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Malperfusion Rather Than Merely Timing of Operative Repair Determines Early and Late Outcomes in Type A Aortic Dissection

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Glossary of Abbreviations:

ACS: Acute Coronary Syndrome

CPR: Cardio Pulmonary Resuscitation

GI: Gastro-Intestinal

IRAD: International Registry of Acute Aortic Dissection

IQR: Inter-quartile range

PATS: Patient Analysis and Tracking System

NSTS: National Health Service Strategic Tracing Service

ABSTRACT

Background:

While generally better outcome is reported for patients undergoing early repair of Type A aortic dissection, patients who survive the first 48 hours self select themselves towards a better outcome too. Malperfusion is also an important determinant of outcome in these patients. Aim of the study was to examine the hypothesis that it is malperfusion and not the timing of operation determining outcome in repair of type A aortic dissection.

Methods: 205 patients underwent operative repairs of acute type A aortic dissection over a 17 year period. Time from onset of symptoms to surgical repair was reliably established in 152 cases. Patients were grouped into those who had undergone an operation early [within 12 hrs] and compared to those who had the operation later [after 12 hrs].

Results: 72 patients (47%) were operated within 12 hrs. 30 day mortality was similar inboth the groups, 19.4% (95% CI 12.0-30.6) vs.13.8% (95%CI 7.9-23.5) p=0.08.
Log-rank test for equality of survivor functions was 0.08. However, malperfusion and haemodynamic compromise was also seen more commonly in those with shorter wait (47% vs. 31%) P = 0.029 and was found to be an independent predictor of long term mortality (hazard ratio 1.90, 95%CI 1.14 to 3.15), p=0.014.

Conclusions: Malperfusion at presentation rather than timing of intervention is the major risk factor of death both in hospital and at long term follow up in patients undergoing Type A aortic dissection.

CENTRAL MESSAGE

Presence or absence of malperfusion is the main determinant of outcome in patients undergoing repair of aortic dissections.

PERSPECTIVE STATEMENT

In Aortic Dissections patients undergoing early repair and those surviving the first 48 hours tend to have better outcome due to absence of malperfusion. Patients' where malperfusion has developed despite early presentation represent more severe pathology and associated with poorer outcomes. While early repair remains standard of care outcome is determined by malperfusion rather than timing of surgery.

Legend for the Central Picture

Survival comparison of patients with and without malperfusion

INTRODUCTION:

Acute type A aortic dissection, can be difficult to diagnose, due to a number of different clinical presentations. Sudden severe chest pain which is the most common presenting symptom often leads the patients to be investigated along the lines of Acute Coronary Syndrome (ACS) but may even be absent in up to 20% of the cases.[1] Other signs and symptoms usually associated with aortic dissection and routine investigations are neither sensitive nor specific for the condition.[2] Misdiagnosis can lead to a delay in surgical repair being carried out in up to 68% of cases.[3]It has therefore been suggested that rapid diagnosis of aortic dissections mandates a high degree of clinical suspicion and clinical algorithms have been developed to offer the best chance of diagnosis.[4, 5]

The delay in surgical repair of acute type A aortic dissection has been thought to be directly related to poor outcomes. In the absence of surgical correction the mortality increases by 1%-2% per hour after onset of symptoms and has been reported to be more than 35% in the first 24 hours.[6] Early diagnosis allows repair to be carried out before the development of cardiac tamponade or renal impairment and provides the patient with the best chance of survival.[7] The importance of malperfusion as a determinant of outcome has also been stressed by the International Registry of Acute Aortic Dissection (IRAD). It identified the presence of myocardial or mesenteric ischemia, kidney failure, hypotension, cardiac tamponade, and limb ischemia more commonly associated in non survivors following aortic dissection.[8]

While there is a sound scientific explanation for better outcome in patients who are operated early [9] it is also generally accepted that patients who survive the first 48 hours self select themselves towards a better outcome following surgical repair perhaps due to the absence of malperfusion.[3] Essentially this group of patients have pathophysiologically escaped developing malperfusion secondary to aortic dissection. The most obvious extension of this being the better natural history of intramural haematoma given that it is not associated with malperfusion.

