IMPACT OF MALNUTRITION ON LONG-TERM SURVIVAL IN ADULT PATIENTS AFTER ELECTIVE CARDIAC SURGERY

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1 Introduction

Malnutrition has been a common problem amongst most hospitalized patients, but for a long time, was believed to not affect the heart. However, recent studies have shown that nutritional support may play a role in obtaining better outcomes for malnourished patients who are being prepared for cardiac surgery.

In a 1976 study, Abel and collaborators observed the outcome of cardiac surgery in 44 malnourished patients. The mortality rate was 16%, whereas in another group of patients who were well-nourished, there were no deaths. In another report, Gibbons and Blackburn and their associates observed 12 clinically malnourished patients who underwent cardiac valve replacement. They found that those who received preoperative nutritional supplements were more likely to survive than those who did not. In a recent study by Chermesh et. al., it was reported that among 403 cardiac patients, 17.9% were at a risk of high malnutrition, which was associated with a 3.8 times higher risk for 30-day mortality. Although these studies were not conducted on a large scale, they suggested that there is some impact of malnutrition on patients who underwent cardiac surgery.

This project aims to analyse the relationship between malnutrition and long-term survival in patients who underwent cardiopulmonary bypass (CPB). Any impact thus found, of malnutrition on cardiac surgery patients, may be useful for malnourished patients, who may benefit from preventive nutritional intervention.

2 Data Collection

The inclusion criteria for patients:

- Age: Older than 18 years
- Have underwent elective cardiac surgery under cardiopulmonary bypass

The exclusion criteria for patients:

- Underwent emergent surgery
- Underwent aortic surgery performed under deep hypothermic circulatory arrest
- Required thrombectomy due to pulmonary thromboembolism
- Underwent off-pump surgery

Nutritional screening using the MUST (Malnutrition Universal Screening Tool) was performed once for 1210 patients out of which 23 were excluded (those operated without CPB (15) and those who underwent surgery under deep hypothermic circulatory arrest (8)). Therefore, the data of 1187 patients were used for the final analysis. Demographic, nutritional, and medical history was collected for each patient. No specific preoperative nutritional intervention had been prescribed. Surgical risk was assessed in accordance with the logistic Euro SCORE and intraoperative data was collected, including CPB time and postoperative characteristics.

For survival data collection, both electronic medical records and phone interviews were used. Long-term follow-up was conducted by phone interviews. If follow-up for a patient was not successful, then the data till the last follow-up date has been considered.

3 Medical Terms

A list of some frequently used medical words throughout the report:

1. **EuroSCORE** (European System for Cardiac Operative Risk Evaluation) is a risk model which calculates the risk of death after a cardiac surgery using logistic regression.
2. **MUST** (Malnutrition Universal Screening Tool) is a five-step screening tool that identifies patients who are malnourished or at a risk of malnutrition.
3. **Albumin** is a protein made by the liver which helps keep fluid in the bloodstream, preventing it from leaking into other tissues.
4. **C-reactive protein** is a protein found in blood plasma, and high CRP levels indicate inflammation in the body.
5. **CAD -** Coronary Artery Disease
6. **HVD -** Heart Valve Disease

4 Statistical Methods and Formulae

4.1 Receiver Operating Characteristic Curves (ROC Curves)

An ROC Curve is a technique for visualizing, organizing, and selecting classifiers based on their performance. A classification model (or classifier) is a mapping from instances to predicted classes.

Given a classifier and an instance, there are four possible outcomes. If the instance is positive and it is classified as positive, it is counted as a true positive; if it is classified as negative, it is counted as a false negative. If the instance is negative and it is classified as negative, it is counted as a true negative; if it is classified as positive, it is counted as a false positive.

Formulae:

1. $Sensitivity\ (True\ Positive\ Rate) = \frac{Positives\ Correctly\ Classified}{Total\ Positives} = \frac{True\ Positives}{True\ Positives + False\ Negatives}$

2. $Specificity\ (True\ Negative\ Rate) = \frac{Negatives\ Correctly\ Classified}{Total\ Negatives} = \frac{True\ Negatives}{True\ Negatives + False\ Positives}$

ROC Curves are the plots of Sensitivity vs. 1-Specificity

4.1.1 Area Under an ROC Curve (AUC)

ROC curves are two-dimensional depictions of classifier performance. To compare classifiers, we want a single scalar value representing expected performance. Area under the ROC curve is often used as this scalar value.

Since the area is a portion of the area of the unit square, its value will always be between 0 and 1. A random classifier will give a diagonal line joining (0, 0) and (1, 1) as the ROC curve. Thus, its AUC will be 0.5.

Statistically, the importance of the AUC is that higher the value of AUC, better are the predictions of the classifier:

1. **<u>AUC = 1</u>**
   This implies that the classifier can perfectly distinguish between all the positives and negatives.
2. **<u>AUC = 0</u>**
   This implies that the classifier predicts all positives as negatives and all negatives as positives.
3. **<u>AUC = 0.5</u>**
   This implies that the classifier is unable to distinguish between the positives and the negatives. Thus, it is equivalent to a random classifier.

Note that when AUC is between 0.5 and 1, it implies that the classifier can detect a greater number of true positives and true negatives than false positives and false negatives. Thus, any ROC curve having an AUC less than 0.5 will not be useful to us as its predictions will be highly inaccurate.

4.1.2 P-Value

The *P*-value for the AUC of a specific model quantifies the extent to which it deviates from a model with AUC = 0.5. Note, however that, a classifier corresponding to AUC = 0.5 does not necessarily need to be a random classifier. The *P*-value is the probability of observing an outcome as extreme as or more extreme than the actual one, given that the null hypothesis is true. In other words, the P value answers this question: **How likely it is that the data obtained has occurred by random chance?**

1. **P-Value ≤ 0.05**
   This indicates that there is less than or equal to a 5% probability that the results are random. Thus, such p-values are statistically significant. We can reject the null hypothesis in this case.

2. **P-Value > 0.05**
   This indicates strong evidence for the null hypothesis, i.e., there is a good chance of the results being random. Hence, p-values greater than 0.05 are not statistically significant.

Note that while calculating p-values we put down the condition that the null hypothesis is true. Thus, p-value ≤ 0.05 does not indicate that there is a 95% or higher probability that the alternative hypothesis is true.

4.1.3 Mann-Whitney U Test

The Mann–Whitney *U* test is a test of the null hypothesis that for randomly selected values *X* and *Y* from two populations, the probability of *X* being greater than *Y* is equal to the probability of *Y* being greater than *X*.

Let $X_1, X_2, \dots, X_n$ be an independent and identically distributed sample from X, and $Y_1, Y_2, \dots, Y_n$ be an independent and identically distributed sample from Y, where X and Y are independent of each other. The corresponding Mann-Whitney U statistic is defined as:

$$U = \sum_{i=1}^{n} \sum_{j=1}^{m} S\left(X_i, Y_j\right),$$

$$\text{where } S(X,Y) = \begin{cases} 1, & if\ X > Y \\ \frac{1}{2}, & if\ X = Y \\ 0, & if\ X < Y \end{cases}$$

The Area under the ROC Curve is equivalent to the Mann-Whitney U Statistic with the relation:

$$AUC = \frac{U}{n_0 \times n_1},$$

where n_0 and n_1 are the number of observations in the non-target and target group respectively.

4.1.4 Youden's J Statistic

Let: $a = True\ Positives, b = False\ Negatives, c = True\ Negatives, d = False\ Positives$

Then, a reasonable measure of success for the positives will be: $\frac{a-b}{a+b}$

Similarly, a reasonable measure of success for the negatives will be: $\frac{c-d}{c+d}$

Assuming that false positives are as undesirable as false negatives, we can take an average of the two measures of success as a "rating" for the model, i.e., how accurate the predictions of the classifier are.

$$J = \frac{1}{2}\left[\frac{a-b}{a+b} + \frac{c-d}{c+d}\right] = \left(\frac{a}{a+b} - \frac{1}{2}\right) + \left(\frac{c}{c+d} - \frac{1}{2}\right) = \frac{a}{a+b} + \frac{c}{c+d} - 1$$

$$\therefore\ J = Sensitivity + Specificity - 1$$

J is known as "Youden's J Statistic" or "Youden's Index"

Thus, the values of J range from 0 to 1, and the higher the value of J, the greater is the accuracy of the classifier.

4.2 Survival Analysis

Survival Analysis: It is a modelling technique used to model time to an event i.e., it is used to determine how long it will take for an event (not necessarily death) to occur.

Survival Function: It is a function which determines if a unit (in the sample) is going to survive beyond the specified time or not. If S is the survival function, then S(t) is the probability that a unit will survive beyond time t.

'Lifetime' in this case is the time until the specified event has occurred.

Let the Lifetime T be a continuous random variable with probability distribution function f and cumulative distribution function F on [0, ∞)

Then, $S(t) = P(T > t) = \int_t^{\infty} f(u)\,du = 1 - F(t)$

In this project, we consider the event to be "death of the patient".

There are several methods for survival analysis; this project only discusses the ones related to our concerned experiment.

4.2.1 Kaplan – Meier Curves

Survival analysis with human subjects often gets complicated when the subjects refuse to remain in the study or when some of the subjects have not experienced the event before the end of the study. For these subjects, we have partial information. Such observations are labelled as "censored". As they still provide some information about the survival, we would not want to completely ignore these observations. In such cases, the Kaplan-Meier estimate is the simplest estimator of the survival function despite all the difficulties associated with subjects or situations.

The Kaplan-Meier survival curve is defined as the probability of surviving at a certain time interval.

The survival probability at any given time interval [t, t + Δt] is calculated as:

$$S_t = \frac{No.of\ subjects\ at\ risk\ at\ t\ - No.of\ subjects\ who\ died\ between\ t\ and\ t+\ \Delta t}{No.of\ subjects\ at\ risk\ at\ t}$$

Subjects who have died or dropped out from the study, are not counted as "at risk". Total probability of survival till that time interval is calculated by multiplying all the probabilities of survival at all time intervals preceding that time.

4.2.2 Cox Proportional Hazards Model

Hazard: It is the probability of occurrence of the event in the next time interval, given that it has not occurred yet.

Hazard Rate: It is the hazard divided by the length of the time interval. Hazard rate represents an instantaneous rate as we consider the length of the time interval to be very small.

Hazard Ratio: It is an estimate of the ratio of the hazard rate of one group to the hazard rate of the other.

4.2.3 Log-Rank Test

Log-Rank Test is a test to compare survival distributions of two groups. It is used to test the null hypothesis that occurrence of an event (in our case – death) at any time has equal probability for each group.

Like Kaplan – Meier Curves, this test considers censored observations in the time interval they became "censored", but not in subsequent time intervals. This test is most likely to detect a difference in groups when the risk of the event is consistently greater for one group than another.

The test statistic is calculated as follows:

$$\chi^2(\log rank) = \frac{\left[\sum_t \left(d_{1t} - r_{1t} \cdot \frac{d_t}{r_t}\right)\right]^2}{\sum_t \frac{r_{1t} r_{2t}\, d_t (r_t - d_t)}{r_t^2 (r_t - 1)}}$$

d_{it}: $Total\ number\ of\ observed\ events\ in\ Group\ i\ at\ time\ t$
r_{it}: $Total\ number\ of\ people\ at\ risk\ in\ Group\ i\ at\ time\ t$

d_t: $Total\ number\ of\ observed\ events\ at\ time\ t$
r_t: $Total\ number\ of\ people\ at\ risk\ at\ time\ t$

The test statistic is compared with a χ^2 distribution with 1 degree of freedom.

There are several variants of the Log-Rank Test. We discuss the ones that have been used in this project.

4.2.3.1 Breslow Test

The Breslow Test gives more weight to early failures whereas log-rank test gives equal weight to all failures. Therefore, log – rank requires a constant hazard ratio over time whereas Breslow test requires a hazard ratio not constant over time.

$$\chi^2(Breslow) = \frac{\left[\sum_t (r_t)\left(d_{1t} - r_{1t} \cdot \frac{d_t}{r_t}\right)\right]^2}{\sum_t \frac{(r_t^2) r_{1t} r_{2t}\, d_t (r_t - d_t)}{r_t^2 (r_t - 1)}}$$

Here, the weight is r_t.

4.2.3.2 Tarone – Ware Test

In situations where survival distributions differ substantially for some values of t but not necessarily elsewhere, neither log – rank nor Breslow tests are very effective. In such cases, tests such as Tarone – Ware test are found to be much more effective.

$$\chi^2(Tarone - Ware) = \frac{\left[\sum_t (\sqrt{r_t})\left(d_{1t} - r_{1t} \cdot \frac{d_t}{r_t}\right)\right]^2}{\sum_t \frac{\left(\sqrt{r_t}^2\right) r_{1t} r_{2t}\, d_t (r_t - d_t)}{r_t^2 (r_t - 1)}}$$

Here, the weight is $\sqrt{r_t}$.

4.3 Regression Analysis

Univariate linear regression determines a relationship between one independent or explanatory variable and one dependent or response variable. Given a dataset of variables (x_i, y_i), where x_i is the explanatory variable and y_i is the dependent variable, the simplest model that could be applied for the relation between two of them is a linear one. This model is known as the Simple Linear Regression model.

Simple linear regression model is as follows:

$$y_i = \beta_0 + \beta_1 x_i + \varepsilon_i$$

This describes a line with slope β_1 and y-intercept β_0. ε_i is a random error component which is added as there might not be a strict deterministic relationship between the variables.

The goal is to find estimated values $\hat{\beta}_1$, $\hat{\beta}_0$ for the parameters β_1 and β_0 respectively, which would provide the best fit in some sense for the data points. This "best" fit can be considered by the least-squares approach: a line that minimizes the sum of squared errors, when the sum of squared errors is 0.

Formulae:

$$\hat{\beta}_1 = \frac{\sum(x_i - \bar{x})(y_i - \bar{y})}{\sum(x_i - \bar{x})^2}$$

$$\hat{\beta}_0 = \bar{y} - \hat{\beta}_1\bar{x}$$

4.3.1 The Coefficient of Correlation

The Coefficient of Correlation – r, is a measure of the strength of the linear relationship between the two variables in concern.

$$r = \frac{\sum(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum(x_i - \bar{x})^2\sum(y_i - \bar{y})^2}}$$

The Coefficient of Correlation lies between -1 and 1, and the closer its value is to 0, the more it suggests that there may not be a linear relationship between the variables. A positive r suggests a positive relationship, i.e., the value of the dependent variable increases as the value of the independent variable increases. A negative r suggests a negative relationship, i.e., the value of the dependent variable decreases as the value of the independent variable increases.

4.3.2 The Coefficient of Determination

The Coefficient of Determination – r^2, represents the proportion of the sample variability around the mean of y, that is explained by the linear relationship between x and y.

$$r^2 = 1 - \frac{\sum(y_i - \hat{y})^2}{\sum(y_i - \bar{y})^2}$$

Mathematically, the Coefficient of Determination is the square of the Coefficient of Correlation, and thus, it is denoted as r^2.

5 Methods for Statistical Analysis

5.1 ROC

Characteristics for cut-off points are specificity and sensitivity. Corresponding values, i.e., threshold levels (that maximized the combined specificity and sensitivity) are taken to be the "Criterion". These values were used for Survival Analysis using Kaplan-Meier Curves.

AUC values for the ROC curves* were computed. P-Values for AUC were determined using the Wilcoxon-Mann-Whitney U-Statistic.

The following risk factors of mortality were analysed:

- Age (years)
- Preoperative Albumin Level (g/l)
- Cardiopulmonary Bypass Time (min)

- Aortic Cross-Clamp Time (min)
- Preoperative Thrombocytes level (109/l)
- Preoperative C-Reactive Protein level (mg/l)
- Left Ventricle Ejection Fraction (%)

The target value for cut-off point was determined by the Youden’s J – Statistic, which was used as the threshold for converting variables into two-level factor variables (low/high, with/without risk).

ROC analysis for HVD, CAD and mixed cohorts was done. 3-year survival and 8-year survival analysis done for mixed cohorts only, while overall survival has been considered for a few HVD and CAD cohorts.

*The ROC Curves used in this project plot sensitivity vs 1-specificity. However, the plot point marking the threshold value is the (specificity, sensitivity)

5.2 Kaplan-Meier

Overall survival was calculated using the Kaplan-Meier method using 95% Confidence Interval.

Comparison of two cohorts was performed by log-rank test, Chi-squared statistic, and p-values. Breslow and Tarone-Ware tests were also performed. Cox Proportional Hazard models were used for analysis of predictors of mortality.

Univariate models were fitted for:

- Logistic Euro SCORE
- MUST > 0
- Cardiopulmonary Bypass Time (min) > Criterion
- Preoperative C-Reactive protein level (mg/l) > Criterion
- Preoperative Albumin Level (g/l) > Criterion

Fitting multivariate models was performed by including all predictors in the model. The optimal model was obtained by step-by-step elimination of predictors with p-values greater than 0.05.

All statistical tests were two-sided.

6 Statistical Analysis

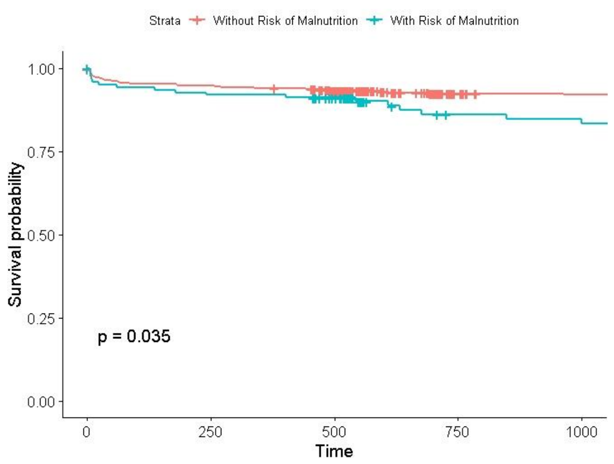
6.1 3-year Survival

6.1.1 Malnutrition

The patients were divided into two groups – patients who are at a risk of malnutrition and patients who are not at a risk of malnutrition.

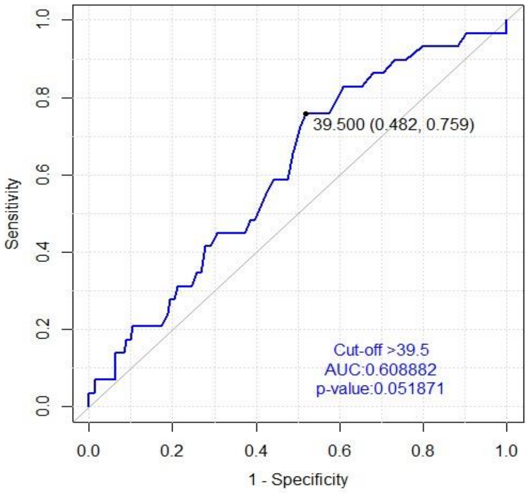
Chi-square (4.4) and P-value (0.035) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the 3-year survival analysis of the patients with respect to the risk factor “Malnourishment”.

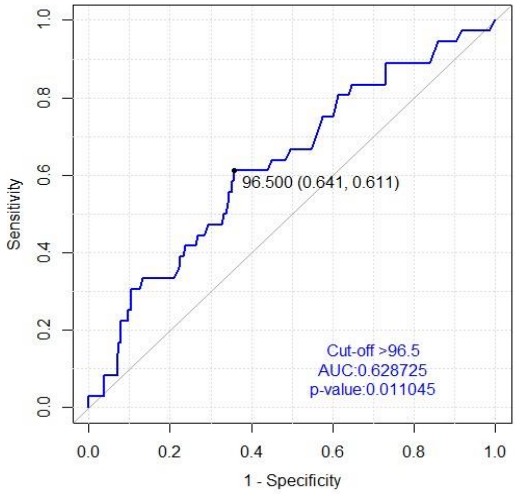


Kaplan Meier curve for 3-year follow up data for MUST

6.1.2 Aortic Cross Clamp Time

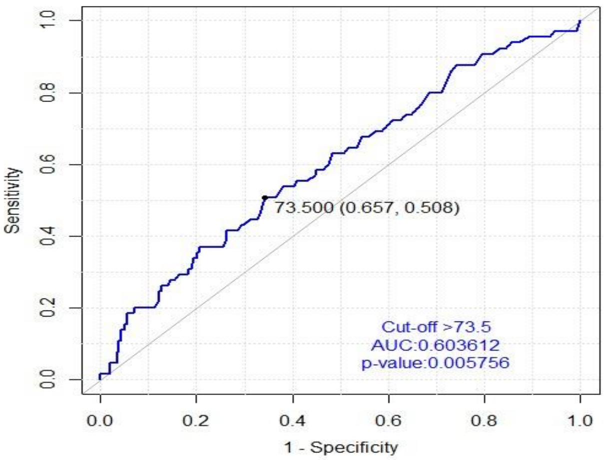


ROC curve for 3-year follow-up of CAD cohort patients for aortic cross clamp time(min).



ROC curve for 3-year follow-up of HVD cohort patients for aortic cross clamp time(min).

The ROC curves for the 3-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with a very small p value. Hence the ROC curve suggests that aortic cross clamp time influences the 3-year survival of the patients.



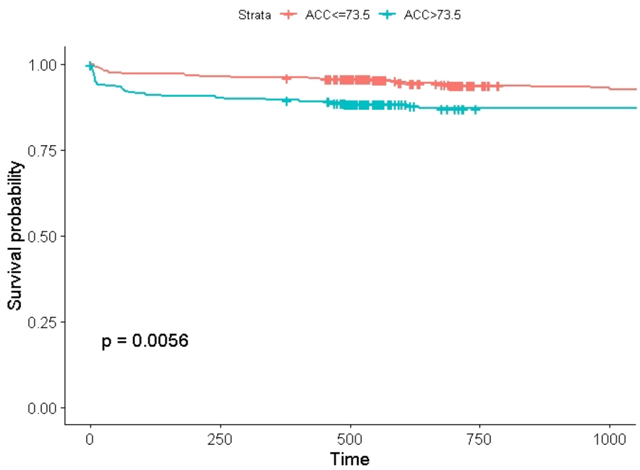
ROC curve for 3-year follow-up of mixed cohort patients for aortic cross clamp time

For the mixed cohort, the ROC curve for 3-year revealed a cut-off value of 73.5 min with a significantly large AUC of 0.604 and p value less than 0.006.

The patients were divided into two groups high ACC time (>73.5 minutes) and low ACC time (≤73.5 minutes). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

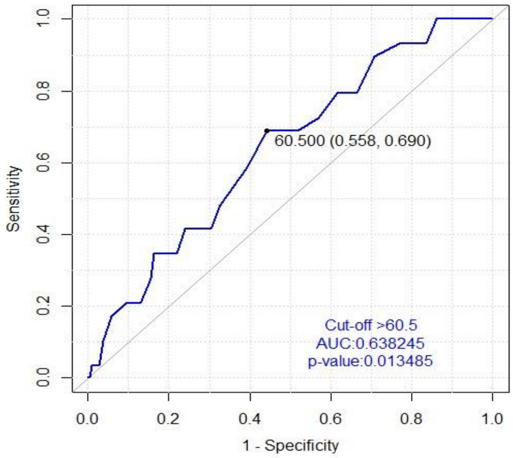
Chi-square (7.7) and P-value (0.0056) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the 3-year survival analysis of the mixed cohort patients with respect to the risk factor “aortic cross clamp time”

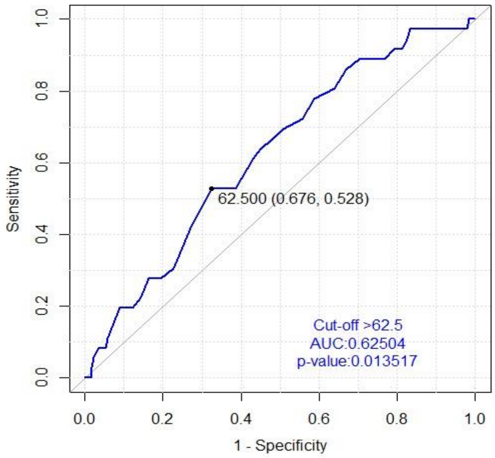


Kaplan Meier curve for 3-year follow up of mixed cohort patients for aortic cross clamp time (min)

6.1.3 Age

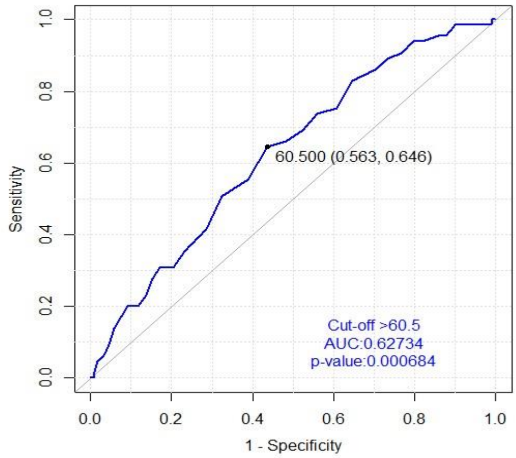


ROC curve for 3-year follow-up of CAD cohort patients for Age (years).



