Clinical Implications of a Positive Prostate Cancer Screen in Patients undergoing Cardiac Transplant Evaluation

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Abstract

Background

Screening the general population for prostate cancer with prostate specific antigen (PSA) testing continues to be controversial. Patients with advanced heart failure undergoing evaluation for cardiac transplantation are often requested to undergo prostate cancer screening, with guiding evidence generated from the general population. The clinical implications of a positive prostate cancer screening result in this patient population has not been determined.

Methods

A retrospective cohort study was performed on all men that were referred to a cardiac transplant center between January, 2000 and December, 2015. Patients were classified as having either a 'positive screen' (PSA ≥ 4ng/ml) or a 'negative screen' (PSA < 4ng/ml) at the point of initial evaluation. The primary outcome of time to listing for cardiac transplant (days) was calculated from the date of referral to the date of listing. A multivariable Cox proportional hazards model was developed to assess the association between a positive prostate cancer screening result and listing for cardiac transplantation. For patients with a positive PSA screen individual chart review was performed to ascertain the subsequent diagnostic evaluation and identify patients with a diagnosis of prostate cancer.

Results

Among the 704 patients included in our analysis, 66 men (9.4%) had a positive prostate cancer screening result. Men with a positive prostate cancer screen were approximately 4 years older (58.5 ± 8.7 years vs 54.1 ± 11.2 years), more likely to have a diagnosis of ischemic cardiomyopathy (74% vs 53%) and to be on mechanical support at the point of

transplant evaluation (61% vs 16%). After adjusting for age, renal function, clinical status at evaluation, history of COPD and the year of evaluation, patients with a positive prostate cancer screen had a 42% reduced likelihood for progressing to cardiac transplant listing compared to those with a negative screen (HR 0.58, 95%CI 0.38-0.91). 4 patients with a positive prostate cancer screen had a confirmed diagnosis of prostate cancer during the evaluation process, representing a positive predictive value of PSA screening of 6.1% and cancer detection rate of 0.6%.

Conclusion

Serum PSA performs poorly as a screening modality for prostate cancer in men undergoing a cardiac transplant evaluation, especially in those who are acutely unwell at the point of evaluation. Patients with a positive screen have more adverse clinical characteristics in addition to a reduced likelihood for progressing to listing for cardiac transplant. Given the unique nature of the decision to perform prostate cancer screening in this population, an individualized approach in particular with regards to timing of PSA screening should be encouraged.

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List of Abbreviations

Body Mass Index	BMI
Chronic Obstructive Pulmonary Disease	COPD
Congestive Heart Failure	HF
Ejection Fraction	EF
Glomerular Filtration Rate	GFR
Lactate Dehydrogenase	LDH
Likelihood Ratio Test	LRT
Organ Procurement and Transplant Network	OPTN
Prostate Specific Antigen	PSA
Thyroid Stimulating Hormone	TSH
U.S. Preventive Services Task Force	USPSTF
United Network of Organ Sharing	UNOS
Variance Inflation Factor	VIF

Chapter 1: Introduction

Heart failure (HF) currently affects 5.8 million adult men and women in the United States and its prevalence is expected to increase to more than 8 million by 2030[1,2]. HF is associated with significant morbidity and the 1-year mortality approaches 50% to 80% in patients with advanced disease[3,4]. Cardiac transplantation is the gold standard treatment for eligible patients and offers significant improvement in both quality of life and long-term survival[4,5]. Since the first cardiac transplant procedure in 1967, significant advances in surgical techniques, immunosuppressive regimens and immune-surveillance have resulted in a median half-life of 13 years among those who survive their first year following transplant[3,5,6]. These advances have also facilitated an expansion in the referral criteria for consideration of a cardiac transplant and there are increasingly favorable outcomes in patients with pre-existing co-morbidities[5,7]. The paucity of donors continues to be the main limiting factor for transplantation[8]. Thus, the appropriate utilization of precious resources places greater emphasis on transplant physicians to correctly apply the strict inclusion and exclusion criteria for cardiac transplant listing[7,9]. The listing criteria represent an international consensus and provide guidance to transplant centers designed to help further improve the long-term survival of the donor heart.

The presence of an active neoplasm is an absolute contraindication to cardiac transplantation[7,9]. In order to identify a pre-existing malignancy in a patient referred for a cardiac transplant evaluation, most transplant centers adhere to strict screening practices, with the implementation often being derived from guidelines targeting the general population[10–13]. The decision to screen for a malignancy is complex and involves balancing the delicate trade-offs between the benefits (early detection to avoid the

morbidity and mortality from advanced cancer) with the harms (false alarms, overdiagnosis and overtreatment)[14]. Unlike the decision-making process required when discussing screening options with the general population, a transplant physician has a unique dichotomy of care; to the patient with end stage organ failure undergoing evaluation and to the unknown individual from whom the donor heart is received. Outside the setting of a transplant evaluation, patients with end-stage heart failure, who are most likely to die from the severity of their underlying condition, the harms of screening would generally outweigh the benefits. The decision framework is further complicated by the increased death rates in de-novo malignancies post-transplant[15–17] and de-novo malignancy being the leading cause of death in those who survive more than 5 years post cardiac transplant[6]. When balancing all these factors in the shared decision-making process the specifics of the screening modality, the characteristics of the malignancy and the population screened matter greatly.

Prostate-specific antigen (PSA) was initially isolated from the prostatic epithelium in 1979[18] and was subsequently developed as a serum biomarker useful in the staging and management of prostatic neoplasm[19–21]. Following the completion of a number of large observational clinical studies, the utility of a PSA finding for the detection of prostate cancer at a cut-off value of 4ng/ml was highlighted as an effective screening modality for the general population[22,23]. At the time (and currently), prostate cancer was the most common malignancy diagnosed in men[24]. Inasmuch, the demonstrable improvement in screening yield through the use of PSA over a digital rectal examination[22], led to this screening modality to be rapidly incorporated into routine clinical practice[25]. However, with greater experience and appreciation that PSA findings are not sensitive for prostate cancer, the considerable harm associated with the invasive

investigations and the indolent nature of prostate cancer, has led to increasing controversy on the use of PSA as a screening tool[26].

To address these and related issues, two large randomized controlled trials the Prostate, Lung, Colorectal and Ovarian (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC) were conducted[27–29]. The PLCO included 76,693 men aged between 55 and 74 years at 10 US centers[27], whereas the ERSPC included 162,243 men age between 50 and 69 years old at multiple centers in 7 European countries[28]. Despite the trials conflicting results in terms of the benefits of screening on reduction in mortality from prostate cancer, they concurred in the high rates of false alarms[28,30,31]. False positive results from benign conditions such as benign prostatic hyperplasia (BPH) are a well appreciated phenomenon[26], however, values for PSA are also elevated in the setting of cardiogenic shock, coronary revascularization and cardio-pulmonary resuscitation[32–34], which could further limit the utility of prostate cancer screening during the transplant evaluation process.

In 2012, the U.S. Preventive Services Task Force (USPSTF) recommended against population based PSA screening for asymptomatic men[10], however with the ongoing uncertainty on the possible benefits in asymptomatic men aged between 55 and 69 years a shared decision making approach is now advocated in 2017[35]. This uncertainty in guideline development reflects the lack of conclusive evidence with regards to the benefits of PSA screening on long-term survival and the significant morbidity associated with prostate biopsies and treatment[27]. The American Cancer Society strongly recommends an individualized patient-driven approach, where the risks and benefits of screening are clearly outlined[36]. Empiric evidence is key to guiding the decision-making process. While the utility of PSA screening has been assessed in

patients who have been evaluated for a renal transplant[37], no studies to date have evaluated the clinical impact of prostate cancer screening with PSA in cardiac transplant candidates. Since approximately 1 in 8 patients who are on a cardiac transplant waiting list die annually[4], any delay to listing and possible transplant can have significant adverse consequences. Using data from patients evaluated for cardiac transplant at a tertiary center, the objective of this study is to assess the clinical impact of prostate cancer screening on listing for cardiac transplant.

Chapter 2: Methods

2.1: Data Source and Time Point Definitions

Following approval from the Tufts Medical Center (TMC) Institutional Review Board (IRB), we performed a retrospective review of information contained in a comprehensive database of all patients that had a cardiac transplant evaluation at TMC between January, 2000 to December, 2015, with follow-up information available to March 31st, 2017. Given the low risk retrospective nature of this study, the expedited IRB review granted a waiver of consent and waiver of Health Insurance Probability and Accountability Act (HIPAA) research authorization. In accordance with the Organ Procurement and Transplantation (OPTN) and United Network of Organ Sharing (UNOS) requirements[38], TMC maintains a comprehensive database of all patients that were referred for a cardiac transplant evaluation that was used to identify the patients.

A standardized data abstraction template was created on the Research Electronic Data Capture (REDCap) web application (Table 5.1). For all patients, socio-demographics and clinical characteristics were collected using a review of the TMC Cardiac Transplant Database and electronic medical records.

The primary study outcome of time to transplant listing was calculated from the date of evaluation to the date of listing as specified in the transplant database. Patients were censored if they failed to reach transplant listing status by March 31st 2017. Censoring time was also calculated as the time from the date of transplant evaluation to censoring. Censoring occurred for patients at the date of death prior to listing, date of the formal 'not listed' decision letter or at the date of discharge in those patients where the

decision not to list occurred as an inpatient and communicated in the discharge summary. Patients that were lost to follow up were classified as 'Not Listed' at the time of their last clinical encounter.

2.2: Cohort Definition and Predictor Variables

Baseline demographic and clinical characteristics were recorded at the point of transplant evaluation as specified by the Cardiac Transplant Database. Patients were excluded if they were female, evaluated for destination ventricular assist device only, had a prior history of treated prostate cancer, age less than 18, or if they did not undergo prostate cancer screening. In keeping with clinical practice at TMC and published guidelines,[27,39] patients with a PSA value greater than or equal to 4ng/ml were classified as having a 'positive screen' and those with a value below 4ng/ml were classified as having a 'negative screen'.

Using a priori rationale on possible confounders in the relationship between a positive PSA test result and transplant, variables strongly related to cardiac transplant listing were identified (Figure 5.1). The baseline demographics and clinical characteristics collected included age at evaluation, ethnicity, height (cm), weight (kg), Body Mass Index (BMI) (kg/m^2), blood group, renal function (measured by GFR (ml/min) using the MDRD equation[40]), established diagnosis of Chronic Obstructive Pulmonary Disease (COPD) and diabetes, ejection fraction (EF) at evaluation, and serum levels of thyroid stimulating hormone (TSH), lactate dehydrogenase (LDH) and total bilirubin at the time of cardiac transplant evaluation.

2.3: Cardiovascular Disease Status

There are a wide variety of underlying cardiovascular conditions that can lead to a referral for evaluation for cardiac transplantation. At the point of data abstraction, the underlying cardiovascular diagnosis was recorded as stated on the transplant database and grouped in one of five categories: 1) Ischemic Cardiomyopathy (ICM), 2) Non-Ischemic Cardiomyopathy (NICM), 3) Hypertrophic Obstructive Cardiomyopathy, 4) Restrictive Cardiomyopathy, and 5) Other. To facilitate the analysis patients with Hypertrophic Obstructive Cardiomyopathy, Restrictive Cardiomyopathy and other were grouped with NICM.

