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ORIGINAL RESEARCH ARTICLE

Utility of routine evaluations for rejection in patients greater than 2 years after heart transplantation

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Abstract

Aims Guidelines support routine surveillance testing for rejection for at least 5 years after heart transplant (HT). In patients greater than 2 years post-HT, we examined which clinical characteristics predict continuation of routine surveillance studies, outcomes following discontinuation of routine surveillance, and the cost-effectiveness of different surveillance strategies.

Methods and results We retrospectively identified subjects older than 18 who underwent a first HT at our centre from 2007 to 2016 and who survived ≥760 days (n = 217) post-HT. The clinical context surrounding all endomyocardial biopsies (EMBs) and gene expression profiles (GEPs) was reviewed to determine if studies were performed routinely or were triggered by a change in clinical status. Subjects were categorized as following a test-based surveillance (n = 159) or a signs/symptoms surveillance (n = 53) strategy based on treating cardiologist intent to continue routine studies after the second post-transplant year. A Markov model was constructed to compare two test-based surveillance strategies to a baseline strategy of discontinuing routine studies. One thousand twenty studies were performed; 835 were routine. Significant rejection was absent in 99.0% of routine EMBs and 99.8% of routine GEPs. The treating cardiologist's practice duration, patient age, and immunosuppressive regimen predicted surveillance strategy. There were no differences in outcomes between groups. Routine surveillance EMBs cost more and were marginally less effective than a strategy of discontinuing routine studies after 2 years; surveillance GEPs had an incremental cost-effectiveness ratio of $1.67 million/quality-adjusted life-year.

Conclusions Acute asymptomatic rejection is rare after the second post-transplant year. Obtaining surveillance studies beyond the second post-transplant year is not cost-effective.

Keywords Transplantation; Cost-effectiveness; Gene expression profile; Endomyocardial biopsy

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Introduction

Routine surveillance testing for rejection is performed frequently in patients after heart transplant (HT) to enable identification and treatment of asymptomatic rejection, which is associated with an outstanding prognosis when treated early. Left untreated, asymptomatic rejection may progress to haemodynamically significant rejection, which carries a much poorer prognosis.[1,2] Surveillance is performed using either endomyocardial biopsies (EMBs) or non-invasive gene expression profiles (GEPs).[3] While the risks of complications associated with a routine EMB are low, they may be significant and include ventricular perforation, pseudoaneurysm, arrhythmias, and damage to the tricuspid valve with the potential for tricuspid insufficiency leading to right heart failure.[4] While GEPs avoid upfront risk, positive studies necessitate a confirmatory EMB as the test's positive predictive value is only 4.3% in patients greater than 6 months after HT.[5]

In the modern transplant era, the incidence of acute rejection is low beyond the first post-transplant year.[4,6–8] However, guidelines continue to support routine EMBs for 5 years post-HT in higher risk patients and beyond 5 years per clinical judgement; GEPs are recommended in low risk patients 6 months to 5 years post-HT (*Table 1*).[3] These recommendations have led to diverse surveillance practices given

Table 1 Select International Society of Heart and Lung Transplantation recommendations for rejection surveillance in heart transplant recipients[3]

Statement	Class	LOE
'The standard of care for adult HT recipients is to perform periodic EMB during the first 6 to 12 post-operative months for surveillance of HT rejection.'	IIa	C
'After the first post-operative year, EMB surveillance for an extended period of time (eg, every 4–6 months) is recommended in HT recipients at higher risk for late acute rejection, to reduce the risk for rejection with hemodynamic compromise, and to reduce the risk of death in African-American recipients.'	IIa	C
'Gene Expression Profiling (Allomap) can be used to rule out the presence of ACR of grade 2R or greater in appropriate low risk patients, between 6 months and 5 years after HT.'	IIa	B

LOE, level of evidence.

providers' concern about the potential consequences of rejection and their individual risk aversion. We examined which clinical characteristics impact a patient's surveillance strategy, clinical outcomes following discontinuation of routine surveillance for rejection, and the cost-effectiveness of different surveillance strategies in patients greater than 2 years after HT at a single centre with heterogeneous practice patterns.