It might be argued, therefore, that the outcome is related less to timing of surgical repair but more to the presence or absence of malperfusion. Timing merely acts as a surrogate marker with immediate operation preventing development of malperfusion and delayed operation selecting patients with minimal or no malperfusion.

We carried out this study to examine the hypothesis that it is malperfusion and not timing that has a direct relation to outcome following surgical repair of type A Aortic Dissection.

METHOD

Patient selection:

All patients undergoing surgical treatment for type A aortic dissection over a period of 17 years at the Bristol Heart Institute, were included in the study. The duration between onset of symptoms and surgical intervention was established through careful case note review. Duration between onset of symptoms and surgical repair and between presentation to our institution and intervention were calculated. The median time between the onset of symptoms and initiation of repair of aortic dissection was 12.5 hours with an inter-quartile range of 9-24.25 hours. We therefore used a cut off of 12 hours in order to have two groups of comparable size. Therefore, patients were grouped into those who had intervention within 12 hours of onset of symptoms and those who had intervention 12 hours after onset of symptoms.

Malperfusion was defined as presence of limb ischaemia including absence of pulse, cerebro-vascular event (syncope, Transient Ischaemic attack or stroke), objective evidence of visceral malperfusion, anuria or persistent oliguria, evidence of myocardial ischaemia and presence of significant haemodynamic compromise or shock secondary to cardiac tamponade or severe aortic regurgitation. Even in presence of malperfusion our strategy was to treat the aortic dissection first and deal with any residual end-organ malperfusion in the post-operative period.

Data Collection and Definitions:

Demographics, pre-, peri- and post-operative data has been collected prospectively on all patients undergoing cardiac surgery and entered into a database (Patient Analysis and Tracking System (PATS, Dendrite Clinical Systems Inc, London UK). The regression model included two variables, one indicated the timing of surgery (<=12 hours vs > 12 hours) and presence or absence of malperfusion. All types of malperfusion were considered together. Shock and rupture were considered as cardiac malperfusion. Deaths post hospital discharge was identified from

mortality data provided by NHS Strategic Tracing Service (NSTS). All patients were successfully matched to the NSTS database. Definitions with respect to the operative priority, pre-morbid conditions and post operative complications are those defined by the National Adult Cardiac Surgical Database and accepted by the Society of Cardiothoracic Surgeons of Great Britain and Ireland available at www.scts.org

Operative techniques:

For dissections extending beyond the ascending aorta an open distal anastomosis was used. Spiral tears extending along the under-surface of the arch were treated with a bevelled distal anastomosis (hemi-arch replacement). With tears within the aortic arch complete aortic arch replacement was performed. Only those operations involving two or more distal anastomoses, one to the distal aorta and one or more aortic arch branches, were considered as aortic arch operations.

Detailed surgical and anaesthetic techniques along with strategies for cerebral protection and blood conservation has been described previously. [10] With regards to malperfusion presenting with aortic dissection we adopted the policy of repairing the aortic dissection first. Any residual end-organ malperfusion was treated in the post-operative period.

Statistical analysis:

Baseline and operative characteristics were compared using the chi-squared or Fisher's exact test (categorical variables) or the Wilcoxon rank sum test (continuous variables). Mortality was estimated using the Kaplan Meier method and compared using log rank test. Cox regression was used to quantify mortality risk and mortality in subgroups compared by adding interaction terms to the Cox regression model. Cox regression model included important baseline and operative characteristics like age, gender, left ventricular ejection fraction, presence of marfan's

disease, re-operative surgery, aortic root replacement, arch replacement, concomitant caornary artery bypass grafting, presence of Malperfusion, duration between symptoms and operation as a linear and non linear term. To assess if a linearity of relation existed between time and survival we used ANOVA to compare time to surgery as a linear versus time to surgery as a non-linear variable. (3 knots spline). All analyses were carried out using Stata® version 9.2 (Stata Corporation, College Station, Texas, USA).