The clinical status of the patients can vary significantly at the time of referral for cardiac transplantation. Using the clinical history and examination findings recorded in the transplant database and the electronic medical records, the reasons for referral were categorized into one of the following: 1) New York Heart Association (NYHA) functional classification III/IV despite optimal medical therapy, 2) reduced functional capacity by exercise testing, 3) inoperable Coronary Artery Disease (CAD) with intractable angina, 4) ventricular arrhythmia refractory to medical therapy, 5) continuous mechanical support (Intra-aortic balloon pump or Ventricular Assist Device), or 6) continuous inotropic support.

2.4: Prostate Cancer Screening and Evaluation

Prostate cancer screening was performed either by the referring institution or at TMC at the time of transplant evaluation. Screening values provided by the referring institution were recorded either directly into the transplant database or were available in the

referring documentation. TMC utilizes second generation assays and provides the total PSA values (Reference <4ng/ml). In patients with a positive prostate cancer test result (total PSA ≥ 4ng/ml) a further detailed review of the patient's medical records was conducted to ascertain the evaluation for the elevated PSA levels. This included determining the location of PSA evaluation (inpatient versus outpatient), patients who had a normal repeat PSA evaluation, patients requiring prostate biopsy, patients diagnosed with prostate cancer. Patients with unclear follow up information were categorized as either a) referred to external provider or Unknown or b) died prior to further evaluation. Pathology reports from either prostate biopsy or surgical specimens following resection were used to confirm the diagnosis of prostate cancer. In the patients with a positive PSA screening result, the clinical and biochemical characteristics, and evaluation outcome is described according to the patient's clinical status at the time of referral i.e. a) Mechanical Support, b) Continuous Inotropic Support, c) other (including NYHA III/IV, Inoperable CAD or Ventricular Arrhythmia refractory to medical treatment).

2.5: Cardiac Transplant Evaluation Outcome

The primary outcome for this study is time to listing (days) from the patient's date of evaluation. In accordance with OPTN and UNOS requirements all patients that are listed for a possible cardiac transplant receive formal written notification[41]. The date of listing and listing status is recorded in the transplant database in addition to the electronic medical records. Patients that were not listed for cardiac transplant by March 31st 2017 were classified as 'not listed'. UNOS requires all patients that are listed for cardiac transplant be assigned an urgency transplant status, with pre-specified criteria for each stage[7,42–44]. Patients assigned a status of 1A are categorized as highest priority in the allocation of a donor heart, followed by status 1B and then status 2. Patients who are

deemed eligible for a cardiac transplant, but have outstanding and reversible medical condition (e.g. active infection) are given a status 7 equivalent to inactive. The date and time of all patients that had received a cardiac transplant was available in the electronic medical record. Patients that were on the cardiac transplant waiting list and had not received a transplant by March 31st 2017 were classified as not having received a transplant.

For patients that were not listed for cardiac transplant over the course of our study, the date and reason for not listing was ascertained from the clinical decision letter or discharge summary present in the patient's medical records. Patients that died during the evaluation process were classified as 'not listed' at the date of death. The primary reason for not listing was categorized as a) continued medical or surgical management of cardiac disease, b) non-cardiac clinical contraindications, c) social or nutritional contraindication, d) died during evaluation, or e) lost to follow up.

2.6: Sensitivity Analysis

In our primary analysis, the outcome of time to listing for cardiac transplant allowed censoring of patients by the time they were not listed. To assess the robustness of the estimates provided in the Cox proportional hazards model used in our primary analyses we used a logistic regression model, which does not account for censoring and a competing risks model accounting for the competing risk of death during transplant evaluation (Appendix 5.3).

2.7: Statistical Analysis

We compared the differences in baseline demographics and clinical characteristics of patients with a positive prostate cancer screen to a negative screen using independent samples t-tests for continuous variables and chi-square tests for categorical variables. In scenarios where the variable distribution was skewed or the sample size was less than 10 in any category a Wilcoxon rank-sum test was used for continuous variables and Fishers exact test for categorical variables. Comparison of the difference in median PSA values in patients with a positive prostate cancer screen on mechanical support to those on inotropic support or 'other' was performed using Wilcoxon rank-sum test.

The difference in proportions in patients being listed for cardiac transplant by screening status was compared using a chi-square test. Amongst those patients that were listed for cardiac transplant, the listing status at the point of listing was compared using a Fishers exact test and a chi-square test was used to determine the difference between those that underwent cardiac transplant. Amongst the patients that were not listed, the difference in proportions in patients that died during the evaluation process was compared using a chi-square test.

2.7.1: Time to Event Analysis

Cox proportional hazard regression models were used to assess the relationship between PSA screening status and our primary outcome of time to listing for cardiac transplant. To control for possible confounding, a variety of a priori defined variables were identified (Figure 5.1). With increased experience in the transplant evaluation

process with time, the year the evaluation took place was also evaluated as a possible contributory variable with categorization into, a) 2000-2004, b) 2005-2009, and c) 2010-2015. To facilitate the analysis certain categorical variables were collapsed: the race and ethnicity variable was categorized as either Non-hispanic/Non-latino:white vs other, cardiac diagnosis was categorized as either Ischemic Heart Disease or other and clinical status at referral was grouped into 3 categories: a) Mechanical Support, b) Continuous Inotropic Support, c) other (including NYHA III/IV, Inoperable CAD or Ventricular Arrhythmia refractory to medical treatment).

Initially, a Kaplan-Meier analysis, stratified by prostate cancer screening status, was used to determine the median time to cardiac transplant listing. A log-rank test was used to compare the time to listing distributions by PSA screening status. Univariate Cox proportional hazard models were used to estimate hazard ratios and accompanying 95% confidence intervals to compare the variables listed above and the outcome of cardiac transplant listing. In building our multivariable Cox proportional hazard model, only variables that significantly influenced cardiac transplant listing i.e. univariate hazard ratio with a p-value less than 0.2 were included. In the final multivariable model, an assessment of the assumption of proportional hazards was made using Schoenfeld residuals. For continuous variables, the assumption of linearity was assessed using Martingale residuals. Interaction terms were used to assess for the presence of effect modification.

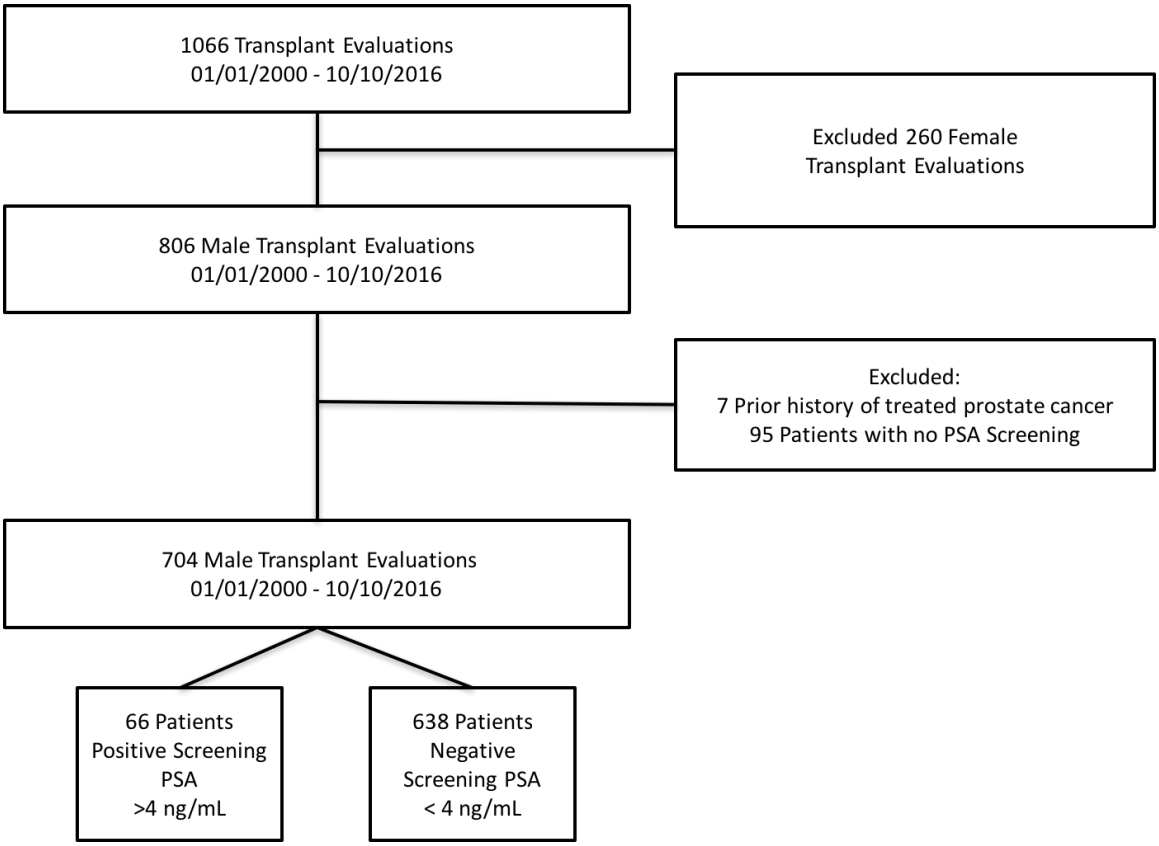
All statistical analyses were performed with the R statistical software platform version 3.2.4 (RStudio version 1.136).

Chapter 3: Results

3.1: Study population

Among the 806 men that underwent cardiac transplant evaluation at TMC between January, 2000 and December, 2015, a total of 704 men (87%) were included in our analysis, patients that did not have evidence of prostate cancer screening in the medical records were excluded (Figure 3.1). 66 men (9.3%) had a positive prostate cancer screen (≥ 4ng/ml). Compared to patients with a negative screening result (PSA <4ng/ml) at the point of evaluation, patients with a positive PSA screening result were significantly older (58.5 vs 54.1 years), have a greater BMI (29.5 vs 28.3 kg/m2), worse renal function (GFR 51.2 vs 61.9 ml/min), were more likely to have a diagnosis of Ischemic Cardiomyopathy (ICM) (74% vs 53%) and be on mechanical support at the point of evaluation (61% vs 16%) (all $p<0.05$) (Table 3.1).

Figure 3.1: Flow chart of patients included in the analysis



PSA = Prostate Specific Antigen

Table 3.1: Baseline Clinical Characteristics at the time of transplant evaluation according to PSA findings

Clinical Variables	Positive Screening PSA >4 ng/ml n=66	Negative Screening PSA <4ng/ml n=638
Age at Evaluation (years, mean +/- sd)	58.5 +/- 8.7	54.1 +/- 11.2
Ethnicity (n, %)		
Non-hispanic/non-latino: White	63 (95)	571 (89)
Non-hispanic/non-latino: Black	1 (1.5)	25 (4)
Hispanic	1 (1.5)	28 (4)
Non-hispanic/non-latino: Other	1 (1.5)	14 (4)
Diagnosis at Evaluation		
Ischemic Cardiomyopathy	49 (74)	336 (53)
Non-Ischemic Cardiomyopathy	17 (26)	260 (41)
Hypertrophic Cardiomyopathy	0	29 (4.5)
Other	0	13 (2)
Clinical status at referral (n, %)		
1. NYHA III/IV	14 (21)	335 (53)
2. Inoperable CAD	1 (1.5)	19 (3)
3. Refractory VT	0	13 (2)
4. Inotropic Dependent	11 (17)	172 (27)
5. Mechanical Support	40 (61)	99 (16)
Blood Type (n (%))		
A	35 (53)	248 (39)
B	7 (11)	76 (12)
AB	3 (5)	27 (4)
O	20 (30)	249 (39)
Ejection Fraction (%, mean +/- sd)	17 (9)	18 (11)
Body Mass Index (kg/m2, mean +/- sd)	29.5 (4.34)	28.3 (5.6)
GFR at Evaluation (mL/min, mean +/- sd)	51.2 (25)	61.9 (22)
Diabetes at Evaluation (n, %)	35 (53)	257 (40)
Chronic Obstructive lung disease (n, %)	4 (6)	77 (12)

3.2: Outcome of Cardiac Transplant Evaluation

A lower proportion (38% vs 60%) of patients with a positive prostate cancer screen were listed for cardiac transplant ($p<0.01$). Of those that were listed, patients with a positive screen were more likely to be listed as UNOS status 1A (56% vs 26%, $p<0.01$), the highest priority for cardiac transplant. In patients who did not get listed for cardiac transplant, patients with a positive prostate cancer screen were more likely to die during the evaluation process (31% vs 16%, $p=0.02$) (Table 3.2).

