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• ***Title.*** Outcome of Pediatric Heart Transplantation in Blood Culture Positive Donors in the United States

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Abstract

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Outcome of Pediatric Heart Transplantation in Blood Culture Positive Donors in the United States

Clinical transplantation

Abstract

Active donor infection at time of organ procurement poses a potential infection risk and may increase post-transplant morbidity and mortality in recipients. Our hypothesis was that pediatric heart transplant recipients from blood culture positive donors (BCPD) would have increased morbidity and mortality compared to non-blood culture positive donors (NBCPD). A retrospective analyses of pediatric heart transplant recipients using the Organ Procurement and Transplant Network (OPTN) between 1987 and 2015 were conducted. Recipient as well as donor data were analyzed. Propensity score matching with 1:2 ratios was performed for recipient variables. Post-transplant morbidity and mortality was compared for recipients of BCPD and NBCPD. Among 9,618 heart transplant recipients, 450 (4.7%) were from culture-positive donors. Recipients of BCPD had a longer duration of Status 1A listing; diagnosis of congenital heart disease or restrictive cardiomyopathy and required support (IV inotropes, Inhaled NO and LVAD) prior to transplant. Post-transplant survival between the two groups were not different. Propensity matched recipients had similar length of stay; stroke rate; need for dialysis; pacemaker implantation and treated rejection episodes in the first year post transplant. Careful acceptance of BCPD may have the potential to increase availability of donor hearts in the pediatric population.

***Keywords*:** Blood culture positive donors; pediatric heart transplant; transplant outcomes; UNOS

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Introduction

Heart transplantation is routinely offered to children with end-stage heart failure due to cardiomyopathies or secondary to various congenital heart diseases (CHD). [1-4] In recent years, survival outcomes for CHD surgery have improved. [5-7] Hence, in addition to children there is now an increasing flux of adults with congenital heart disease requiring heart transplantation. [8, 9]

Limited donor availability of hearts remains a challenge, for which measures to maximize the donor pool are warranted. One of the many ways to increase the availability of organs is by using high-risk donors or suboptimal organs. Pediatric studies using high risk donors, donors previously refused and donors with depressed ventricular function have been successful. [10-12]

Donor transmitted infections are known to occur in 0.2-1.7% of all transplant procedures. [13, 14] Immunosuppressants following organ transplantation further lowers immunity [15-17], making the recipient more susceptible to overt clinical infection or reactivation of a latent infection. Such infections, in turn, are reported to increase post-transplant morbidity and mortality in heart transplant recipients. [18, 19]

A recent multi-center study by Forest et al. [20] evaluated short and long term heart transplant outcomes in adults following heart transplantation from blood culture positive donors (BCPD) vs. non-blood culture positive donors (NBCPD). Recipients of BCPD had higher rates of co-morbidities, but overall survival was no different at 1 year (86 vs. 87%, p =0.2585) and at 15 years (34% vs. 36%, p =0.0929). There is paucity of data, however, on post-transplant outcomes of pediatric recipients receiving hearts from BCPD. In this study, we compared morbidity and mortality outcomes of pediatric patients who received hearts from BCPD vs. NBCPD.

Methods

Study design and data collection

This was a retrospective analysis of data obtained from the United Network of Organ Sharing Database (UNOS) Standard Transplant Analysis and Research files. UNOS is the regulatory agency responsible for the oversight of all solid organ transplantation in the United States. UNOS data include donor and recipient characteristics and follow-up outcomes of all patients who have undergone solid organ transplantation. The study was determined to be exempt from review by the Institutional Review Board of the Children's Hospital of Michigan and Wayne State University as all protected health information was de-identified.

Pediatric patients ≤ 18 years of age, either gender, undergoing single organ (heart) transplantation in the United States from 1987-2015 were included for this study. Adult patients (>18 years); and multi-organ transplants were excluded. Moreover, outcome variables with <50% reported values were excluded from analysis.

Donor variables included for analysis were: age; gender; ethnicity; weight; body surface area (BSA); body mass index (BMI); ABO blood type; cause of death; Hepatitis B and Hepatitis C status; cytomegalovirus (CMV) status; tattoos; source of infection (pulmonary, urine, other); risk status for blood-borne transmission; history of drug abuse (cocaine, intravenous (IV) or other drug use); ischemic time; receipt of IV inotropes; previous cardiopulmonary resuscitation (CPR); and left ventricular ejection fraction.