ROC curve for 3-year follow-up of HVD cohort patients for Age (years).

The ROC curves for the 3-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with small p-values. Hence the ROC curve suggests that age is influencing the 3-year survival of the patients.



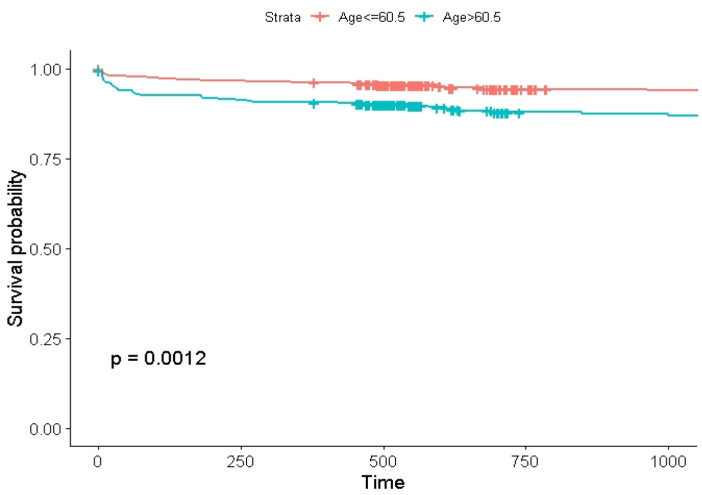
ROC curve for 3-year follow-up of mixed cohort patients for Age (years).

For the mixed cohort the ROC curve for 3-year revealed a cut-off value of 60.5 years with a significantly large AUC of 0.627 and p-value less than 0.001.

The patients were divided into two groups - Age ≤ 60.5 years. This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

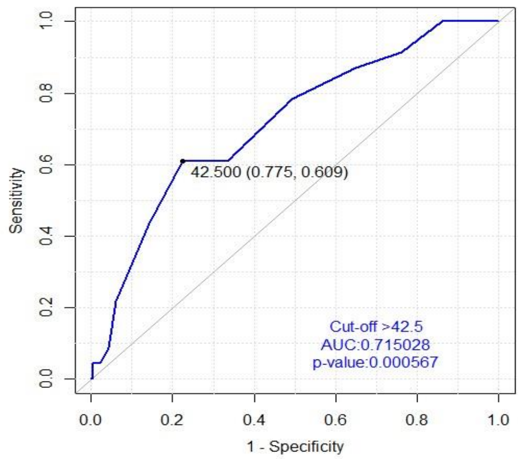
Chi-square (10.4) and P-value (0.0012) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the survival analysis of the mixed cohort patients with respect to the risk factor “Age”.

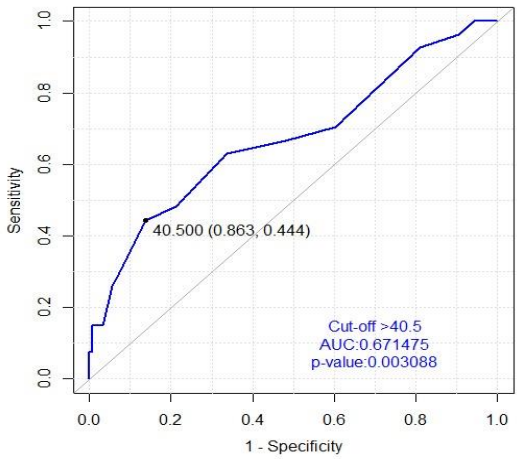


Kaplan Meier curve for 3-year follow up of mixed cohort patients for Age (years).

6.1.4 Albumin

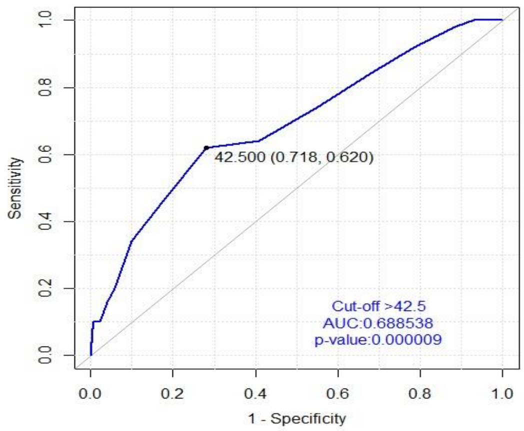


ROC curve for 3-year follow-up of CAD cohort patients for preoperative Albumin(g/L).



ROC curve for 3-year follow-up of HVD cohort patients for preoperative Albumin (g/L).

The ROC curves for the 3-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with a small p-value. Hence the ROC curve suggests that preoperative albumin level influences the 3-year survival of the patients.



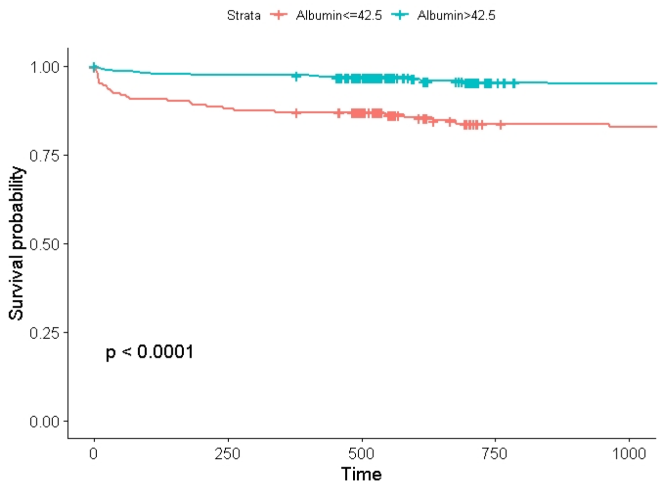
ROC curve for 3-year follow-up of mixed cohort patients for preoperative Albumin(g/L).

For the mixed cohort the ROC curve for 3-year revealed a cut-off value of 42.5 g/l with a significantly large AUC of 0.689 and p-value less than 0.001.

The patients were divided into two groups – Albumin level > 42.5 g/l and Albumin level ≤ 42.5 g/l. This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

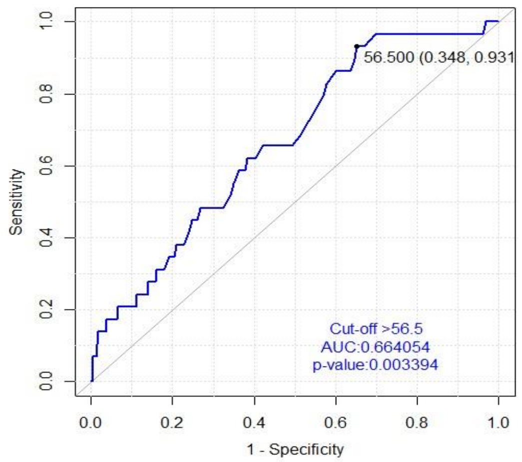
Chi-square (25.8) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the 3-year survival analysis of the mixed cohort patients with respect to the risk factor "Preoperative Albumin level".

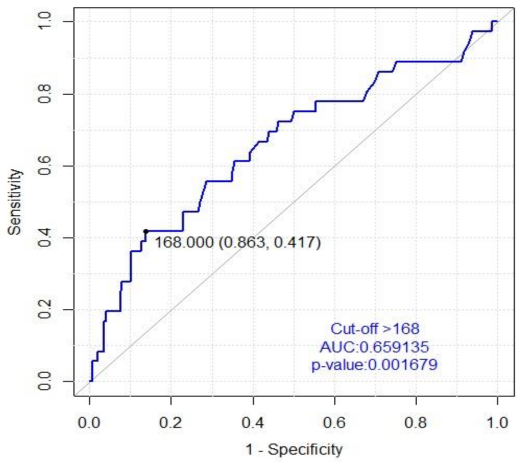


Kaplan Meier curve for 3-year follow up of mixed cohort patients for preoperative Albumin (g/l)

6.1.5 Cardiopulmonary Bypass Time

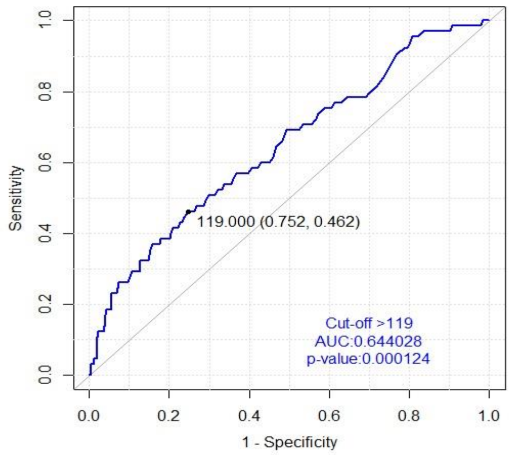


ROC curve for 3-year follow-up of CAD cohort patients for CPB time(min).



ROC curve for 3-year follow-up of HVD cohort patients for CPB time(min).

The ROC curves for the 3-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with a small p value. Hence the ROC curve suggests that CPB time influences the 3-year survival of the patients.



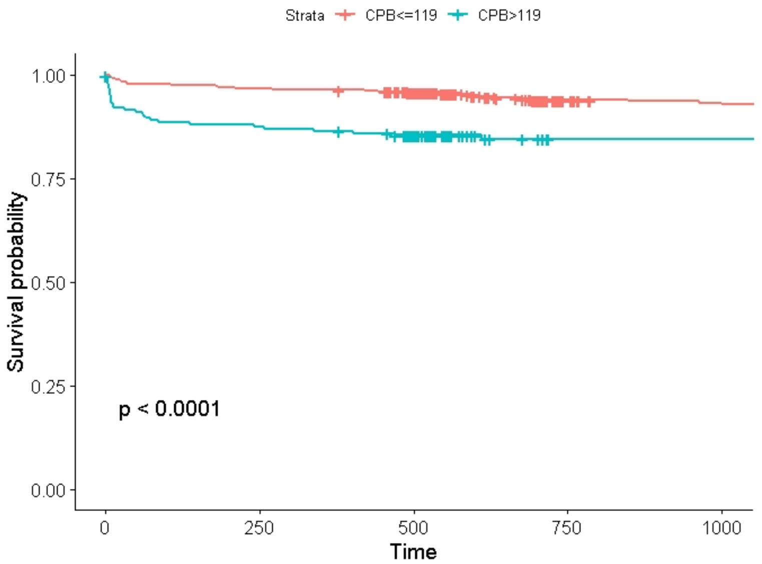
ROC curve for 3-year follow-up of mixed cohort patients for CBP time(min).

For the mixed cohort the ROC curve for 3-year revealed a cut-off value of 119 minutes with a significantly large AUC of 0.644 and p-value less than 0.001.

The patients were divided into two groups – high CPB time (>119 minutes) and low CPB time (≤119 minutes). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

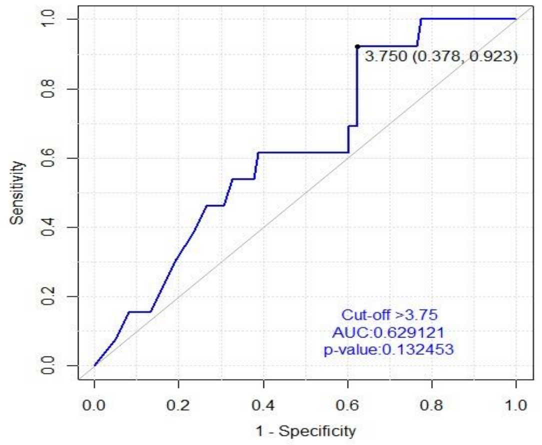
Chi-square (15.6) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the 3-year survival analysis of the mixed cohort patients with respect to the risk factor “CPB time”.

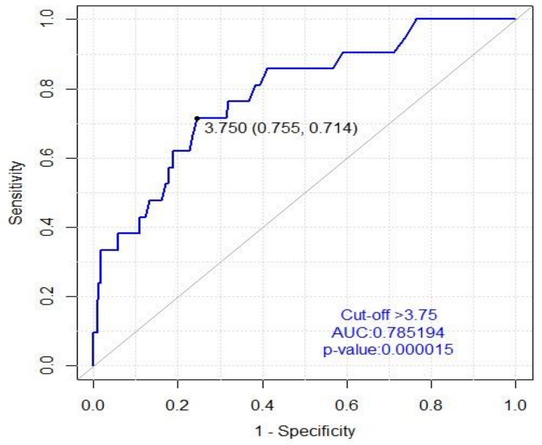


Kaplan Meier curve for 3-year follow up of mixed cohort patients for CBP time(min).

6.1.6 Preoperative C-Reactive Protein Level

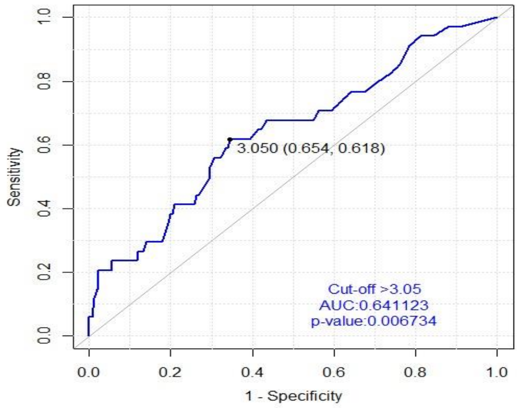


ROC curve for 3-year follow-up of CAD cohort patients for Preoperative C-reactive protein level (mg/l).



ROC curve for 3-year follow-up of HVD cohort patients for Preoperative C-reactive protein level (mg/l).

The ROC curves for the 3-year follow up of CAD and HVD cohorts were plotted. In the HVD cohort AUC was observed to be considerably large with a very small p-value, suggesting that CRP influences the 3-year survival of patients in the cohort. However, in the CAD cohort the p-value was considerably large suggesting no considerable influence of CRP on the 3-year survival of patients from this cohort.



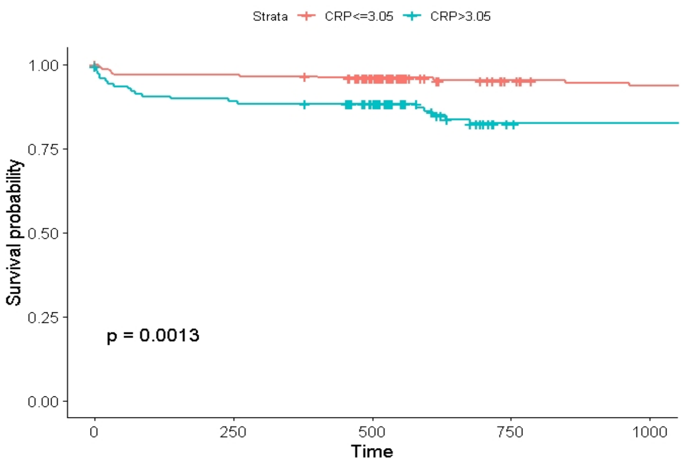
ROC curve for 3-year follow-up of mixed cohort patients for Preoperative C-reactive protein level (mg/l).

For the mixed cohort the ROC curve for 3-year revealed a cut-off value of 3.05 mg/l with a significantly large AUC of 0.641 and p-value less than 0.05.

The patients were divided into two groups for – high CRP level (>3.05 mg/l) and low CRP levels (≤3.05 mg/l). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

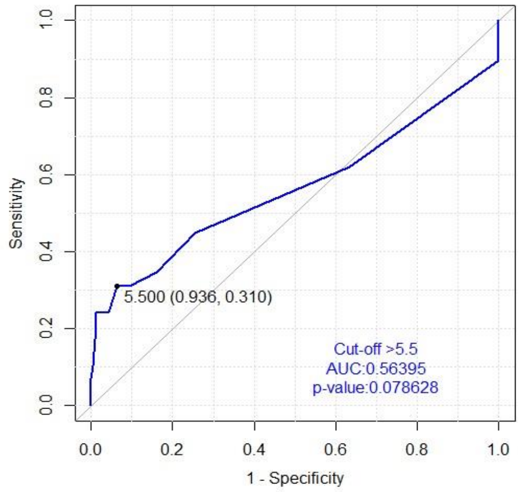
Chi-square (10.3) and P-value (0.0013) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the 3-year survival analysis of the mixed cohort patients with respect to the risk factor “CRP level”.

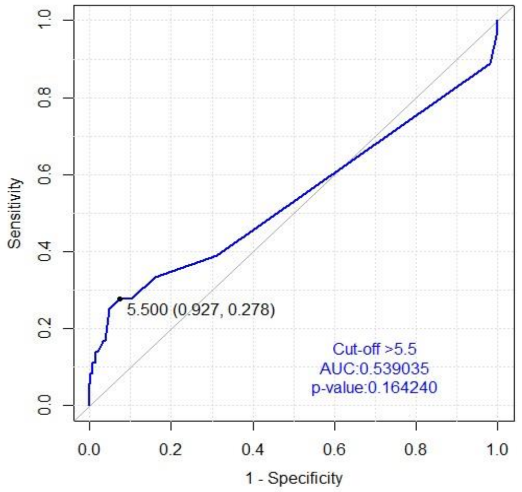


Kaplan Meier curve for 3-year follow up of mixed cohort patients for Preoperative C-reactive protein level (mg/l).

6.1.7 ICU Stay

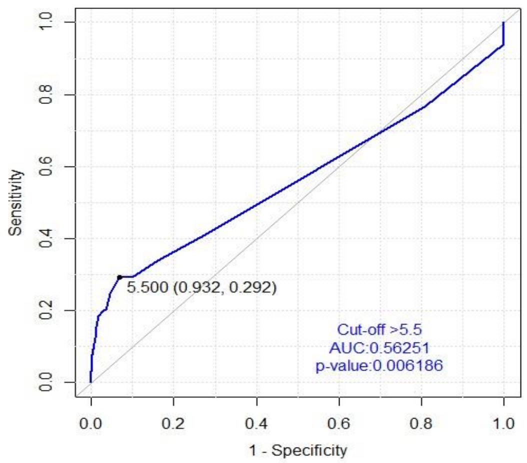


ROC curve for 3-year follow-up of CAD cohort patients for ICU stay(days).



ROC curve for 3-year follow-up of HVD cohort patients for ICU stay(days).

The ROC curves for the 3-year follow up of CAD and HVD cohorts were plotted. In both the cohorts, the p-value was considerably large suggesting no considerable influence of ICU Stay on the 3-year survival of the patients.



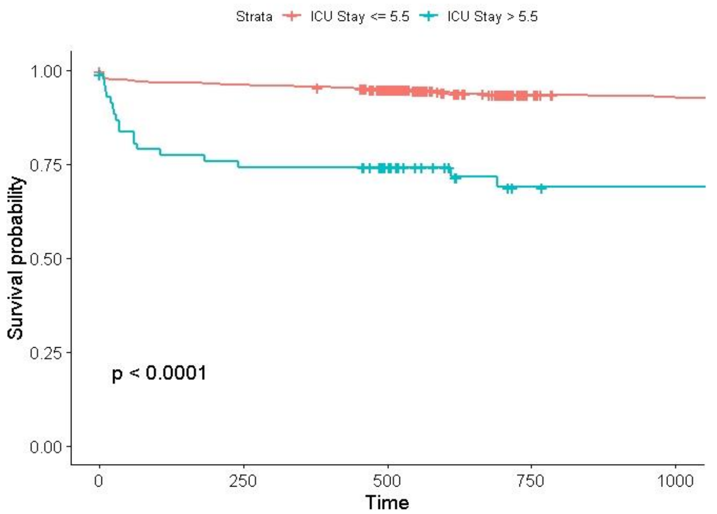
ROC curve for 3-year follow-up of mixed cohort patients for ICU stay(days).

For the mixed cohort the ROC curve for 3-year revealed a cut-off value of 5.5 days with a significantly large AUC of 0.562 and p-value less than 0.01.

The patients were divided into two groups for – more days in ICU (>5.5 days) and less days in ICU (≤5.5 days). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

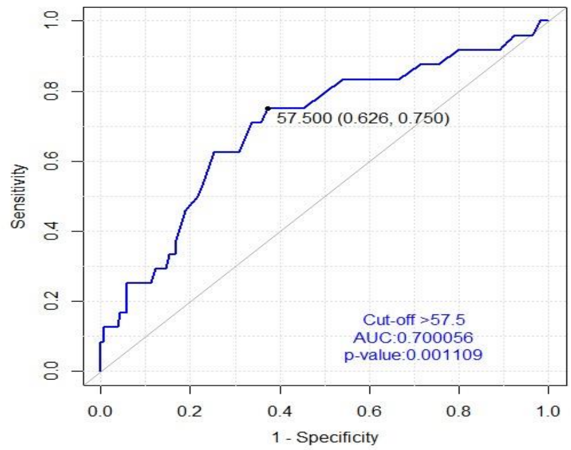
Chi-square (43.8) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the 3-year survival analysis of the mixed cohort patients with respect to the risk factor "ICU Stay".

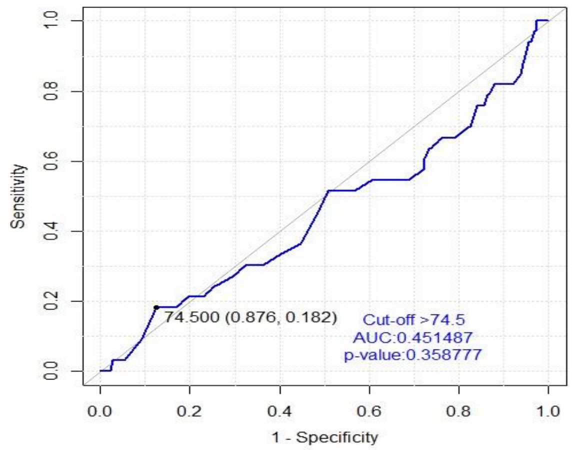


Kaplan Meier curve for 3-year follow up of mixed cohort patients for ICU stay (days).

6.1.8 Left Ventricle Ejection Fraction

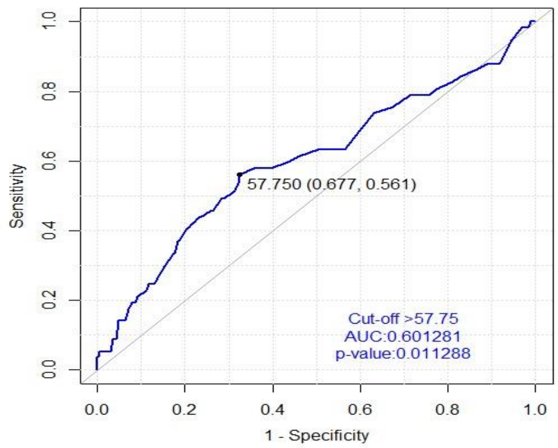


ROC curve for 3-year follow-up of CAD cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).



ROC curve for 3-year follow-up of HVD cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).

The ROC curves for the 3-year follow up of CAD and HVD cohorts were plotted. In the CAD cohort AUC was observed to be considerably large with a very small p-value, suggesting that LVEF influences the 3-year survival of patients in the cohort. However, in the HVD cohort the AUC was observed to be less then 0.5 suggesting no considerable influence of LVEF on the 3-year survival of patients from this cohort.



