)  # 12 EVPs
sum(look_at$trials)  # 114 points

# look at only the points identified above
wn_diag[c(25, 73), ]

# what are the actual values for the cutoffs
# of cooks d and leverage h?
4/nrow(wn)
2 * p / nrow(wn)
3 * p / nrow(wn)

# do any EVPs violate all criteria?
# no, they don't
which_violate_all <-
  abs(wn_diag$std_res) > 2 &
  wn_diag$cooks_d > 4 / nrow(wn) &
  wn_diag$h > 3*p / nrow(wn)
any(which_violate_all)

# EVP 25 contains 22 observations
# its Cook's distance and leverage are above the cutoffs
# however, only slightly on both accounts
# not enough for us to justify removing this many points
# EVP 73 has 2 observations
# it is above the residual cutoff thus above the delta X^2 cutoff
# again, this is only a minor violation

```



```

# not quite strong enough for us to consider removing.

# as for the remaining EVPs
# the ones that do violate the cutoffs do so only slightly
# additionally, they mostly surpass one cutoff, not two
# lastly, almost all of them contain more than 6 original points, up to 14
# we will proceed with the model as is

# note: in the analysis we used the examine.logistic.reg function
# because of it's interactivity
# the plots in the report were made with the following code

# add relevant values (cooks d, etc.) to data
aug_diag <- augment(diag_fit,
                    data = wn,
                    type.predict = "response")

# for some reason, augment() is only returning deviance residuals
aug_diag <- aug_diag %>%
  mutate(
    .std.resid = rstandard(diag_fit, type = "pearson")
  )

# make diagnostic plots.
# same plots as examine.logistic.reg but using ggplot2

ggplot(aug_diag, aes(x = .fitted, y = .std.resid)) +
  geom_point() +
  geom_hline(yintercept = 2, linetype = "dotted") +
  geom_hline(yintercept = 3, linetype = "dotted") +
  geom_hline(yintercept = -2, linetype = "dotted") +
  geom_hline(yintercept = -3, linetype = "dotted")

cook_cutoff <- 4 / nrow(wn)
h_cutoff2 <- 2 * p / nrow(wn)
h_cutoff3 <- 3 * p / nrow(wn)

ggplot(aug_diag, aes(x = .hat, y = .cooks.d)) +
  geom_point() +
  geom_vline(xintercept = h_cutoff2, linetype = "dotted") +
  geom_vline(xintercept = h_cutoff3, linetype = "dotted") +
  geom_hline(yintercept = cook_cutoff, linetype = "dotted") +
  ylab("Cook's Distance") +
  xlab("Leverage") +
  theme_classic()

ggplot(aug_diag, aes(x = .fitted, y = .std.resid^2)) +

```

```

geom_point() +
geom_hline(yintercept = 4) +
geom_hline(yintercept = 9) +
ylab("Squared Residuals") +
xlab("Fitted Values") +
theme_classic()

# Hosmer-Lemeshow goodness-of-fit test

source(here("reports", "prostate-cancer", "code", "HLTest.R"))

# 6 groups used b/c that's minimum number such that expected counts are
# greater than 5
hl_test <- HLTest(diag_fit, 6)
hl_test

# contingency table of observed vs. expected
cbind(hl_test$observed, hl_test$expect)

# =====
# ===== INFERENCE =====
# =====

final_fit <- glm(penetrates ~ dre + psa + gleason,
                 data = prostate,
                 family = binomial(link = "logit"))

# summary and confidence intervals for final fit
final_fit
summary(final_fit)
confint(final_fit)

# also via the broom package
tidy(final_fit, conf.int = TRUE)

# ---- predictive power ----

fit_roc <- roc(prostate$penetrates, predict(final_fit, type = "response"))
plot(fit_roc, legacy.axes = TRUE, print.auc = TRUE)

# or using ggplot
data.frame(
  sensitivity = fit_roc$sensitivities,
  specificity = fit_roc$specificities
) %>%
  ggplot(aes(x = 1 - specificity, y = sensitivity)) +

```

```

geom_line() +
geom_abline(slope = 1, intercept = 0) +
annotate("text", label = paste0("AUC = ", round(fit_roc$auc, 2)),
         x = 0.75, y = 0.5)

# --- future predictions ---

# hypothetical new data
new_data <- data.frame(
  dre = c("no nodule", "unilobar right", "no nodule"),
  psa = c(15.26, 8.70, 80.42),
  gleason = c(6, 4, 8)
)

predict(final_fit, newdata = new_data, type = "response")