Recipient variables included for analysis were: age; gender; ethnicity; weight; BSA; BMI; days listed as UNOS status 1A; primary transplant vs. re-transplant; primary cardiac diagnosis - dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), hypertrophic cardiomyopathy (HCM), congenital heart disease, Heart re-transplant and Other); ABO blood type; patient status prior to transplant (out of hospital, in hospital, ICU); support prior to transplant (ventilator, ECMO, IABP, IV inotropes, Dialysis, Inhaled nitric oxide, Other); ventricular assist device (VAD) use prior to transplant; Panel Reactive Antibody (PRA); prior cardiac surgery; serum albumin; year of transplant; infection requiring IV drug therapy 2 weeks before transplant; and donor-recipient ABO match.

Our primary outcome was patient survival post-transplant. Our secondary outcomes were post-transplant hospital length of stay; events prior to hospital discharge (stroke, dialysis, pacemaker implantation); and treated rejection episodes in the first year post transplant.

Statistical analysis

Summary statistics are presented as median (interquartile range), mean ± standard deviation, or number (percent) as appropriate. Recipient and donor characteristics were compared across groups using the Chi-square or Fischer's exact tests for categorical variables and the Student's t-test or Wilcoxon rank-sum test for continuous variables, as appropriate, depending upon variable distribution. Cochrane-Armitage test was utilized to evaluate trend of utilization of BCPD overtime.

SAS PSMATCH [21] procedure utilizing the optimal method of propensity score matching with 1:2 ratios was performed to achieve unbiased estimation of treatment effect in an observational study. Optimal method selects all matches simultaneously without replacement to minimize the total absolute difference in propensity score across all matches. The variables used in the above procedure included gender; ethnicity (white vs. non-white); ventilator , ECMO, VAD and dialysis prior to transplant; underlying diagnosis (congenital heart disease vs. others); year of transplant (before 2010 vs. 2010 and after); days as status 1A (≤ 7 days, 8-30 days, > 30 days); and age (< 1 year, 1-10 years, 10-18 years). The PSMATCH procedure resulted in 449 cases and 898 controls.

The characteristics and outcomes of the two study groups were compared using t-tests and chi-square tests after the propensity score matching. Kaplan-Meier survival curves along with log-rank test were used to compare graft and overall survival of the two study groups. The conventional p-value < 0.05 was used to determine statistical significance. All data analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC).

Results

A total of 9618 pediatric heart transplants were performed during the study period and 450 (4.7%) children received organ from BCPD. There was a progressive increase in utilization of BCPD for heart transplantation over the years (p <0.0001). **(Figure 1)**

Donor characteristics

Demographic characteristics of BCPD and NBCPD were similar with respect to gender, weight, body mass index (BMI), ABO blood type and Hepatitis B and C status. BCPD were more likely to be older [11-18 years (29.9 vs. 23.8%, p=0.04)]; of African American or Hispanic ethnicity (23.8 vs. 19%; 21.3 vs. 17% respectively, p=0.001); have died from anoxia (19.1 vs. 13.9%, p<0.0001) or drug intoxication (3.6 vs. 1.2%, p <0.0001); and more likely to have tattoos (7.8 vs. 5.3%, p=0.03) on their body. Moreover, they were more likely (4.4 vs. 2.4%, p= 0.01) to be a

Public Health Service increased risk donor [donors which were deemed to be at higher risk for HIV prior to 2013 and HIV, HBV and HCV after 2013], and to have a source of infection. History of drug abuse, however, was no different between two groups. **(Table 1)**

Recipient characteristics

Recipients of BCPD were no different than NBCPD with respect to age, gender, weight, BMI and previous history of transplant. However, recipients of BCPD were listed for a longer duration as UNOS status 1 [34.6 (29.4-39.9) vs. 24.9 (23.8-26.1) days, p=0.0004); more frequently had a history of congenital heart disease (19.1 vs. 13.7%; p=0.0003) or restrictive cardiomyopathy (6.4 vs. 4.3%, p=0.0003); and were more likely to be on IV inotropic support (46.2 vs. 38.3%, p=0.0009) and inhaled nitric oxide (1.3 vs. 0.5%, p=0.02) prior to transplant. Also, recipients of BCPD were more likely to be on left ventricular assist device (LVAD) support (8.2 vs. 4.5, p=0.0009) prior to transplant. Moreover, recipients of BCPD were more likely to have received IV drug therapy for infection two weeks prior to transplant (25.3 vs. 16.3%, p <0.0001). **(Table 2)**

