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Incidence of Acute Rejection Compared With Endomyocardial Biopsy Complications for Heart Transplant Patients in the Contemporary Era

Vincenzo Cusi, BS,[1] Florin Vaida, PhD,[2] Nicholas Wettersten, MD,[3] Nicholas Rodgers, BS,[1] Yuko Tada, MD, PhD,[1] Bryn Gerding, BS,[1] Marcus Anthony Urey, MD,[1] Barry Greenberg, MD,[1] Eric D. Adler, MD,[1] and Paul J. Kim, MD, MAS[1]

Background. The reference standard of detecting acute rejection (AR) in adult heart transplant (HTx) patients is an endomyocardial biopsy (EMB). The majority of EMBs are performed in asymptomatic patients. However, the incidence of treated AR compared with EMB complications has not been compared in the contemporary era (2010–current). **Methods.** The authors retrospectively analyzed 2769 EMBs obtained in 326 consecutive HTx patients between August 2019 and August 2022. Variables included surveillance versus for-cause indication, recipient and donor characteristics, EMB procedural data and pathological grades, treatment for AR, and clinical outcomes. **Results.** The overall EMB complications rate was 1.6%. EMBs performed within 1 mo after HTx compared with after 1 mo from HTx showed significantly increased complications (OR, 12.74, $P<0.001$). The treated AR rate was 14.2% in the for-cause EMBs and 1.2% in the surveillance EMBs. We found the incidence of AR versus EMB complications was significantly lower in the surveillance compared with the for-cause EMB group (OR, 0.05, $P<0.001$). We also found the incidence of EMB complications was higher than treated AR in surveillance EMBs. **Conclusions.** The yield of surveillance EMBs has declined in the contemporary era, with a higher incidence of EMB complications compared with detected AR. The risk of EMB complications was highest within 1 mo after HTx. Surveillance EMB protocols in the contemporary era may need to be reevaluated.

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INTRODUCTION

Acute rejection (AR) has been historically associated with early death after heart transplantation (HTx). Because of the initially high morbidity and mortality of AR, endomyocardial biopsy (EMB) was developed to detect AR early in HTx patients.[1] Although recent advancements in noninvasive imaging and blood-based biomarkers show promise in replacing surveillance EMBs,[2-5] EMB continues to be used for surveillance of AR in asymptomatic patients at most institutions in the first year after HTx.

Previous studies have described various complications associated with EMBs that range from 1% to 5% in HTx patients.[6-10] Although EMB complications rates remain unchanged, the incidence of AR detected by EMBs has

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[1] UC San Diego Health, San Diego, CA.

[2] Department of Family Medicine and Public Health, UC San Diego, La Jolla, CA.

[3] Cardiology Section, Veterans Affairs San Diego Healthcare System, San Diego, CA.

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Correspondence: Paul J. Kim, MD, MAS, Division of Cardiovascular Medicine, Department of Medicine, UC San Diego Health, 9452 Medical Center Dr, MC 7411, La Jolla, CA 92037. (pjk017@health.ucsd.edu).

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decreased from 54% to 5%.[11,12] Deaths because of AR have also decreased.[13] This shift has been attributed to advances in post-HTx care, particularly improved immunosuppression regimens.

Because of the marked reduction in AR and also the concern for over immunosuppression,[14] the role for surveillance EMB in HTx patients is being reevaluated.[15,16] However, a direct comparison of the incidence of treated AR versus EMB complications in both surveillance and for-cause EMBs has not been performed in the contemporary era (2010–current).

In the present single-center study, our aim was to provide an update to the incidence of treated AR versus procedure-related complications for surveillance and for-cause EMBs among HTx patients.

MATERIALS AND METHODS

Data Sharing

The data that support the findings of this study are openly available in Mendeley Data (doi:10.17632/vyrdvb8fv9.1).

Study Design

This study was a retrospective, observational study of consecutive EMBs performed on HTx patients at the University of California, San Diego Health (UC San Diego Health), between August 2019 and August 2022. Eligible patients were HTx recipients who were 18 y of age or older who survived to their first EMB. All EMBs at UC San Diego Health are fluoroscopy guided and at least 3 separate passes for EMB samples are attempted.[17] For this study, the authors (V.C., N.R., and B.G.) extracted patient data and clinical outcomes from the electronic medical record. Estimated glomerular filtration rate was calculated using the chronic kidney disease epidemiology collaboration equation, which does not include a race factor.[18] Approval for this study was provided by the UC San Diego Health Office of IRB Administration (No. 805675). This study adheres to the principles of the Declaration of Helsinki formulated by the World Medical Association and the US Federal Policy for the Protection of Human Subjects.