# or via broom
augment(final_fit, newdata = new_data, type.predict = "response")

# =====
# ===== ADDITIONAL FUNCTIONS =====
# =====

#####
# NAME: Chris Bilder #
# DATE: 7-30-13 #
# UPDATE: #
# Purpose: Automate part of the logistic regression diagnostic #
#           procedures into one function. #
# # #
# NOTES: #
# 1) This function needs to be run just once before it is used. Below is an #
#    example of how to use the function the first time: #
# #
#    source(file = "C:\\Chris\\examine.logistic.model.R") #
#    mod.fit1 <- glm(formula = y/n ~ x, data = EVP.form, weight = n, #
#    family = binomial(link = logit)) #
#    examine.logistic.reg(mod.fit1) #
#    mod.fit2 <- glm(formula = y/n ~ x + I(x^2), data = EVP.form, weight = n, #
#    family = binomial(link = logit)) #
#    examine.logistic.reg(mod.fit2) #
# #
# 2) Arguments: #
#    mod.fit.obj = model fit object from glm() #
#    identify.points = identify points on the plot by mouse clicks #
#    bubble = produce plots where plotting point is proportional in size #
#             to a third dimension (number of trials or Cook's D) #

```

```

#   scale.n, scale.cookd = scaling to use with bubble size; the default is   #
#   the original numerical scale of the quantity; it can be helpful to use   #
#   a transformation, like sqrt, when there is a large difference in         #
#   numerical values.                                                         #
#   pearson.dev = specifies whether "Pearson" or "deviance" based residuals   #
#   should be given in the plots                                              #
#####

examine.logistic.reg <- function(mod.fit.obj = mod.fit,
                                identify.points = TRUE, bubble = TRUE,
                                scale.n = I,
                                scale.cookd = I,
                                pearson.dev = "Pearson"){

  pearson <- residuals(mod.fit.obj, type = "pearson") #Pearson residuals
  # Standardized Pearson residuals
  stand.resid <- rstandard(model = mod.fit.obj, type = "pearson")
  deltaXsq <- stand.resid^2
  pred <- mod.fit.obj$fitted.values
  n <- mod.fit.obj$prior.weights # Number of observations per EVP
  df <- mod.fit.obj$df.residual
  cookd <- cooks.distance(mod.fit.obj)
  h <- hatvalues(mod.fit.obj)
  dev.res <- residuals(mod.fit.obj, type = "deviance")
  # Standardized deviance residuals
  stand.dev.resid <- rstandard(model = mod.fit.obj, type = "deviance")
  deltaD <- dev.res^2 + h*stand.resid^2
  pear.stat <- sum(pearson^2)
  dev <- mod.fit.obj$deviance
  p <- length(mod.fit.obj$coefficients)

  # Type of residuals to include on plots
  resid.plot11 <- stand.resid
  resid.plot21 <- deltaXsq
  plot.label11 <- "Pearson"
  plot.label21 <- "Delta X^2"
  if (pearson.dev == "deviance") {
    resid.plot11 <- stand.dev.resid
    resid.plot21 <- deltaD
    plot.label11 <- "deviance"
    plot.label21 <- "Delta D"
  }
}

#####
# Four plots

# Open a new plotting window

```

```

#x11(width = 8, height = 6, pointsize = 12)
# Divide the plot into three rows and two columns.
# The last row is only 1cm in height to make sure
# there is some room for the printed GOF statistics
layout(mat = matrix(c(1,2,3,4,5,5), byrow = TRUE, ncol = 2),
        height = c(1,1,1cm(1)))
# layout.show(5)

# Standardized residual vs predicted prob.
plot(x = pred, y = resid.plot11, xlab = "Estimated probabilities",
     ylab = "Standardized residuals",
     main = paste("Standardized", plot.label11, "residuals vs. est. prob."),
     ylim = c(min(-3, stand.resid), max(3, stand.resid)))
abline(h = c(-3, -2, 0, 2, 3), lty = "dotted", col = "blue")
if(identify.points == TRUE) {
  # labels(pred) uses the row names from the original data set
  # This can be helpful, rather than the default of 1:n in identify(),
  # when observations have been removed from the data set
  # (i.e., the same row names will be used
  # as with the original data set)
  identify(x = pred, y = resid.plot11, labels = labels(pred))
}

order.pred <- order(pred)
smooth.stand <- loess(formula = resid.plot11 ~ pred, weights = n)
lines(x = pred[order.pred], y = predict(smooth.stand)[order.pred],
      lty = "solid", col = "red")
# The ordering of pred leads to one line drawn across the plot.
# Otherwise, multiple lines will be drawn
# between each pred and predict() pair, which may cause a
# zig-zag-like pattern of lines