Post-transplant outcomes of recipients from BCPD vs. NBCPD

There were no differences in median patient survival between unmatched recipients of BCPD and NBCPD (p=0.15). **(Figure 2a)** In the matched cohort, there was no difference in 1-month survival (94.1 vs. 95.1%, p=0.51) and 6-month survival (88.9 vs. 89.9%, p=0.63) post-transplant. Moreover, long-term patient survival between matched recipients was also no different (p=0.72). **(Figure 2b)**

Propensity matched BCPD and NBCPD recipients had similar median hospital length of stay [27.2 (24.3-30.2) vs. 27.5 (25.3-29.7) days, p=0.90); stroke rates (3.2 vs. 2.4%; p=0.36), need for dialysis (7 vs. 6.9%, p=0.91) and pacemaker implantation (0.9 vs. 1.1, p=1) post-transplant. The numbers of treated rejection episodes in the first year post transplant were also no different between both groups (28.7 vs. 29.2%, p 0=88). **(Table 3)**

Discussion

Most recent UNOS/OPTN estimates (2011-2014) reveal that median waiting times for pediatric patients listed for heart transplants ranged from 72-188 days (the longest for children 1-

5 years of age). [22] During the same time, the number of pediatric patients who were successfully transplanted was around 61.4-74.5% with the lowest number in infants. In view of the limited supply of donor hearts, there has been a quest to evaluate outcomes following heart transplantation from suboptimal donors.

In our study, blood culture positive donors were utilized for transplants in only a minority of patients (4.7%). Whether this was because of fewer BCPD in the United States or the fact that there was low utilization of such donors is not known. It has been shown that there is a risk of transmitting donor infections to the recipient via transplant and such infections can increase early and late morbidity and mortality. [13, 14, 23-27] Moreover, pediatric patients do not have as many co-morbidities (diabetes, hypertension and end stage renal disease) as adults and hence centers tend to wait for an “ideal” donor organ. [28, 29] Thus the donor pool is often limited for use by these patients.

Although ideally transplanting centers would like to have all information (clinical and microbiological) about the donor, time constraints in which such screening must be carried out make it less likely that transplanting centers would have all this information until after transplant. [30] In our study, we found characteristics of donors who were more likely to be blood culture positive (adolescent; of African American or Hispanic ethnicity; death from drug intoxication; and have other focus of infection). These characteristics may be used by the recipient center as a screening tool to identify such donors.

As expected, recipients who received BCPD had higher acuity of illness at time of transplant (longer duration as UNOS status 1A; underlying cardiac diagnosis of congenital heart disease or restrictive cardiomyopathy; on IV inotropes, inhaled nitric oxide and VAD support pre-transplant) and would have likely died on the waitlist as shown in other studies [31-35] if centers had not accepted a BCPD. Interestingly, recipients of BCPD were more likely to have received IV drug therapy for infection in the two weeks prior to transplant. These patients were probably more prone to infection because they were more likely to have been on ECMO or VAD support, both of which are known to be associated with an increased infection risk. [36-40].

The survival in both unmatched and propensity matched analyses was comparable between BCPD and non-BCPD groups. Morbidities and hospital length of stay was also similar. These results, given the higher acuity of the BCPD recipients, are encouraging. These findings are similar to the adult study evaluating outcomes of blood culture positive donors in kidney [41], liver [42] and heart transplantation. [20] Selective use of PHS "increased risk" donors have been shown in other analysis to result in similar post-transplant survival. [10] Donors at high risk of positive blood culture or those with known positive blood culture likely comprise some of this "increased risk" pool for which post-transplant survival is not impacted and therefore if all else with the donor seems suitable for transplant (considering the candidate's risk profile) then donor should not be declined solely on the basis of positive blood culture or likely positive blood culture.

Certain measures can be taken to decrease transmission of donor-derived infections to the recipients. Such measures include: (a) surveillance cultures of the transplant recipient to detect any infection post-transplant. (b) depending on the organism isolated from the donor, post-transplant antibiotics directed against the organism for appropriate duration. [43-46] The use of BCPD, along with active surveillance and judicious use of antibiotics in such recipients will allow an expansion of the donor pool for pediatric heart transplantation recipients without increasing morbidity and mortality.