Methods

Patient population and data collection

We retrospectively identified subjects age 18 or older who underwent a first HT at the University of Michigan from January 2007 until January 2016 and who survived at least 760 days post-HT. Last follow-up was April 2018. Information was collected through a chart review on patient characteristics and treating cardiologist. The study was approved by the University of Michigan Institutional Review Board. Informed consent was not required given the retrospective nature of this work. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Definitions

Rejection was defined according to the 2004 revised International Society of Heart and Lung Transplant (ISHLT) criteria.[9] Significant rejection was defined as 2R or 3R acute cellular rejection (ACR), antibody-mediated rejection (AMR), or haemodynamically significant biopsy-negative rejection. Consistent with guideline recommendations, 1R cellular rejection in the absence of signs or symptoms of rejection is not treated at our institution.[3] The clinical context surrounding all EMBs and GEPs was reviewed to determine if they were performed routinely or were triggered by a change in clinical status. We evaluated studies after day 760 as we assumed that routine studies scheduled for the end of the second year could be delayed by up to 30 days. Studies were considered triggered if they (i) deviated from the subject's previously defined surveillance schedule and a rationale for doing so was provided; (ii) were performed in follow-up of a positive GEP, as defined by the treating cardiologist; or (iii) were performed within 360 days of a significant episode of rejection, irrespective of the time of the initial positive biopsy.

Surveillance biopsy protocols

At our centre, surveillance biopsy practices are determined for each recipient by their transplant cardiologist though suggested protocols are available for reference (Supporting Information, *Table S1*). Subjects were categorized into two groups based on their stated surveillance strategy at 2 years: 'test-based (TB) surveillance' versus 'signs/symptoms (SS) surveillance'. Subjects following a TB surveillance strategy underwent routine studies to survey for rejection per their treating cardiologist; those following a SS surveillance strategy only underwent testing in the setting of signs or symptoms suggestive of rejection or in follow-up of a recent episode of rejection, as defined earlier. The intended surveillance strategy was determined by reviewing provider documentation at the end of year 2 and, if not available, explicitly through ordering practices. For example, in the latter case, a provider who orders no surveillance studies for 4 years post-HT then orders an EMB can be assumed to be following a SS surveillance strategy. In five instances, we were unable to ascertain whether the provider intended to continue routine studies; these subjects were excluded from analyses of surveillance strategy. For analysis of covariates predictive of surveillance strategy, treating cardiologist was only defined for subjects followed by a single adult cardiologist in the third post-transplant year and beyond and when the cardiologist followed at least three subjects in this cohort.

Cost-effectiveness analysis

The methods for the cost-effectiveness analysis are described in detail in the Supporting Information. In brief, a Markov model was constructed to compare three strategies from months 24–60 after transplant: (i) a SS surveillance strategy, (ii) routine EMB every 6 months, and (iii) routine GEP every 6 months. In all strategies, patients underwent an EMB for signs or symptoms of rejection. The analysis was performed with TreeAge Pro 2019 Software (Williamstown, MA).

Patients entered the model after 24 months of routine management. The Markov model cycle length was 30 days. Patients could enter each cycle well or with signs or symptoms of rejection (*Figure 1*). Patients who entered into the model well could either remain well, die, or undergo routine screening with either a GEP or an EMB, as appropriate. Elevated GEP scores led to a follow-up EMB. Patients then progressed to ACR, AMR, the well state, or the dead state. Patients who entered into the model with signs or symptoms of rejection could either die or undergo an EMB. After an EMB, patients transitioned to ACR, AMR, the well state, or the dead state. After AMR or ACR, patients transitioned to alive or dead. The model cycled until 60 months post-HT.

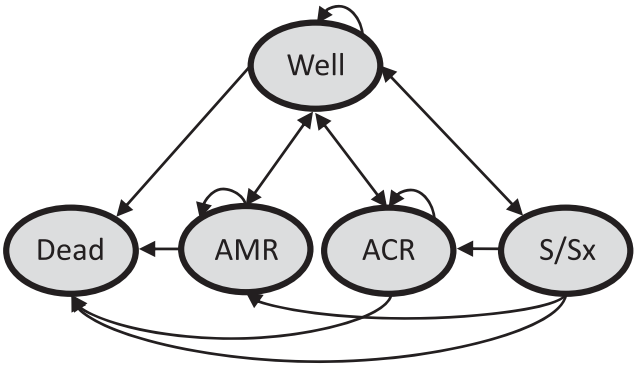
Hospitalization costs for rejection, in 2015 US dollars, were based on the Healthcare Cost and Utilization Project,[10] and costs for tests and procedures on the Medicare & Medicaid Services Physician fee schedule (Supporting Information, *Table S6*).[11] Medication costs were derived from an internal University of Michigan pharmacy database. Patients were assumed to be treated as an inpatient for AMR and symptomatic ACR and as an outpatient for asymptomatic ACR.