EMB Complications

Potential EMB complications included: new pericardial effusions that required intervention, new pericardial effusions moderate or greater in size that was increased by >1 grade, tricuspid valve injury, inadvertent arterial access, failed venous access attempts, atrial or ventricular arrhythmias, atrioventricular block, pneumothorax, hemothorax, access site infection or hematoma, arteriovenous fistula, pseudoaneurysm, vasovagal reaction, and coronary artery fistula. To meet criteria for a procedure-related pericardial effusion, there had to be prior cardiac imaging by echocardiography or computed tomography for comparison to demonstrate that the pericardial effusion was a new finding after the procedure. To meet criteria for a procedure-related tricuspid valve injury, there had to be a prior echocardiogram for comparison with a new diagnosis of moderate or greater tricuspid valve regurgitation that was increased by >1 grade and was found to be persistent in subsequent echocardiograms.[6] All EMB complications were adjudicated by 2 experienced HTx cardiologists (NW and PJK). Where there was disagreement, a third cardiologist (YT) made the final determination.

For-Cause Versus Surveillance

At UC San Diego Health, the typical EMB surveillance protocol includes EMBs performed biweekly for the first 3 mo and monthly afterward during the first-year post-HTx. After 1-y post-HTx, EMBs were typically performed as for-cause EMBs. For-cause refers to an EMB performed for clinical suspicion of rejection, which includes: signs or symptoms of congestive heart failure, echocardiographic evidence of graft dysfunction (left ventricular ejection fraction <50%), new arrhythmias, repeat EMB requested to confirm the resolution of a recent episode of AR, and development of a de novo donor specific antibody (DSA). EMBs performed with concurrent but not de novo DSA were considered surveillance unless there was documentation indicating clinical suspicion for rejection. Typical induction and AR treatment protocols for UC San Diego Health has been described previously.[19]

Biopsy-defined Rejection

We followed the International Society for Heart and Lung Transplantation classification scheme for clinically significant acute cellular rejection (ACR) and used the pathological antibody-mediated rejection (pAMR) grading scheme for antibody-mediated rejection (AMR).[17,20] AR refers to either clinically significant ACR, AMR, or both (mixed ACR and AMR).[3] At UC San Diego Health, a weekly pathological review of all EMB samples is performed as previously described.[19] Treatment for AR refers to a significant change in a subject's immunomodulatory regimen including: initiation or increase in corticosteroids to a prednisone equivalent of 40 mg/d or higher, intravenous immune globulin, plasmapheresis, rituximab, thymoglobulin, and/or bortezomib use.

Clinical Outcomes

All HTx patients were followed for all-cause death. Cause of death was adjudicated by NW, PJK, and YT. Additional days of hospitalization after an EMB complication refer to the number of days beyond the initial projected hospitalization discharge date.

Statistical Analyses

Categorical variables were expressed as frequency and percentage and compared with the use of either the Pearson chi-square or Fisher exact test. Continuous variables were expressed as mean ± SD for normally distributed variables or median and interquartile range (IQR) for nonnormally distributed variables and compared with the use of the Student t-test or Wilcoxon rank-sum test as appropriate.

We calculated the proportions of EMB complications, AR, and treated AR and compared differences in proportions between the surveillance and for-cause groups. The agreement rate of the initial adjudication for EMB complications was analyzed by Cohen's kappa statistics. For EMB complications, treated AR, and to identify candidate predictors for prediction models, we performed mixed effects logistic regression with forward model selection to

take into account within-subject correlation and determine significant predictors at a subject level using a $P<0.15$ threshold. Poisson models were used to evaluate the ratio of treated AR incidence versus EMB complications in the for-cause compared with surveillance groups via an interaction term to account for within-subject correlation.

Analysis was conducted in R (R Core Team, 2022). We used the Bonferroni-Holm procedure whenever multiple comparisons were performed while implementing a particular statistical hypothesis test. The corrected P values are designated as p_c. For single hypothesis testing, we report the unadjusted P value. P or $p_c<0.05$ are considered significant.

RESULTS

Characteristics of the Study Population

A total of 2769 consecutive EMBs from 326 unique HTx patients were included in this study. All cases were included for the primary outcome of EMB complications (Figure 1). For-cause EMBs accounted for 499 (18.0%) samples, whereas surveillance EMBs accounted for 2270 (82.0%) samples.