Study Limitations

Our study is based on analysis of registry data, which often depends on accurate data input by the participating centers. Post-transplant outcomes such as early in hospital mortality, post-transplant sepsis, long term morbidity, and coronary allograft vasculopathy were not available and hence could not be analyzed. We limited the outcomes analysis to only those variables that had more than 50% reported rates, thus reducing but definitely not eliminating a type II error. We didn't have detailed information about the bacterial strains. This information is important as virulent bacterial infections may have worse post-transplant outcomes than community acquired bacteria. Also, there is a possibility that a portion of blood culture positive donors may include individuals who have cultures that are positive for common contaminants such as coagulase negative staphylococcus which may not increase post-transplant morbidity or mortality. Finally, we didn't have information for blood culture positive donors that never got utilized for transplantation. Whether the BCPD who were accepted for transplantation differed in some systematic way from those that were not accepted is unknown, and certainly possible.

Conclusions

In this study, we utilized the largest national transplant registry to assess the characteristics and outcomes of BCPD in the pediatric population. Recipients of such BCPD donors were more likely to have higher acuity of illness and a higher likelihood of dying while waiting for transplant. Even though recipients of BCPD were sicker, post-transplant morbidity and mortality was not inferior to recipients receiving NBCPD. These findings suggest that careful acceptance of BCPD may have the potential to increase the availability of donor hearts without increasing post-transplant morbidity and mortality in children with end-stage heart failure.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the journal.

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Table 1. Demographic and Clinical Characteristics of donors

	No. of Patients n= 9618 n (%)	BCPD n=450 Mean [95% CI], or n (%)	NBCPD n= 9168 Mean [95% CI], or n (%)	p value
Age, y				
0-≤1	8714 (90.6)	83 (20.3)	1953 (23.5)	
1-10		136 (33.4)	2945 (35.5)	**0.04***
11-18		122 (29.9)	1980 (23.8)	
>18		67 (16.4)	1428 (17.2)	
Weight	9126 (94.9)	34.8 [32.4-37.2]	32.6 [32.1-33.1]	0.08
Donor BMI	8563 (89)	19.6 [19.1-20]	19.1 [19-19.2]	0.06
Gender				
Male	9617 (99.9)	250 (55.6)	5240 (57.2)	0.53
Female		200 (44.4)	3927 (42.8)	
Ethnicity				
Caucasian	9433 (98.1)	235 (53.3)	5622 (62.5)	**0.001***
African American		105 (23.8)	1704 (19)	
Hispanic		94 (21.3)	1530 (17)	
Other		7 (1.6)	136 (1.5)	
ABO blood type				
O	9448 (98.2)	286 (63.6)	5421 (60.3)	0.51
Cause of death				
Anoxia *	9485 (98.6)	86 (19.1)	1254 (13.9)	
Trauma #		190 (42.2)	4039 (44.7)	**<0.0001***
Cardiovascular		30 (6.7)	564 (6.2)	
Drug intoxication		16 (3.6)	105 (1.2)	
Other †		128 (28.4)	3073 (34)	
Hepatitis B positivity	9618 (100)	2 (0.44)	70 (0.76)	0.78
Hepatitis C positivity	9618 (100)	2 (0.44)	7 (0.08)	0.06
CMV positivity	9618 (100)	265 (58.9)	4635 (50.6)	**0.0006***
Donor Tattoos	9618 (100)	35 (7.8)	490 (5.3)	**0.03***
Donor source of infection				
Pulmonary	9618 (100)	292 (64.9)	2142 (23.4)	
Urine		186 (41.3)	502 (5.5)	**<0.0001***
Other		47 (10.4)	302 (3.3)	
Donor at risk for blood-borne disease transmission £	9618 (100)	20 (4.4)	217 (2.4)	**0.01***
Source of infection				
Pulmonary	9618 (100)	292 (64.9)	2142 (23.4)	
Urine		186 (41.3)	502 (5.5)	**<0.0001***
Other		47 (10.4)	302 (3.3)	
Donor history of drug abuse				
Cocaine	9618 (100)	4 (0.9)	62 (0.7)	0.55
IV drug use		0 (0)	11 (0.12)	1
Other Drug use		28 (6.2)	448 (4.9)	0.22
Ischemic time > 4	9618 (100)	186 (41.3)	3312 (36.1)	**0.03***
Vasoactive support at	9618 (100)	186 (41.3)	2446 (26.7)	**<0.0001***

procurement				
Previous CPR	9618 (100)	27 (6)	451 (4.9)	0.32
Donor left ventricular ejection fraction	5713 (59.4)	63.6 [62.5-64.6]	62.8 [62.5-63.1]	0.17

* Drowning, Seizure, Asphyxiation # Gunshot wound, stab, Gunshot/stab wound, blunt injury, electrical † SIDS, Intracranial hemorrhage/stroke, Death from natural causes, None of the above.