The probabilities used in the analysis were derived from the 159 patients (4645 cycles) following a TB surveillance strategy after the second post-transplant year, as described earlier (Supporting Information, *Table S7*). To estimate rejection rates with the SS surveillance strategy, we applied rejection rates from the two TB surveillance arms and assumed that all patients with routinely detected rejection would instead present with signs or symptoms of haemodynamically significant rejection and then die at the end of the cycle. Utilities were based on literature review and, when unavailable, expert opinion (Supporting Information, *Table S8*). In a sensitivity analysis, we quadrupled the overall rate of rejection detected by routine studies (Supporting Information, *Table S7*).

Statistical analysis

Data were evaluated for normality and summarized as mean ± standard deviation or median [25th, 75th percentile]. Patient characteristics by surveillance strategy were compared using the chi-square or Fischer's exact test for categorical variables and the *t*-test for continuous variables. Univariable logistic regression was performed on clinical characteristics to identify those predictive of surveillance strategy; stepwise multivariable logistic regression was used to determine independent predictors of surveillance strategy. A Cox proportional hazards model was used to compare outcomes by surveillance strategy. Linear regression was used to evaluate which clinical characteristics predicted number of studies performed after post-transplant year 2. Univariable models identified candidate variables ($P < 0.15$) for the final multivariable linear regression model utilizing a stepwise selection process. For all multivariable analyses, a P-value <0.05 was considered significant. All statistical analyses were performed in SAS (version 9.4, Cary, NC).

Figure 1 Markov model. Patients move between health states on the basis of transition probabilities assuming 30 day cycles. Patients can enter the model in the well state or with signs or symptoms of rejection. During each cycle, patients can either (i) remain well; (ii) experience asymptomatic rejection, if following a pathway of routine GEPs or EMBs; (iii) experience symptomatic acute rejection; or (iv) die. Patients with rejection detected within 90 days of a prior rejection episode were assumed to enter the model with signs or symptoms of rejection. ACR, acute cellular rejection; AMR, antibody-mediated rejection; EMB, endomyocardial biopsy; GEP, gene expression profile; S/Sx, signs and symptoms.



Results

Patient characteristics

Between January 2007 and January 2016, 251 adult subjects underwent a first HT at the University of Michigan. Thirty-one subjects died or transferred care to another centre prior to day 760, and three were followed by a paediatric cardiologist; 217 subjects were included in the analysis (*Table 2*). Most were male (76%) and White (82%) with a mean age of 51.5 ± 13.0 years at the time of transplant. Fifty-six subjects experienced 70 episodes of 2R or 3R cellular rejection in the first 2 years after HT; 60 episodes in 52 subjects in post-transplant year 1 and 10 episodes in 10 subjects in post-transplant year 2. One subject had AMR 15 months post-HT. At the end of the second post-transplant year, 133 (61.3%) subjects were on prednisone at a median dose of 2.5 mg [2.5, 5.0]. Three-drug and two-drug regimens including a calcineurin inhibitor were used by 44.2% and 35.9% of study subjects, respectively. Mean duration of follow-up was 6.3 ± 2.7 years.