# Very similar way to get the loess model plotted
# smooth.stand <- loess(formula = resid.plot11 ~ pred, weights = n)
# x.axis <- seq(from = min(pred), to = max(pred),
#               by = (max(pred) - min(pred))/100)
# pred.data <- predict(object = smooth.stand, newdata =
#                      data.frame(pred = x.axis))
# lines(x = x.axis, y = pred.data, lty = "solid", col = "red")

# Cook's distance vs. leverage
plot(x = h, y = cookd, ylim = c(0, max(4/length(cookd), cookd)),
     xlim = c(0, max(3*p/length(h), h)),
     xlab = "Leverage (hat matrix diagonal)", ylab = "Cook's distance",
     main = "Cook's distance vs. leverage")
abline(h = c(4/length(cookd), 1), lty = "dotted")

```

```

abline(v = c(2*p/length(h), 3*p/length(h)), lty = "dotted")
if(identify.points == TRUE) {
  identify(x = h, y = cookd, labels = labels(h))
}

# Delta X^2 or D vs. predicted prob. with plotting point proportional to n
if(bubble == TRUE) {
  symbols(x = pred, y = resid.plot21, xlab = "Estimated probabilities",
    circles = scale.n(n),
    ylab = plot.label21,
    main = paste(
      plot.label21,
      "vs. est. prob. \n with plot point proportional to number of trials"),
    inches = 0.1, ylim = c(0, max(9, resid.plot21)))
  abline(h = c(4, 9), lty = "dotted", col = "blue")
  if(identify.points == TRUE) {
    identify(x = pred, y = resid.plot21, labels = labels(pred))
  } }
else {
  plot(x = pred, y = resid.plot21, xlab = "Estimated probabilities",
    ylab = plot.label21,
    main = paste(plot.label21, "vs. est. prob."),
    ylim = c(0, max(9, resid.plot21)))
  abline(h = c(4, 9), lty = "dotted", col = "blue")
  if(identify.points == TRUE) {
    identify(x = pred, y = resid.plot21)
  } }

```

```

# Print deviance/df on plot
dev.df <- dev/df
gof.threshold <- round(c(1 + 2*sqrt(2/df), 1 + 3*sqrt(2/df)), 2)
mtext(text = paste("Deviance/df = ", round(dev.df, 2),
  "; GOF thresholds: 2 SD = ",
  round(gof.threshold[1], 2), ", 3 SD = ",
  round(gof.threshold[2], 2), sep = ""),
  side = 1, line = 6, cex = 1.0, adj = 0)

```

```

# Delta X^2 or D vs. predicted prob.
# with plotting point proportional to Cook's distance
if(bubble == TRUE) {
  symbols(x = pred, y = resid.plot21, circles = scale.cookd(cookd),
    xlab = "Estimated probabilities",
    ylab = plot.label21,
    main = paste(
      plot.label21,

```

```

    "vs. est. prob. \n with plot point proportional to Cook's distance"),
    inches = 0.1, ylim = c(0, max(9, resid.plot21)))
abline(h = c(4, 9), lty = "dotted", col = "blue")
if(identify.points == TRUE) {
  identify(x = pred, y = resid.plot21, labels = labels(pred))
} }
else {
  # Empty plot because the last plot would be exactly the same
  plot(x = c(0, 1), y = c(0,1), type = "n", axes = FALSE, xlab = " ",
        ylab = " ")
}

# Return to normal layout
layout(mat = 1)

# Information is stored in the object, but not printed unless requested
invisible(list(pearson = pearson, stand.resid = stand.resid,
               stand.dev.resid = stand.dev.resid,
               deltaXsq = deltaXsq, deltaD = deltaD, cookd = cookd,
               pear.stat = pear.stat, dev = dev, dev.df = dev.df,
               gof.threshold = gof.threshold, pi.hat = pred, h = h))
}

HLTest = function(obj, g) {

  # first, check to see if we fed in the right kind of object

  stopifnot(family(obj)$family == "binomial" && family(obj)$link == "logit")

  y = obj$model[[1]]

  trials = rep(1, times = nrow(obj$model))

  if(any(colnames(obj$model) == "(weights)"))

    trials <- obj$model[[ncol(obj$model)]]

  # the double bracket (above) gets the index of items within an object

  if (is.factor(y))

    y = as.numeric(y) == 2 # Converts 1-2 factor levels to logical 0/1 values

  yhat = obj$fitted.values
  # Creates factor with levels 1,2,...,g
  interval = cut(yhat, quantile(yhat, 0:g/g), include.lowest = TRUE)

```