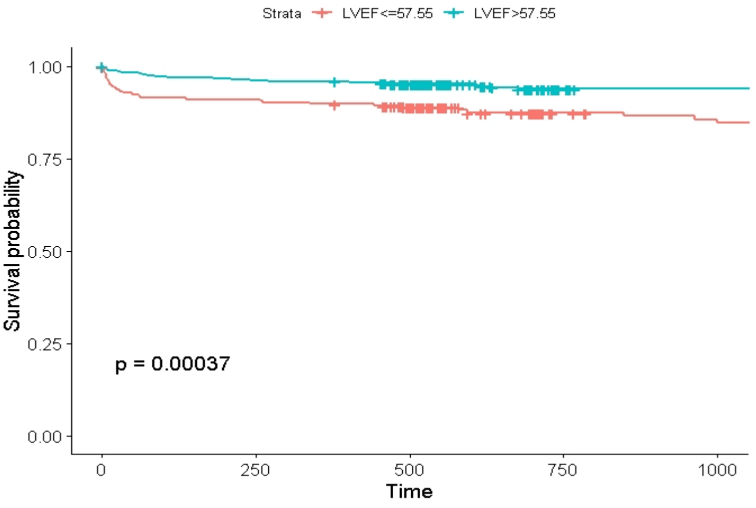
ROC curve for 3-year follow-up of mixed cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).

For the mixed cohort the ROC curve for 3-year revealed a cut-off value of 57.75 % with a significantly large AUC of 0.601 and p value less than 0.05.

The patients were divided into two groups for – high LVEF (>57.55%) and low LVEF (≤57.55 %). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

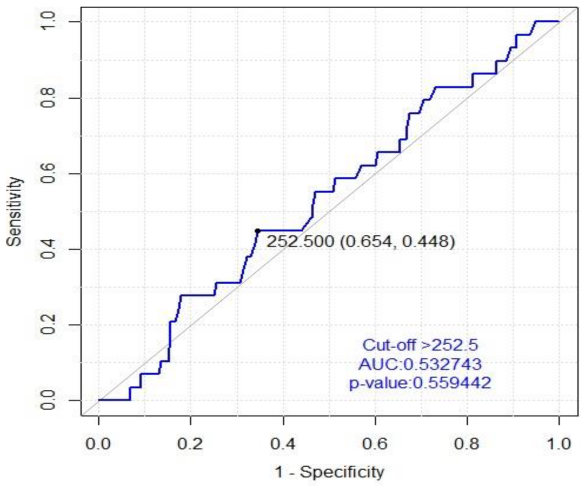
Chi-square (12.7) and P-value (0.00037) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the 3-year survival analysis of the mixed cohort patients with respect to the risk factor “LVEF”.

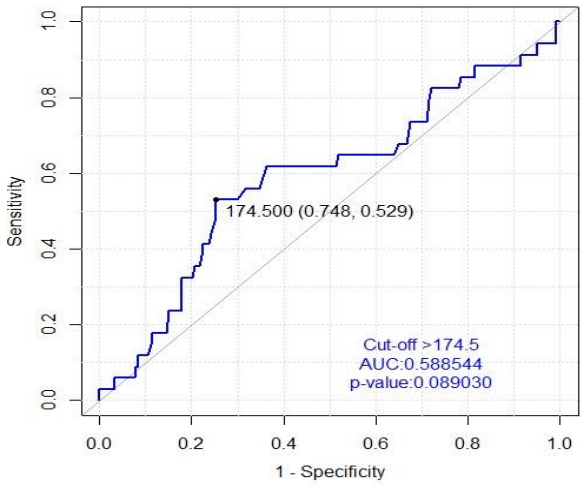


Kaplan Meier curve for 3-year follow up of mixed cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).

6.1.9 Preoperative Thrombocytes Level

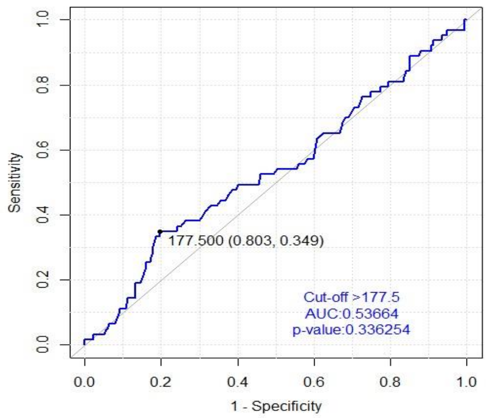


ROC curve for 3-year follow-up of CAD cohort patients for Preoperative Thrombocytes level (x10^9/l).



ROC curve for 3-year follow-up of HVD cohort patients for Preoperative Thrombocytes level (x10^9/l).

The ROC curves for the 3-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be near 0.5 with a large p-value. Hence the ROC curve suggests that the preoperative thrombocytes level does not influence the 3-year survival of the patients.



ROC curve for 3-year follow-up of mixed cohort patients for Preoperative Thrombocytes level (x10^9/l).

For the mixed cohort the ROC curve for 3-year revealed a cut-off value of 177.5 x 10^9/l with AUC close to 0.5 and a large p-value.

Thus, we do not plot the corresponding Kaplan-Meier curve as there is not enough evidence suggesting that preoperative thrombocytes level affects 3-year survival.

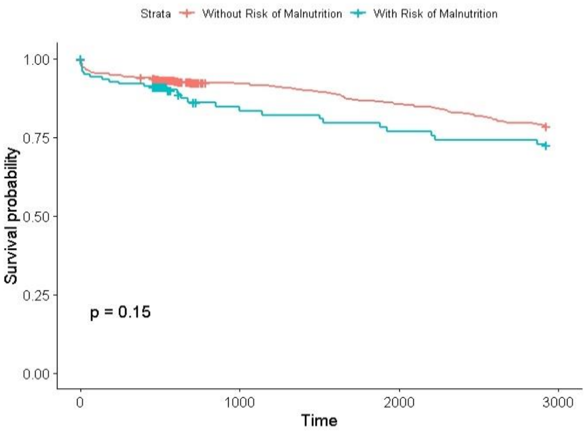
6.2 8-year Survival

6.2.1 Malnutrition

The patients were divided into two groups – patients who are at a risk of malnutrition and patients who are not at a risk of malnutrition.

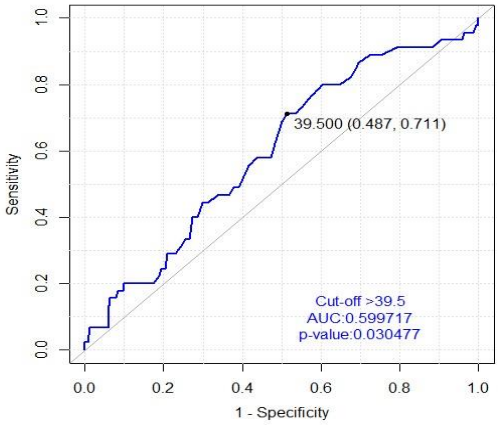
Chi-square (2.1) and P-value (0.15) was obtained. The low p-value suggests that there are no statistically significant differences in the 8-year survival of the two groups.

This constituted the 8-year survival analysis of the patients with respect to the risk factor “Malnourishment”.

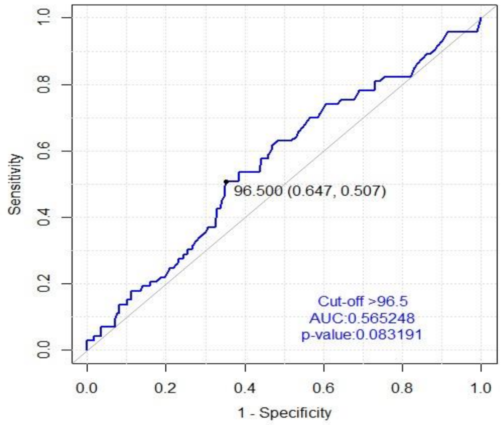


Kaplan Meier curve for 8-year follow up data for MUST

6.2.2 Aortic Cross Clamp Time

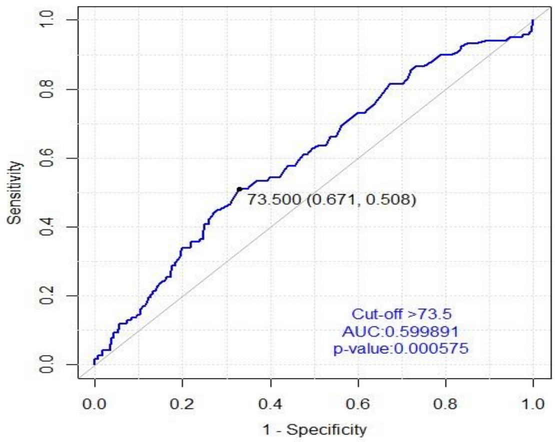


ROC curve for 8-year follow-up of CAD cohort patients for aortic cross clamp time(min).



ROC curve for 8-year follow-up of HVD cohort patients for aortic cross clamp time(min).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In the CAD cohort, AUC was observed to be considerably large with a small p value. Hence the ROC curve suggests that aortic cross clamp time influences the 8-year survival of the patients in this cohort. However, in the HVD cohort, the AUC was near 0.5 and had a large p-value. Thus, the ROC curve suggested that ACC time does not affect the 8-year survival of the patients in the HVD cohort.



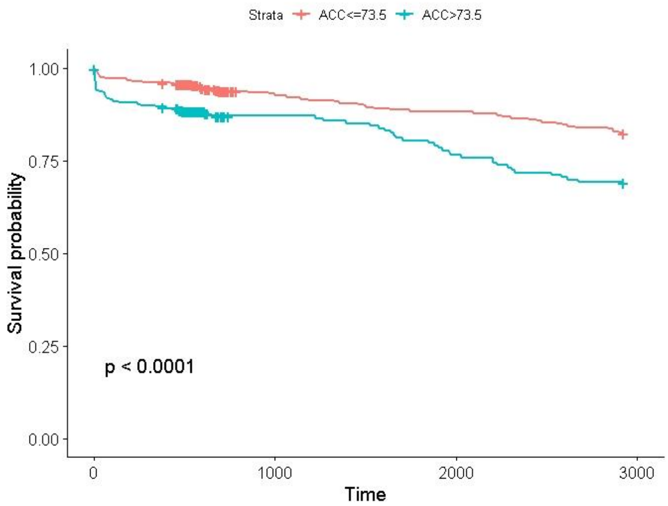
ROC curve for 8-year follow-up of mixed cohort patients for aortic cross clamp time

For the mixed cohort, the ROC curve for 8-year revealed a cut-off value of 73.5 min with a significantly large AUC of 0.6 and p value less than 0.001.

The patients were divided into two groups for – high ACC time (>73.5 minutes) and low ACC time (≤73.5 minutes). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

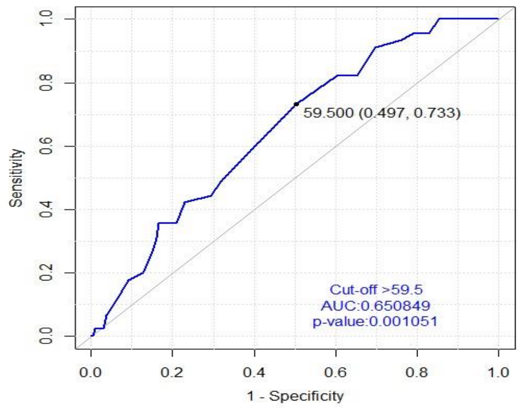
Chi-square (15.7) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the 8-year survival of the two groups.

This constituted the 8-year survival analysis of the mixed cohort patients with respect to the risk factor “aortic cross clamp time”.

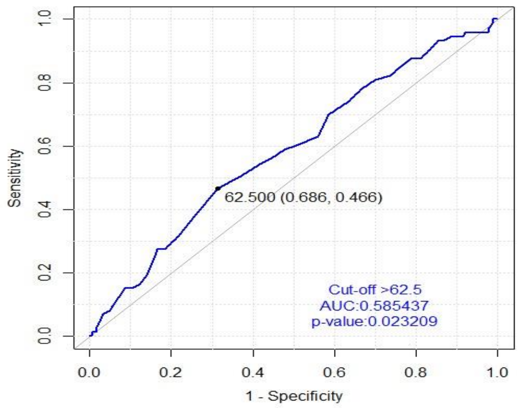


Kaplan Meier curve for 8-year follow up of mixed cohort patients for aortic cross clamp time (min)

6.2.3 Age

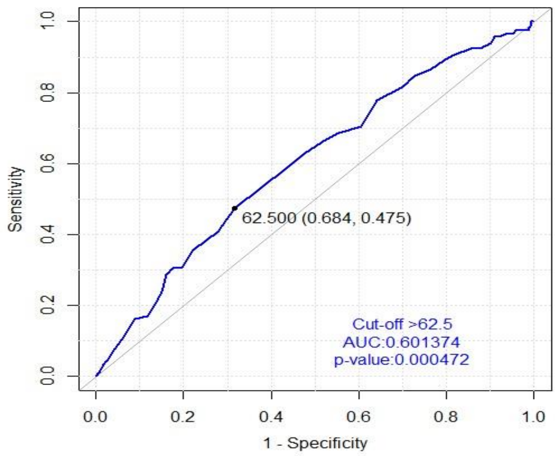


ROC curve for 8-year follow-up of CAD cohort patients for Age (years).



ROC curve for 8-year follow-up of HVD cohort patients for Age (years).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with small p-values. Hence the ROC curve suggests that age is influencing the 8-year survival of the patients.



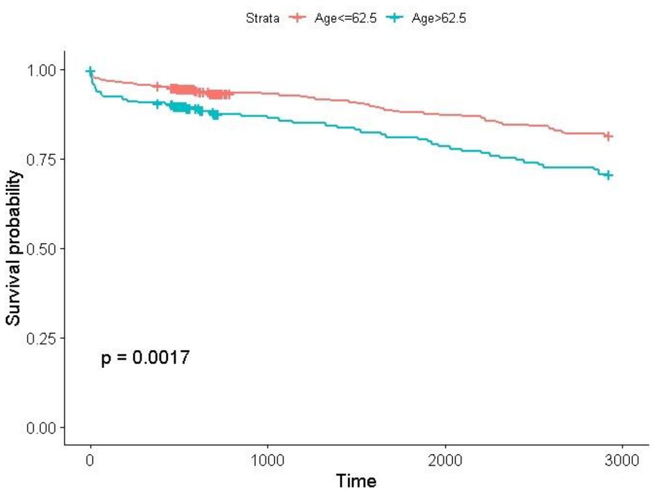
ROC curve for 8-year follow-up of mixed cohort patients for Age (years).

For the mixed cohort the ROC curve for 8-year revealed a cut-off value of 62.5 years with a significantly large AUC of 0.601 and p-value less than 0.001.

The patients were divided into two groups – Age > 62.5 years and Age ≤ 62.5 years. This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

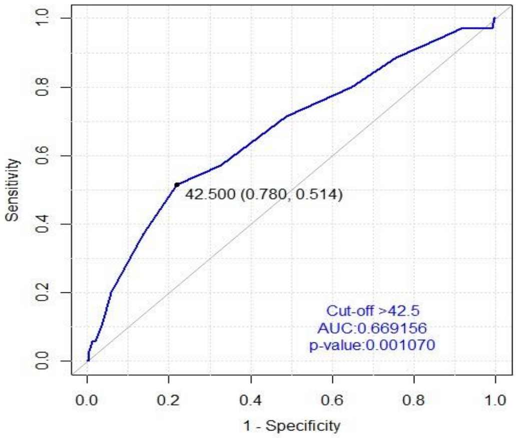
Chi-square (9.8) and P-value (0.0017) was obtained. The low p-value suggests that there are statistically significant differences in the 8-year survival of the two groups.

This constituted the 8-year survival analysis of the mixed cohort patients with respect to the risk factor "Age".

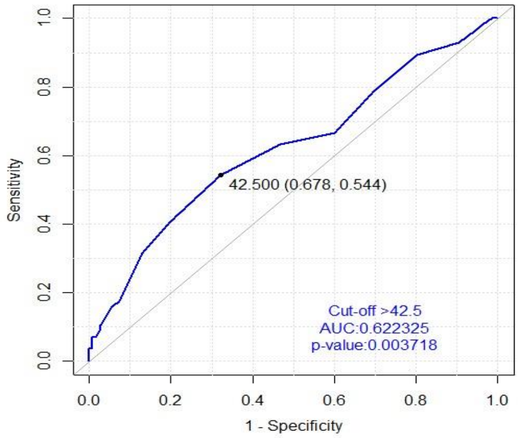


Kaplan Meier curve for 8-year follow up of mixed cohort patients for Age(years).

6.2.4 Albumin

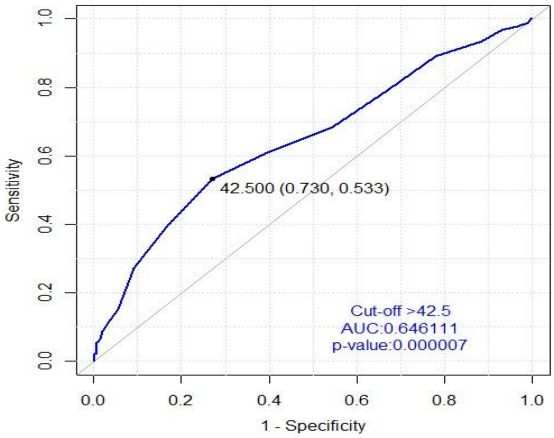


ROC curve for 8-year follow-up of CAD cohort patients for preoperative Albumin(g/L).



ROC curve for 8-year follow-up of HVD cohort patients for preoperative Albumin (g/L).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with a small p-value. Hence the ROC curve suggests that preoperative albumin level influences the 8-year survival of the patients.



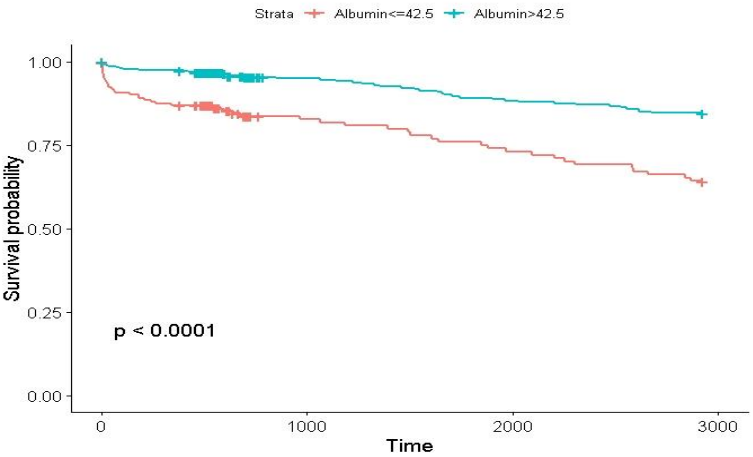
ROC curve for 8-year follow-up of mixed cohort patients for preoperative albumin(g/L).

For the mixed cohort the ROC curve for 8-year revealed a cut-off value of 42.5 g/l with a significantly large AUC of 0.646 and p-value less than 0.001.

The patients were divided into two groups – Albumin level > 42.5 g/l and Albumin level ≤ 42.5 g/l. This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

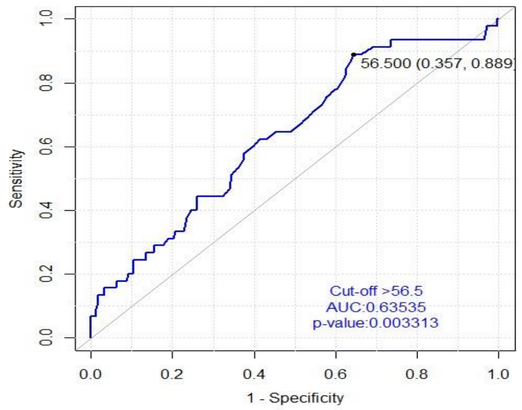
Chi-square (29.6) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the 8-year survival of the two groups.

This constituted the 8-year survival analysis of the mixed cohort patients with respect to the risk factor "Preoperative Albumin level".

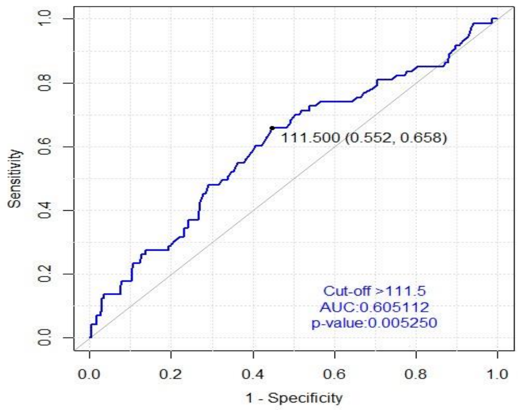


Kaplan Meier curve for 8-year follow up of mixed cohort patients for preoperative Albumin (g/l).

6.2.5 Cardiopulmonary Bypass Time

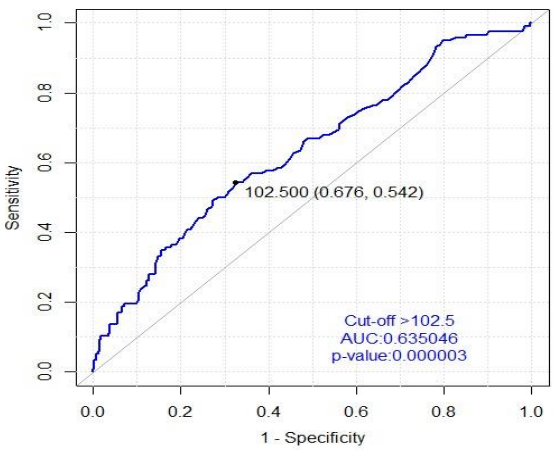


ROC curve for 8-year follow-up of CAD cohort patients for CPB time(min).



ROC curve for 8-year follow-up of HVD cohort patients for CPB time(min).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with a small p value. Hence the ROC curve suggests that CPB time influences the 8-year survival of the patients.



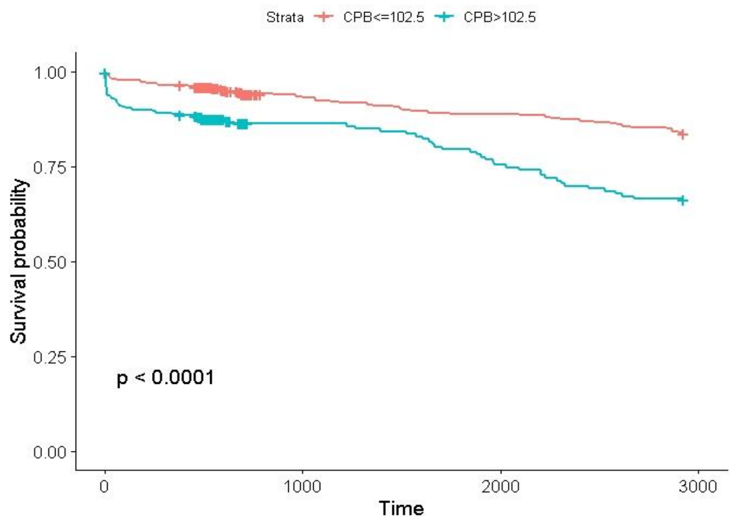
ROC curve for 8-year follow-up of mixed cohort patients for CBP time(min).

For the mixed cohort the ROC curve for 8-year revealed a cut-off value of 102.5 minutes with a significantly large AUC of 0.635 and p-value less than 0.001.

The patients were divided into two groups – high CPB time (>102.5 minutes) and low CPB time (≤102.5 minutes). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

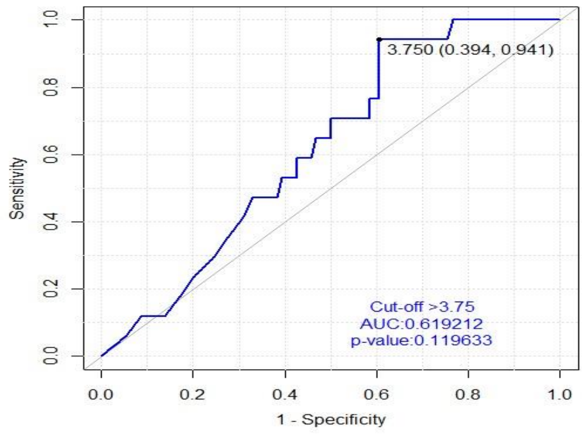
Chi-square (24.7) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the 8-year survival of the two groups.

This constituted the 8-year survival analysis of the mixed cohort patients with respect to the risk factor "CPB time".