Results of routine and triggered studies

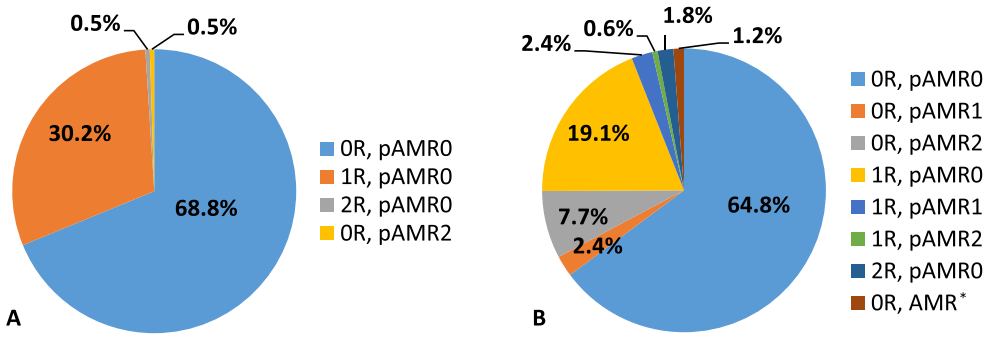
We evaluated the differential yield of routine and triggered studies. After day 760, 1020 studies were performed in 169 of 217 subjects of which 370 were EMBs and 650 GEPs. A total of 835 (81.9%) studies were routine of which 634 (75.9%) were GEPs and 201 (24.1%) EMBs, with the decision to pursue routine EMBs versus GEPs driven by perceived patient risk (Supporting Information, *Table S1*). Routine surveillance EMBs were negative for significant rejection in 99.0% of cases (*Figure 2*). One patient, with no prior history of rejection, had 2R ACR on a routine surveillance EMB 782 days after HT. That subject had a BNP level of 183 pg/mL on the day the study was performed, increased from 116 pg/mL when last checked, and a level of 428 pg/mL on the day the biopsy

Table 2 Baseline characteristics by surveillance strategy

	Total cohort (n = 217)[a]		SS surveillance (n = 53)		TB surveillance (n = 159)		
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	P-value
Demographics							
Patient age at transplant, years		51.5 (13.0)		54.6 (10.0)		50.6 (13.7)	0.02
Female gender	52 (24.0)		12 (22.6)		38 (23.9)		0.85
White	178 (82.0)		47 (88.7)		128 (80.5)		0.17
Transplant characteristics							
Indication, ischaemic CMP	71 (32.7)		16 (30.2)		55 (34.6)		0.56
Donor age		33.5 (10.2)		31.5 (11.8)		33.9 (12.1)	0.20
Episodes 2R or 3R cellular rejection, year 1	52 (24.0)			0.3 (0.5)		0.3 (0.5)	0.88
Episodes 2R or 3R cellular rejection, year 2	10 (4.6)			0.02 (0.1)		0.06 (0.2)	0.15
Biopsy-negative rejection, years 1 and 2	5 (2.3)		2 (3.8)		3 (1.9)		0.60
Antibody-mediated rejection, years 1 and 2	1 (0.5)		0 (0.0)		1 (0.6)		1.00
Immunosuppression at 2 years							
Tacrolimus	203 (93.6)		51 (96.2)		150 (94.3)		0.73
Mycophenolate mofetil	144 (66.4)		33 (62.3)		108 (57.9)		0.45
Prednisone	133 (61.3)		27 (50.9)		103 (64.8)		0.07
Proliferation signal inhibitor	28 (12.9)		6 (11.3)		22 (13.8)		0.64
Immunosuppression group							0.22
Group 1	96 (44.2)		17 (32.1)		77 (48.4)		
Group 2	78 (35.9)		24 (45.3)		53 (33.3)		
Group 3	34 (15.7)		10 (18.9)		23 (14.5)		
Other	9 (4.1)		2 (3.8)		6 (3.8)		
Co-morbid conditions at time of transplant							
BMI, kg/m^2		27.1 (4.6)		26.8 (4.0)		27.2 (4.7)	0.59
Diabetes mellitus	81 (37.3)		22 (41.5)		56 (35.2)		0.41
Hypertension	132 (60.8)		31 (58.5)		96 (60.4)		0.81
CKD (eGFR $<$ 60 mL/min/1.73 m^2)	87 (40.1)		20 (37.7)		66 (41.5)		0.63

Counts and percentages are presented for categorical variables. Mean values with standard deviations are presented for continuous variables. Only patient age at transplant differed significantly between the two groups. For immunosuppression group, group 1 (a three-drug regimen including a CNI + two of the following: MMF, AZA, PSI, or prednisone), group 2 (a two-drug regimen including a CNI + either MMF, AZA, or PSI), group 3 (a two-drug regimen containing CNI + prednisone). AZA, azathioprine; BMI, body mass index; CNI, calcineurin inhibitor; CKD, chronic kidney disease; CMP, cardiomyopathy; eGFR, estimated glomerular filtration rate; MMF, mycophenolate mofetil; PSI, proliferation signal inhibitor; SD, standard deviation; SS surveillance, signs/symptoms; TB surveillance, test-based.
[a]Five subjects could not be categorized as following a TB surveillance strategy versus a SS surveillance strategy.