```

Y1 <- trials*y
Y0 <- trials - Y1
Y1hat <- trials*yhat
Y0hat <- trials - Y1hat

obs = xtabs(formula = cbind(Y0, Y1) ~ interval)

expect = xtabs(formula = cbind(Y0hat, Y1hat) ~ interval)

if (any(expect < 5))
  warning("Some expected counts are less than 5. Use smaller number of groups")

pear <- (obs - expect)/sqrt(expect)

chisq = sum(pear^2)

P = 1 - pchisq(chisq, g - 2)

# by returning an object of class "htest", the function will perform like the
# built-in hypothesis tests

return(structure(list(

  method = c(paste("Hosmer and Lemeshow goodness-of-fit test with", g, "bins",
    sep = " ")),

  data.name = deparse(substitute(obj)),

  statistic = c(X2 = chisq),

  parameter = c(df = g-2),

  p.value = P,

  pear.resid = pear,

  expect = expect,

  observed = obs

), class = 'htest'))
}

```


References

- American Cancer Society. 2016. “About Prostate Cancer.” <https://www.cancer.org/content/dam/CRC/PDF/Public/8793.00.pdf>.
- . 2017. “Understanding Your Pathology Report: Prostate Cancer.” <https://www.cancer.org/treatment/understanding-your-diagnosis/tests/understanding-your-pathology-report/prostate-pathology/prostate-cancer-pathology.html>.
- Auguie, Baptiste. 2017. *GridExtra: Miscellaneous Functions for “Grid” Graphics*. <https://CRAN.R-project.org/package=gridExtra>.
- Mayo Clinic. 2018. “Prostate Cancer.” <https://www.mayoclinic.org/diseases-conditions/prostate-cancer/symptoms-causes/syc-20353087>.
- Müller, Kirill. 2017. *Here: A Simpler Way to Find Your Files*. <https://CRAN.R-project.org/package=here>.
- . 2018. *Bindrcpp: An ‘Rcpp’ Interface to Active Bindings*. <https://CRAN.R-project.org/package=bindrcpp>.
- National Cancer Institute. 2017. “Prostate-Specific Antigen (Psa) Test.” <https://www.cancer.gov/types/prostate/psa-fact-sheet>.
- R Core Team. 2018. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing. <https://www.R-project.org/>.
- Ripley, Brian. 2018. *MASS: Support Functions and Datasets for Venables and Ripley’s Mass*. <https://CRAN.R-project.org/package=MASS>.
- Robin, Xavier, Natacha Turck, Alexandre Hainard, Natalia Tiberti, Frédérique Lisacek, Jean-Charles Sanchez, and Markus Müller. 2018. *PROC: Display and Analyze Roc Curves*. <https://CRAN.R-project.org/package=pROC>.
- Robinson, David, and Alex Hayes. 2018. *Broom: Convert Statistical Analysis Objects into Tidy Tibbles*. <https://CRAN.R-project.org/package=broom>.
- WebMD. 2018. “Digital Rectal Exam for Prostate Problems.” <https://www.webmd.com/prostate-cancer/guide/prostate-cancer-digital-rectal-exam>.
- Wickham, Hadley. 2018. *Forcats: Tools for Working with Categorical Variables (Factors)*. <https://CRAN.R-project.org/package=forcats>.
- Wickham, Hadley, Winston Chang, Lionel Henry, Thomas Lin Pedersen, Kohske Takahashi, Claus Wilke, and Kara Woo. 2018. *Ggplot2: Create Elegant Data Visualisations Using the Grammar of Graphics*. <https://CRAN.R-project.org/package=ggplot2>.
- Wickham, Hadley, Romain François, Lionel Henry, and Kirill Müller. 2018. *Dplyr: A Grammar of Data Manipulation*. <https://CRAN.R-project.org/package=dplyr>.
- Wickham, Hadley, Jim Hester, and Romain Francois. 2017. *Readr: Read Rectangular Text Data*. <https://CRAN.R-project.org/package=readr>.
- Xie, Yihui. 2018a. *Bookdown: Authoring Books and Technical Documents with R Markdown*.

<https://CRAN.R-project.org/package=bookdown>.

———. 2018b. *Knitr: A General-Purpose Package for Dynamic Report Generation in R*. <https://CRAN.R-project.org/package=knitr>.

Zhu, Hao. 2018. *KableExtra: Construct Complex Table with 'Kable' and Pipe Syntax*. <https://CRAN.R-project.org/package=kableExtra>.