Table 3.2: Outcome of cardiac transplant evaluation

Variable	Screening PSA >4 ng/ml n=66	Screening PSA <4ng/ml n=638	p-value
Listed (n, %)	25 (38)	380 (60)	p<0.01
List Status (n, % listed)			p<0.01
1A	14 (56)	98 (26)	
1B	5 (20)	109 (29)	
2 or 7	6 (24)	173 (45)	
Transplant (n, % listed)	13 (56)	213 (56)	0.85
Died during evaluation (n, % not listed)	13 (31)	42 (16)	0.02

3.3: Time to listing for Cardiac Transplant

The Kaplan-Meier analysis revealed the median time to cardiac transplant listing was greater in patients with a positive prostate cancer screening result (119 days vs 49 days, p=0.03) (Figure 3.2). Following a univariate analysis with Cox proportional hazard models, the patient's age at evaluation, renal function, the year of evaluation and pre-existing diagnosis of COPD were used in a multivariable Cox proportional hazard model (Table 3.3). After adjusting for these variables, the hazard of transplant listing was significantly lower in men that had a positive prostate cancer screen (HR 0.58, 95% CI 0.38-0.91, p=0.02). There was no violation of the assumption of proportional hazards, linearity, and no presence of effect modification (Appendix 5.4).

Figure 3.2: Kaplan-Meier Curve

The Kaplan-Meier curve compares the time to cardiac transplant listing in men with a positive prostate cancer screen (Elevated prostate specific antigen (PSA) >4ng/ml) to men with a negative screen (Normal PSA <4ng/ml). The median time to listing in patients with a positive screen was 119 days versus 49 days in those with a negative screen (p=0.03)

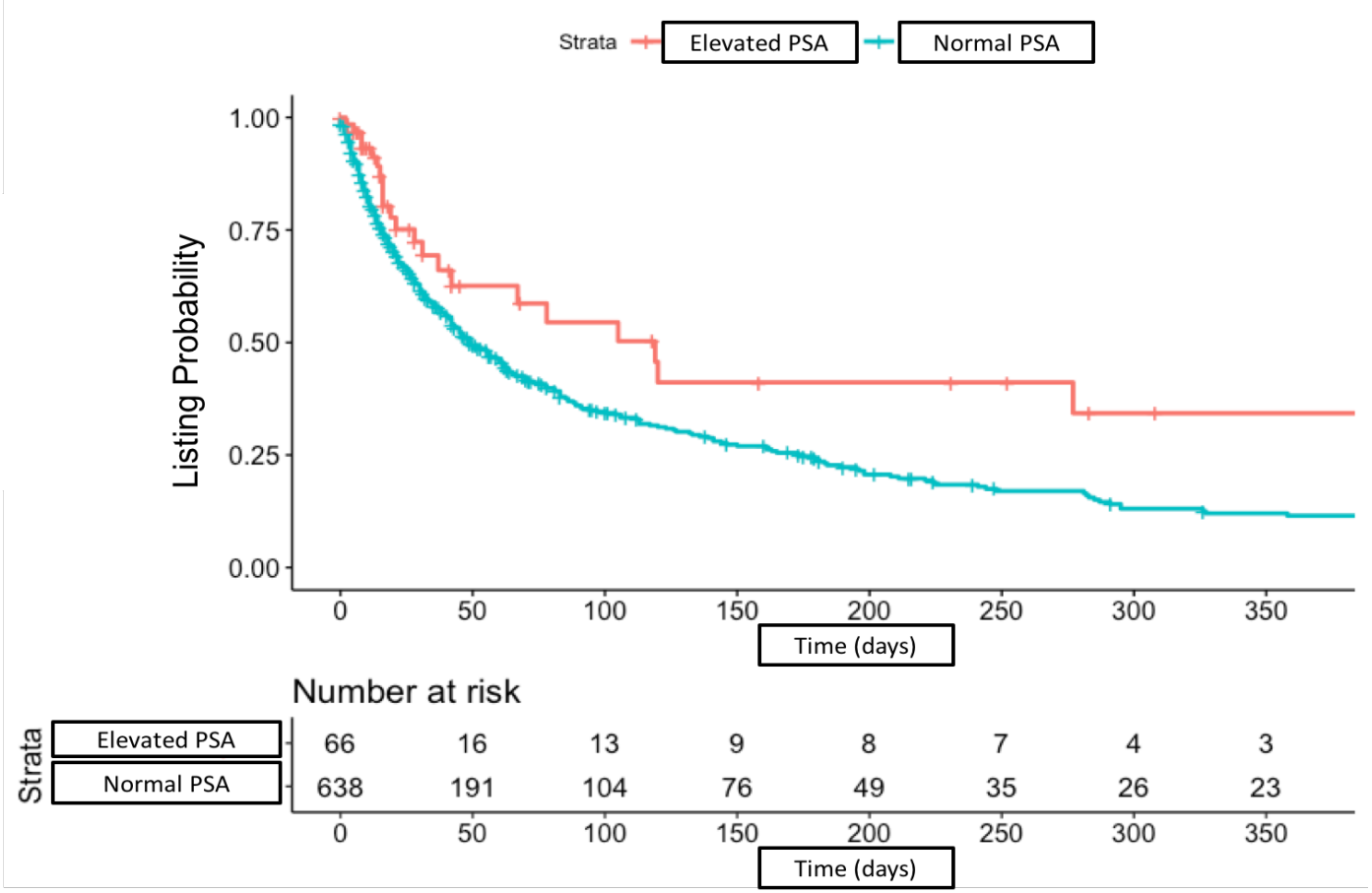


Table 3.3: Univariable and multivariable Cox proportional hazards analysis on the association between positive prostate cancer screen and cardiac transplant listing.

Variable	Univariate Screen			Multivariable Model		
	HR	95% CI	p-value	HR	95% CI	p-value
Elevated PSA >4ng/ml	0.64	0.43-0.96	0.03	0.58	0.38-0.91	0.02
Age at Evaluation (year)	0.98	0.97-0.99	<0.01	0.99	0.98-1.00	0.01
Body Mass Index (kg/m^2)	1.00	0.98-1.02	0.71			
Year of Evaluation						
2010 - 2015	Ref			Ref		
2005 - 2009	1.25	0.99–1.56	0.06	1.30	1.04-1.63	0.02
2000 – 2004	1.40	1.08–1.81	0.01	1.51	1.17-1.97	<0.01
Race						
White	0.97	0.71-1.32	0.82			
Clinical Status at Referral						
Continuous Mechanical Support	Ref			Ref		
Continuous Inotropic Support	1.58	1.17–2.15	<0.01	1.47	1.07-2.03	0.02
Other	0.82	0.62-1.09	0.17	0.70	0.52-0.96	0.02
Ischemic Cardiomyopathy	0.90	0.74-1.10	0.34			
Renal Function (GFR (ml/min))	1.01	1.00-1.02	0.06	1.00	0.99-1.01	0.23
Blood Group						
A	Ref					
B	1.07	0.55-1.65	0.70			
O	0.97	0.78-1.21	0.78			
AB	0.96	0.55-1.65	0.87			
Diagnosis of COPD (yes)	0.62	0.44-0.86	<0.01	0.66	0.47-0.92	0.02
Diagnosis of Diabetes (yes)	0.98	0.80-1.20	0.85			

3.4: Outcome of patients with a positive Prostate Cancer screen

Among the 66 patients that had an elevated PSA finding (≥4ng/ml), 40 patients (61%) were requiring continuous mechanical support at the point of evaluation, 11 patients (17%) were requiring continuous inotropic support and 15 patients (22%) were referred for either NYHA class III/IV symptoms refractory to medical treatment, Inoperable CAD or ventricular arrhythmia refractory to medical treatment (referred to as 'other' (Table 3.4)). 58 (88%) patients had their PSA evaluation performed during an inpatient admission. Patients who required continuous mechanical support at the time of evaluation had a median PSA value (12.5 ng/ml (IQR 6.5-24.5 ng/ml)), which was significantly higher than patients on continuous inotropic support (7.3ng/ml (IQR 6.0-9.7), $p<0.01$) and those referred for 'other' reasons (6.2ng/ml (IQR 5.1-8.1), $p<0.01$). The follow up for the elevated PSA varied considerably, however 18 (28%) patients had a repeat PSA that was normal (<4ng/ml), 20 (31%) were referred to an external provider not at TMC, 13 (20%) died prior to further evaluation. 9 patients required prostate biopsy and 4 patients (6.1%) received a subsequent diagnosis of prostate cancer (Table 3.4). Of the 4 patients to receive a diagnosis of prostate cancer during the evaluation process, 2 were listed for transplant following surgery.

Table 3.4: Clinical evaluation of patients with a positive prostate cancer screen

Variables	Positive PSA Screen
	N=66
Location of PSA	
Inpatient (%)	58 (88)
PSA Value by clinical status at Evaluation (median (IQR))	
Continuous Mechanical Support (n = 40)	12.45 (6.5 - 24.5)
Continuous Inotropic Support (n = 11)	7.3 (6.4 - 9.7)
Other (n=15)	6.2 (5.1 - 8.1)
Evaluation of Elevated PSA (n (%))	
Repeat PSA - Normal	18 (28)
Negative Prostate Biopsy	5 (8)
Alternative non-cancer diagnosis	6 (9)
Referred to External Provider	20 (31)
Died prior to further investigation	13 (20)
Prostate Cancer Diagnosed	4 (6)

PSA = Prostate Specific Antigen

Chapter 4: Discussion

This study provides the largest single center experience on the yield of screening for prostate cancer in patients with advanced HF. Consistent with prior work[33,34], we demonstrate that the prostate cancer screening result determined by serum Prostate Specific Antigen (PSA) is influenced by the clinical status of the patient. We found that patients with a positive PSA screen (greater than or equal to 4ng/ml) were more likely to have a diagnosis of Ischemic Cardiomyopathy (ICM) and be on mechanical circulatory support at the point of evaluation. These men were more likely to die during the transplant evaluation process and less likely to be listed for a cardiac transplant.

