**Question 1**

|  |  |  |  |
| --- | --- | --- | --- |
| ***Variable*** | | ***Did not relapse***  ***(28, 56%)*** | ***Relapsed***  ***(22, 44%)*** |
| Age, mean (SD) | | 66.71 (5.84) | 68.36 (5.68) |
| Nadir PSA, mean (SD) | | 4.12 (17.28) | 31.94 (52.50) |
| Pretreatment PSA (mean, SD) | | 617.19 (1252.08) | 732.35 (1357.34) |
| Performance score, mean (SD) | | 83.93 (9.56) | 76.50 (11.82) |
| Bone scan score, n (%) | |  |  |
|  | 1 | 5 (17.86) | 0 (0.00) |
|  | 2 | 9 (32.14) | 4 (20.00) |
|  | 3 | 14 (50.00) | 16 (80.00) |
| Tumor grade, n (%) | |  |  |
|  | 1 | 7 (29.17) | 3 (17.65) |
|  | 2 | 8 (33.33) | 7 (41.18) |
|  | 3 | 9 (27.50) | 7 (41.18) |

**Question 2**

1. From this adjusted logistic regression analysis, we estimate each 1 ng/mL higher PSA blood level is associated with 1.034 times higher odds of relapse among men of the same performance status and bone scan score. Under the null hypothesis of no PSA level effect (H0: β1 = 0 or OR = 1) and type 1 error rate of 0.05, we find that this result is not beyond what we would expect to observe by chance alone (95% CI of the odds ratio indicates that the odds relapse for each 1 ng/mL higher PSA level was 0.987 to 1.083 times higher). We have insufficient evidence to reject the null hypothesis, in favor of the alternative hypothesis.
2. , therefore doubling (r = 2) nadir PSA is associated with a 1.815 (95% CI: 1.174, 2.456) times the odds of relapse after 24 months adjusting for performance status and bone scan score. From this adjusted logistic regression analysis, we estimate that doubling the PSA blood level is associated with 1.815 times higher odds of relapse among men of the same performance status and bone scan score. Under the null hypothesis of no PSA level effect (H0: β1 = 0 or OR = 1) and type 1 error rate of 0.05, we find that this result is beyond what we would expect to observe by chance alone (95% CI of the odds ratio indicates that the odds relapse for each 1 ng/mL higher PSA level was 1.174 to 2.456 times higher). We have sufficient evidence to reject the null hypothesis, in favor of the alternative hypothesis.
3. When nadir PSA was modeled using linear splines at 1ng/mL, 4ng/mL and 8ng/mL as cutoffs, there was a significant association between nadir PSA and relapse in 24 months (χ2 (4 df)= 11.05, p = 0.0260). The graph below shows the predicted probabilities of relapse in 24 months for nadir PSA, modeled as linear splines, at the mean performance status (80.83) and mean bone scan score (0.4792)



1. Intercept interpretations:
2. Model a: The odds of relapse in a man with a nadir PSA of 0 ng/mL, but the most disease (bone scan score of 3—recoded to 0) and worst performance (performance score = 0), was 37.45 (95% CI: 0.187, 7502.983)
3. Model b: The odds of relapse in a man with a nadir PSA of 1 ng/mL, but the most disease (bone scan score of 3—recoded to 0) and worst performance (performance score = 0), was 39.492 (95% CI: 0.1278, 12200.47)
4. The odds of relapse in a man with a nadir PSA of 0 ng/mL, but the most disease (bone scan score of 3—recoded to 0) and worst performance (performance score = 0), was 1.279 (95% CI: 0.0011588, 1411.401)

It is unlikely that a man with prior prostate cancer would regress back to a nadir PSA of 0. Therefore extrapolation to this level might be misleading.

**Question 3**



where



I performed a linear regression on the raw scale nadir PSA, estimating standard errors using the robust Huber-White sandwich estimator.