RESULTS:

During the study period 205 procedures were performed. Time from admission to the hospital to intervention was ascertained in all cases. However, time from onset of symptoms to surgical repair could be determined reliably for 152 cases (74%). Median time between onset of symptoms and operation was 12.5 hours inter-quartile range (IQR) 9 - 24.25 hours. 72 patients (47%) were operated within 12 hours and 80 patients (53%) were operated beyond 12 hours of onset of symptoms. The median time between presenting to our centre and undergoing a surgical repair was 3 hours (IQR 1.5- 7 hours).

Malperfusion was present in 60/152 cases (39%) of patients. In patients undergoing early surgical repair evidence of organ malperfusion was also more common but not statistically significant [35 (48.6%) vs. 25(31.3%); p=0.29]. A summary of different organ malperfusion across the two groups are detailed in Table 1. All other baseline characteristics were similar in both the groups. [Table 2] Apart from a significantly higher proportion of patients requiring an aortic valve replacement or repair/re-suspension in the early group the surgical procedures carried out across the 2 groups were essentially similar. [Table 2]. With regards to post –operative morbidity there was no difference in outcome between the 2 groups either.[Table 3] Early mortality between the 2 groups was also similar. In patients undergoing early surgical intervention there were 14 (19.4%; 95% CI 12.0-30.6) deaths within 30 days as opposed to 11(13.8%95%CI 7.9-23.5) deaths in the group where operation was delayed beyond 12 hours (p= 0.08). Time to surgery as a non-linear variable showed an inverse relationship with late mortality (univariate P=0.03) with a first phase showing a decrease in mortality during the first 24 hours and a second steady phase. The effect of time from symptoms to surgery was no longer significant after multivariate adjustment (P=0.09) [Table 4]

In the group undergoing early surgical repair, mortality was slightly higher at 1 year, 5 years and 10 years follow up but this did not achieve statistical significance with a hazard ratio for late death being 0.64, 95% CI (0.38-1.06). [Figure 1]

Malperfusion on the other hand was associated with significantly increased risk of death (hazard ratio 1.90, 95%CI 1.14 to 3.15), p=0.014. [Table 6] No significant interaction was found between malperfusion and time to surgery on survival (P=0.34) [Figure 3]

.Malperfusion was confirmed as a risk factor for late mortality in both linear as well as non linear models [Figure 2].[Figure 2]

DISCUSSION:

The main findings of our study were that almost 40% of patients undergoing repair of type A Aortic Dissection had evidence of malperfusion. The second important finding was that presence of malperfusion was associated with significantly increased risk of death both in the short and long term follow up. With regards to timing, delayed operation had a reduced risk but this was not significant when malperfusion was accounted for.

Interesting information has emerged with regard to time dependent outcome from different studies and registries. Analysis of the IRAD data shows that there is an incremental risk of death of 1-2% every hour without repair.[6] After 24 hours there is a slightly lower risk of death[11] which continues to decrease between days 5 and 30 at a rate of 1% per day.[12] However, acute type A aortic dissection remains a true surgical emergency and the consensus opinion is surgical repair as soon as possible especially in the first 48 hours and more so in the presence of malperfusion.[6] The variability in outcome apparently influenced by time can be explained by the onset and progression of malperfusion and thus time related outcome is essentially a function of time related changes in organ perfusion. It has been proposed that malperfusion is a dynamic process and patients can present in different stages of organ perfusion. These stages can be categorized into no malperfusion, sub-clinical malperfusion, defined as organ malperfusion with preserved function and malperfusion syndrome with overt clinical organ dysfunction.[13, 14] So timing merely represents patients in different points of this malperfusion scale. Apart from the above three groups there is another group of patients who despite the aortic dissection do not seem to develop malperfusion and may account for the improved late results reported in some studies. In addition of course those with intramural haematoma do not experience malperfusion and have better outcomes.

In our study, we found that the patients who were operated early had slightly higher mortality but this was statistically not significant Moreover, the proportion of patients with malperfusion in this group was also higher and once malperfusion was accounted for there was no difference in outcome between the two groups..