When screening the general population for prostate cancer, a PSA value of greater than or equal to 4.0 ng/ml is seen as an acceptable tradeoff in sensitivity and specificity to justify further investigation.[45,46] At 4.0 ng/ml, the positive predictive value for a diagnosis of prostate cancer in the general population is 30% and the cancer detection rate (proportion of patients screened that were diagnosed with prostate cancer) is 3%.[31,46] However, when using the same threshold to classify a positive screen in our patient population, provided a cancer detection rate of less than 1% and a positive predictive value of 6%. In contrast to screening patients for colorectal cancer with colonoscopy, where a patient's clinical stability is essential for safe and effective use of the screening modality[47], serum PSA can be easily checked at any point during a patient's transplant evaluation course. Given that the value of PSA is dynamic[48] and influenced by multiple conditions besides prostate cancer, approximately 1 in 4 patients in our analysis had normalization of their PSA values following an initial positive screen. This suggests that improved timing of serum PSA sampling i.e. performed when the patient is in a stable hemodynamic state, ideally in an outpatient setting, could help

prevent the anxiety associated with a positive screening result.[49] Adding to the complexity of the decision to perform screening with PSA, is determining the optimal method for managing patients with screening detected prostate cancer. In the general population, Hamdy *et al.* demonstrated that in patients with screening detected localized prostate cancer, active monitoring is equivalent to radical treatment over a median follow up of 10-years.[50] There were only four diagnoses of prostate cancer in the transplant evaluation process over the course of our study, thus no firm conclusions can be derived. Notably, two of these patients did receive a cardiac transplant following radical prostatectomy. A combination of the performance characteristics of PSA as a screening tool, the harms of the subsequent invasive investigations and the indolent nature of prostate cancer continue to make prostate cancer screening recommendations so controversial[51]. Even when targeting the general population most guidelines fail to come to a common consensus. However, they do counsel in unison against screening for prostate cancer if a patient's life-expectancy is less than 10 years[31]. Nearly all patients with advanced HF, in the absence of a transplant, will die from their underlying cardiac condition and will gain limited to no benefit from screening.

Vitiello *et al.* assessed the utility of prostate cancer screening with PSA in patients with end-stage renal failure undergoing renal transplant evaluation[37]. With their larger sample size and the heterogeneity in their screening practices, the authors were able to compare screened patients with non-screened patients. They showed a 41% reduced likelihood of receiving a renal transplant in patients with a positive prostate cancer screen result (PSA ≥ 4ng/ml) compared to those with no screening. Similar to our findings, their cohort of patients with a positive PSA screening result waited longer for renal transplant listing, in addition to a prolonged time to renal transplant[37]. Their yield of screening in this study was also lower than the general population, with a positive

predictive value of 25.8% and cancer detection rate of approximately 2%.[37] In our unadjusted analysis, patients with a positive PSA screen had a longer median time to transplant listing (Figure 3.2) and when adjusting for common confounders these patients have a 42% reduced likelihood of being listed for cardiac transplant compared to those with a negative screen (Table 3.3).

4.1: Strengths and Limitations

In ideal circumstances, long-term mortality from prostate cancer would be the most suitable outcome to assess the utility of screening in the transplant evaluation process. However, national databases[41,52,53] only begin to collect information on transplant related outcomes following listing or receiving a transplant, thus assessing the role of cancer screening using these databases will be prone to selection bias. By utilizing time to listing as our primary outcome, our work advances the current gap in the literature on the clinical outcomes associated with prostate cancer screening in this patient population. Nevertheless, this analysis has several limitations. Unlike the criteria for listing for transplant, for which there are published and updated guidelines[7,42], there is no such robust criteria for referral for evaluation for cardiac transplantation. Thus, there is significant heterogeneity in the clinical status of patients being referred for a transplant evaluation and subsequently multiple competing risks for not being listed for transplant. Unlike prior analyses[37], our sensitivity analyses attempts to assess the impact of death during evaluation as a competing risk for listing for cardiac transplant, where we demonstrate that the analytic approach to account for the competing risk of death during the transplant evaluation can alter our findings (Appendix 5.3). Furthermore, given the numerous different reasons for a patient to be not listed, and the imbalance of factors between those with versus without a positive screening result, our quoted hazard ratio

likely overestimates the causal effect of a positive screen on transplant listing. We performed detailed individual patient chart abstraction on confounders that were identified *a priori*, but with the clinical complexity of the patients being evaluated and the observational nature of the study the possibility for residual confounding remains high. Not all the patients received follow-up of their positive prostate cancer screen at our institution, thus our findings represent the lowest estimate of the yield of prostate cancer screening. In the extreme and unrealistic scenario that all patients that were followed up at different institutions were subsequently diagnosed with prostate cancer, the cancer detection rate within our study would rise to 3% and the positive predictive value of a positive PSA screen of 36%. Finally, our analysis represents a single center experience, where majority of patients were non-hispanic/non-latino: white with ICM and thus may not be generalizable to the practices of other cardiac transplant centers.

4.2: Future Directions

For the foreseeable future, the availability of the donor heart will be the limiting step in the management of patients eligible for a cardiac transplant. The rationale for screening pre-transplant candidates for an asymptomatic malignancy is related to the poor prognosis seen in immunosuppressed patients with de-novo malignancies post-transplant[15–17], increased cancer specific mortality in patients with a pre-transplant malignancy who receive a transplant[54] and ultimately the drive to improve the longevity of the donor organ. What remains uncertain is the effectiveness of screening this population using technology and guidelines aimed at the general population. A systematic review of cancer screening practice guidelines aimed at transplant physicians showed that majority of the published guidelines reflect expert opinion without the backing empiric evidence.[55] Furthermore there is significant variability in the

recommendations depending on the region and organ type. Our work highlights the need for further collaborative multicenter studies that will provide sufficient power to assess the role of cancer screening during the transplant evaluation process.

Given the goals of cancer screening in patients being evaluated for a transplant is different to that of the general population, there is a need for specific technology and guidelines aimed at this population. With the vast improvement in next generation sequencing techniques the identification of tumor DNA circulating in the blood is now possible[56–58]. Furthermore, unlike protein based biomarkers like PSA, recent studies have shown that this technique has the possibility to improve cancer screening specificity to over 99%[59]. Future studies assessing the utility of this novel screening technology will focus on its application to the general population, however investigators should also consider separately assessing their utility in this unique population also.

4.3: Conclusion

Our data provides the largest single center experience on the clinical effects of prostate cancer screening in patients undergoing a cardiac transplant evaluation. In this population, screening for prostate cancer with PSA performs poorly in particular for patients who are acutely unwell at the point of evaluation. Men with a positive screen had a longer time to listing for a cardiac transplant and a reduced likelihood for transplant listing.

Chapter 5: Appendix

5.1: REDCap Abstraction Template

A standardized template was created on the Research Electronic Data Capture (REDCap) web application to abstract patient specific data (Table 5.1).

Table 5.1: Standardized Data Abstraction Code Book

Field Name	Field Type	Field Label
record_id	text	Record ID
ethnicity	text	Ethnicity
race	text	Race
diagnosis	text	Diagnosis
sex	text	Sex
date_of_psa	text	Date of PSA
psa	text	PSA
psanormalhigh	text	PSA Normal or High
ageateval	text	Age at Evaluation
doe	text	Date of Evaluation
listedyn	text	Patient Listed Y/N
listdate	text	List Date
liststatus	text	List Status
timetolisting	text	Time to Listing
transplantyn	text	Transplant Y/N
dotx	text	Date of Transplant
txstatus	text	Transplant Status
timetotransplant	text	Time to Transplant
removedfromlistdate	text	Removed from list date
removedfromlistreason	text	Removed from list reason
deathdate	text	Death Date
reasonnottransplanted	text	Reason not Transplanted
statusatdeath	text	Status at Death
causeofdeath	text	Cause of Death
location_of_psa	dropdown	Location of PSA

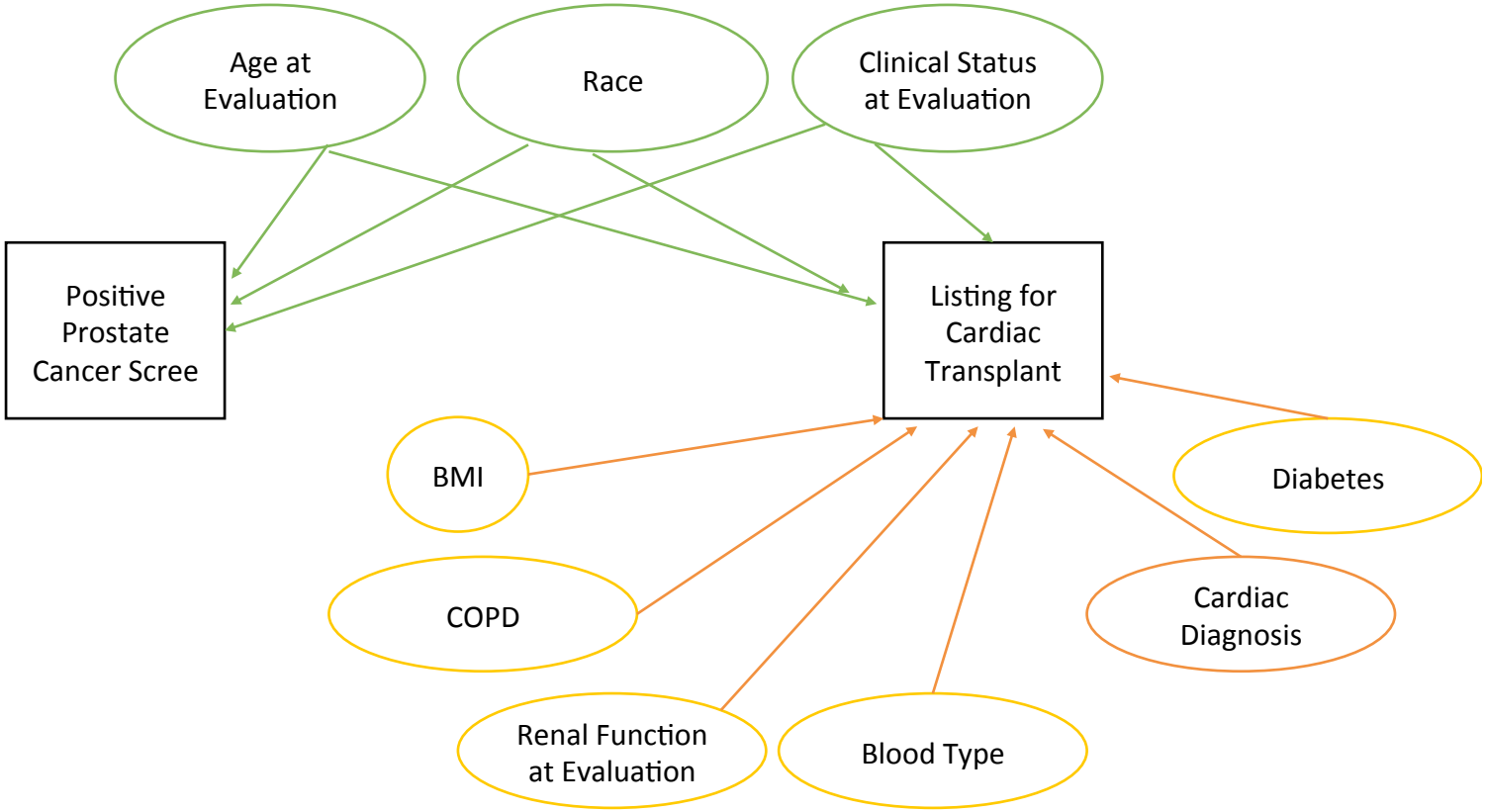
reason_for_referral	dropdown	Reason for Referral
other_cause_for_referral	text	Other Cause for Referral
lvad	yesno	LVAD
relevant_transplant_info	notes	Relevant Transplant Info
weight	text	weight
htf	text	height (feet)
hti	text	height inches
bsa	text	Body Surface Area
bmi	text	Body Mass Index
blood_type	dropdown	Blood Type
htn	yesno	Hypertension
hld	yesno	Hyperlipidemia
dm	yesno	Diabetes
dm_type	dropdown	Diabetes Type
hba1c	text	HbA1c
rhythm	dropdown	Rhythm
other_rhythm	text	Other Rhythm
ejection_fraction	text	Ejection Fraction
pacemaker	yesno	Pacemaker
reason_pacemaker	text	Reason pacemaker
icd	yesno	ICD
reason_icd	text	Reason ICD
copd	yesno	Chronic Obstructive Pulmonary Disease
pulmonary_function_test	yesno	Pulmonary Function Test
fvc	text	FVC
fev1	text	FEV1
fev1_fvc	text	FEV1/FVC
ckd	yesno	Chronic Kidney Disease
ckd_stage	dropdown	CKD Stage
creat_at_listing	text	Creat at Evaluation
gfr_at_evaluation	text	GFR at Evaluation
cirrhosis	yesno	Cirrhosis
t_bili	text	Total. Bilirubin
ldh	text	LDH
tsh	text	TSH
microbiology	checkbox	Microbiology
abnormal_chest_x_ray	yesno	Abnormal Chest X-ray
chest_x_ray_abnormality	text	Chest X-ray Abnormality