Figure 2 Results of (A) routine and (B) triggered endomyocardial biopsies. A total of 370 endomyocardial biopsies were performed after post-transplant day 760, 201 of which were routine. AMR, antibody-mediated rejection; asterisk (*) denotes grade unspecified.



result became available. The second subject, who had experienced a previous episode of ACR 128 days after HT, experienced AMR grade 2 on an EMB 912 days after HT. Earlier that day, the subject had presented to clinic with signs of heart failure with a BNP of 571 pg/mL, increased from 65 pg/mL when last checked. Thus, these subjects had BNP trends and, in one subject, a clinical presentation that may have otherwise triggered an evaluation for rejection. While routine BNPs are not required as part of our surveillance protocol (Supporting Information, *Table S1*), they are frequently performed at our institution, and a change in BNP $>$ 100 pg/mL has previously been shown at our institution to predict increased risk of $\geq$2R rejection with high sensitivity and a high positive predictive value.[12]

One-hundred twelve (17.7%) of 634 routine GEPs had scores $\geq$34; 36 GEPs led to a follow-up EMB. Only one EMB 825 days after HT demonstrated 2R ACR, which was treated with prednisone as an outpatient given the patient's lack of symptoms, normal BNP, and unchanged echocardiogram. In two instances, one asymptomatic patient received prednisone between his GEP and a grade 0 EMB 854 days and 1404 days after transplant. In the first instance, he was presumptively treated with a standard oral prednisone burst and taper as he was travelling far from the transplant centre. In the second instance, he was treated by his primary care physician with 2 days of oral prednisone for coincident gout prior to his EMB. Given the low yield of GEPs, these most likely represent false positive test results. While it is conceivable that rejection was treated prior to the EMB, this is less likely, especially in the second instance in which treatment duration was brief. When considering only routine GEPs obtained within 5 years of HT, consistent with ISHLT guideline recommendations (*Table 1*),[3] 73 (16.3%) of 449 GEPs had scores $\geq$34, which led to 29 EMBs, only one of which demonstrated ACR (3.4% of EMBs; 0.2% of all GEPs).

There were 185 triggered studies of which 169 (91.4%) were EMBs and 16 (8.6%) GEPs (*Figure 2*). There was AMR on 24 triggered EMBs from five subjects with 22 of 24 episodes occurring in three subjects with persistent AMR. Three studies demonstrated 2R cellular rejection. Seven subjects were treated for biopsy-negative rejection.

Predictors of surveillance strategy

In total, 159 (75%) subjects followed a TB surveillance strategy and 53 (25%) a SS surveillance strategy (*Table 2*). Follow-up was nominally but not significantly shorter for the TB surveillance group compared with the SS surveillance group (5.7 ± 2.5 years vs. 6.5 ± 2.7 years; P = 0.06). After day 760, 17 studies were performed in the SS surveillance group and 965 studies in the TB surveillance group. A multivariable logistic regression model which included treating cardiologist practice duration (dichotomized as $\leq$20 years and $>$ 20 years based on clustering in practice duration), patient age, and immunosuppressive regimen predicted surveillance strategy, accounting for a large amount of the variability (c-statistic 0.85). The model was overwhelmingly driven by the treating cardiologist's practice duration (*Table 3*; Supporting Information, *Table S2*). Subjects were more likely to follow a TB surveillance strategy if they were younger, managed by a cardiologist who had been in practice for $\leq$20 years, or were on a three-drug immunosuppressive regimen with a calcineurin inhibitor. In a multivariable Cox proportional hazards model adjusting for patient age at the time of transplant, there were no differences in time to death, heart failure hospitalization, myocardial infarction/revascularization, or their composite by surveillance strategy (Supporting Information, *Table S3*).

We additionally evaluated the number of studies performed per subject, adjusting for duration of follow-up. Treating cardiologists' practice duration and subjects' histories of rejection predicted the number of studies per subject (Supporting Information, *Table S4*). Across cardiologists, the number of studies after post-transplant year 2 ranged from 0.31 studies/patient-year to 2.20 studies/patient-year (Supporting Information, *Table S5*).