In keeping with the finding of our study, malperfusion is reported to be present in almost one third of the patients presenting with acute type A aortic dissection.[15, 16] While sub-clinical malperfusion does not seem to increase the operative risk,[13] presence of clinical malperfusion is associated with poorer outcomes.[14] The outcome also varies with the type of associated malperfusion. Mesenteric ischemia is associated with the worst outcome and even though it occurs in a small proportion of patients it is associated with mortality in up to two-thirds of cases.[17,18] Cerebral malperfusion is associated with not only increased mortality but also leads to significant impairment of quality of life, even if the patient survives.[19] The incidence of coronary malperfusion due to type A aortic dissection has been reported in up to 15% cases.[20] However, it can be difficult to evaluate and leads to an increase in mortality both in the short term and at 5 years follow up.[10, 11] Hemodynamic instability, when associated with malperfusion at presentation has an extremely poor prognosis and this has been shown to be independent of patient age.[21]

The time related outcome, therefore, is merely a representative of malperfusion related outcomes. Prevention or reversal of malperfusion is the primary goal of operative repair. [16] Very early repair may treat the aortic dissection before it has a chance to cause organ malperfusion. Even after malperfusion has developed prompt repair allows perfusion to be restored to all compromised organ systems and helps in minimizing complications. [16] When malperfusion occurs before operative repair can be carried out the outcome is often poor. In some cases delayed operative repair is possible and often results from diagnostic delay and is usually associated with better outcome because these patients self select themselves to a better outcome as they do not have organ malperfusion . Essentially, the time related outcome

is merely a representation of malperfusion related outcome. Moreover, while time related outcomes can be conflicting, outcomes based on presence or absence of malperfusion seem to be associated with more consistent findings and better association with the pathology.

Limitations: One of the important limitations of the study was including different types of malperfusions as a single variable. Thus cardiogenic shock was included together with limb malperfusion. However, due to extremely low numbers of more serious malperfusions, like cardiogenic shock (n=2) analysing them individually was not possible. Moreover, the sample size was relatively small in our study was small, which may have led to absence of significant differences between the groups.

In conclusion, malperfusion at presentation rather than timing of intervention is the major risk factor of death both in the short and long term follow up in patients undergoing Type A aortic dissection. However, early operation remains the standard of care in managing type A aortic dissections as it prevents development of malperfusion and in those cases where malperfusion has already set in, it offers the best possible option to restore normal perfusion and limit the adverse effects of malperfusion.

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Table 1

Type of malperfusion seen in patients operated early and late for type A aortic dissection

	Early (<12 hours) (n=72)	Late (>12 hours) (n=80)
Cardiogenic shock needing Pre-op CPR	2	0
Cardiac Tamponade	7	4
Severe Aortic Regurgitation	8	3
Renal malperfusion	6	9
Limb ischemia	11	12
Cerebral malperfusion	5	11
GI Malperfusion	0	2

CPR = cardiopulmonary resuscitation; GI = gastro-intestinal

Table2

Baseline Characteristics

	Early (n=72)	Late (n=80)	P-value
Age (yrs)	62 (54 – 69)	63(49 – 70)	0.42
Male gender	56 (77.8%)	55(68.8%)	0.21
Hypertension	41 (57.8%)	38(48.7%)	0.27
Redo	4 (6.5%)	7(9.7%)	0.49
Peripheral Vascular Disease	6 (8.3%)	4(5.1%)	0.43
EuroSCORE	9 (7 – 12)	9(6 – 12)	0.96
Malperfusion	35 (48.6%)	25(31.3%)	0.029
Marfans	1(1.38%)	7(8.75%)	0.06
Concomitant coronary artery disease	4(5.55%)	8(10%)	0.37
CPB time (min)	166 (132-195)	152 (125-189)	0.36
Cross clamp time (min)	73 (57-101)	76 (61-108)	0.60
Circulatory arrest time (min)	36 (27 – 51)	37 (28 – 62)	0.78
Concomitant CABG	9 (12.5%)	10(12.5%)	>0.99
Concomitant MVR	1(1.4%)	2 (2.6%)	>0.99
Arch replacement	5 (6.9%)	8 (10.4%)	0.46
Valve replacement	17(23.6%)	21(26.9%)	0.015
repair / re suspension	15(20.8%)	4 (5.1%)	