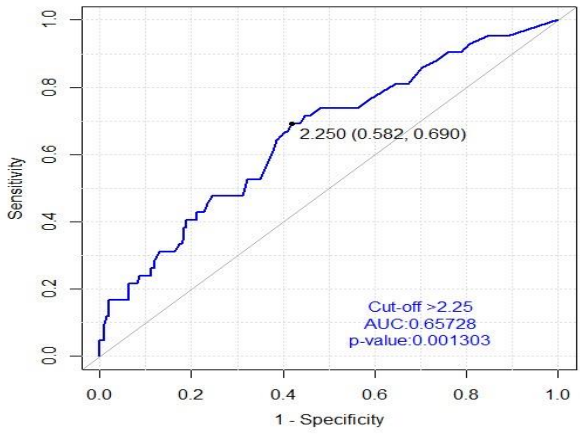


Kaplan Meier curve for 8-year follow up of mixed cohort patients for CBP time (min).

6.2.6 Preoperative C-Reactive Protein Level

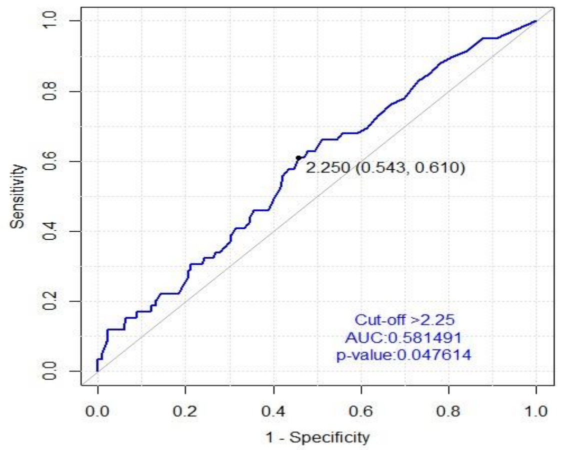


ROC curve for 8-year follow-up of CAD cohort patients for Preoperative C-reactive protein level (mg/l).



ROC curve for 8-year follow-up of HVD cohort patients for Preoperative C-reactive protein level (mg/l).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In the HVD cohort AUC was observed to be considerably large with a small p-value, suggesting that CRP influences the 8-year survival of patients in the cohort. However, in the CAD cohort the p-value was considerably large suggesting no considerable influence of CRP on the 8-year survival of patients from this cohort.



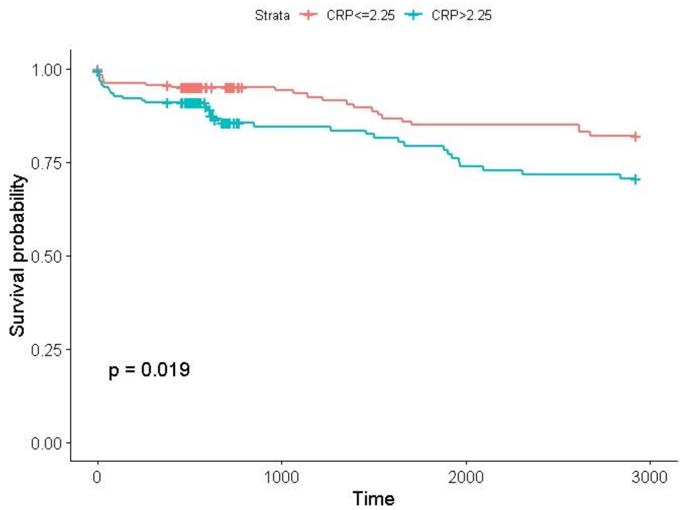
ROC curve for 8-year follow-up of mixed cohort patients for Preoperative C-reactive protein level (mg/l).

For the mixed cohort the ROC curve for 8-year revealed a cut-off value of 2.25 mg/l with a significantly large AUC of 0.581 and p-value less than 0.05.

The patients were divided into two groups for – high CRP level (>2.25 mg/l) and low CRP levels (≤2.25 mg/l). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

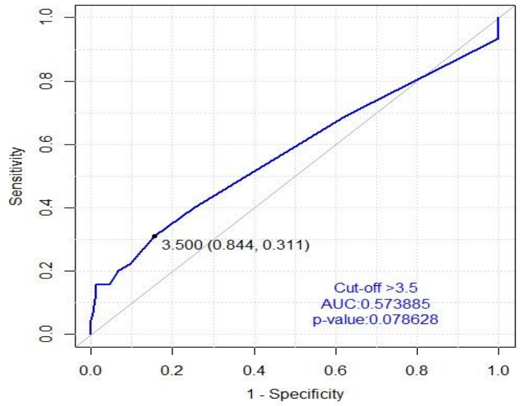
Chi-square (5.5) and P-value (0.019) was obtained. The low p-value suggests that there are statistically significant differences in the 8-year survival of the two groups.

This constituted the 8-year survival analysis of the mixed cohort patients with respect to the risk factor "CRP level".

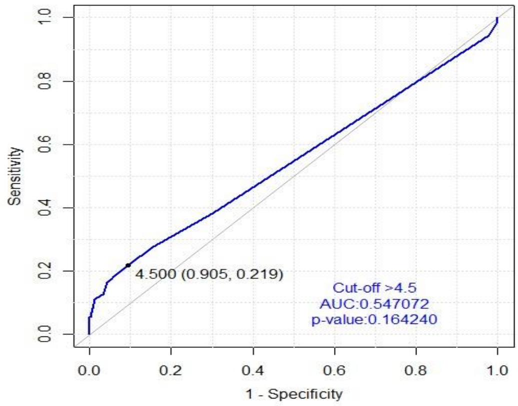


Kaplan Meier curve for 8-year follow up of mixed cohort patients for Preoperative C-reactive protein level (mg/l).

6.2.7 ICU Stay

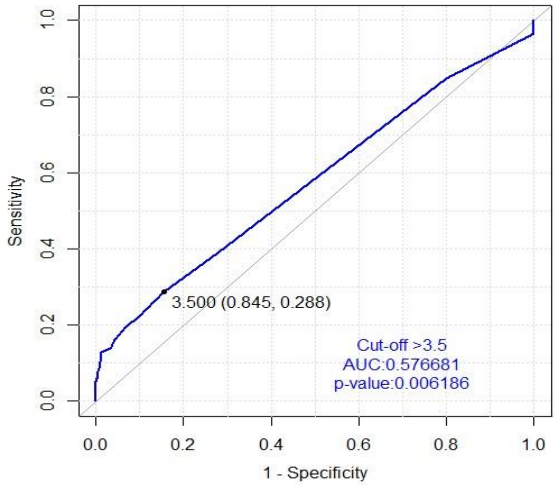


ROC curve for 8-year follow-up of CAD cohort patients for ICU stay(days).



ROC curve for 8-year follow-up of HVD cohort patients for ICU stay(days).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In both the cohorts, the p-value was considerably large suggesting no considerable influence of ICU Stay on the 8-year survival of patients.



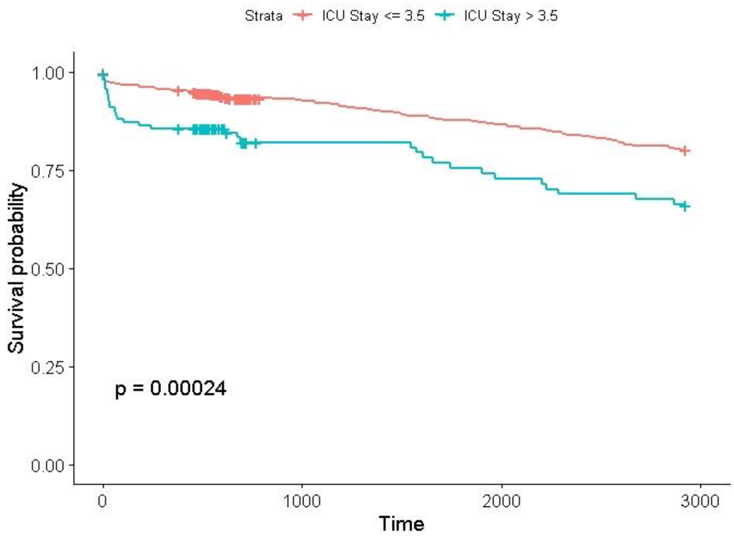
ROC curve for 8-year follow-up of mixed cohort patients for ICU stay(days).

For the mixed cohort the ROC curve for 8-year revealed a cut-off value of 3.5 days with a significantly large AUC of 0.577 and p-value less than 0.01.

The patients were divided into two groups for – more days in ICU (>3.5 days) and less days in ICU (≤3.5 days). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

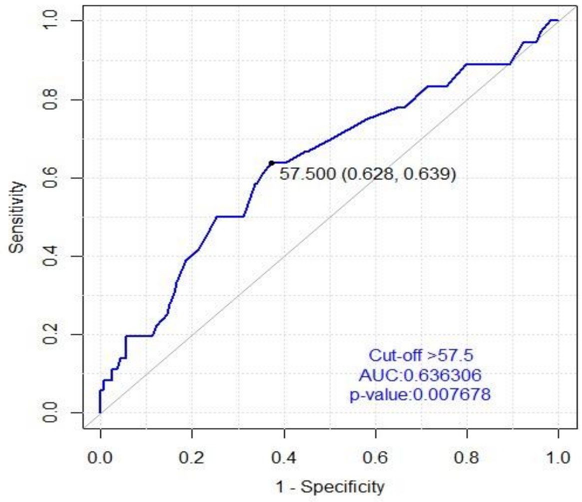
Chi-square (13.5) and P-value (0.00024) was obtained. The low p-value suggests that there are statistically significant differences in the 8-year survival of the two groups.

This constituted the 8-year survival analysis of the mixed cohort patients with respect to the risk factor “ICU Stay”.

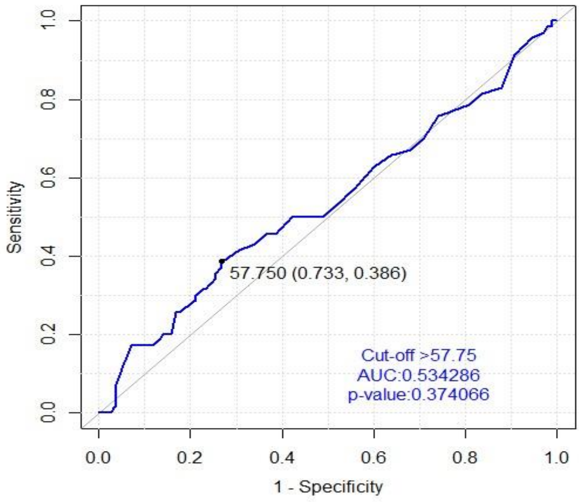


Kaplan Meier curve for 8-year follow up of mixed cohort patients for ICU stay(days).

6.2.8 Left Ventricle Ejection Fraction

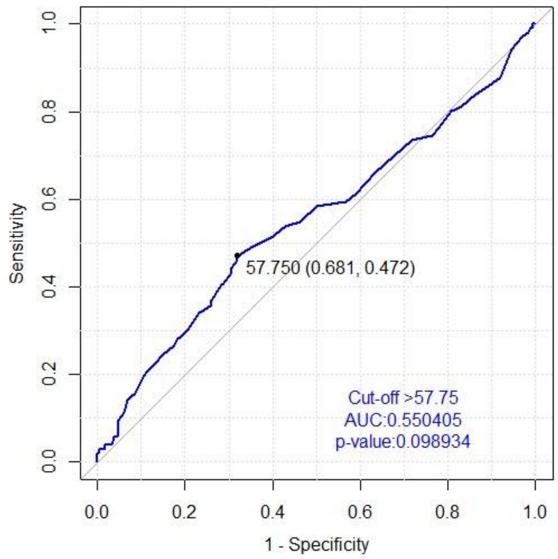


ROC curve for 8-year follow-up of CAD cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).



ROC curve for 8-year follow-up of HVD cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In the CAD cohort AUC was observed to be considerably large with a very small p-value, suggesting that LVEF influences the 8-year survival of patients in the cohort. However, in the HVD cohort the AUC was observed to be nearly 0.5 with a large p-value suggesting no considerable influence of LVEF on the 8-year survival of patients from this cohort.

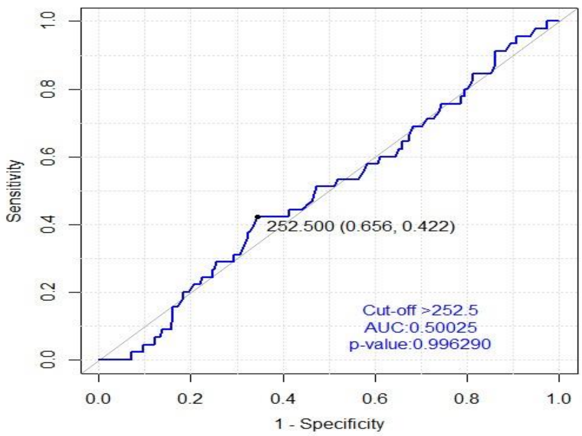


ROC curve for 8-year follow-up of mixed cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).

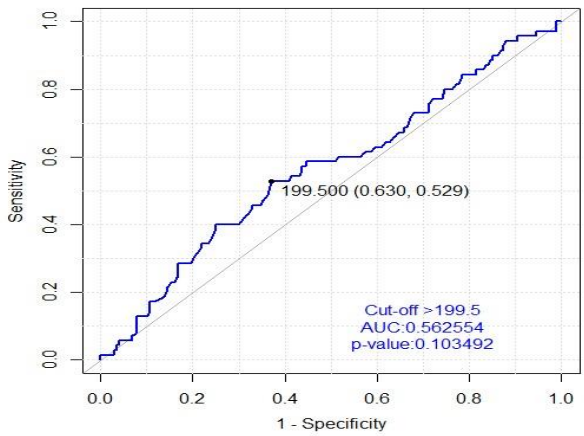
For the mixed cohort the ROC curve for 8-year revealed a cut-off value of 57.75 % with a low AUC (0.550) and p value greater than 0.05.

Thus, we do not plot the corresponding Kaplan-Meier curve as there is not enough evidence suggesting that LVEF affects 8-year survival

6.2.9 Preoperative Thrombocytes Level

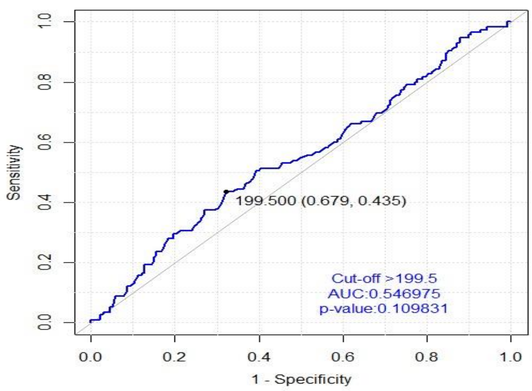


ROC curve for 8-year follow-up of CAD cohort patients for Preoperative Thrombocytes level (x10^9/l).



ROC curve for 8-year follow-up of HVD cohort patients for Preoperative Thrombocytes level (x10^9/l).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be near 0.5 with a large p-value. Hence the ROC curve suggests that the preoperative thrombocytes level does not influence the 8-year survival of the patients.



ROC curve for 8-year follow-up of mixed cohort patients for Preoperative Thrombocytes level (x10^9/l).

For the mixed cohort the ROC curve for 8-year revealed a cut-off value of 199.5 x 10^9/l with AUC close to 0.5 and a large p-value.

Thus, we do not plot the corresponding Kaplan-Meier curve as there is not enough evidence suggesting that preoperative thrombocytes level affects 8-year survival.

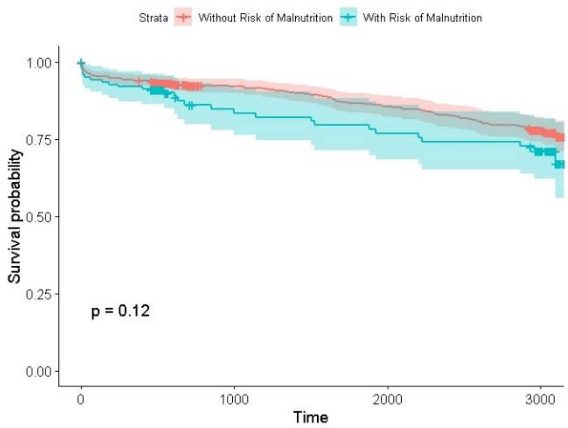
6.3 Overall Survival

6.3.1 Malnutrition

The patients were divided into two groups – patients who are at a risk of malnutrition and patients who are not at a risk of malnutrition.

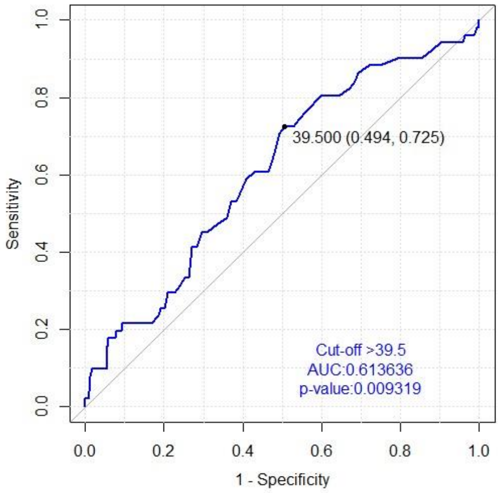
Chi-square (2.4) and P-value (0.12) was obtained. The high p-value suggests that there are no statistically significant differences in the overall survival of the two groups.

This constituted the overall survival analysis of the patients with respect to the risk factor “Malnourishment”.

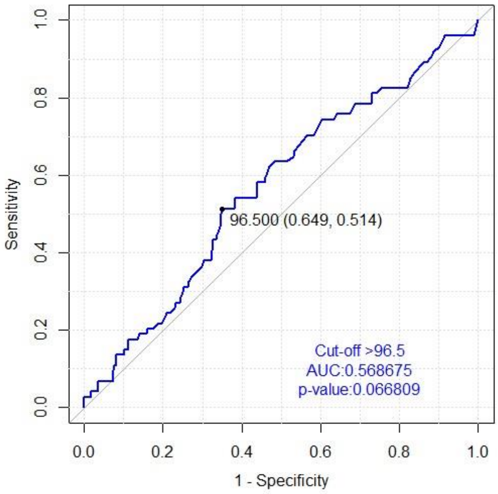


Kaplan Meier curve for Overall Survival data for MUST

6.3.2 Aortic Cross Clamp Time

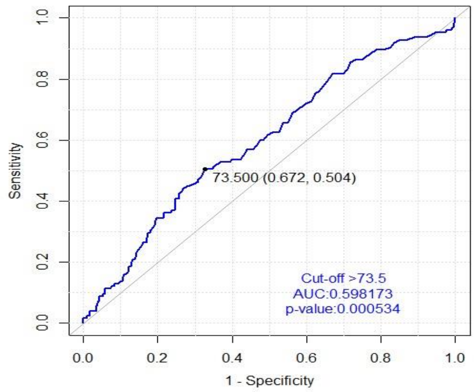


ROC curve for overall survival follow-up of CAD cohort patients for aortic cross clamp time(min).



ROC curve for overall survival follow-up of HVD cohort patients for aortic cross clamp time(min).

The ROC curves for overall survival of CAD and HVD cohorts were plotted. In the CAD cohort, AUC was observed to be considerably large with a small p value. Hence the ROC curve suggests that aortic cross clamp time influences the overall survival of the patients in this cohort. However, the HVD cohort had a large p-value. Thus, the ROC curve suggested that ACC time does not affect the overall survival of the patients in the HVD cohort.



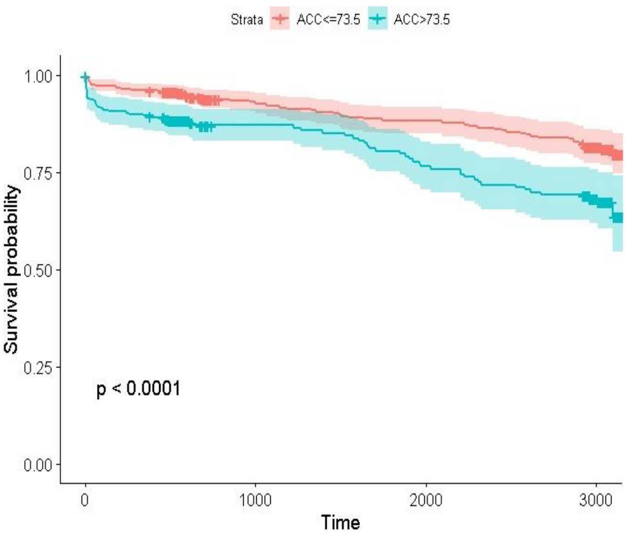
ROC curve for overall survival follow-up of mixed cohort patients for aortic cross clamp time

For the mixed cohort, the ROC curve for overall survival revealed a cut-off value of 73.5 min with a significantly large AUC of 0.598 and p value less than 0.006.

The patients were divided into two groups for – high ACC time (>73.5 minutes) and low ACC time (≤73.5 minutes). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

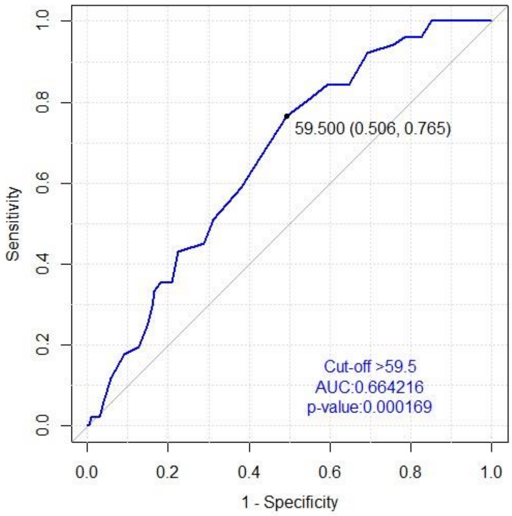
Chi-square (16.3) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the overall survival of the two groups.

This constituted the overall survival analysis of the mixed cohort patients with respect to the risk factor “aortic cross clamp time”.

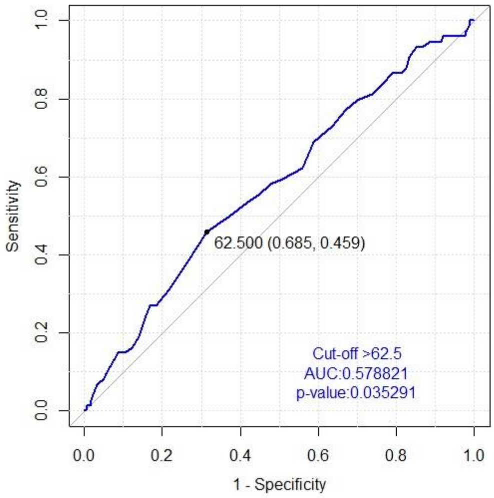


Kaplan Meier curve for overall survival of mixed cohort patients for Aortic Cross Clamp Time (min)

6.3.3 Age

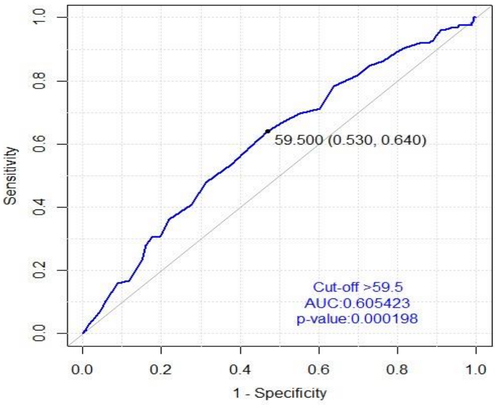


ROC curve for overall survival *of CAD cohort patients for Age (years).*



ROC curve for overall survival *of HVD cohort patients for Age (years).*

The ROC curves for the overall survival of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with small p-values. Hence the ROC curve suggests that age is influencing the overall survival of the patients.



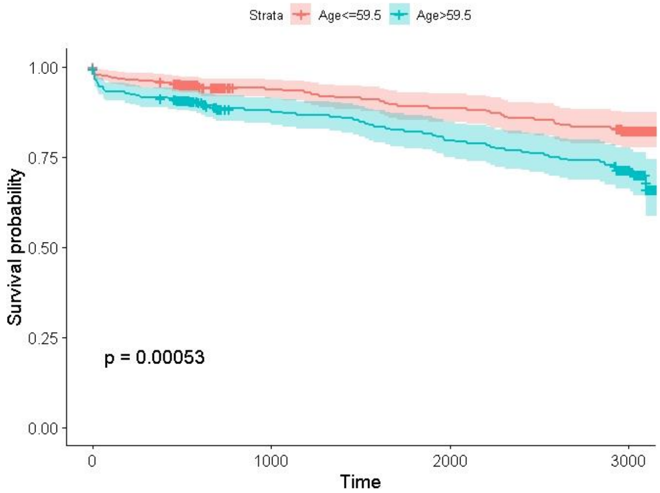
ROC curve for overall survival of mixed cohort patients for Age (years).