abnormal_carotid_non_invas	yesno	Abnormal Carotid Non-Invasive
carotid_us_abnormality	text	Carotid US Abnormality
abnormal_us_abdo	yesno	Abnormal US Abdo
reason_for_abnormality	yesno	Reason for Abnormality US Abdo
psychiatry_concerns	yesno	Psychiatry Concerns
mental_health_concern	checkbox	mental health concern
substance_misuse	yesno	Substance Misuse
alcohol	yesno	Alcohol
smoking	yesno	Current Smoker
former_smoker	yesno	Former Smoker
pack_year_exposure	text	Pack Year Exposure
social_services_concern	yesno	Social Services Concern
ss_concern	text	Social Services Concern
nutrition_concerns	yesno	Nutrition Concerns
nutrition_concern_type	text	Nutrition Concern Type
other_concern	yesno	Other Concern
other_concern_type	text	Other Concern Type
reason_not_listed	text	Reason Not Listed
coumadin	yesno	Coumadin
other_anti_coagulant	text	Other Anti-coagulant
psa_work_up	yesno	PSA Work Up
psa_work_up_type	checkbox	PSA Work Up Type
psa_work_up_complication	notes	PSA Work-Up complication
prostate_cancer_diagnosis	yesno	Prostate Cancer Diagnosis
prostate_cancer_pre_listin	yesno	Prostate Cancer Pre Listing
other_relevant_info	notes	Other Relevant Info

5.2: Directed Acyclic Graph

A priori rationale was used to identify confounders in the association between screening status and being listed for cardiac transplant, in addition to variables strongly associated with listing for cardiac transplant (Figure 5.1).

Figure 5.1: Directed Acyclic Graph
The Directed Acyclic Graph demonstrates a priori rationale on key variables in the association between prostate cancer screening and cardiac transplant listing.



BMI = Body Mass Index, COPD = Chronic Obstructive Pulmonary Disease

5.3: Sensitivity Analyses

We assessed the robustness of the estimates provided in the Cox proportional hazards model used in our primary analyses by using a logistic regression model, which does not account for censoring and a competing risks model accounting for the competing risk of death during transplant evaluation.

5.3.1: Multivariable Logistic Regression Model

Using a priori rationale confounders in the relationship between prostate cancer screening status and transplant listing, in addition to variables associated with achieving transplant listing were identified (Figure 5.1). These variables were included in a logistic regression model with listing for cardiac transplant as the binary outcome. The listing status (either listed for cardiac transplant or not) of each patient referred between January, 2000 to December 2015 was ascertained until March 31st 2017. There were no patients that did not have a formal outcome for the transplant evaluation over this timeframe. The median time from referral to transplant referral outcome was 22 days (IQR 10-62 days).

To facilitate the analysis certain categorical variables were collapsed: the race and ethnicity variable was categorized into either Non-hispanic/Non-latino:white vs other, the cardiac diagnosis were categorized into either Ischemic Heart Disease or other and clinical status at referral was grouped into 3 categories: a) Mechanical Support, b) Continuous Inortropic Support, c) other (including NYHA III/IV, Inoperable CAD or Ventricular Arrhythmia refractory to medical treatment). Odds ratios for transplant listing for each identified variable with accompanying 95% CI was estimated by using logistic regression. Following the univariate screen, variables associated with transplant listing

were included within the multivariable logistic regression model if the p-value was less than 0.20. To build a parsimonious model, a backward elimination process was performed until the p-value was less than 0.1. A Likelihood Ratio Test (LRT) was used to compare the models at each step, comparing the more parsimonious model with the model that included all the variables following the univariate screen. Model diagnostics included: 1) assessment for co-linearity using variance inflation factor (VIF), 2) assessment of the assumption of linearity for the continuous variables and 3) assessment of individual patient level Pearson residuals. The concordance statistic (c-statistic) and the Hosmer-Lemeshow test were used to assess goodness of fit for the final logistic regression model. We used interaction terms to assess for the presence of effect modification.

In an unadjusted analysis, a positive prostate cancer screen was associated with a lower odds for cardiac transplant listing (OR 0.41, 95% CI 0.24-0.69). Table 5.2 describes the relationship of the covariates included in univariable analysis and listing for cardiac transplant. The presence of a diagnosis of ICM, diagnosis of COPD in addition to the patient's age, renal function and clinical status at evaluation met the pre-specified cutoff (p-value <0.2) for use in the multivariable analysis. After adjusting for age, renal function and clinical status at evaluation a positive prostate cancer screen was no longer significantly associated with cardiac transplant listing (aOR 0.58, 95% CI 0.38-1.02) (Table 5.3). There was no significant interaction between prostate cancer screening status and the covariates used in the multivariable model (Table 5.4). In the final multivariable logistic regression model there was no evidence of co-linearity or violation of assumption of linearity for the continuous variables. The Hosmer-Lemeshow test for goodness of fit was not significant (p=0.80) and the concordance statistic (c-statistic) for

the final model was 0.65 (Figure 5.2). Individual patient residual diagnostics failed to reveal outliers i.e. those with Pearson residuals greater than 3 (Figure 5.2).

Table 5.2: Univariate logistic regression analysis

Variables	Odds Ratio	95% CI	p-value
Elevated PSA >4ng/ml	0.41	0.24-0.69	<0.01
Age at Evaluation (year)	0.97	0.95-0.98	<0.01
Body Mass Index ($kg/m^{2)}$	1.01	0.99-1.04	0.33
Race			
White	0.78	0.46-1.29	0.34
Clinical Status at Referral			
Continuous Mechanical Support	Ref		
Continuous Inotropic Support	2.47	1.57–3.91	<0.01
Other	1.62	1.09-2.40	0.05
Ischemic Cardiomyopathy	0.63	0.47-0.85	<0.01
Renal Function (GFR ml/min)	1.01	1.00-1.02	<0.01
Blood Group			
A	Ref		
B	1.02	0.62-1.67	0.94
O	1.14	0.81-1.61	0.43
AB	0.68	0.31-1.45	0.32
Diagnosis of Diabetes (yes)	1.01	0.74-1.37	0.94
Diagnosis of COPD (yes)	0.72	0.45-1.15	0.17

Table 5.3: Multivariable logistic regression analysis

	Multivariable Model 1		Multivariable Model 2		Multivariable Model 3		
	aOR	p-value	aOR	p-value	aOR	95% CI	p-value
Elevated PSA >4ng/ml	0.60	0.08	0.59	0.07	0.58	0.32-1.02	0.06
Age at Evaluation (year)	0.97	<0.01	0.97	<0.01	0.97	0.95-0.98	<0.01
Clinical Status at Referral							
Continuous Mechanical Support	Ref		Ref		Ref		
Continuous Inotropic Support	2.47	<0.01	2.52	<0.01	2.45	1.50 – 4.00	<0.01
Other	1.49	0.07	1.52	0.06	1.48	0.97 – 2.28	0.05
Ischemic Cardiomyopathy	0.87	0.41					
Renal Function (GFR ml/min)	1.01	0.06	1.01	0.06	1.01	0.99-1.01	0.07
Diagnosis of COPD (yes)	0.80	0.37	0.79	0.34			
Likelihood Ratio Test			Model 2 vs 1	0.41	Model 3 vs 1	0.32	

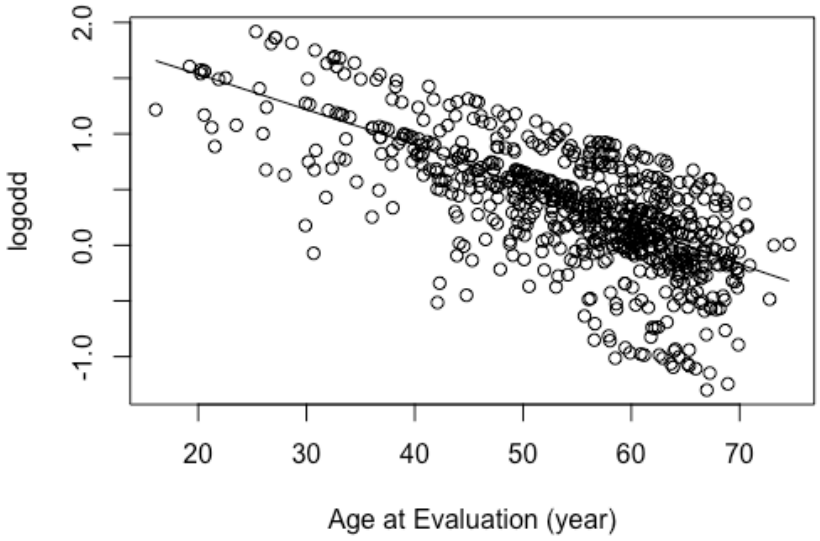
For each multivariable model 698 patients were included, 6 patients that had missing values on their renal function and were excluded. 403 patients were listed for transplant.