Table 3

Post-operative Outcomes

	Early (n=72)	Late (n=80)	P-value
Neurological complication	10(15.6%)	10(13.3%)	0.70
Renal failure	8 (11.1%)	11 (13.8%)	0.62
Re-operation for bleeding	8 (11.4%)	9 (11.4%)	>0.99
Tracheostomy	10 (15.4%)	19(26.4%)	0.12
Septicemia	6 (9.8%)	9 (14.8%)	0.41
ICU stay (days)	4 (2 – 6)	5 (3 – 12)	0.06
Hospital stay (days)	13 (10 – 19)	14 (10 – 22)	0.45

Table 4

Multivariate analysis of different variables on outcome

	Hazard Ratio	Confidence Interval 95%	p-value
Age	1.02	[0.99;1.06]	0.1734
Female Gender	1.14	[0.50;2.63]	0.7558
Marfan's disease	0.30	[0.03;2.61]	0.2726
Left Ventricular Function	1.52	[0.63;3.64]	0.3507
Re-operative surgery	2.07	[0.45;9.50]	0.3494
Root replacement	1.29	[0.50;3.33]	0.5966
Arch replacement	0.63	[0.20;1.99]	0.4290
Concomitant coronary artery bypass grafting	3.03	[1.12;8.19]	0.0292
Malperfusion	2.65	[1.21;5.79]	0.0146
Time between symptom and operation as a linear variable	1.01	[0.99;1.02]	0.2600
Time between symptom and operation as a non-linear variable	0.51	[0.23-1.14]	0.09