For the mixed cohort the ROC curve for overall survival revealed a cut-off value of 59.5 years with a significantly large AUC of 0.605 and p-value less than 0.001.

The patients were divided into two groups – Age > 59.5 years and Age ≤ 59.5 years. This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

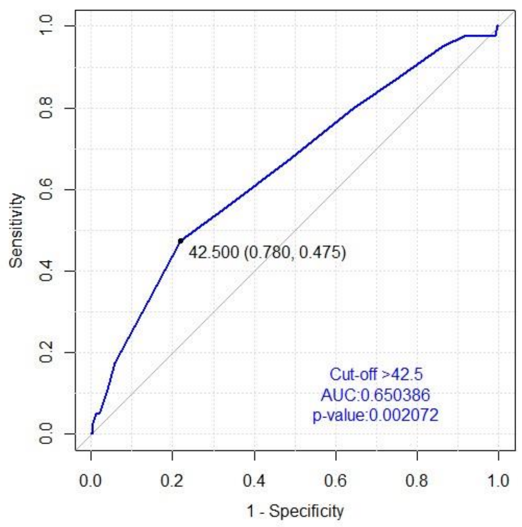
Chi-square (12) and P-value (0.00053) was obtained. The low p-value suggests that there are statistically significant differences in the overall survival of the two groups.

This constituted the overall survival analysis of the mixed cohort patients with respect to the risk factor “Age”.

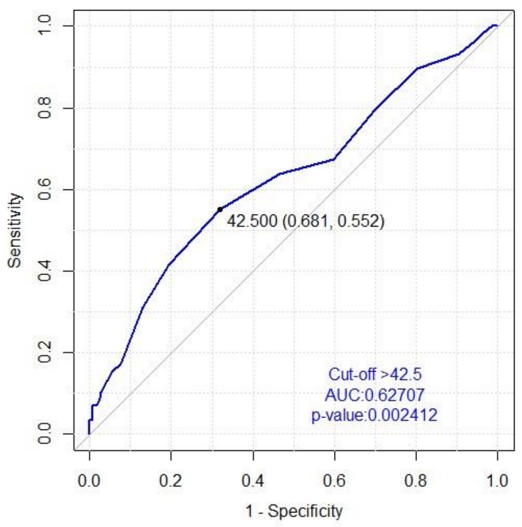


Kaplan Meier curve for overall survival of mixed cohort patients for Age (years)

6.3.4 Albumin

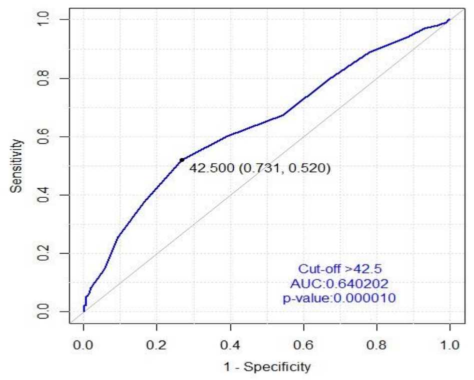


ROC curve for overall survival of CAD cohort patients for preoperative Albumin(g/L).



ROC curve for overall survival of HVD cohort patients for preoperative Albumin (g/L).

The ROC curves for the overall of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with a small p-value. Hence the ROC curve suggests that preoperative albumin level influences the overall survival of the patients.



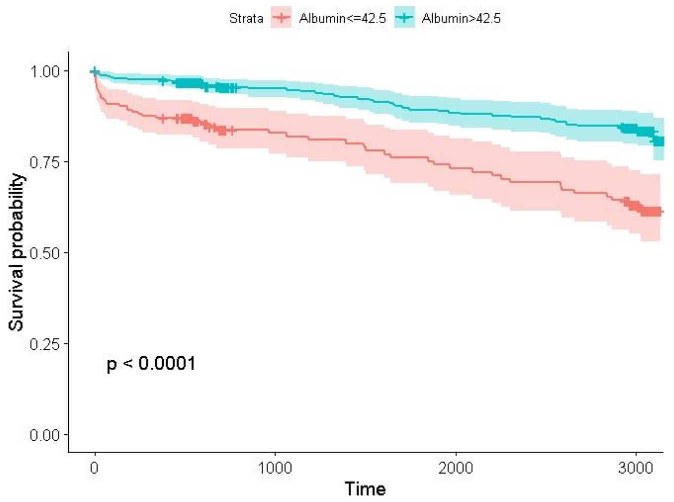
ROC curve for overall survival of mixed cohort patients for preoperative Albumin(g/L).

For the mixed cohort the ROC curve for overall survival revealed a cut-off value of 42.5 g/l with a significantly large AUC of 0.640 and p-value less than 0.001.

The patients were divided into two groups – Albumin level > 42.5 g/l and Albumin level ≤ 42.5 g/l. This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

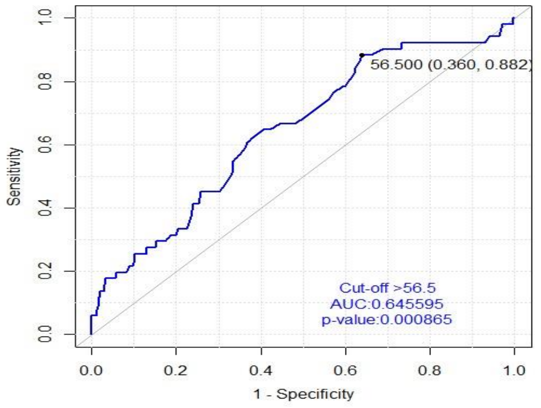
Chi-square (30.2) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the 3-year survival of the two groups.

This constituted the overall survival analysis of the mixed cohort patients with respect to the risk factor "Preoperative Albumin level".

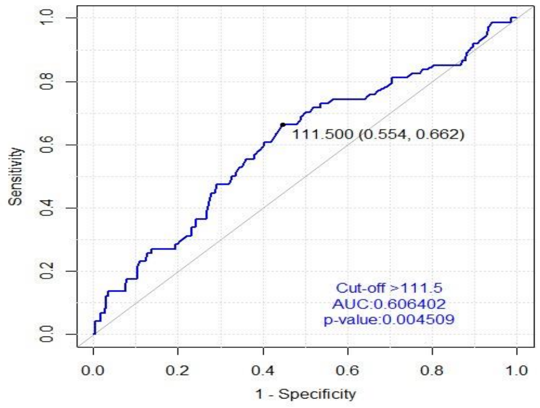


Kaplan Meier curve for overall survival of mixed cohort patients for Preoperative Albumin (g/L)

6.3.5 Cardiopulmonary Bypass Time

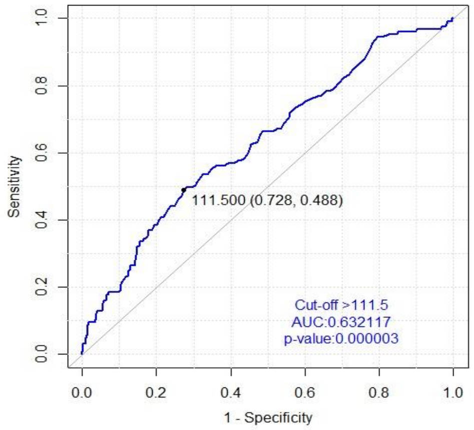


ROC curve for overall survival of CAD cohort patients for CPB time(min).



ROC curve for overall survival of HVD cohort patients for CPB time(min).

The ROC curves for the overall survival of CAD and HVD cohorts were plotted. In both the cohorts AUC was observed to be considerably large with a small p value. Hence the ROC curve suggests that CPB time influences the overall survival of the patients.



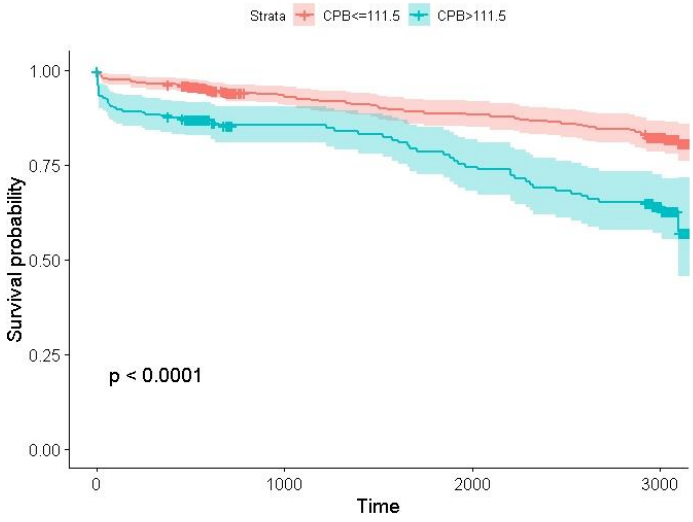
ROC curve for overall survival of mixed cohort patients for CBP time(min).

For the mixed cohort the ROC curve for overall survival revealed a cut-off value of 111.5 minutes with a significantly large AUC of 0.632 and p-value less than 0.001.

The patients were divided into two groups – high CPB time (>111.5 minutes) and low CPB time (≤111.5 minutes). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

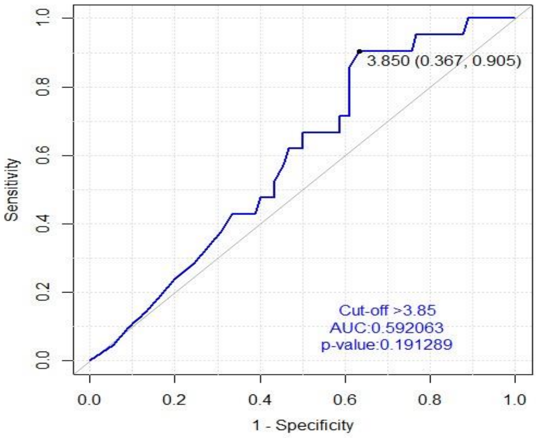
Chi-square (27.7) and P-value (<0.0001) was obtained. The low p-value suggests that there are statistically significant differences in the overall survival of the two groups.

This constituted the overall survival analysis of the mixed cohort patients with respect to the risk factor "CPB time".

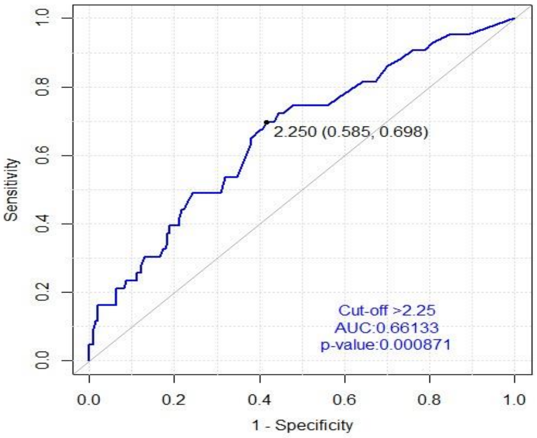


Kaplan Meier curve for overall survival of mixed cohort patients for CPB time (min)

6.3.6 Preoperative C-Reactive Protein Level

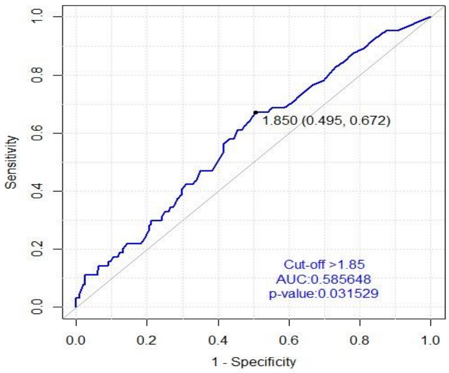


ROC curve for overall survival of CAD cohort patients for Preoperative C-reactive protein level (mg/l).



ROC curve for overall survival of HVD cohort patients for Preoperative C-reactive protein level (mg/l).

The ROC curves for the overall survival of CAD and HVD cohorts were plotted. In the HVD cohort AUC was observed to be considerably large with a very small p-value, suggesting that CRP influences the overall survival of patients in the cohort. However, in the CAD cohort the p-value was considerably large suggesting no considerable influence of CRP on the overall survival of patients from this cohort.



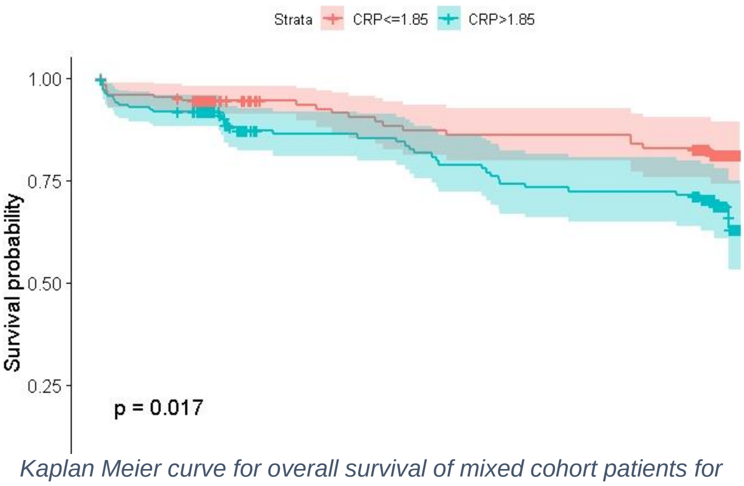
ROC curve for overall survival of mixed cohort patients for Preoperative C-reactive protein level

For the mixed cohort the ROC curve for overall survival revealed a cut-off value of 1.85 mg/l with AUC of 0.586 and p-value less than 0.05.

The patients were divided into two groups for – high CRP level (>1.85 mg/l) and low CRP levels (≤1.85 mg/l). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

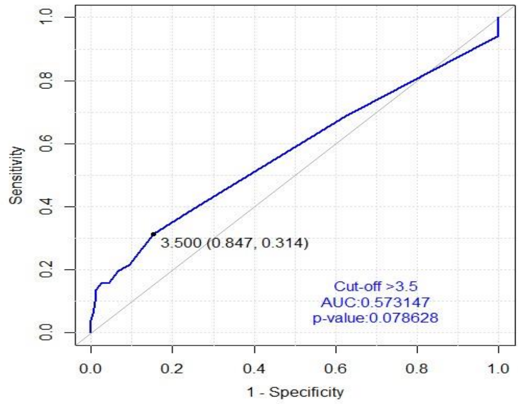
Chi-square (5.7) and P-value (0.017) was obtained. The low p-value suggests that there are statistically significant differences in the overall survival of the two groups.

This constituted the overall survival analysis of the mixed cohort patients with respect to the risk factor “CRP level”.

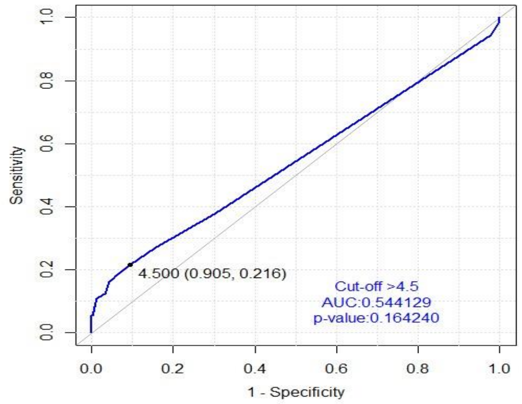


Kaplan Meier curve for overall survival of mixed cohort patients for Preoperative C-reactive protein level

6.3.7 ICU Stay

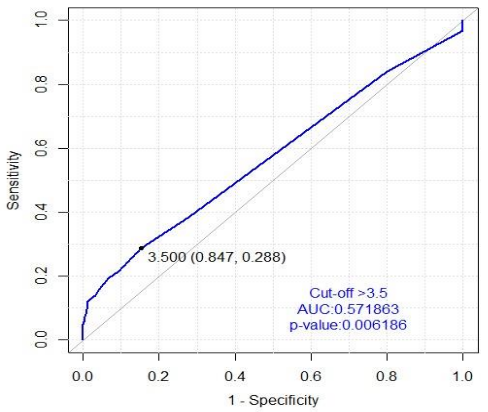


ROC curve for overall survival of CAD cohort patients for ICU stay(days).



ROC curve for overall survival of HVD cohort patients for ICU stay(days).

The ROC curves for the 8-year follow up of CAD and HVD cohorts were plotted. In both the cohorts, the p-value was considerably large suggesting no considerable influence of ICU Stay on the overall survival of patients.



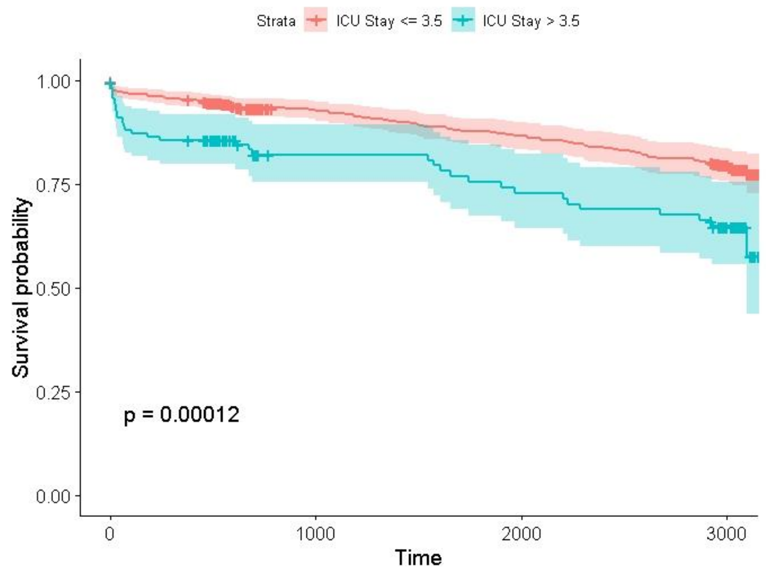
ROC curve for overall survival of mixed cohort patients for ICU stay(days).

For the mixed cohort the ROC curve for overall survival revealed a cut-off value of 3.5 days with AUC of 0.572 and p-value less than 0.01.

The patients were divided into two groups for – more days in ICU (>3.5 days) and less days in ICU (≤3.5 days). This threshold value was obtained from ROC Analysis. Kaplan-Meier curve was then plotted.

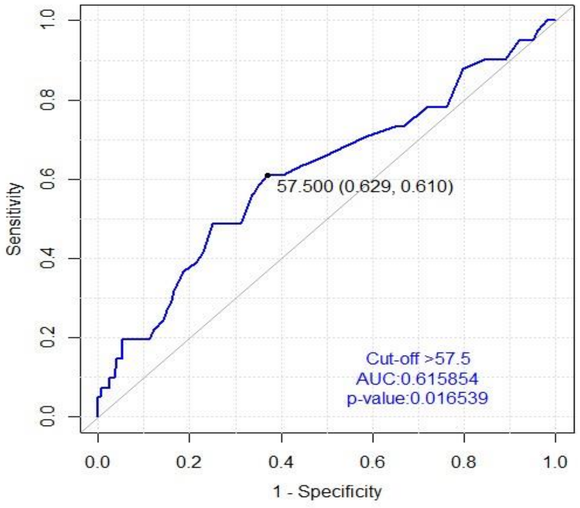
Chi-square (14.7) and P-value (0.00012) was obtained. The low p-value suggests that there are statistically significant differences in the overall survival of the two groups.

This constituted the overall survival analysis of the mixed cohort patients with respect to the risk factor “ICU Stay”.

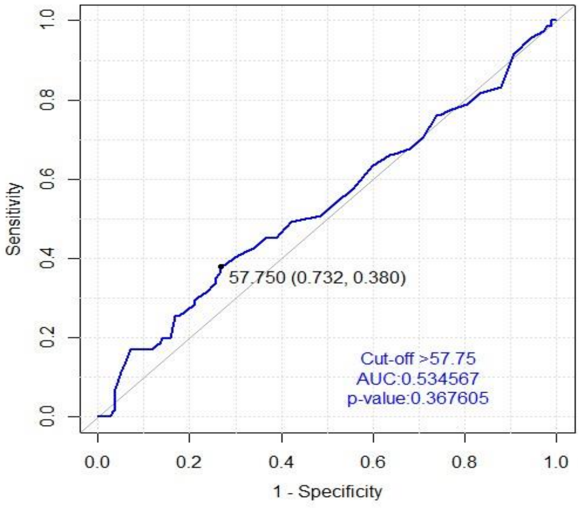


Kaplan Meier curve for overall survival of mixed cohort patients for ICU stay(days).

6.3.8 Left Ventricle Ejection Fraction

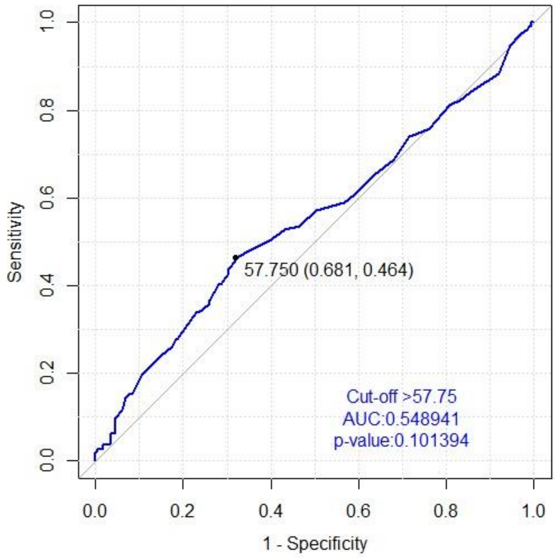


ROC curve for overall survival of CAD cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).



ROC curve for overall survival of HVD cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).

The ROC curves for the overall survival of CAD and HVD cohorts were plotted. In the CAD cohort AUC was observed to be considerably large with a very small p-value, suggesting that LVEF influences the overall survival of patients in the cohort. However, in the HVD cohort the AUC was observed to be less than 0.5 suggesting no considerable influence of LVEF on the overall survival of patients from this cohort.

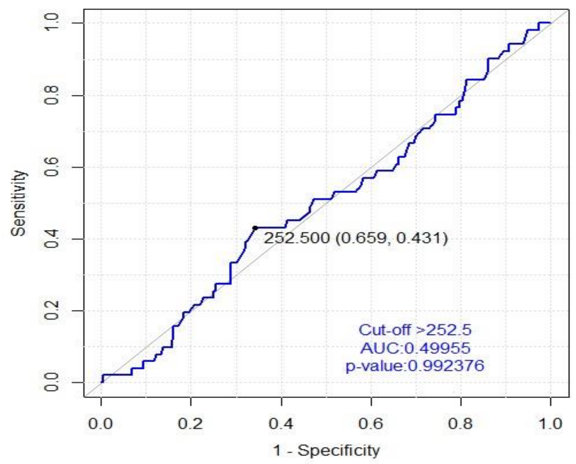


ROC curve for overall survival of mixed cohort patients for Left Ventricle Ejection Fraction (LVEF) (%).

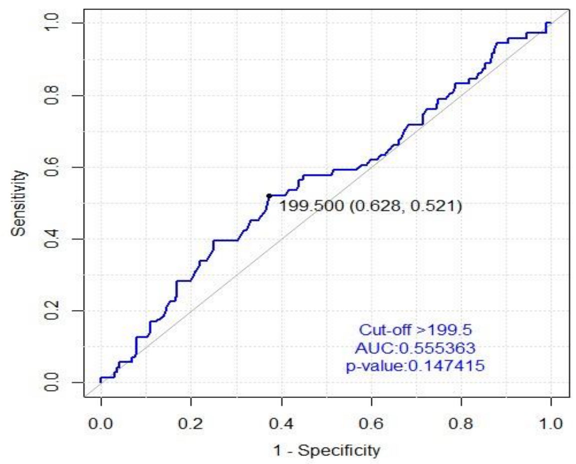
For the mixed cohort the ROC curve for overall revealed a cut-off value of 57.75 % with AUC of 0.549 and p value greater than 0.05.