Table 3 Multivariable logistic regression of clinical variables predicting likelihood of following a TB surveillance strategy after post-transplant year 2

	Odds ratio (95% CI)	χ^2	*P*-value	Reduction in −2 LogL
Patient age at transplant, years	0.960 (0.928–0.993)	5.605	0.018	5.080
Treating cardiologist practice duration (ref = ≤ 20 years)	0.013 (0.002–0.102)	17.199	0.013	52.428
Immunosuppression group (ref = group 1)				
Group 2	0.265 (0.108–0.647)	8.498	0.004	9.423
Group 3	0.408 (0.126–1.322)	2.234	0.135	

Stepwise multivariable logistic regression was used to determine independent predictors of surveillance strategy with exit and entry criteria of $P < 0.05$. Reduction in −2 log likelihood was used to select variables for the final model. Subjects whose transplant cardiologist had been in practice for ≤20 years, who were younger, or who were on a three-drug immunosuppressive regimen with a calcineurin inhibitor were more likely to follow a TB surveillance strategy. For immunosuppression group, group 1 (a three-drug regimen including a CNI + two of the following: MMF, AZA, PSI, or prednisone), group 2 (a two-drug regimen including a CNI + either MMF, AZA, or PSI), group 3 (a two-drug regimen containing CNI + prednisone). AZA, azathioprine; CNI, calcineurin inhibitor; CI, confidence intervals; LogL, log likelihood; MMF, mycophenolate mofetil; PSI, proliferation signal inhibitor; TB, test-based.

Cost-effectiveness analysis

In the 159 subjects following a TB surveillance strategy, two episodes of rejection were detected between years 2 and 5 at a gross cost of $967 014.80 per episode. In our cost-effectiveness analysis, compared with a baseline strategy of performing studies only for signs or symptoms of rejection, TB surveillance EMBs were less effective and cost more; surveillance GEPs had an incremental cost-effectiveness ratio of $1.67 million/quality-adjusted life-year (QALY), grossly in excess of the 'willingness to pay' threshold of $100 000 per QALY often invoked in the USA to define cost-effective interventions (*Table* 4; supplemental results). In a sensitivity analysis in which the overall rate of rejection was quadrupled, both surveillance EMBs and surveillance GEPs were marginally more effective than the baseline strategy though substantially more costly (Supporting Information, *Table S9*).

Table 4 Routine EMBs and GEPs are not cost-effective

	Incremental Cost ($)	Effectiveness (QALY)	ICER ($/QALY)
Baseline		28.76	
Surveillance EMB	$18 783.07	28.76	−2 568 087.01[a]
Surveillance GEP	$16 900.34	28.77	1 668 196.90

All displayed columns are in reference to a baseline strategy of performing studies only for signs or symptoms of rejection. Compared with the baseline strategy, surveillance EMBs were less effective and cost more; surveillance GEPs were marginally more effective though cost significantly more. EMB, endomyocardial biopsy; GEP, gene expression profile; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
[a]The negative value reflects that EMBs were less effective and cost more than the baseline strategy.

Discussion

Current guidelines support routine EMBs for at least 5 years post-HT in higher risk patients and routine GEPs 6 months to 5 years post-HT in low risk patients. In light of these permissive guidelines, routine surveillance for rejection is often continued beyond the second post-transplant year. At our institution, 75% of transplant cardiologists intended to continue routine surveillance studies beyond this time point. In the prospective Outcomes Allomap Registry, of the 933 patients enrolled within the first year post-transplant, 20.2% continued routine surveillance GEPs beyond the second post-transplant year (Jeffrey Teuteberg, personal correspondence).

This high frequency of testing is continued despite the observed temporal decline in the incidence of rejection.[2,13] In the ISHLT registry, 12.6% of patients transplanted between 2010 and 2016 were treated for rejection between hospital discharge and 1 year post-transplant, an approximately 50% decline when compared with 2004–2006.[14] In a second single-centre study, only 1.5% of asymptomatic patients had rejection detected on a routine EMB between 2000 and 2011 compared with 6.1% of patients between 1990 and 2000.[6] The risk for rejection declines even further with greater time from transplant. In a large multicentre registry, there was a 2.4-fold decrease in the risk of rejection when comparing patients 2 versus 5 years post-transplant.[2] We similarly found a low risk for acute rejection on routine studies. Two of 201 (1.0%) routine EMBs demonstrated acute rejection; 449 routine GEPs between 2 and 5 years post-transplant lead to 29 EMBs (6.5%), only one of which demonstrated ACR (3.4% of EMBs; 0.2% of all GEPs). Thus, when performed consistent with guideline recommendations, even a positive test results in a very low likelihood of rejection in this low risk population.