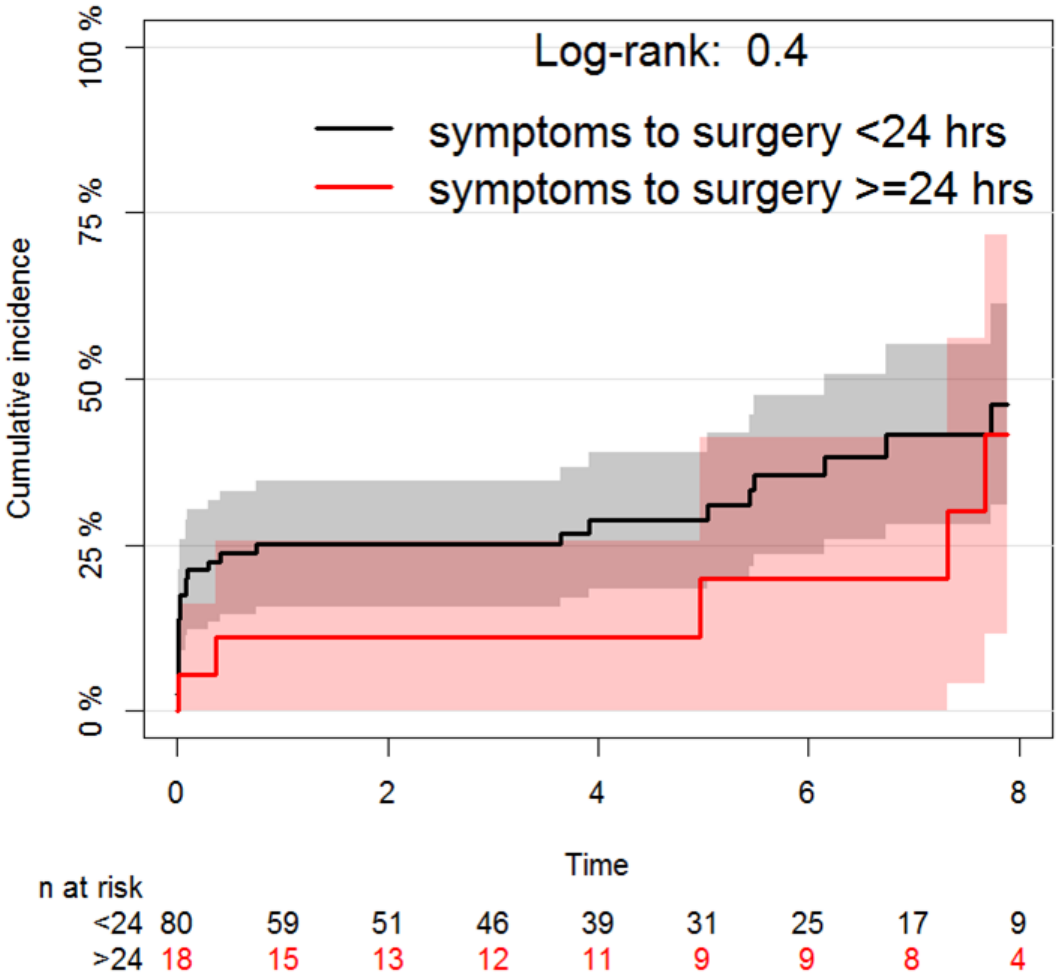

FIGURE 1. Survival comparison of patients undergoing early (12 hours) operations

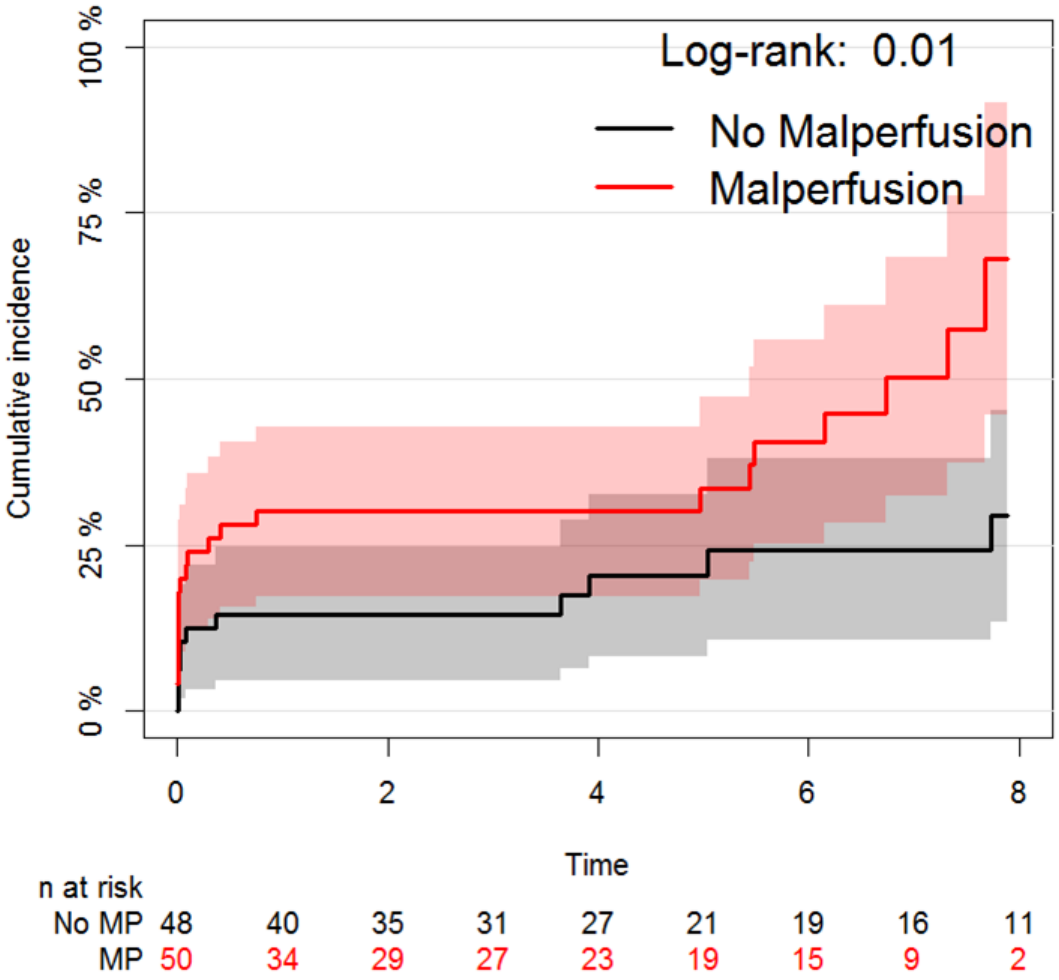

FIGURE 2. Survival comparison of patients with and without malperfusion. MP, Malperfusion.