Table 5.4: Assessment of effect modification in the multivariable logistic regression model

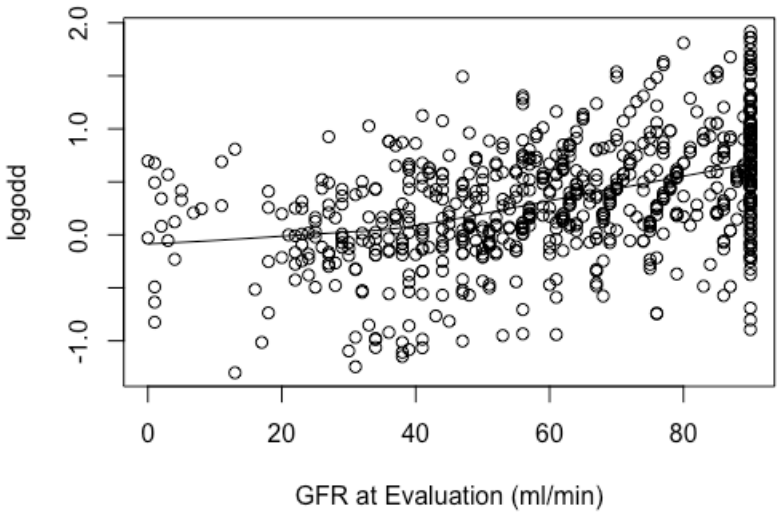
Variables			
			p-value
Effect Modification by Age at Evaluation			
Interaction Term Age at Evaluation x PSA Screening Status			0.78
Effect Modification by Clinical status at Referral			
Interaction Term Inotropic Support x PSA Screening Status			0.73
Interaction Term 'Other' x PSA Screening Status			0.13
Effect Modification by Renal Function			
Interaction Term Renal Function x PSA Screening Status			0.45

Figure 5.2: Model diagnostics for the multivariable logistic regression analysis

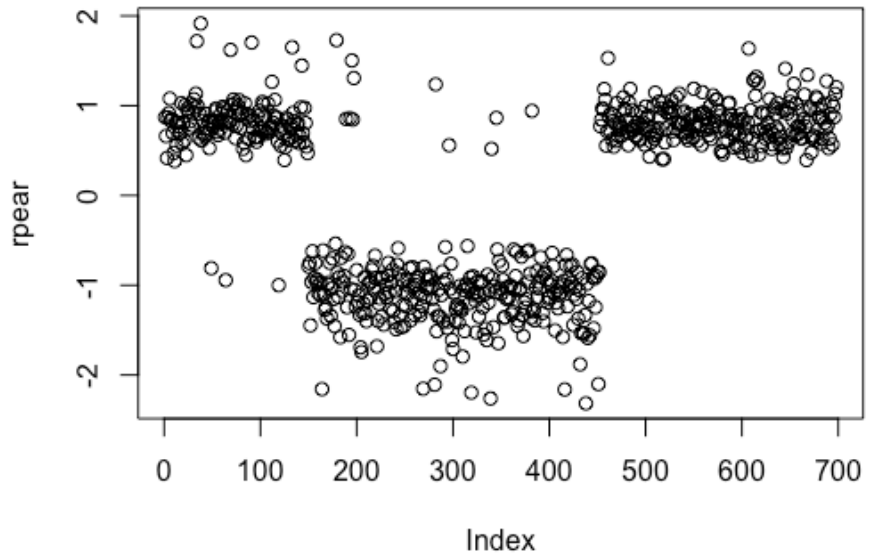
A) Assessment of the assumption of linearity using a plot of Age at evaluation with the log-odds. The line represents the lowess curve.



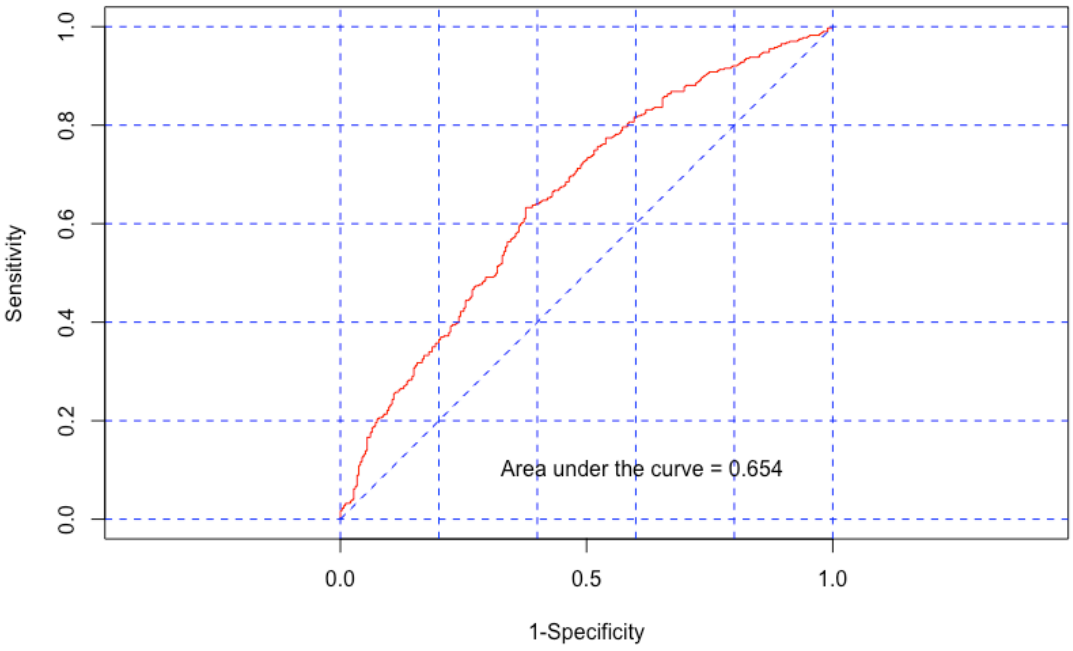
B) Assessment of the assumption of linearity using a plot of Renal function with the log-odds. The line represents the lowess curve.



C) Assessment of outliers using a plot of individual patient's Pearson residuals



D) Receiver Operating Characteristic (ROC) curve. The area under the ROC curve (AUC) is an assessment of the discriminative strength of the multivariable model 3 used to analyze the association between positive prostate cancer screen and cardiac transplant listing.



5.3.2: Competing Risks Model

In our cohort of patients, 55 (7.8%) died prior to the decision for transplant listing. Our primary interest is the time from referral to transplant listing and whether this differs by the PSA screening status. Thus, in our primary analysis, death prior to cardiac transplant listing is a competing risk for being listed for cardiac transplant and the assumption of independence of the censoring distribution may be violated.

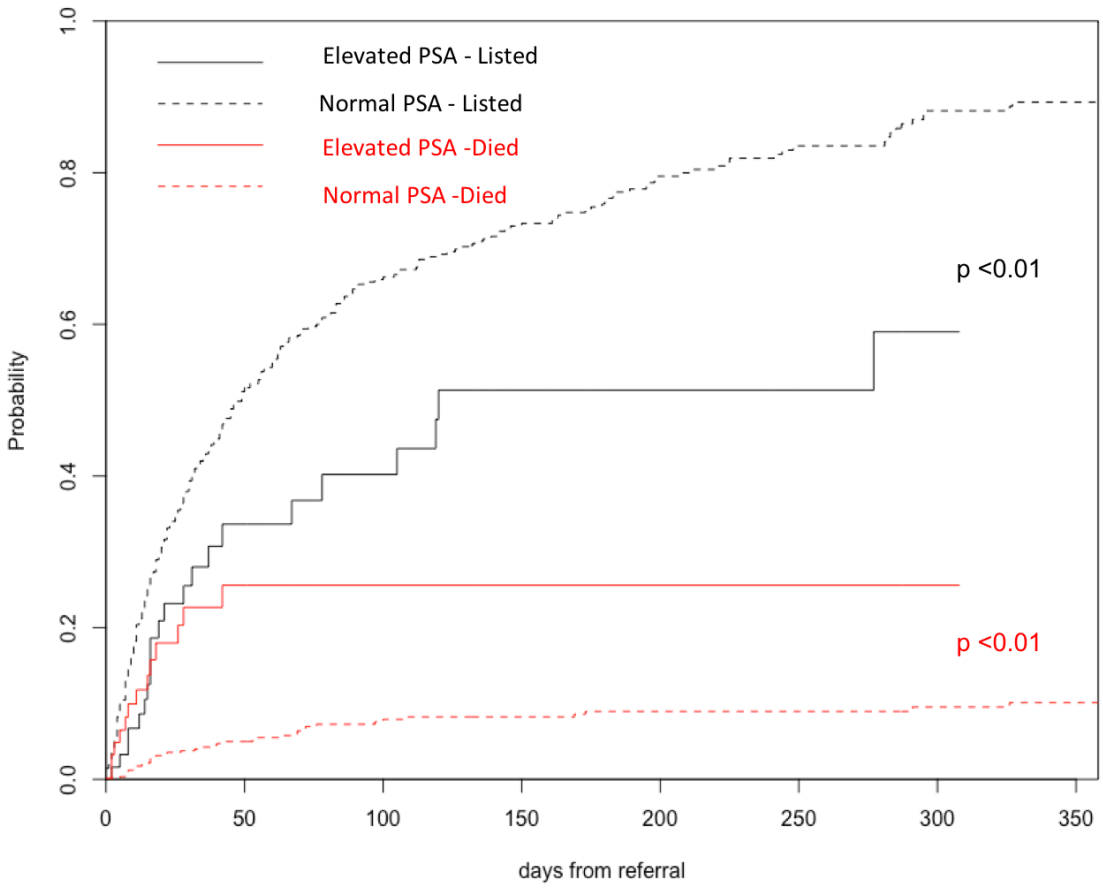
To analyze this further, we calculated the cause specific hazard for, a) being listed for cardiac transplant and b) dying during the cardiac transplant process by PSA screening status. To do this, a univariate Cox proportional hazard model was used to calculate the hazard ratio and accompanying 95% CI by screening status. When calculating the hazard ratio for being listed for transplant, patient that were not listed were censored (including those that died during the evaluation) and when calculating the hazard ratio for death during evaluation, patients that were listed and not listed for reasons other than death during evaluation were censored. In a further sensitivity analysis, we calculated the impact on classifying patients as 'listed for transplant' at their time of death on the hazard ratio for listing by screening status. Finally, in an analysis restricted to the patients that had their outcome in the first 365 days (excluding 25 patients whose evaluation decision occurred after this time point), we utilized the Fine and Gray methods for calculating cumulative incidence function of both listing for transplant and death during evaluation[60–62]. We plotted the cumulative incidence curves for each outcome stratified by a patient's screening status and compared the equality of the cumulative incidence functions across the groups by using the log-rank test developed by Gray *et al.*[60]

In a univariate analysis, patients with a positive PSA screening result (≥4ng/ml) had reduced likelihood to be listed for cardiac transplant (HR 0.64 95% CI 0.43-0.94) and an increased likelihood for dying during the transplant evaluation process (HR 3.15 95% CI 1.68-5.89). In our sensitivity analysis, where all patients that died during the transplant evaluation process were categorized as 'listed for transplant' at their date of death, there is no association between PSA screening status and time to listing or death (Table 5.5). The cumulative incidence curves demonstrate, similar to the values quoted by the cause specific proportional hazards ratios quoted above, that patients with a positive PSA screening result are indeed more likely to die during the transplant evaluation and less likely to be listed for transplant (Figure 5.3). Given the sample size and outcomes, further multivariable competing risks analyses was beyond the scope of this analysis.

Table 5.5: Cause specific hazards including the competing risk of death during evaluation.