Thus, we do not plot the corresponding Kaplan-Meier curve as there is not enough evidence suggesting that preoperative thrombocytes level affects overall survival.

6.3.9 Preoperative Thrombocytes Level

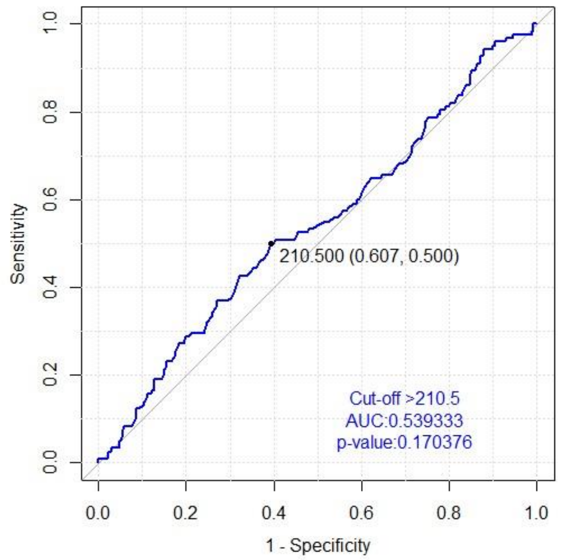


ROC curve for overall survival of CAD cohort patients for Preoperative Thrombocytes level (x10^9/l).



ROC curve for overall survival of HVD cohort patients for Preoperative Thrombocytes level (x10^9/l).

The ROC curves for the overall survival of CAD and HVD cohorts were plotted. In the CAD cohort AUC was observed to be less than 0.5 with a large p-value. In the HVD cohort, the AUC is greater than 0.5 but the p-value is large. Hence the ROC curve suggests that the preoperative thrombocytes level does not influence the overall survival of the patients.

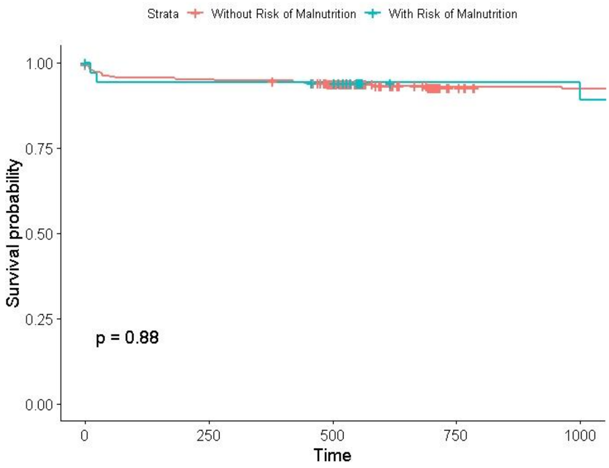


ROC curve for overall survival of mixed cohort patients for Preoperative Thrombocytes level (x10^9/l).

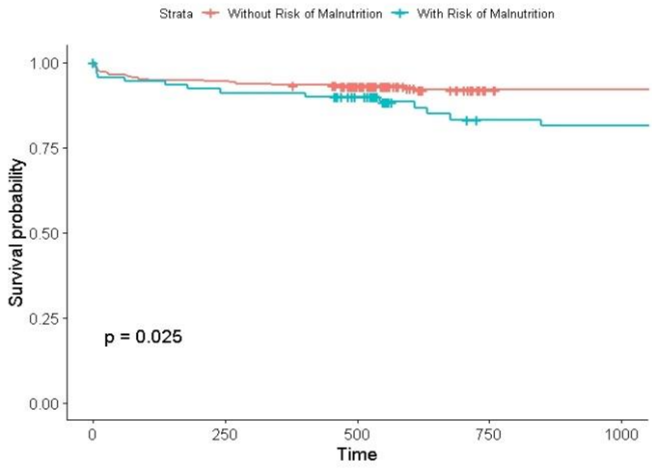
For the mixed cohort the ROC curve revealed a cut-off value of 210.5 x 10^9/l with AUC close to 0.5 and a large p-value.

Thus, we do not plot the corresponding Kaplan-Meier curve as there is not enough evidence suggesting that preoperative thrombocytes level affects overall survival.

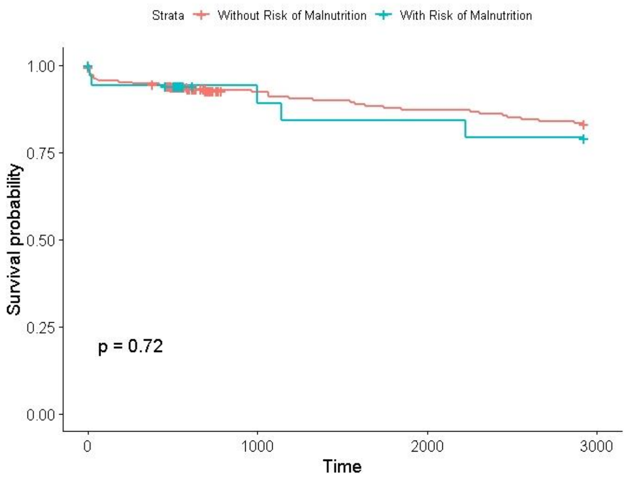
6.4 Kaplan – Meier Curves for Malnutrition in groups stratified by primary pathology



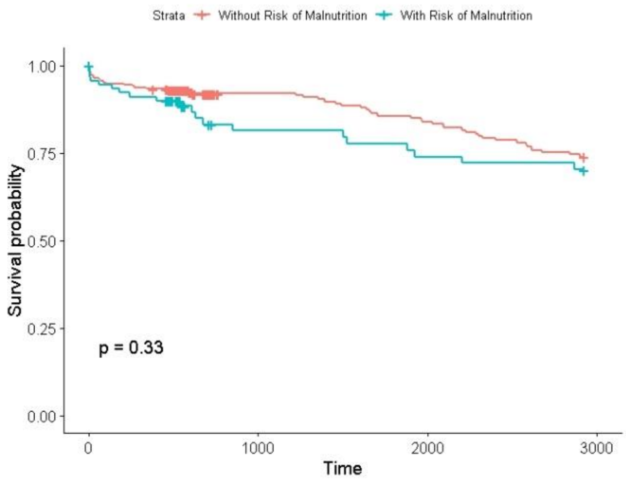
Kaplan Meier curve for 3-year Survival of CAD Cohort patients for MUST



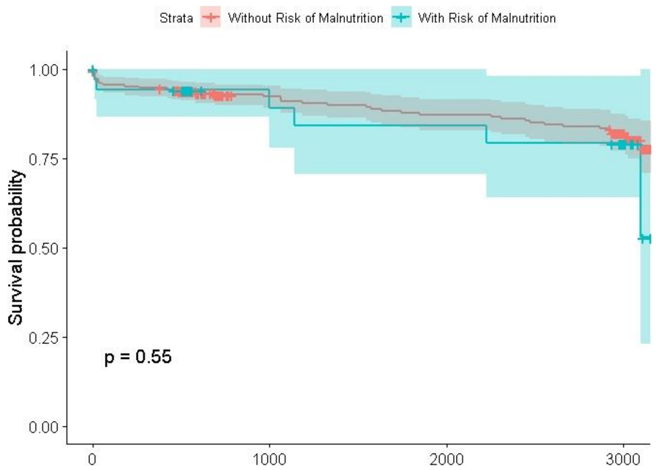
Kaplan Meier curve for 3-year Survival of HVD Cohort patients for MUST



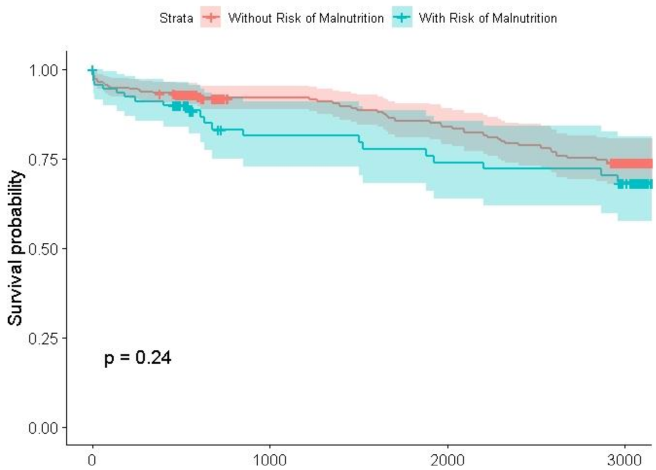
Kaplan Meier Curve for 8-year Survival of CAD Cohort patients for MUST



Kaplan Meier Curve for 8-year Survival of HVD Cohort patients for MUST



Kaplan Meier for Overall Survival of CAD Cohort patients for MUST



Kaplan Meier for Overall Survival of HVD Cohort patients for MUST

6.5 Summary Tables

ROC Table For 3-Year Follow-Up of Patients					
Variable	**Specificity**	**Sensitivity**	**Criterion**	**AUC**	**P**
Mixed cohort					
Albumin	0.718	0.62	42.5	0.688538	0.000009
CRP	0.654	0.618	3.05	0.641123	0.006734
CPB time	0.752	0.462	119	0.644028	0.000124
Aortic cross clamp	0.657	0.508	73.5	0.603612	0.005756
Thrombocytes	0.803	0.349	177.5	0.53664	0.336254
ICU stay	0.932	0.292	5.5	0.56251	0.006186
LVEF	0.677	0.561	57.75	0.601281	0.011288
Age	0.563	0.646	60.5	0.62734	0.000684
CAD cohort					
Albumin	0.775	0.609	42.5	0.715028	0.000567
CRP	0.378	0.923	3.75	0.629121	0.132453
CPB time	0.348	0.931	56.5	0.664054	0.003394
Aortic cross clamp	0.482	0.759	39.5	0.608882	0.051871
Thrombocytes	0.654	0.448	252.5	0.532743	0.559442
ICU stay	0.936	0.31	5.5	0.56395	0.078628
LVEF	0.626	0.75	57.5	0.700056	0.001109
Age	0.558	0.69	60.5	0.638245	0.013485
HVD cohort					
Albumin	0.863	0.444	40.5	0.671475	0.003088
CRP	0.755	0.714	3.75	0.785194	0.000015
CPB time	0.863	0.417	168	0.659135	0.001679
Aortic cross clamp	0.641	0.611	96.5	0.628725	0.011045
Thrombocytes	0.748	0.529	174.5	0.588544	0.08903
ICU stay	0.927	0.278	5.5	0.539035	0.16424
LVEF	0.876	0.182	74.5	0.451487	0.358777
Age	0.676	0.528	62.5	0.62504	0.013517

ROC Table For 8-Year Follow-Up of Patients					
Variable	**Specificity**	**Sensitivity**	**Criterion**	**AUC**	**P**
Mixed cohort					
Albumin	0.73	0.533	42.5	0.646111	0.000007
CRP	0.543	0.61	2.25	0.581491	0.047614
CPB time	0.676	0.542	102.5	0.635046	0.000003
Aortic cross clamp	0.671	0.508	73.5	0.599891	0.000575
Thrombocytes	0.679	0.435	199.5	0.546976	0.109831
ICU stay	0.845	0.288	3.5	0.576681	0.006186
LVEF	0.681	0.472	57.75	0.550405	0.098934
Age	0.684	0.475	62.5	0.601374	0.000472
CAD cohort					
Albumin	0.78	0.514	42.5	0.669156	0.00107
CRP	0.394	0.941	3.75	0.619212	0.119633
CPB time	0.357	0.889	56.5	0.63535	0.003313
Aortic cross clamp	0.487	0.711	39.5	0.599717	0.030477
Thrombocytes	0.656	0.422	252.5	0.50025	0.99629
ICU stay	0.844	0.311	3.5	0.573885	0.078628
LVEF	0.628	0.639	57.5	0.636306	0.007678
Age	0.497	0.733	59.5	0.650849	0.001051
HVD cohort					
Albumin	0.678	0.544	42.5	0.622325	0.003718
CRP	0.582	0.69	2.25	0.65728	0.001303
CPB time	0.552	0.658	111.5	0.605112	0.00525
Aortic cross clamp	0.647	0.507	96.5	0.565248	0.083191
Thrombocytes	0.63	0.529	199.5	0.562554	0.103492
ICU stay	0.905	0.219	4.5	0.547072	0.16424
LVEF	0.733	0.386	57.75	0.534286	0.374066
Age	0.686	0.466	62.5	0.585437	0.023209

ROC table for Overall Survival of patients

Variable	Specificity	Sensitivity	Criterion	AUC	P
Mixed cohort					
Albumin	0.731	0.52	42.5	0.640202	0.00001
CRP	0.495	0.672	1.85	0.585648	0.031529
CPB time	0.728	0.488	111.5	0.632117	0.000003
Aortic cross clamp	0.672	0.504	73.5	0.598173	0.000534
Thrombocytes	0.607	0.5	210.5	0.539333	0.170376
ICU stay	0.847	0.288	3.5	0.571863	0.006186
LVEF	0.681	0.464	57.75	0.548941	0.101394
Age	0.53	0.64	59.5	0.605423	0.000198
CAD cohort					
Albumin	0.78	0.475	42.5	0.650386	0.002072
CRP	0.367	0.905	3.85	0.592063	0.191289
CPB time	0.36	0.882	56.5	0.645595	0.000865
Aortic cross clamp	0.494	0.725	39.5	0.613636	0.009319
Thrombocytes	0.659	0.431	252.5	0.49955	0.992376
ICU stay	0.847	0.314	3.5	0.573147	0.078628
LVEF	0.629	0.61	57.5	0.615854	0.016539
Age	0.506	0.765	59.5	0.664216	0.000169
HVD cohort					
Albumin	0.681	0.552	42.5	0.62707	0.002412
CRP	0.585	0.698	2.25	0.66133	0.000871
CPB time	0.554	0.662	111.5	0.606402	0.004509
Aortic cross clamp	0.649	0.514	96.5	0.568675	0.066809
Thrombocytes	0.628	0.521	199.5	0.555363	0.147415
ICU stay	0.905	0.216	4.5	0.544129	0.16424
LVEF	0.732	0.38	57.75	0.534567	0.367605
Age	0.685	0.459	62.5	0.578821	0.035291

Kaplan - Meier Table		
Variable	**Chi-square Statistic**	**p-value**
3-Year Analysis		
MUST	4.4	0.035
Albumin	25.8	<0.0001
CRP	10.3	0.0013
CPB Time	15.6	<0.0001
Aortic Cross Clamp	7.7	0.0056
ICU Stay	43.8	<0.0001
LVEF	12.7	0.00037
Age	10.4	0.0012
8-Year Analysis		
MUST	2.1	0.15
Albumin	29.6	<0.0001
CRP	5.5	0.019
CPB Time	24.7	<0.0001
Aortic Cross Clamp	15.7	<0.0001
ICU Stay	13.5	0.00024
Age	9.8	0.0017
Overall Survival Analysis		
MUST	2.4	0.12
Albumin	30.2	<0.0001
CRP	5.7	0.017
CPB time	27.7	<0.0001
Aortic Cross Clamp	16.3	<0.0001
ICU stay	14.7	0.00012
Age	12	0.00053

Preoperative variables	Total (n=1187)	Malnutrition risk*, (n=201)	No malnutrition risk, (n=986)
Age (years)	58.832 ± 10.065	58.612 ± 10.419	58.877 ± 9.996
Age >65 years	315 (26.5375)	52(25.871)	263(26.673)
Female Sex	444(37.405)	93(46.269)	351(35.599)
LVEF <35%	37(3.117)	9(4.478)	28(2.839)
NYHA class			
0	1(0.0842)	1(0.498)	0(0)
I	24(2.0219)	4(1.990)	20(2.0284)
II	234(19.7136)	25(12.4378)	209(21.1968)
III	895(75.4002)	162(80.5970)	733(74.3408)
IV	33(2.7801)	9(4.4776)	24(2.4341)
Logistic EuroScore	5.4304 ± 5.5993	6.7597 ± 6.4551	5.1798 ± 5.3907
Primary Diagnosis			
Coronary Artery Disease	579 (48.778)	50 (24.876)	529 (53.651)
Mitral Stenosis	183(15.417)	55(27.363)	128(12.982)
Mitral Insufficiency	134(11.289)	41(20.398)	93(9.432)
Aortic Stenosis	194(16.344)	33(16.418)	161(16.329)
Aortic Insufficiency	73(6.150)	18(8.955)	55(5.578)
Tricuspid Insufficiency	23(1.938)	4(1.990)	19(1.927)
Pulmonary Artery Stenosis	1(0.0842)	0(0)	1(0.1014)
BMI, kg/m^2	28.944 ± 5.222	26.083 ± 5.827	29.529 ± 4.891

6.6 Cox Proportional Hazards Model

Although, the main objective of this project is to check if malnutrition has a significant effect on the survival of patients who have had cardiac surgery, we analyse different variables to ensure that we are getting accurate results. The sample could have patients with underlying conditions, who also are malnourished, such that these conditions affect their survival rather than malnourishment. To avoid these errors, we analyse several variables independently to explore the significant predictors of survival.

Receiver Operating Characteristic (ROC) Analysis was performed for the variables, and those having p-value less than 0.05 and variables judged to be clinically significant, were further analysed using Cox Multivariate Regression, by stepwise backward Wald selection. The results are presented as Hazard Ratios of the predictors with a 95% Confidence Interval, in the following table:

	Univariate Models				Full Mixed Cox Model				Optimal Mixed Cox Model (Backward Wald selection)				Optimal Mixed Cox Model*			
Characteristics	*HR*	*95% CI*		*p*	*HR*	*95% CI*		*p*	*HR*	*95% CI*		*p*	*HR*	*95% CI*		*p*
3-Year Follow-Up Cox Regression Models																
Logistic EuroSCORE	1.06439	1.039	1.09	< 0.001	1.01759	0.96	1.0786	0.5574					1.03512	0.9813	1.0919	0.20518
MUST > 0	1.7953	1.032	3.122	0.0382	1.45839	0.63612	3.3436	0.3727								
CPB > 119	2.5789	1.583	4.2	0.000141	4.19172	1.06689	16.4688	0.0401					2.08438	0.9851	4.4103	0.05477
CRP > 3.05	2.9402	1.472	5.874	0.00225	2.66613	1.20931	5.8779	0.0151	2.5469	1.1838	5.4794	0.0168				
Albumin > 42.5	0.2532	0.143	0.4483	< 0.001	0.40182	0.17814	0.9064	0.028	0.3485	0.1593	0.7623	0.00177	0.30986	0.1445	0.6646	0.00262
Age > 60.5	2.2623	1.361	3.762	0.00165	1.13169	0.4973	2.5753	0.7681								
ACC > 73.5	1.9651	1.208	3.196	0.00648	0.34927	0.09204	1.3254	0.1221								
ICU > 5.5	1.042	1.029	1.055	<0.001	2.22814	0.8333	5.9578	0.1104	3.0967	1.2617	7.6006	0.0136				
8-Year Follow-Up Cox Regression Models																
Logistic EuroSCORE	1.053917	1.035	1.073	< 0.001	1.03274	0.9913	1.076	0.1235	1.0397	1.0012	1.0797	0.043	1.0397	1.0012	1.0797	0.043
MUST > 0	1.3801	0.8874	2.146	0.153	1.12475	0.5972	2.118	0.7159								
CPB > 102.5	2.437	1.696	3.502	< 0.001	2.10211	0.86	5.138	0.1033	1.7976	1.0259	3.1497	0.0404	1.7976	1.0259	3.1497	0.0404
CRP > 2.25	1.851	1.097	3.124	0.0212	1.58252	0.8962	2.794	0.1136								
Albumin > 42.5	0.3374	0.2239	0.5084	< 0.001	0.59506	0.3286	1.078	0.0866	0.5232	0.2973	0.9208	0.0247	0.5232	0.2973	0.9208	0.0247
Age > 62.5	2.0325	1.25	3.305	0.00426	1.02238	0.5652	1.849	0.9416								
ACC > 73.5	2.0431	1.424	2.932	0.000105	0.757	0.3181	1.801	0.5291								
ICU > 3.5	1.043	1.031	1.055	<0.001	1.45807	0.7647	2.78	0.2521								
Overall Survival Cox Regression Models																
Logistic EuroSCORE	1.052065	1.033	1.071	<0.001	1.02723	0.9857	1.0705	0.20161					1.03799	0.9984	1.0791	0.05996
MUST > 0	1.3986	0.9133	2.142	0.123	1.18239	0.6483	2.1566	0.5848								
CPB > 111.5	2.4921	1.753	3.542	<0.001	3.65789	1.541	8.6828	0.00328	2.6169	1.5488	4.4214	0.000324	2.39331	1.4121	4.0563	0.00119
CRP > 1.85	1.8738	1.112	3.158	0.0184	1.61631	0.9129	2.8617	0.09949	1.7989	1.034	3.1294	0.037666				
Albumin > 42.5	0.3443	0.2312	0.5125	<0.001	0.52591	0.3019	0.9162	0.02327	0.4604	0.2722	0.7786	0.003811	0.48841	0.2849	0.8374	0.00918
Age > 59.5	2.0267	1.212	3.388	0.00704	1.23007	0.696	2.1738	0.47601								
ACC > 73.5	2.0329	1.431	2.888	<0.001	0.56398	0.242	1.3142	0.18453								
ICU > 3.5	1.043	1.031	1.055	<0.001	1.12937	0.5978	2.1337	0.70781								

*There are two Optimal mixed Cox Models. The second set of Cox Models are the models shown in the paper we are trying to recreate. However, some of the variables used in these models had p-value greater than 0.05. Hence, we have written both our result and the given result in the paper.

6.7 Linear Regression Models

Taking into account that serum albumin level can be affected by C-Reactive Protein level, MUST, and the New York Heart Association (NYHA) class, we investigate their relation using regression analysis.

We used two methods:

1. **<u>Remove NULL observations:</u>**

   - CRP and Albumin: $r^2 = 0.0486$, $r = -0.22$, $p < 0.0001$
   - MUST and Albumin: $r^2 = 0.0245$, $r = -0.156$, $p < 0.0001$
   - NYHA and Albumin: $r^2 = 0.0134$, $r = -0.116$, $p = 0.0003$

2. **<u>Replace NULL observations by mean:</u>**

   - CRP and Albumin: $r^2 = 0.0219$, $r = -0.148$, $p < 0.0001$
   - MUST and Albumin: $r^2 = 0.0201$, $r = -0.142$, $p < 0.0001$
   - NYHA and Albumin: $r^2 = 0.0105$, $r = -0.102$, $p = 0.0004$

7 Extended Analysis

In this section, we mention a few extra analyses we have done:

- Extension of ROC Analysis to overall survival rather than restricting it to 8-year survival.
- Extension of Kaplan-Meier Curves to overall survival for all predictor variables.
- Extension of Cox Univariate Models to all significant predictors of survival.
- Extension of Cox Models to overall survival.
- Extension of 8-year and overall survival analysis for CAD and HVD Cohort patients.

We now try to extend our analysis by testing if our Cox Proportional Hazard models are valid or not.

7.1 Cox PH Models vs Kaplan-Meier

As we already had Kaplan-Meier curves, it seems unnecessary to perform Cox Regression. However, the Cox PH models has an advantage over Kaplan-Meier Curves. Getting Kaplan-Meier curves for sample divided into more than two groups is a very inefficient and time-consuming process. However, we can do this in an efficient way using Cox Models. Thus, we perform Cox Regression Analysis.

However, in section 4.2.2, we had stated that the Cox Proportional Hazards models assume that the hazard ratio is constant over time. Hence, we want to check if our models are accurate up to a significant level or not.

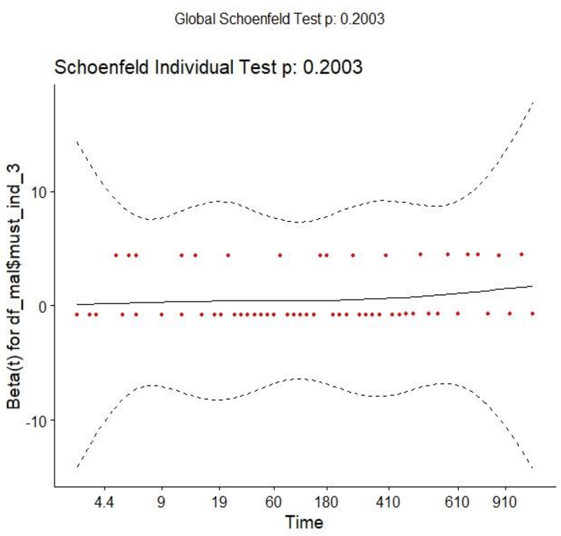
7.2 Schoenfeld Residual Tests

To check our assumption of proportional hazards, we use the Schoenfeld Residual Test. We do not discuss the Schoenfeld and Scaled Schoenfeld Residuals; however, we do state the fact that these residuals are not defined for censored observations. Instead of delving into the mathematical details, we test the proportional hazards assumption graphically.