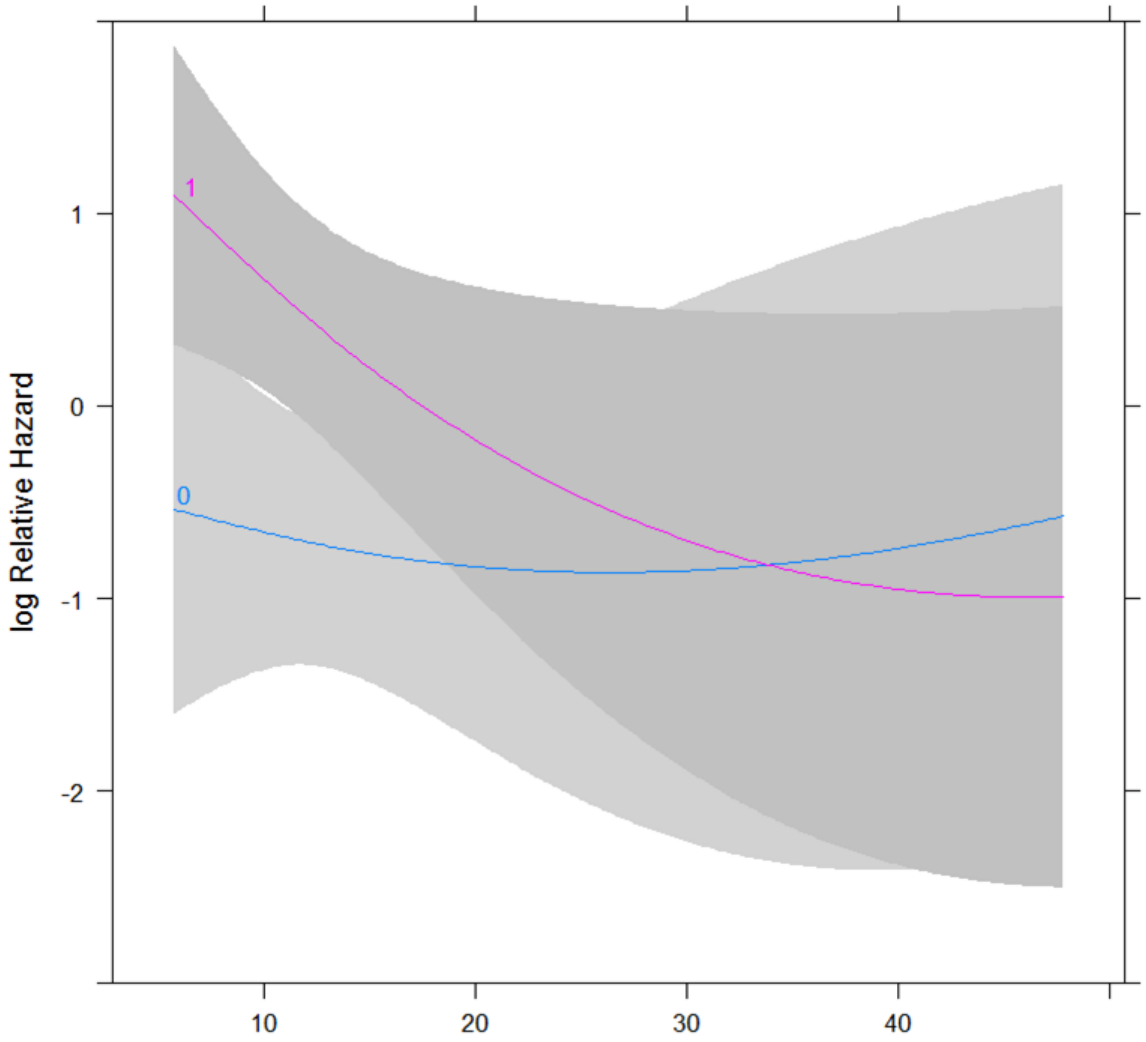

FIGURE 3. Risk-adjusted interaction between malperfusion (1, presence of malperfusion; 0, no malperfusion) and time.