Baseline characteristics of the study population are depicted in Table 1. Patients were typically male (78.8%) and non-Hispanic White (39.0%) with a mean age of 55.5 ± 13.8 y. There were 944.8 person-years in this study from HTx to end of follow-up.

EMB procedural characteristics are summarized in **Table S1** (**SDC**, http://links.lww.com/TP/C942). All EMBs were performed using fluoroscopy guidance, and the majority were performed using the right internal jugular vein as access (84.5%). Eight different HTx cardiologists performed EMBs for this study. The median number of samples per EMB was 4 (IQR, 4–5). The median number of EMB per patient was 9 (IQR, 6–12). As the study analyzed consecutive EMBs rather than consecutive HTx, approximately 30% of HTx patients were not transplanted during the study time period, resulting in a reduced median number of EMB per patient. Most EMBs were performed in an outpatient setting (78.8%).

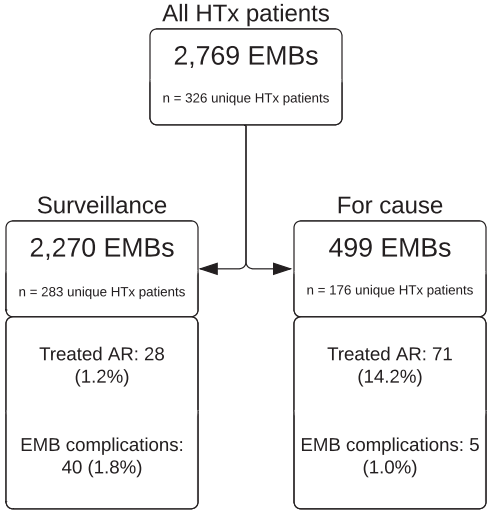

FIGURE 1. Flow diagram. AR, acute rejection; EMB, endomyocardial biopsy.

TABLE 1.
Characteristics of subjects and endomyocardial biopsies

	N	
Donor characteristics		
Age, y, mean (SD)	321	33.3 (10.7)
Male, N (%)	326	267 (81.9)
Recipient characteristics		
Age, y, mean (SD)	326	55.5 (13.8)
Male, N (%)	326	257 (78.8)
Race		
Asian, N (%)	326	24 (7.4)
Black, N (%)	326	44 (13.5)
Native American, N (%)	326	2 (0.6)
Other Race, N (%)	326	27 (8.3)
Pacific Islander, N (%)	326	4 (1.2)
White, N (%)	326	225 (69.0)
Ethnicity		
Hispanic or Latino, N (%)	326	98 (30.1)
Not Hispanic or Latino, N (%)	326	228 (69.9)
Sensitized patients (PRA ≥ 10%)	319	58 (18.2)
VAD use, N (%)	326	108 (33.1)
Indication for transplant		
NICM, N (%)	326	188 (57.7)
ICM, N (%)	326	113 (34.7)
Congenital, N (%)	326	18 (5.5)
Retransplant, N (%)	326	7 (2.1)
Transplant characteristics		
Multiorgan transplant, N (%)	326	53 (16.3)
Total donor ischemic time, min, mean (SD)	319	211 (70)
Sex mismatch, N (%)	326	54 (16.6)
PHM difference, % recipient PHM, mean (SD)	321	5.9 (21.7)
Induction therapy		
Thymoglobulin, N (%)	326	109 (33.4)
Basiliximab, N (%)	326	26 (8.0)
Eculizumab, N (%)	326	2 (0.6)
DCD, N (%)	326	65 (19.9)
NRP-CSS	326	49 (15.0)
DPP-NMP	326	16 (4.9)
Endomyocardial biopsy characteristics		
Time posttransplant, d, median (IQR)	2769	100 (48–217)
De novo DSA, N (%)	2757	74 (2.7)
Concurrent cardiac allograft dysfunction, N (%)	2769	135 (4.9)

DCD, donation after circulatory death; DPP-NMP, direct procurement perfusion-normothermic machine perfusion; DSA, donor specific antibody; ICM, ischemic cardiomyopathy; IQR, interquartile range; NICM, nonischemic cardiomyopathy; NRP-CSS, normothermic regional perfusion-cold static storage; PHM, predicted heart mass; PRA, panel reactive antibodies; VAD, ventricular assist device.