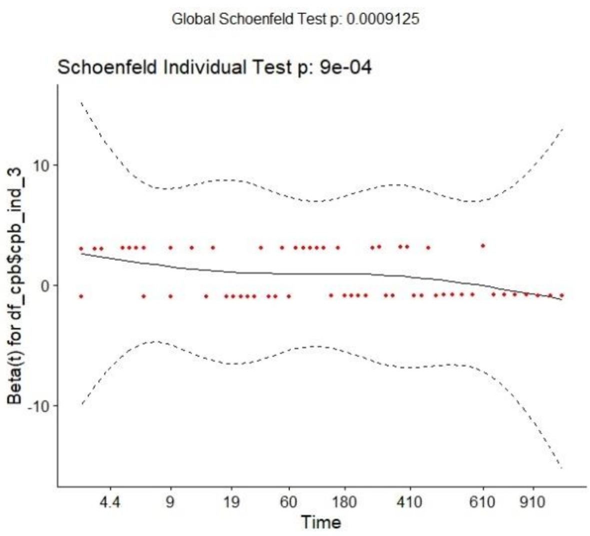
We plot a graph where the y-axis represents the log of the hazard ratio and x-axis is for time. Similar to linear regression, we get a 'curve' which best represents the data. Our null hypothesis is that the hazard ratio is constant throughout, which means that log of the hazard ratio should also be a constant. Thus, the curve we get should have a slope close to 0. The points represent scaled Schoenfeld Residuals.

The plot also contains a 95% Confidence Interval, and a p-value. We do not want our null hypothesis to be rejected, and thus, we want this p-value to be greater than or equal to 0.05.

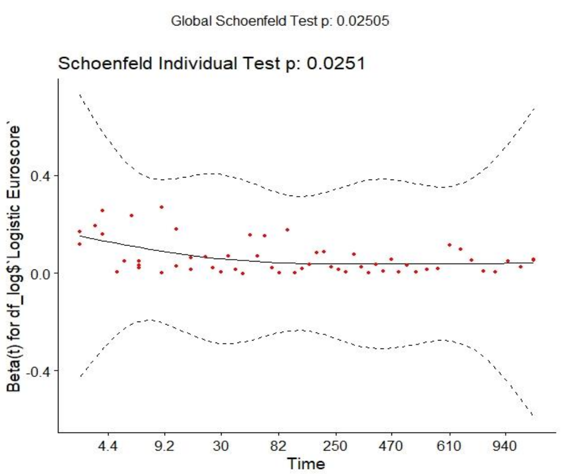
7.3 3-year Plots



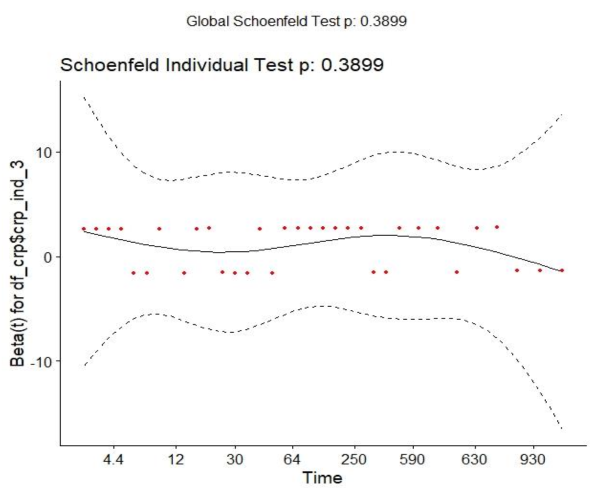
3-Year Malnutrition



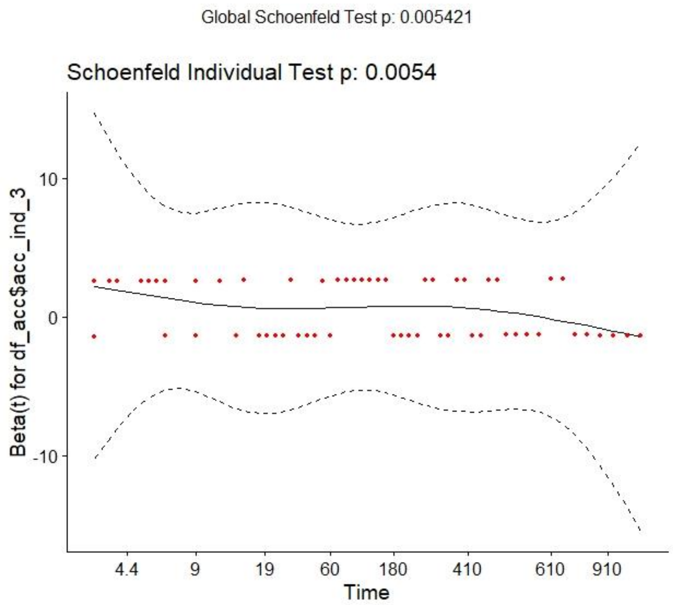
3 -Year Cardiopulmonary Bypass Time



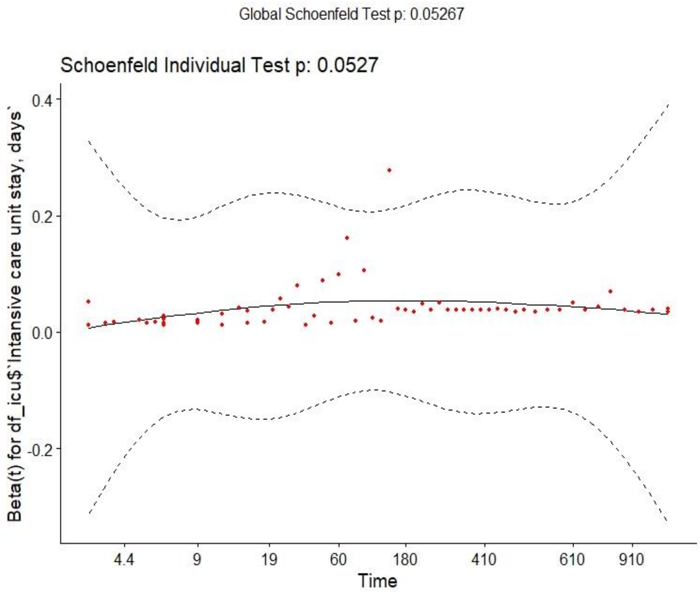
3-Year Logistic EuroSCORE



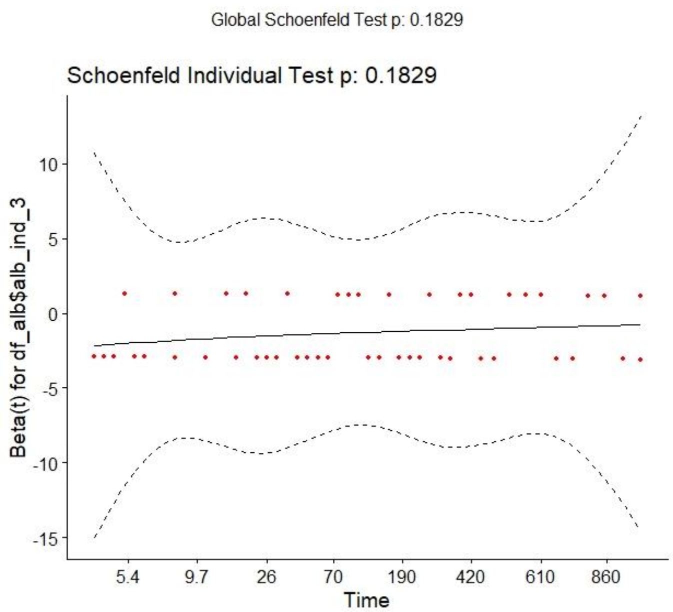
3-Year C-Reactive Protein Level



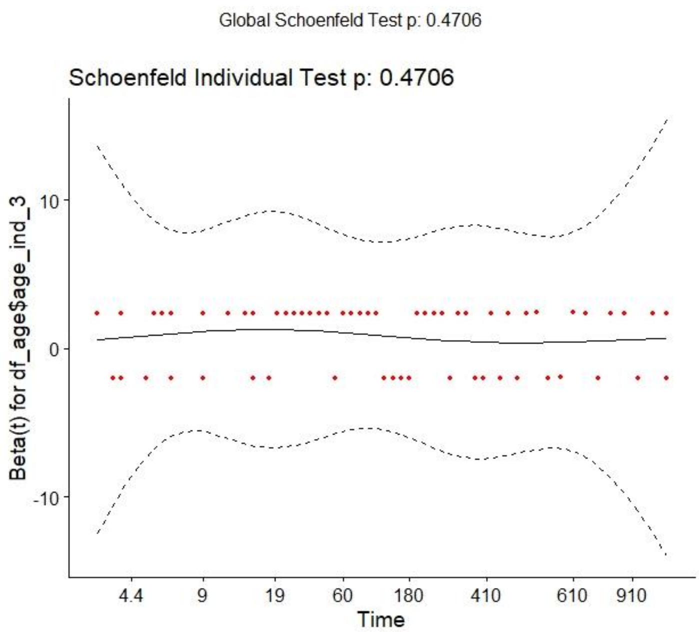
3-Year Aortic Cross Clamp Time



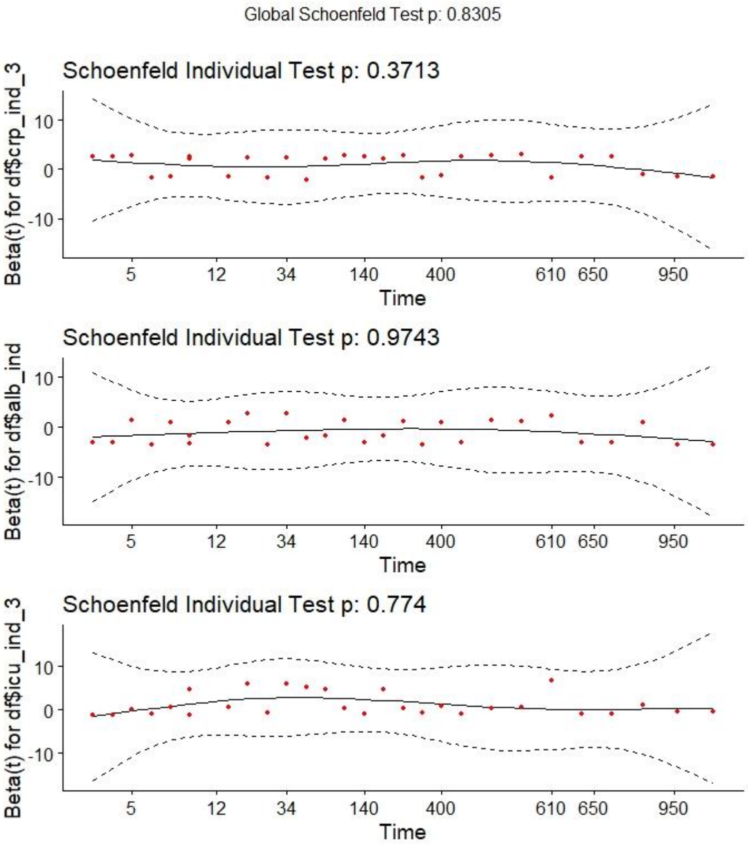
3-year ICU stay



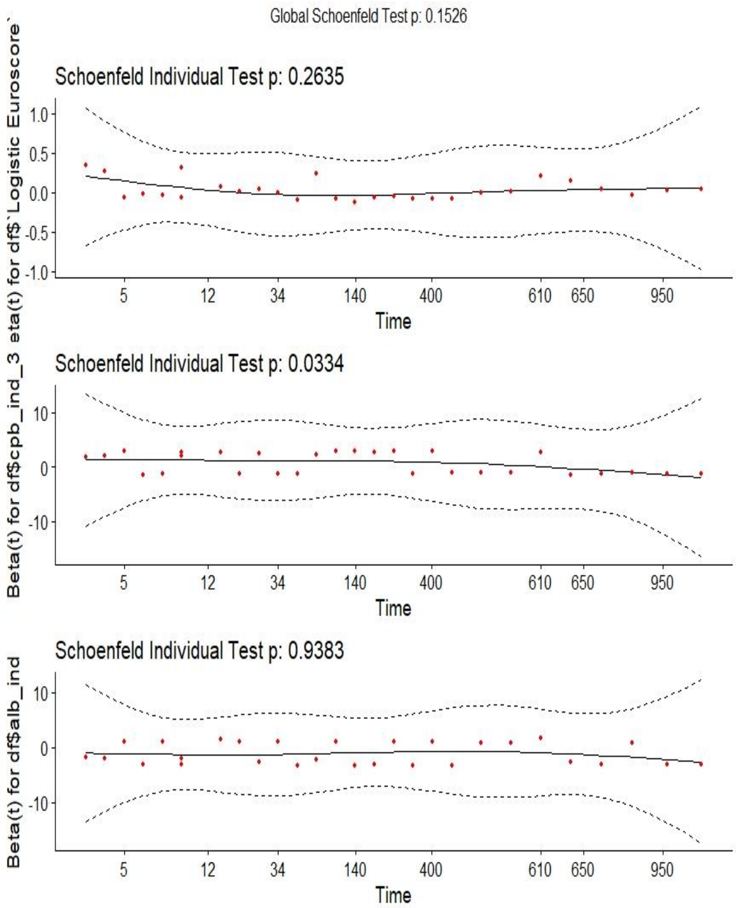
3-Year Preoperative Albumin level



3-Year Age

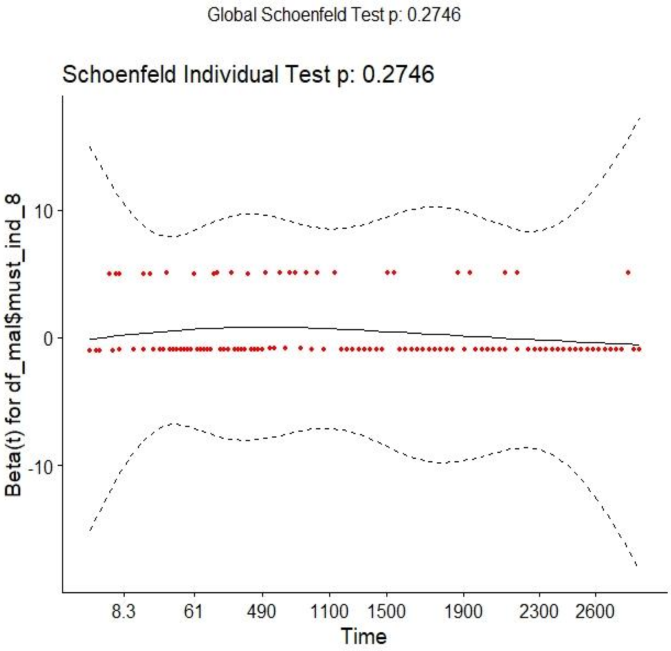


3-year optimal models

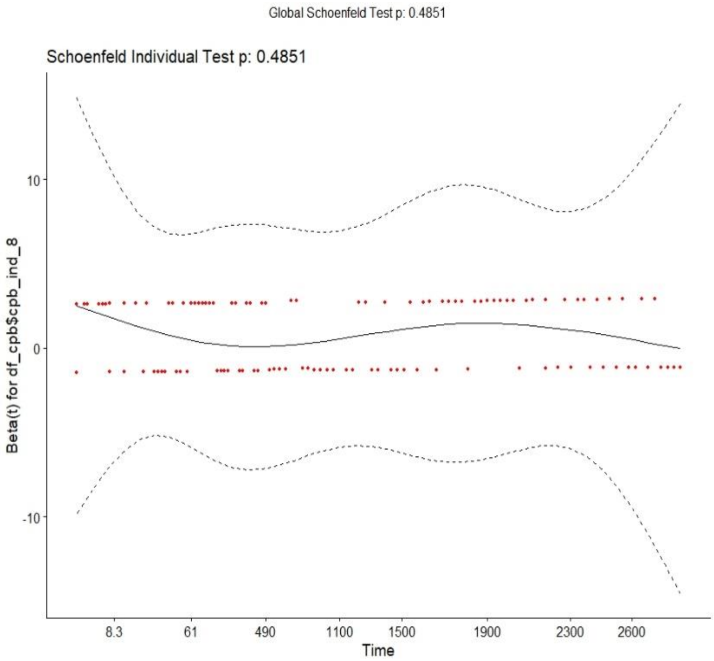


3-Year Optimal Model (in reference paper)