	HR	95% CI
Cause specific hazard for listing for transplant		
Elevated PSA >4ng/ml	0.64	0.43-0.94
Cause specific hazard of death during evaluation		
Elevated PSA >4ng/ml	3.15	1.68 – 5.89
Categorizing patients that died during evaluation as being 'listed' at the time of death		
Elevated PSA >4ng/ml	0.89	0.64-1.24

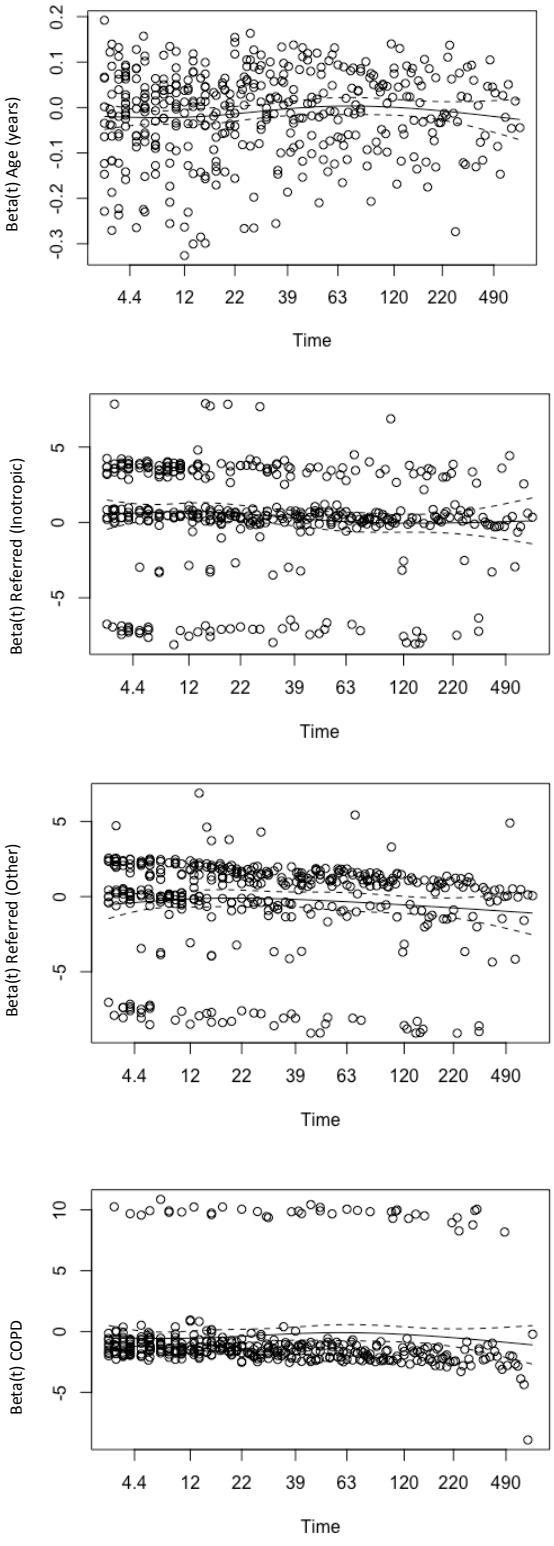
Figure 5.3: Cumulative incidence curves for the outcomes listed for transplant and death during transplant evaluation stratified by screening status.

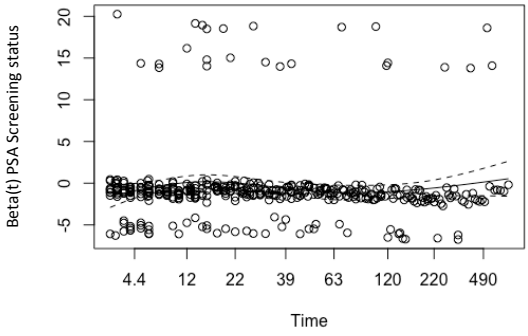


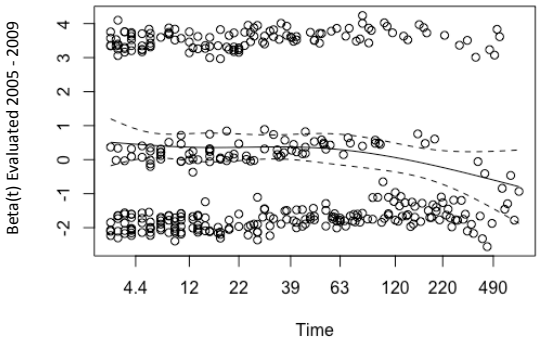
5.4: Model Diagnostics of Cox Proportional Hazards Model

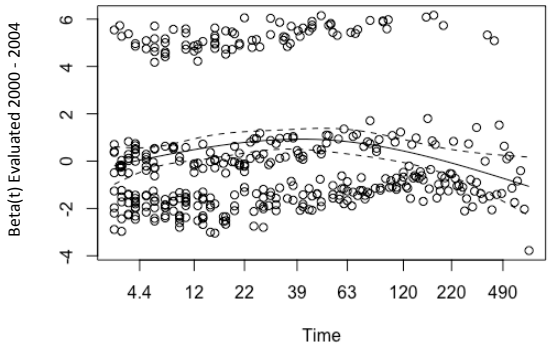
Using Schoenfeld residuals, we found that there was no violation of the assumption of proportional hazards in the multivariable Cox proportional hazards model used in the primary analysis (Figure 5.4). There was no violation of the linearity assumption of the continuous variables (Figure 5.5). Using interaction terms in the multivariable Cox model, we found that there was no evidence of effect modification in the association of a positive prostate cancer screen and time to listing for cardiac transplant (Table 5.6).

Figure 5.4: Assessment of proportional hazards assumption using Schoenfeld residuals




Beta(t) PSA Screening status
20
15
10
5
0
-5
4.4
12
22
39
63
120
220
490
Time


Beta(t) Evaluated 2005 - 2009
4
3
2
1
0
-1
-2
4.4
12
22
39
63
120
220
490
Time


Beta(t) Evaluated 2000 - 2004
6
4
2
0
-2
-4
4.4
12
22
39
63
120
220
490
Time

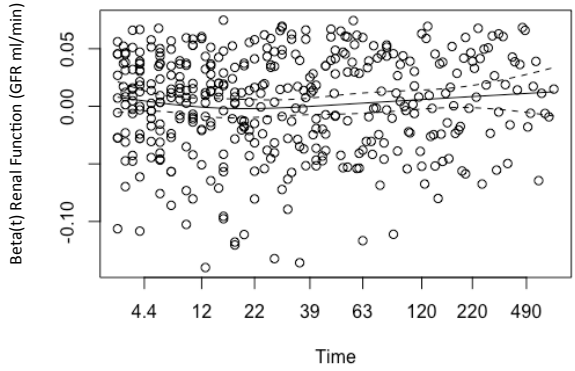
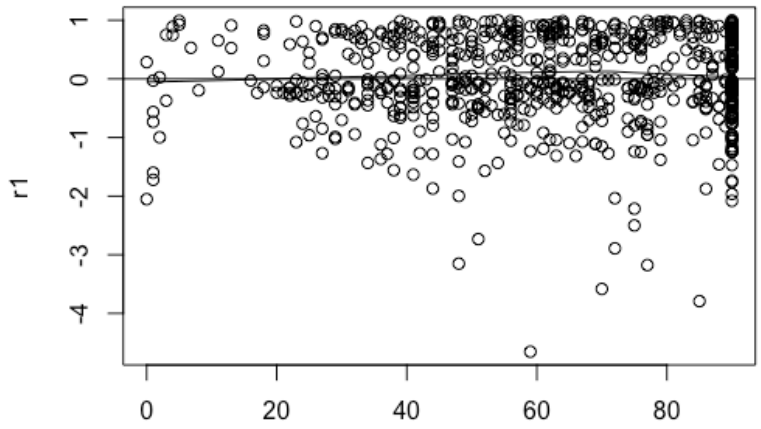

Beta(t) Renal Function (GFR ml/min)
0.05
0.00
-0.10
4.4
12
22
39
63
120
220
490
Time

Figure 5.5: Assessment of the assumption of linearity in the multivariable Cox proportional hazards model

A) Renal Function (GFR ml/min)



B) Age at Evaluation (Years)

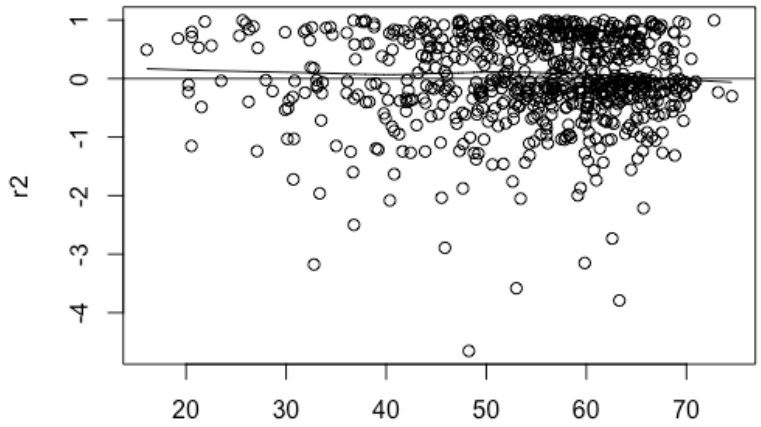


Table 5.6: Assessment of effect modification in the multivariable Cox proportional hazards model.

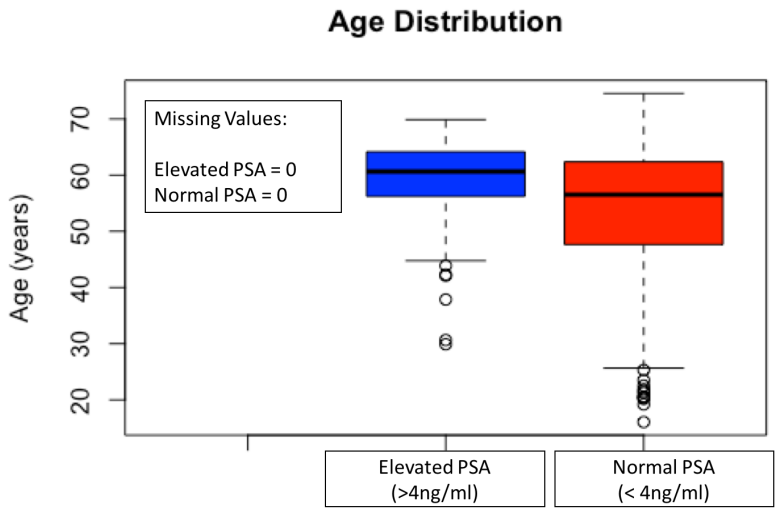
Variables			
			p-value
Effect Modification by Age at Evaluation			
Interaction Term Age at Evaluation x PSA Screening Status			0.58
Effect Modification by Year Category			
Interaction Term '2000-2004' x PSA Screening Status			0.88
Interaction Term '2005-2009' x PSA Screening Status			0.13
Effect Modification by Clinical status at Referral			
Interaction Term Inotropic Support x PSA Screening Status			0.50
Interaction Term 'Other' x PSA Screening Status			0.65
Effect Modification by COPD Status			
Interaction Term Renal Function x PSA Screening Status			0.77
Effect Modification by Renal Function			
Interaction Term Renal Function x PSA Screening Status			0.10

5.5: Missing values

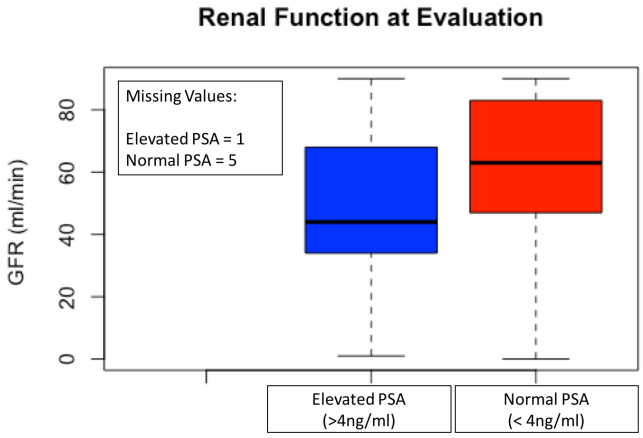
The multivariable Cox proportional hazard model used in our primary analysis excluded 6 patients that were missing data on the covariates included. The distribution and missing values for each of the continuous variables used in the model building process is represented in Figure 5.6. For the categorical variables, there were 39 patients that were missing data on their blood type (1 patient with a positive PSA screen), there were no other missing values for the categorical variables.