EMB Complications

In the study population, 45 (1.6%) total complications occurred in 41 unique HTx patients. Initial adjudication of EMB complications was in agreement 90.6% of the time with a Cohen's kappa of 0.81 (0.64, 0.97; $P<0.001$). There were 33 (73.3%) clinically significant pericardial effusions and 26 of the 33 pericardial effusions required a percutaneous or surgical intervention, for an effusion of moderate or larger size not previously observed by echocardiography. Other complications were less frequent and are shown in Table 2. There was a mean of 4.0 (95% CI,

TABLE 2.
Endomyocardial biopsy complications

	Endomyocardial cases	Unique heart transplant patients
Clinically significant pericardial effusion—No. of patients/total No. (%)	33/45 (73.3)	31/41 (75.6)
Pericardiocentesis with pericardial drain—No. of patients/total No.	25/33	24/31
Surgical pericardial window—No. of patients/total No.	1/33	1/31
Tricuspid valve injury—No. of patients/total No. (%)	3/45 (6.7)	3/41 (7.3)
Inadvertent arterial access—No. of patients/total No. (%)	3/45 (6.7)	3/41 (7.3)
Failed venous access attempt—No. of patients/total No. (%)	4/45 (8.9)	4/41 (9.8)
Right atrial lead dislodgement—No. of patients/total No. (%)	1/45 (2.2)	1/41 (2.4)
Extraction of embedded bioptome—No. of patients/total No. (%)	1/45 (2.2)	1/41 (2.4)

2.89-5.11; $P<0.001$) additional days of hospitalization because of an EMB complication. Clinically significant pericardial effusions occurred separately twice in 2 HTx patients, and no HTx patient had >2 EMB complications. There were 11 (0.4%) nondiagnostic EMB samples in our study. Repeat EMB was performed in 7 of the 11 nondiagnostic cases. No repeat EMBs were associated with complications, and 4 of the 7 repeat EMBs were performed in the first month after HTx.

We evaluated 47 predictors for EMB complications (**Table S2, SDC**, http://links.lww.com/TP/C942) using single predictor logistic regression. Using multipredictor logistic regression, only time since HTx was found to be a significant predictor for EMB complications with the highest risk period to be within 1 mo after HTx (OR 12.74; 95% CI, 6.67-24.40; $p_c<0.001$; Figure 2A and 2B). There was a nonsignificant trend for increased EMB complications with surveillance indication ($P=0.230$). Other factors including access site, bioptome size, different operators, trainee involvement, anticoagulant use, and elevated intracardiac filling pressures were not found to be significantly associated with EMB complications after adjusting for multiple covariates.

The rate of significant pericardial effusions, defined as pericardial effusions moderate or greater in size, was low at 1.7%. We found no significant association for donor-recipient predicted heart mass mismatch (ie, small donor heart transplanted in a large HTx recipient) and incidental pericardial effusion ($P=0.120$). The majority of pericardial effusions were adjudicated as EMB complications (67.3%; 95% CI, 52.3%-79.6%). Although ACR was not associated with pericardial effusions, AMR demonstrated a significant correlation with incidental pericardial effusions (OR, 3.63; 95% CI, 1.39-9.49; $P=0.009$). However, AMR did not significantly correlate with pericardial effusions that were adjudicated as EMB complications ($P=0.725$).

Sensitivity analysis with EMB-related pericardial effusion as the outcome was also performed. Only EMBs performed within 1 mo after HTx (OR, 43.25; 95% CI, 14.91-125.50; $p_c<0.001$) were found to be significantly associated with EMB-related pericardial effusion.

Treated AR by EMB

AR was diagnosed in 133 (4.8%) EMB samples from 67 (20.6%) unique HTx patients (**Table S3, SDC**, http://links.lww.com/TP/C942). However, only 99 (3.6%) AR samples from 61 (18.7%) unique HTx patients were treated. There was 1 EMB sample negative for ACR and AMR that was treated in the setting of focal myocyte necrosis and inflammation and concurrent cardiac allograft dysfunction. All untreated samples showed AMR without ACR (ie, ACR 0R or 1R grades). Of the 35 untreated AMR samples, 28 were pAMR1 and 7 were pAMR2, including 2 patients that recently received immunomodulatory therapy and 1 patient that refused treatment.