£ Refers to Public Health Service Increased risk donors which are donors deemed to be at higher risk for HIV prior to 2013 and HIV, HBV and HCV after 2013.

Table 2. Demographic and Clinical Characteristics of recipients

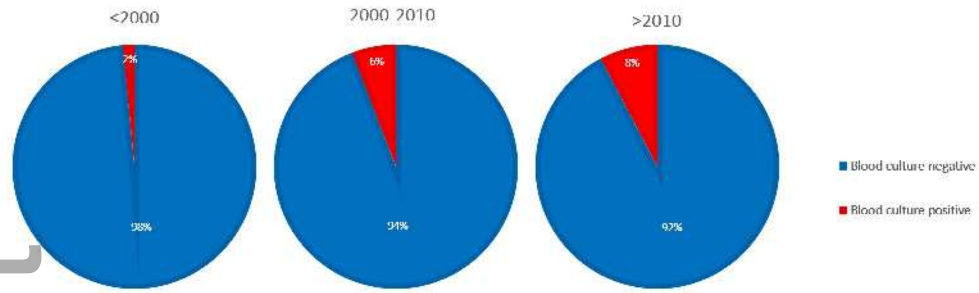
	No. of Patients n= 9618 n (%)	**BCPD n=450 Mean [95% CI], or n (%)**	**NBCPD n= 9168 Mean [95% CI], or n (%)**	**p value**
Age at listing				
0-≤1	9618 (100)	139 (30.9)	3244 (35.4)	
1-5		65 (14.4)	1235 (13.5)	0.18
6-10		75 (16.7)	1291 (14)	
11-18		171 (38)	3398 (37.1)	
Gender				
Male	9618 (100)	235 (52.2)	4916 (53.6)	0.56
Female		215 (47.8)	4252 (46.4)	
Ethnicity				
Caucasian		264 (60.6)	5797 (65.4)	**0.014***
African American	9304 (96.7)	73 (16.7)	1559 (17.6)	
Hispanic		82 (18.8)	1307 (14.7)	
Other		17 (3.9)	205 (2.3)	
Weight, kg	9469 (98.5)	27.5 [25.4-29.5]	26.6 [26.1-27]	0.41
BMI				
Underweight		326 (72.4)	6674 (72.8)	
Normal	9618 (100)	84 (18.7)	1884 (20.5)	0.22
Overweight		27 (6)	381 (4.2)	
Obese		13 (2.9)	229 (2.5)	
Days as UNOS status 1	9523 (99)	34.6 [29.4-39.9]	24.9 [23.8-26.1]	**0.0004***

Re-transplant	9618 (100)	20 (4.4)	538 (5.9)	0.25
Cardiac Diagnosis				
Restrictive CMP	9491 (98.7)	29 (6.5)	390 (4.3)	**0.0003***
CHD		86 (19.1)	1241 (13.7)	
Other		335 (74.4)	7410 (82)	
Patient status prior to transplant				
Out of hospital	9593 (99.7)	160 (35.6)	3294 (36)	
In hospital/Intensive Care		290 (64.4)	5849 (64)	0.88
Source of infection				
Pulmonary	9618 (100)	292 (64.9)	2142 (23.4)	
Urine		186 (41.3)	502 (5.5)	**<0.0001***
Other		47 (10.4)	302 (3.3)	
Life support prior to transplant				
Ventilator	9615 (99.9)	80 (17.8)	1702 (18.6)	0.71
ECMO	9618 (100)	31 (6.9)	440 (4.8)	0.06
IABP	9618 (100)	3 (0.7)	25 (0.3)	0.14
IV Inotropes	9618 (100)	208 (46.2)	3511 (38.3)	**0.0009***
Inhaled NO	9618 (100)	6 (1.3)	42 (0.5)	**0.02***
Other mechanism of life support	9618 (100)	6 (1.3)	215 (2.4)	0.19
LVAD prior to transplant	9615 (99.9)	37 (8.2)	416 (4.5)	**0.0009***
Albumin ≤3.5 g/dl	5476 (56.9)	181 (51.9)	2480 (48.4)	0.22
Dialysis between listing and transplant	9615 (99.9)	12 (2.7)	188 (2.1)	0.39
Infection requiring IV Drug therapy two weeks before transplant	9618 (100)	114 (25.3)	1491 (16.3)	**<0.0001***
Donor –Recipient Blood type				
Incompatible	9617 (99.9)	11 (2.4)	156 (1.7)	0.31
Donor- Recipient weight ratio	9036 (93.9)	1.36 [1.32-1.41]	1.38 [1.37-1.39]	0.49
Total bilirubin				
>2 mg/dl	7299 (75.9)	59 (14.5)	996 (14.5)	1