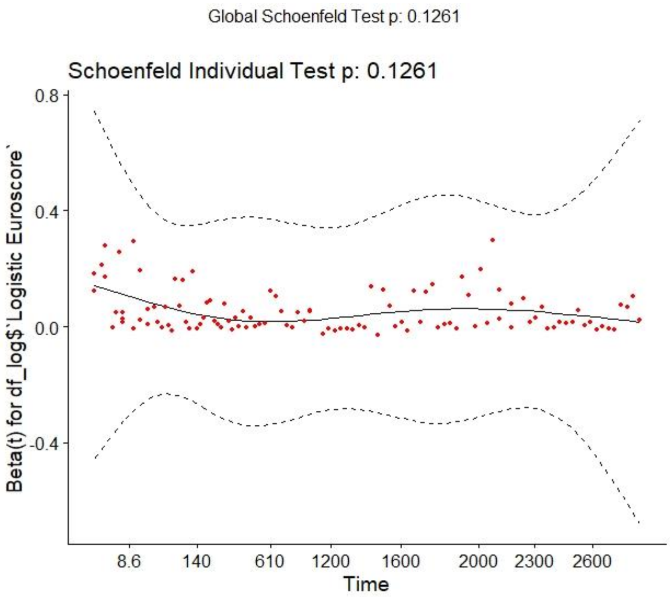
7.4 8-year Plots



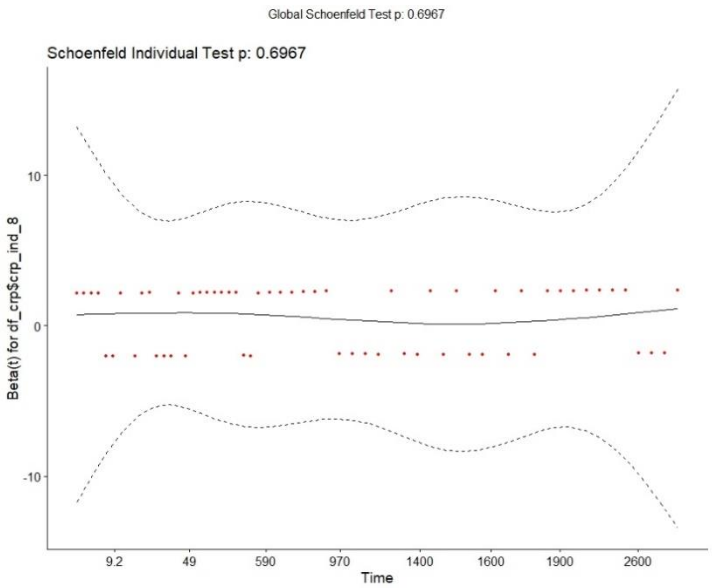
8-Year Malnutrition



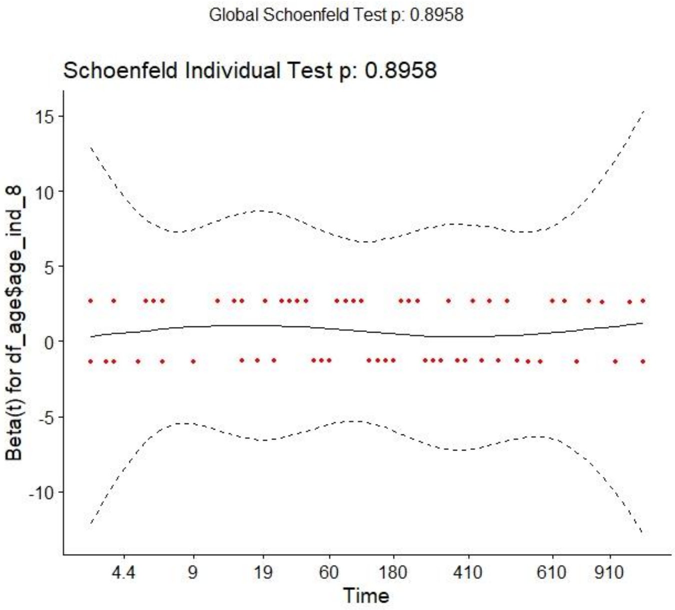
8-Year Cardiopulmonary Bypass Time



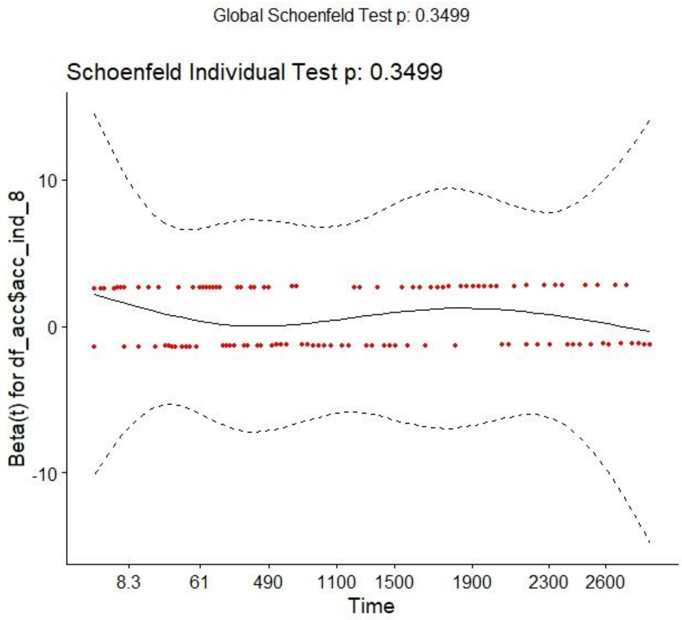
8-Year Logistic EuroSCORE



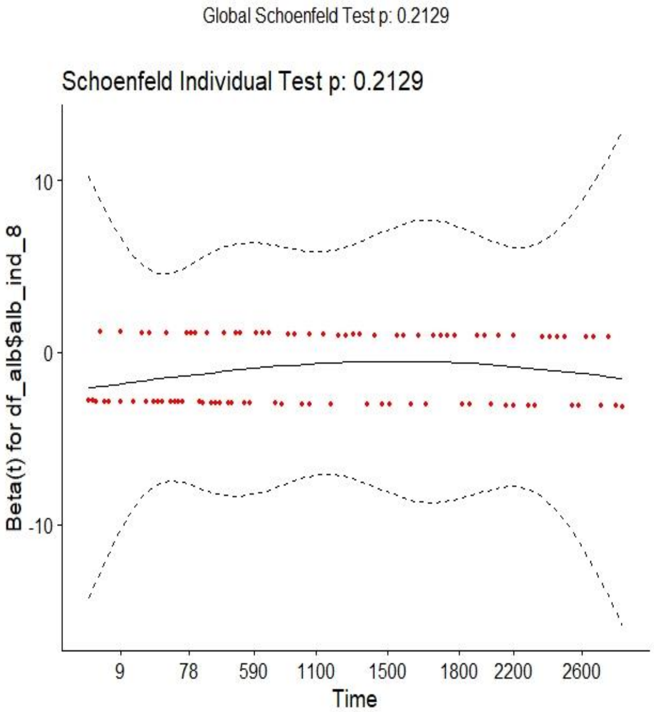
8-Year C-Reactive Protein Level



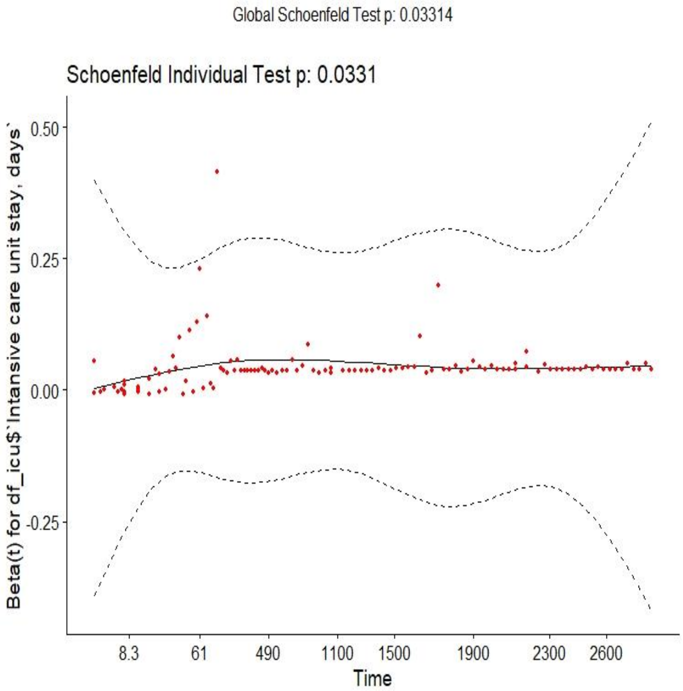
8-Year Age



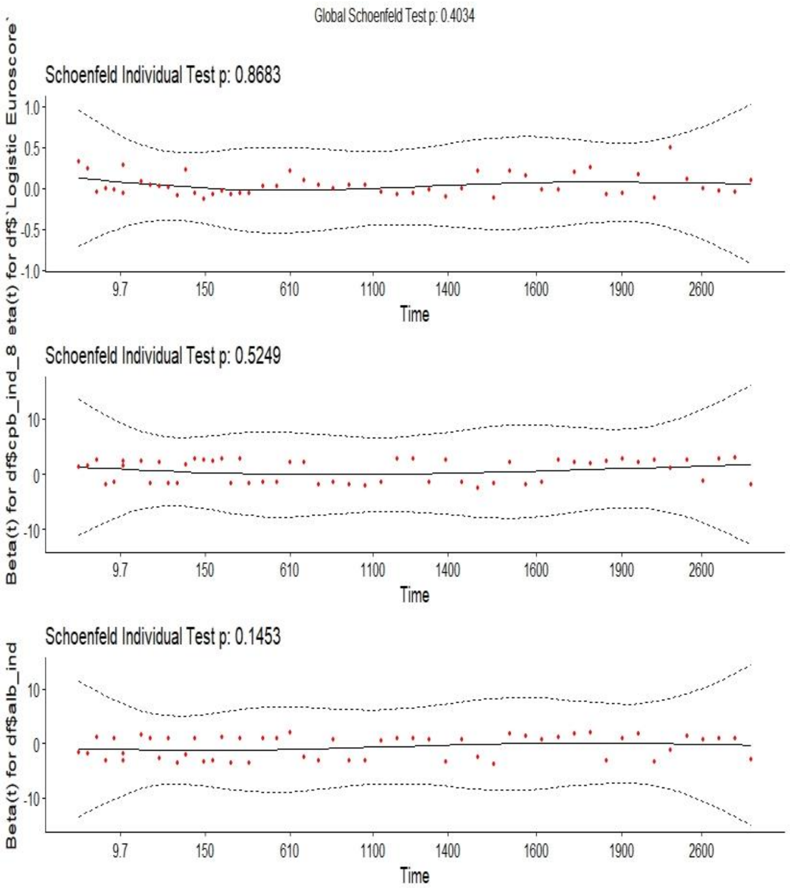
8-Year Aortic Cross Clamp Time



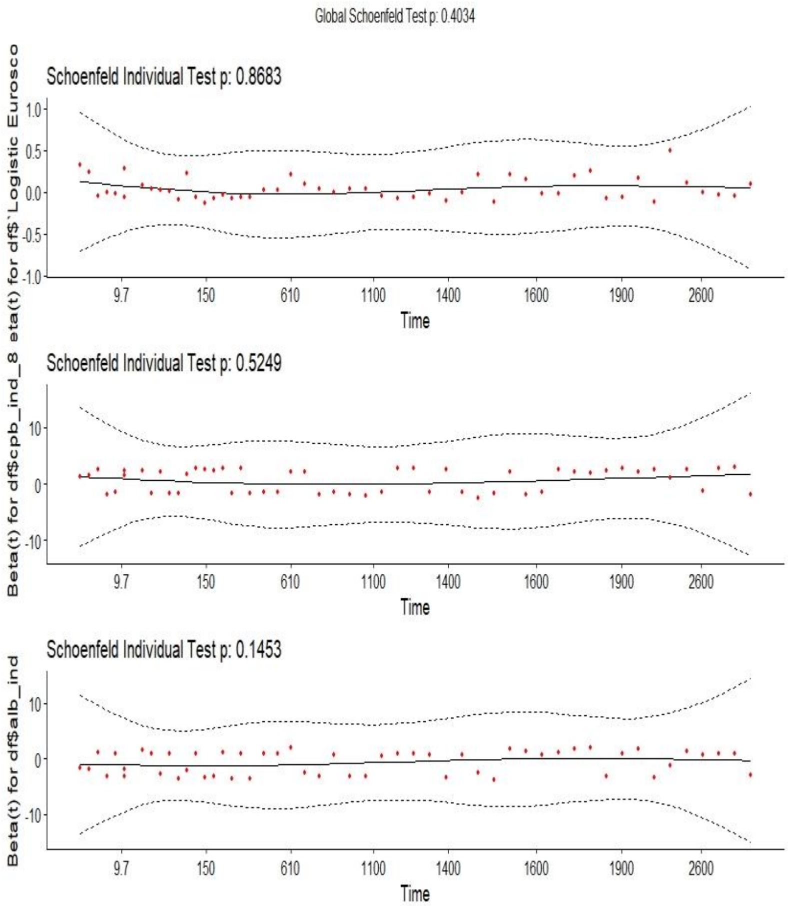
8-Year Preoperative Albumin level



8-year ICU stay

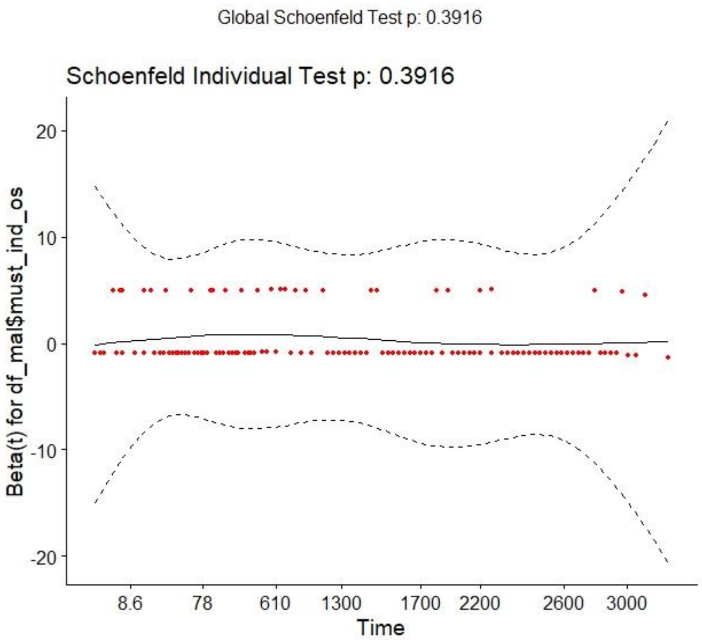


8-Year Optimal Model

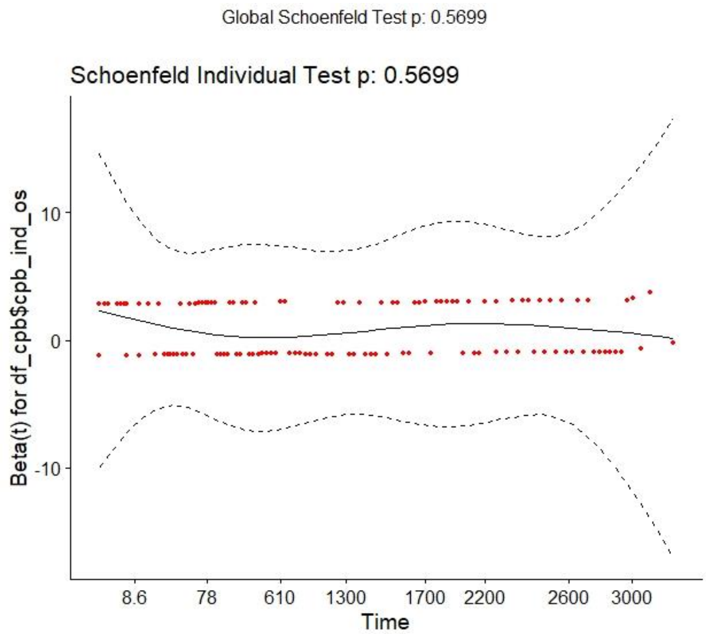


8-Year Optimal Model (in reference paper)

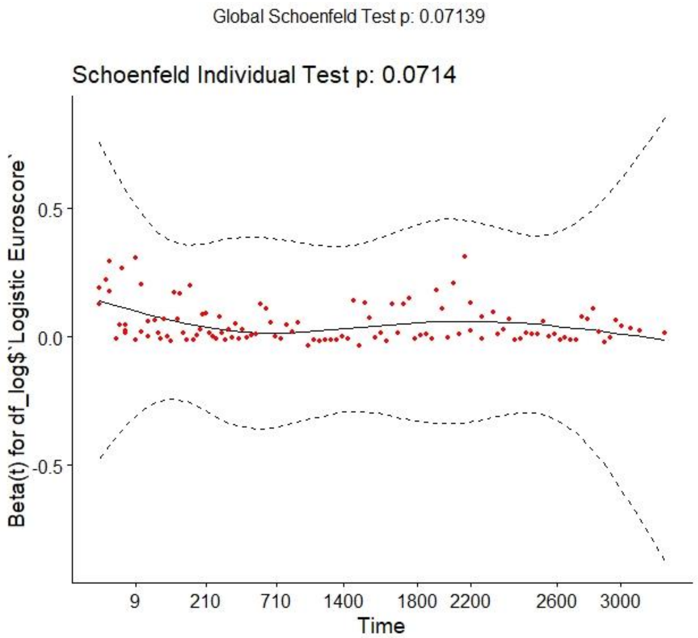
7.5 Overall Survival Plots



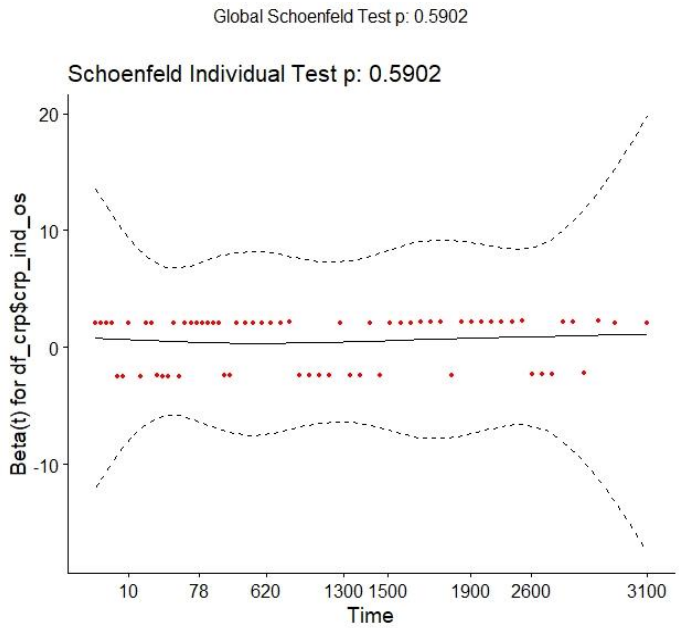
Overall Survival Malnutrition



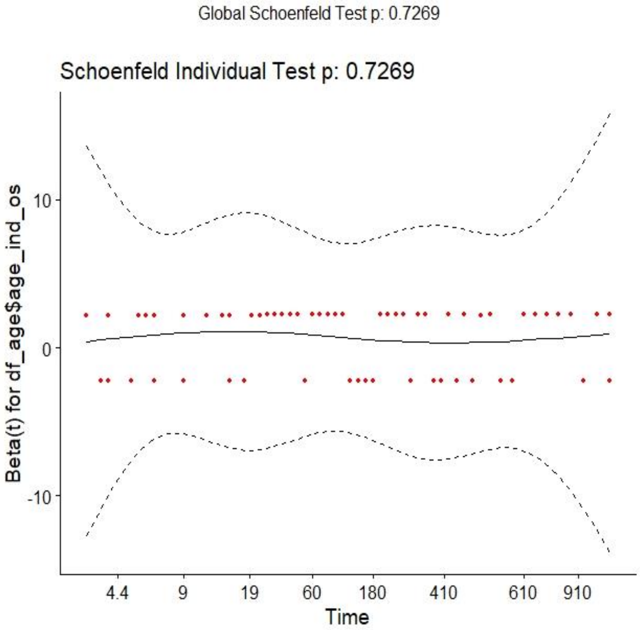
Overall Survival Cardiopulmonary Bypass Time



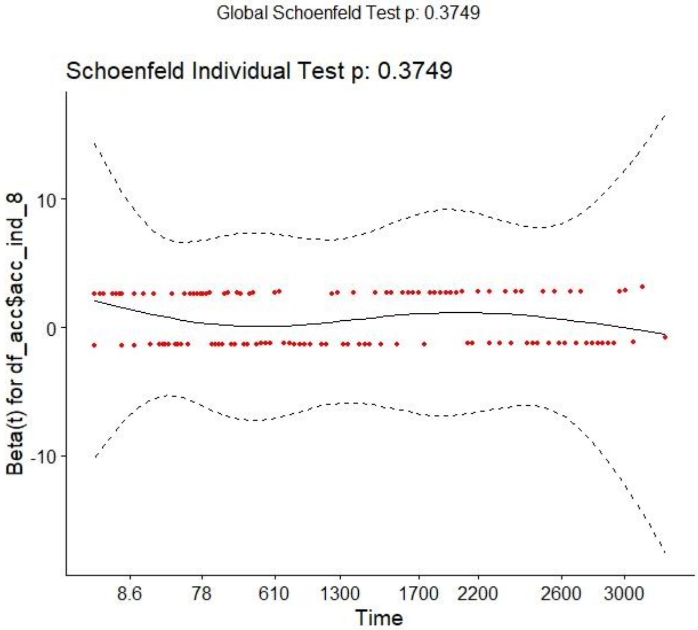
Overall Survival Logistic EuroSCORE



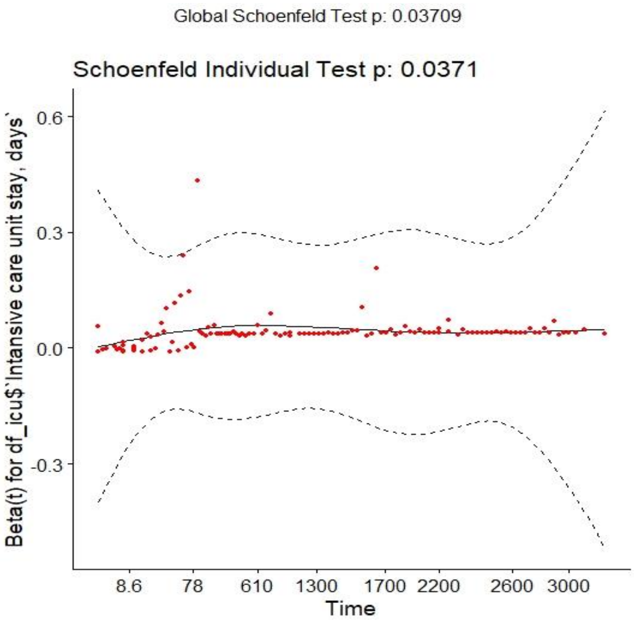
Overall Survival C-Reactive Protein Level



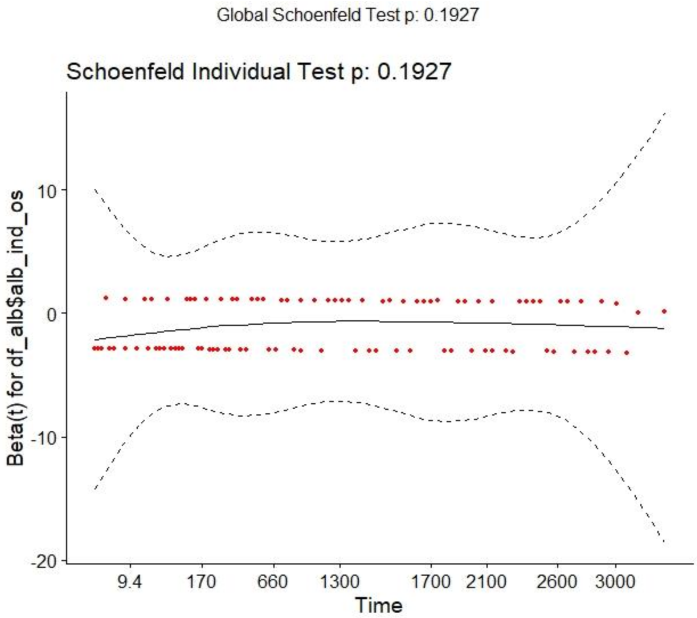
Overall Survival Age



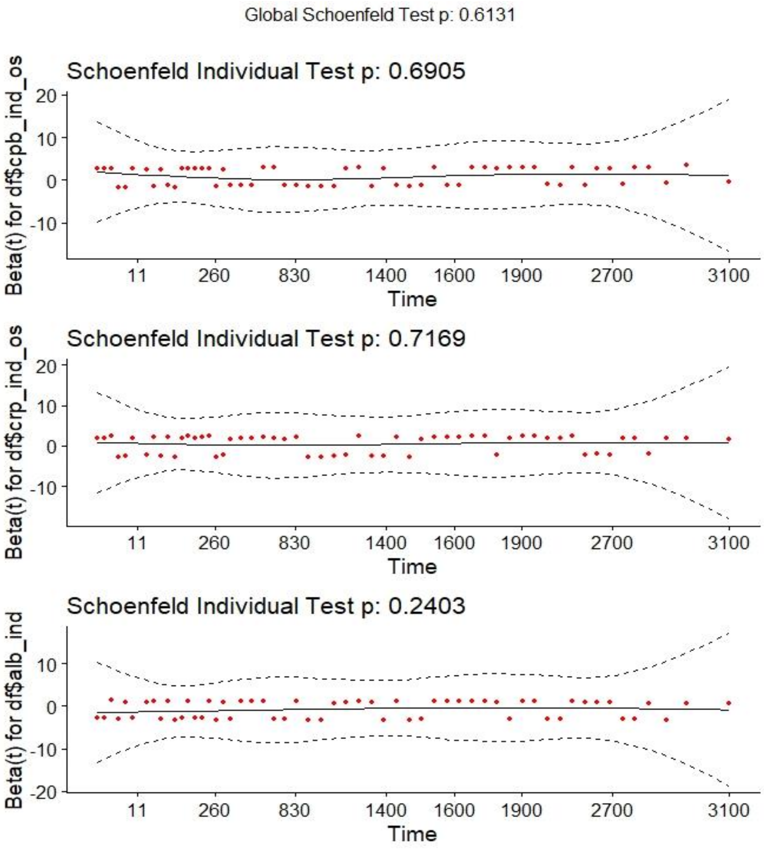
Overall Survival Aortic Cross Clamp Time



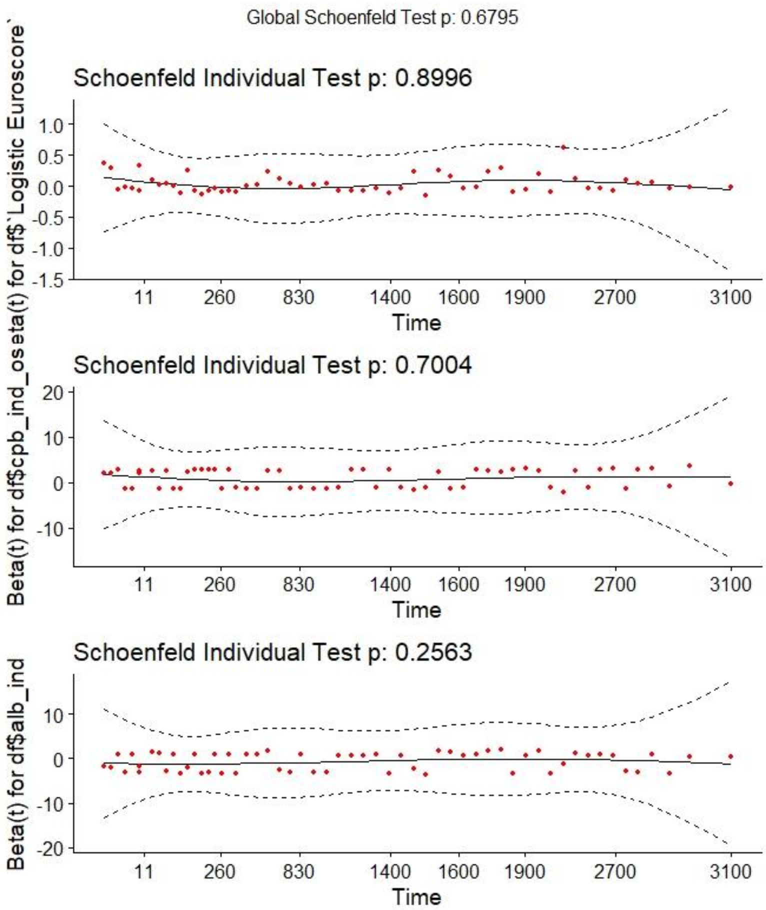
OS for ICU stay



Overall Survival Preoperative Albumin level



Overall Survival Optimal Model



Overall Survival Optimal Model (in reference paper)

7.6 Results

The results obtained from 7.3, 7.4, and 7.5 are the following:

- For 3-year survival, only the univariate Cox models for 'Malnutrion', 'CRP', 'Age', 'ICU Stay', and 'Albumin' can be considered valid. We reject the null hypothesis for the remaining predictor variables.
- For 3- year survival, all multivariate models can be considered valid.
- For 8-year survival, all Cox models can be considered valid except the univariate Cox model for 'ICU Stay'.
- For Overall Survival, all Cox models can be considered valid except the univariate Cox model for 'ICU Stay'.

8 Conclusion

After all analyses, we can conclude that:

- Malnutrition is associated with worse 3-year survival outcome after cardiac surgery.
- Significant differences in survival disappear over time.
- Preoperative Albumin level with a threshold of 42 g/L predicts overall survival in patients.

9 Limitations

There are several limitations to this study:

- 449 of the 1187 patients were lost to follow-up after hospital discharge. However, as the prevalence of censored cases was almost equal among the malnourished and non-malnourished patients. Thus, we can assume that "Malnutrition" itself does not increase the likelihood of follow-up loss.
- Surgical risk was evaluated using Logistic EuroSCORE, which has now been replaced with more sensitive EuroSCORE.
- Survival is the only outcome parameter of this study. Measure of quality of life, hospitalization, and measure of cerebrovascular complications should also be considered.

10 Discrepancies

There were several discrepancies found within the paper, and between obtained and given results:

- In the two papers provided, the values found in Cox Models were different in each paper.
- Under "8-year survival curves", the paper has overall survival curves in most places.
- The outputs from regression analysis have replaced the missing values with mean for relation between Preoperative Albumin level and MUST. However, for relation between Albumin

level and CRP, and that between Albumin level and NYHA Class, values given in the paper are found by removing the missing values.

11 R Packages

The R Packages used in this project are:

- readxl
- survival
- survminer
- pROC

12 References

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- “Survminer Package”: https://www.rdocumentation.org/packages/survminer/versions/0.4.9
- “On distribution-free tests for equality of survival distributions”
    - BY ROBERT E. TARONE AND JAMES WARE
- “Statistics review 12: Survival analysis”
    - Viv Bewick1, Liz Cheek1 and Jonathan Ball2
- Cox Model Assumptions http://www.sthda.com/english/wiki/cox-model-assumptions