This high frequency of testing exposes patients to potentially unnecessary risks and comes at a high cost to both the patient and society. Consistent with Bayes theorem, a positive test result in a low risk patient will only marginally raise the post-test probability for disease, leading to a large number of false positive test results. If a sequential testing strategy of GEPs followed by EMBs when positive is employed, unnecessary downstream testing will result. In our cost-effectiveness analysis, surveillance EMBs were associated with lower quality of life adjusted survival than the baseline strategy yet cost significantly more. Similarly, GEPs resulted in a marginal improvement in quality of life adjusted survival (+0.01) but cost significantly more than the baseline strategy with an incremental cost-effectiveness ratio of $1.67 million/QALY. We obtained these results despite a very conservative assumption that patients who experienced a rejection event in the SS surveillance arm would present with signs or symptoms of haemodynamically significant rejection and then die at the end of the cycle. In reality, a very high percentage of late asymptomatic rejection resolves spontaneously without any augmentation in immunosuppression,[15] making routine EMBs and GEPs even less effective than our analysis would suggest.

Differences in surveillance strategies were primarily driven by providers' practice duration and likely reflect their varying levels of discomfort with low though ever present risk. Our mental calculus, however, differentially weights clinical outcomes and may fail to account for the risks and costs associated with unnecessary testing. At our centre, we found less experienced physicians more likely to continue routine surveillance studies. Whether provider surveillance practices differ at our centre by perception of risk or acceptance of risk cannot be determined from this study. While different centres will vary at what threshold they are willing to accept missed episodes of rejection, we believe these data justify revising our institutional post-transplant protocols. Thus, we are now requiring physicians to provide justification for routinely ordered surveillance studies after post-transplant year 2.

Our study should be interpreted in the context of several limitations. First, we evaluated patients from a single-centre with a relatively small number of African American patients[2]; thus, our lessons learned may not be applicable to all transplant centres or all populations. Secondly, studies were classified as routine or triggered based on retrospective chart review. By classifying all studies within 1 year of a positive EMB as triggered, we artificially decreased the yield of routine studies, potentially impacting the results of our cost-effectiveness analysis. Our low incidence of rejection, however, is consistent with real world data from the Outcomes Allomap Registry.[8] Next, we classified patients as following a TB surveillance versus a SS surveillance strategy based on review of clinical documentation. While treating cardiologist practice duration was a strong predictor of surveillance strategy, we cannot exclude the possibility that unmeasured covariates influenced provider practice pattern. Finally, for our cost-effectiveness analysis, we did not explicitly account for the false negative rate of GEPs nor for the potential complications of EMBs. The latter, however, would lower the utility and increase the cost of surveillance EMBs, which were already the least effective and most costly strategy. Additionally, our results are consistent with a prior cost-effectiveness analysis modelling EMB surveillance strategies in post-transplant years 2 and 3.[16]

In conclusion, acute asymptomatic rejection is exceedingly rare after the second post-transplant year. GEPs obtained beyond this time are highly cost ineffective, and EMBs come at a high cost without any gain in quality-adjusted survival. Both come at a cost to the patient and society. Our analyses support discontinuation of routine surveillance studies after 2 years for the majority of HT recipients.

Acknowledgements

None.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. University of Michigan suggested post-transplant surveillance schedule.
Table S2. Unadjusted logistic regression model predicting likelihood of following a TB-surveillance strategy.
Table S3. Clinical outcomes by surveillance strategy.
Table S4. Multivariable linear regression model predicting number of surveillance studies performed after post-transplant day 760.
Table S5. Studies per cardiologist.
Table S6. Costs (US$ 2015) used in analysis.
Table S7. Probabilities used in analysis.
Table S8. Utilities used in analysis.

Table S9. Routine EMBs and GEPs are not cost-effective when rejection rates are quadrupled.

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