The mean nadir PSA is significantly higher by 23.518 ng/mL (on average) among men who relapsed with in 24 months after adjusting for bone scan score and performance status. This result is significantly different from zero (p = 0.046), with a 95% confidence interval suggesting that such observed results would not be unusual if the true difference in mean PSA between those who relapsed and those who did not relapse anywhere from 0.4765 to 46.5588, with the relapsed group tending towards higher average PSA. We therefore reject the null hypothesis that the mean PSA does not differ between men who relapse and those who do not relapse in favor of the alternative, that men who relapse have higher PSA.

1. 

where



I fit a linear regression on the log-transformed nadir PSA, estimating standard errors using the robust Huber-White sandwich estimator.

The geometric mean nadir PSA tends towards a significant 13.657 times higher among men who relapsed with in 24 months after adjusting for bone scan score and performance status. This result is significantly different from zero (p < 0.001), with a 95% confidence interval suggesting that such observed results would not be unusual if men who relapsed truly tended to anywhere between 4.1296 to 45.1629 times higher geometric mean PSA compared to men who did not relapse. We therefore reject the null hypothesis that the geometric mean PSA does not differ between men who relapse and those who do not relapse in favor of the alternative, that men who relapse have higher geometric mean PSA.

**Question 4**

1. Analysis 2a) is may be misleading because it attempts to fit a linear trend over all possible values of nadir PSA. From a fitted versus nadir PSA plot, it is clear that at very small values of PSA, the potential increase in probability of relapse is very high while at higher values of PSA, increase in PSA is leads to more modest increases in probability of relapse. i.e., at low PSA, the marginal effect of nadir PSA is large while at high PSA it is more modest. The relationship is clearly non-linear (actually logarithmic). Therefore fitting this model misses this important nuance. The main merit of this analysis is that the interpretation is easy. It is easy to isolate the meaning of the coefficient from the model, as a difference in log (odds), or log (odds ratio).

Analysis 2b) handles the logarithmic relationship observed (even anticipated *a priori*) and answers a more clinically relevant question of the impact of multiplicative changes in PSA on relapse. However, deciphering the meaning of the coefficient on the POI is not straightforward. With a little algebraic manipulation, the coefficient can be interpreted, as is the odds ratio of relapse for an r-fold increase in the nadir PSA.

Analysis 2c) is advantageous because it is a flexible way to model the relationship. However, because of this flexibility, describing the relationship succinctly becomes difficult as we now have several slope estimates to consider. The easiest way to demonstrate the relationship is to draw a curve.Analysis 3a) is advantageous because of its simplicity and ease of interpretation of the coefficient estimates. We can use the Huber-White sandwich estimator to estimate somewhat more appropriate standard errors in the face of heteroskedasticity, hence inference is potentially not misleading. Note however, that because the sample size is small (n=50), the sandwich estimator may be misleading. This analysis also does not exploit the full power of the longitudinal design because we are modeling what would be the POI as the outcome and the outcome as the POI. We loose the ability to point towards causality in this analysis. Also the non-linearity and large amounts of heteroskedasticity may still be problematic.



Analysis 3b) is a better analysis than 3c) above because log transformation of the nadir PSA, potentially takes care of the non-linearity and heteroskedasticity problems. However, it changes the linearity of the relationship and changes the interpretation, to one that may not be as intuitive.

*A priori*, I would prefer analysis in 2b) because in addition to being able to answer the question of whether there is an association between nadir PSA and relapse probability, it preserves the directionality of this association. It also considers what is a more clinically relevant question of the impact of multiplicative changes in nadir PSA on relapse.

1. The problem in this study, I believe, is in the definition of nadir PSA as “*the lowest value of PSA observed post-therapy*” and time observed in remission. This potentially makes the effective observation time (from exposure to outcome) for each patient different because different patients could have different rates of PSA decay and thus a nadir PSA would in theory occur at different times for different men. Essentially unaccounted-for exposure time becomes an important confounder of the association and we are unable to adjust for this in any of the analyses that can be done with the data as presented. The other definitional problem with using the lowest value of PSA observed post-therapy and time observed in remission is that this effectively becomes a cross-sectional study, making answering the primary question almost impossible. It may be difficult to know what came first.