Figure 5.6: Box plots demonstrating the distribution of the continuous variables according to screening status.

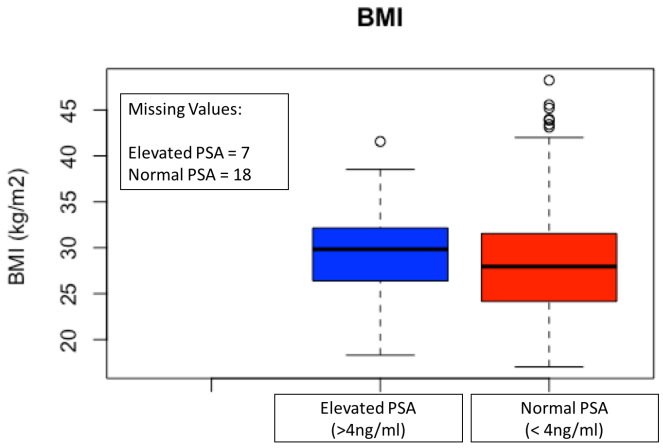
a) Box Plot of Age at the point of evaluation



b) Box plot of renal function at the point of evaluation



c) Box plot of Body Mass Index



PSA = Prostate Specific Antigen
BMI = Body Mass Index
GFR = Glomerular Filtration Rate

5.6: Excluded patients without prostate cancer screening

Out of the 806 men that received a cardiac transplant evaluation over the timeframe of the study, 95 (12%) had no evidence of screening with PSA. These patients were excluded from the primary analysis. When examining the available characteristics of these patients, they were of similar age to the patients with a negative PSA screening result (54.9 year +/- 13.1) and 27 (28%) were listed for transplant. Among the patients that were listed for transplant the median time to listing was 43 days (IQR-14-81 days) (Table 5.7).

Table 5.7: Listing outcomes of patients with no PSA screening

Variable	**No PSA performed** **n=95**
Age at Evaluation (mean +/- SD)	54.9 (13.4)
Listed (n (%))	27 (28.4)
List Status (n (%))	
1A	5 (5)
1B	1 (1)
2 or 7	21 (22)
Median Time to Listing (days (IQR))	43 (14-81)
Transplant (n, % listed)	10 (37)

5.7: Patients Listed for Cardiac Transplant

405 (58%) patients were listed for cardiac transplant over the timeframe of this study. Most transplant evaluation occurred between 2010 and 2015, however the proportions of patients that were eventually listed for transplant were similar at each category (Table 5.8). 51% of patients with a diagnosis of Ischemic Cardiomyopathy (ICM) or a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) were listed for cardiac transplant. Differing proportions of patients were listed for cardiac transplant according to their clinical status at referral (Table 5.8).

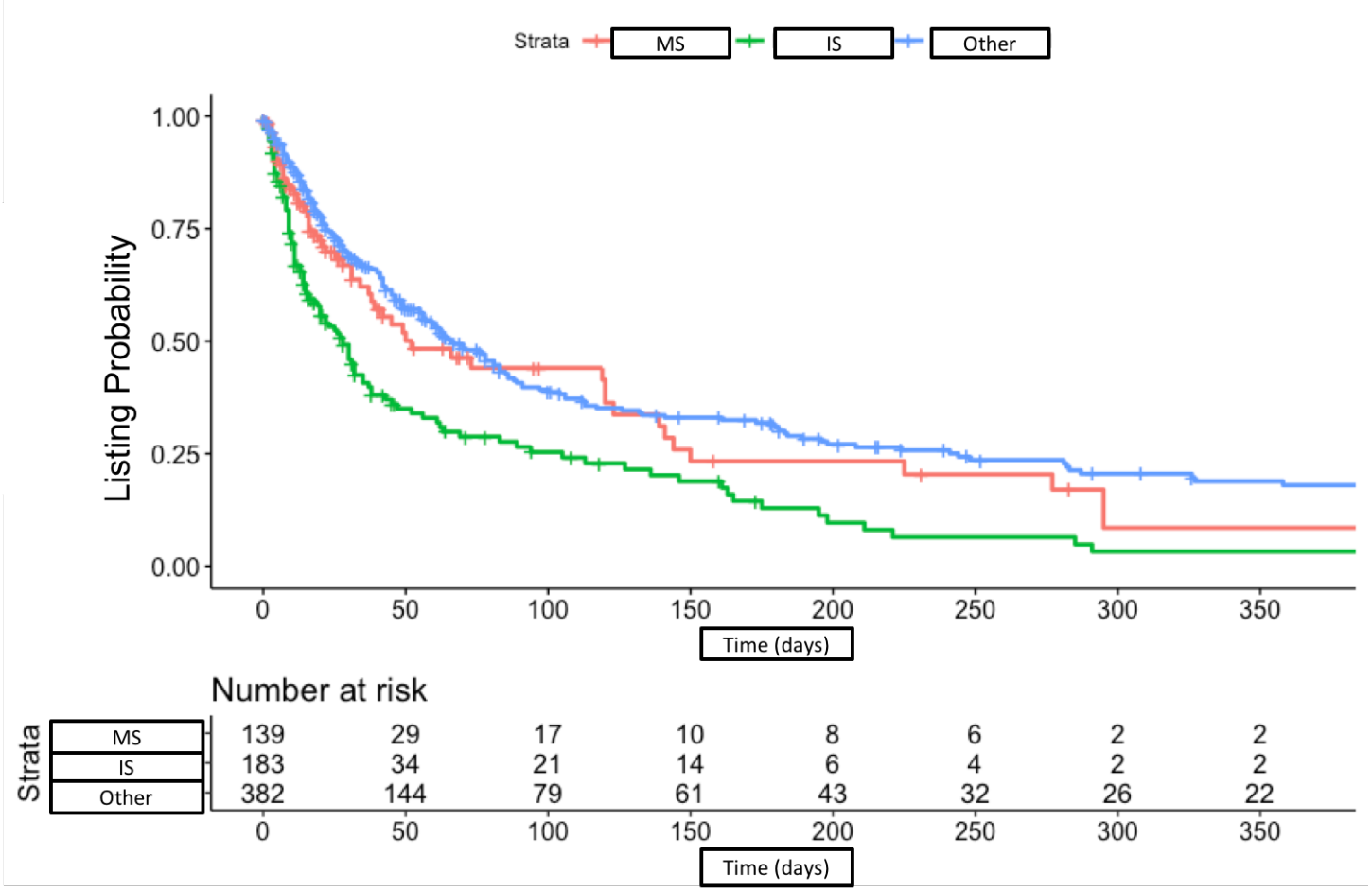
Table 5.8: Proportion of patients listed for cardiac transplant according to baseline variables

Variable	Listed for Transplant (%)
Year of Evaluation	
2010 – 2015 (N=355)	199 (56)
2005 – 2009 (N = 206)	122 (59)
2000 – 2004 (N=143)	84 (59)
Clinical Status at Referral	
Continuous Mechanical Support (N=139)	63 (45)
Continuous Inotropic Support (N=183)	123 (67)
Other (N=382)	219 (57)
Diagnosis of Ischemic Cardiomyopathy (N=385)	202 (52)
Diagnosis of COPD (N = 81)	40 (51)

The estimate provided by the Cox proportional hazards model in the primary analysis and the logistic regression model in the sensitivity analysis differed significantly by the clinical status of the patients at referral. We conducted a Kaplan-Meier analysis to determine the median time to listing for cardiac transplant stratified by clinical status at referral (Figure 5.7). The median time for patients on inotropic support was 28 days (95% CI – 20-35 days), mechanical support was 52 days (95% CI – 38-123 days) and

those with NYHA class III or IV symptoms, Inoperable CAD or Ventricular Arrhythmia refractory to medical treatment (referred to as ‘other’) had a median time to listing of 66 days (95% CI 56-83 days). Thus, the difference between the two models likely represents the differing listing and censoring distributions between the categories.

Figure 5.7 Kaplan-Meier curve of time to listing for Cardiac Transplant according to clinical status at referral. The median time for patients on inotropic support (IS) was 28 days (95% CI – 20-35 days), mechanical support (MS) was 52 days (95% CI – 38-123 days) and those with NYHA class III or IV symptoms, Inoperable CAD or Ventricular Arrhythmia refractory to medical treatment (referred to as 'other') had a median time to listing of 66 days (95% CI 56-83 days).



5.8: Patients not Listed for Cardiac Transplant

299 (42%) patients that were evaluated for cardiac transplant were subsequently not listed for transplant following evaluation. The reasons for a patient to be not listed for transplant is shown in Table 5.9.

Table 5.9: Reasons for a patient not to be listed for transplant according to screening status

Variable	Screening PSA >4 ng/ml n=66	Screening PSA <4ng/ml n=638
Died during Evaluation (%)	13 (19)	42 (7)
Medical or Surgical Intervention or Too well	12 (18)	87 (14)
Non-Cardiac Clinical Contraindication	9 (14)	70 (11)
Social or Nutritional Contraindications	2 (3)	53 (8)
Lost to follow up	5 (8)	6 (1)

5.9: Biochemical characteristics of patients with a positive screen

58 (88%) of patients with a positive PSA screening result had their values checked during an inpatient admission. Furthermore, patients with a positive screening result were more likely to be on continuous mechanical support compared to those patient with a negative screen. We explored further, whether the values of other commonly performed biochemistry tests performed during evaluation also varied by the clinical status of the patient at the point of referral. Our exploratory analyses found that patients on mechanical support were more likely also to have deranged thyroid function tests and elevated Lactate Dehydrogenase (LDH) (Table 5.10). Clinically, the elevated lactate dehydrogenase is to be expected as patients on mechanical support are more likely to suffer from hemolysis, which is known to elevate LDH[63]. Similarly, a patient with acute critical illness is more likely to have sick euthyroid syndrome[64] with low levels of circulating thyroid stimulating hormone (TSH). The changes in PSA during an acute cardiovascular event is not fully elucidated, with some studies suggesting that patient with more severe cardiac disease will have greater rises in serum PSA[32].

Table 5.10: Biochemical characteristics of patients with a positive PSA screening result

Variables	Mechanical Support	Inotropic Support	Other
	N=40	N=11	N=15
Biochemical Characteristics			
PSA Value (median (IQR))	12.5 (6.5 – 24.5)	7.3 (6.0 – 9.7)	6.2 (5.1 – 8.1)
Renal Function at Evaluation (GFR(ml/min))	43 (34 - 77)	49 (39 - 59)	42 (29 - 65)
Thyroid Stimulating Hormone (N (%))			
Normal	30 (75)	10 (91)	15 (100)
Elevated	2 (5)	1 (9)	0 (0)
Low	6 (15)	0 (0)	0 (0)
Lactate Dehydrogenase (median (IQR))	579 (351 - 1056)	222 (174 - 261)	246 (215 - 365)

Chapter 6: Bibliography

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