We found treated AR diagnosed more frequently in for-cause samples (14.2%) compared with surveillance EMB samples (1.2%; $P<0.001$). The for-cause indication demonstrated a significantly increased OR of 9.17 (95% CI, 4.56-18.46; $p_c<0.001$; **Table S4, SDC**, http://links.lww.com/TP/C942) for the diagnosis of treated AR. We found time from HTx was not significantly associated with treated AR after adjusting for multiple covariates ($p_c=0.909$; Figure 3). We did not observe a significantly increased time interval between EMBs for treated AR samples compared with samples without treated AR (3.7 ± 2.4 versus 3.4 ± 2.1 wk; $P=0.300$).

Of the EMB samples within 1 mo after HTx, 382 (88.2%) were surveillance and 51 (11.8%) were for-cause (**Table S5, SDC**, http://links.lww.com/TP/C942). For this study, if an EMB was previously scheduled as a surveillance EMB but the clinical team noted concerns for possible AR before the procedure, the EMB was recategorized as for-cause EMB. Of the EMB samples after 1 mo HTx, 1888 (80.8%) were surveillance and 448 (19.2%) were for-cause. The number of EMB samples performed for-cause was significantly increased after 1 mo HTx compared with surveillance (OR, 1.78; 95% CI, 1.30-2.47; $P=0.002$). Among surveillance EMB within 1 mo after HTx, we found 5 out of 11 AR samples prompted treatment. The 6 surveillance AR cases that were not treated were all pAMR1 without concurrent DSA. Among the for-cause EMB within 1 mo after HTx, we found 10 out of 11 AR samples were treated and the 1 untreated AR sample was a pAMR1 (I+) without concurrent DSA that was subsequently followed by repeated EMB until resolution of the AMR.

Incidence of Treated AR Compared With EMB Complications in For-cause Versus Surveillance EMBs

The overall treated AR versus EMB complications ratio was 2.2. In the for-cause EMB group, we found the treated AR versus EMB complications ratio increased to 14.2 (Figure 4). In contrast, we found the treated AR versus EMB complications ratio decreased to 0.7 in the surveillance EMB group. As a result, the ratio of treated AR

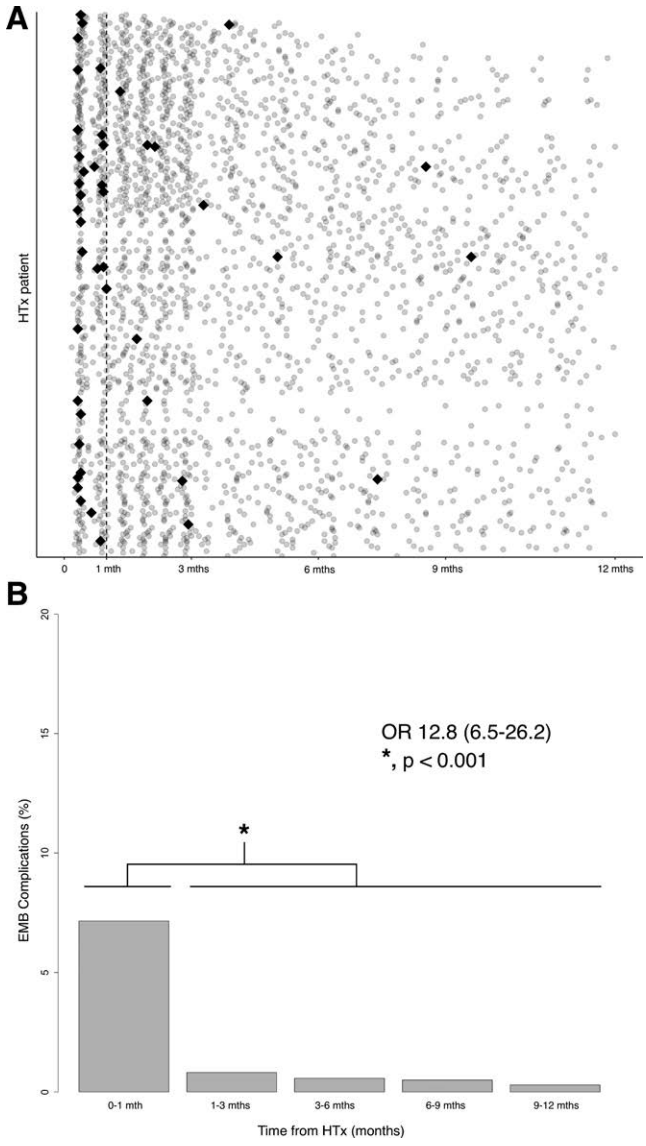

FIGURE 2. EMB complications over time since HTx. A, Scatterplot of EMBs for all 326 HTx patients. Each gray dot represents an EMB sample negative for EMB complications and each black diamond represents an EMB sample associated with a complication. EMB complications show a pattern of occurring within the first month after HTx. B, Barplot showing percentage of EMB complications within each time interval. There is a significant difference in percentage of EMB complications occurring in the first month compared with the rest of the first year after HTx ($P < 0.001$). EMB, endomyocardial biopsy; HTx, heart transplantation.