Table 3. Post-transplant outcomes in patients transplanted with blood culture positive vs. propensity matched non-blood culture positive donors

	BCPD n=449 Mean [95% CI], or n (%)	NBCPD n= 898 Mean [95% CI], or n (%)	p value
Hospital length of stay (days)	27.2 [24.3-30.2]	27.5 [25.3-29.7]	0.90
Stroke	14 (3.2)	20 (2.4)	0.36
Dialysis	31 (7)	59 (6.9)	0.91
Pacemaker implantation	4 (0.9)	9 (1.1)	1
Treated rejection episodes in first year post transplant	86 (28.7)	195 (29.2)	0.88

List of Figures



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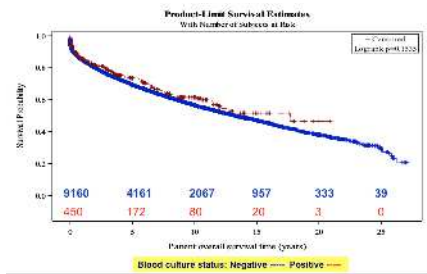

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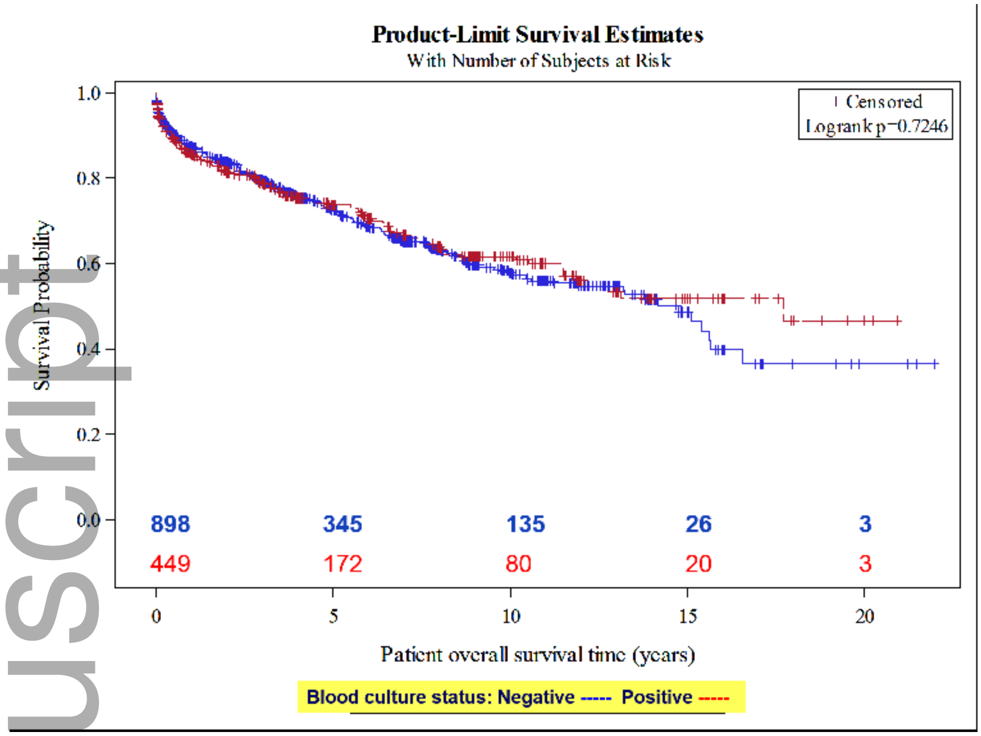

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