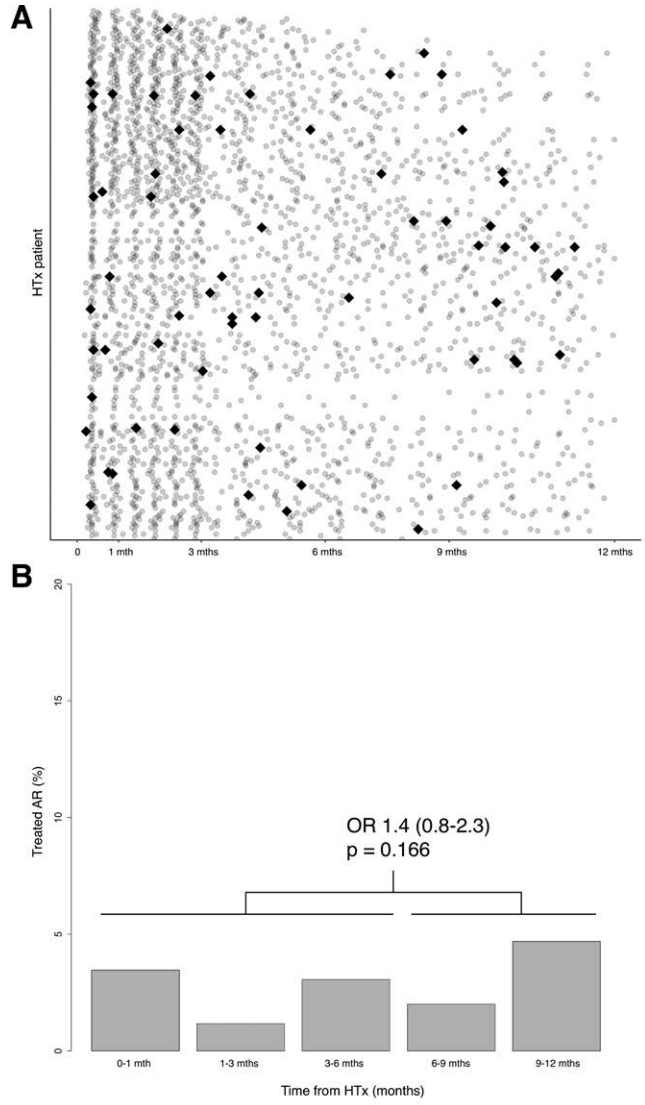

FIGURE 3. Treated AR over time since HTx. A, Scatterplot of EMB for all 326 HTx patients. Each gray dot represents an EMB sample negative for treated AR, and each black diamond represents an EMB sample positive for treated AR. B, Barplot showing percentage of treated AR within each time interval. There is no significant difference in the percentage of treated AR in 0–6 mo compared with 6–12 mo after HTx ($P = 0.17$). AR, acute rejection; EMB, endomyocardial biopsies; HTx, heart transplantation.

versus EMB complications ratios comparing surveillance to for-cause EMB groups was significantly decreased at 0.05 ($P < 0.001$).

Incidence of Treated AR Compared With EMB Complications Performed Before and After 1 mo From HTx

We found the treated AR versus EMB complications ratio was significantly improved in surveillance EMB when comparing EMBs performed after 1 mo from HTx versus within 1 mo after HTx (OR, 11.59; 95% CI, 3.28-49.31; $P < 0.001$). However, we did not observe the treated AR versus EMB complications ratio in for-cause EMBs to be significantly different when comparing EMBs performed after 1 mo from HTx versus within 1 mo after HTx (OR, 3.96; 95% CI, 0.30-39.39; $P = 0.200$).

Clinical Outcomes

There were 24 deaths (7.4%; **Table S6, SDC**, http://links.lww.com/TP/C942) and 1 retransplant. The majority of the deaths (45.8%) were because of infection. Of the 11 deaths because of infection, 7 (63.6%) were on either triple or quadruple immunosuppression and 10 (90.9%) were still taking prednisone. We did not observe any treated AR episodes in the preceding EMB before the diagnosis of the fatal infection. AR accounted for 3 (12.5%) deaths, and all were because of AMR. However, the AMR deaths were outside of the surveillance biopsy window (129.0 ± 33.1 wk), and all 3 patients were noted to have a history of

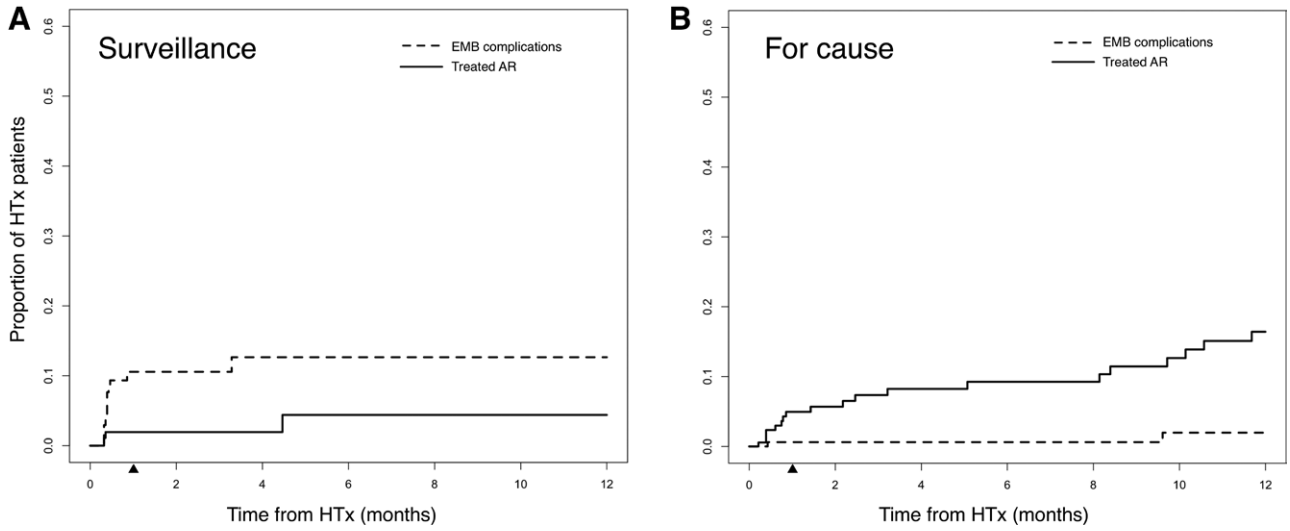

FIGURE 4. EMB and treated AR over time since HTx. A, Surveillance EMB cumulative incidence curves for treated AR and EMB complications. EMB complications incidence significantly increases within the first month (black arrow) after HTx. Incidence of treated AR does not increase above the rate of EMB complications for surveillance EMBs. B, For-cause EMB cumulative incidence curves for treated AR and EMB complications. The incidence of treated AR increases above the rate of EMB complications in for-cause EMBs within the first month (black arrow) after HTx and continues to increase over the first year after HTx. AR, acute rejection; EMB, endomyocardial biopsies; HTx, heart transplantation.

nonadherence. All AMR episodes were determined by for-cause EMBs.

DISCUSSION

In this retrospective single-center study, several key findings were observed. First, the incidence of treated AR compared with EMB complications was significantly lower in surveillance compared with for-cause EMBs. Second, we found the highest risk period for EMB complications to be within 1 mo after HTx. Third, in the contemporary era, EMB complications incidence occurred at a higher rate than treated AR in surveillance EMBs. The treated AR versus EMB complications ratio for surveillance EMBs improved after 1 mo HTx, not because of any increase in detection of treated AR but because of the significant decrease in EMB complications. Fourth, treatment of AMR is inconsistent in the contemporary era and almost half of AMR EMBs do not lead to a change in treatment.

We found the EMB complications rate to be low (1.6%) with rates similar to previous studies.[6,7] Although not a direct cause of death, EMB complications did contribute to increased morbidity, additional interventions, and a significant increase in time hospitalized by 4 d per EMB complication. Historically, tricuspid valve injury and vascular complications made up a significant portion of EMB complications.[7,21] However, pericardial effusions contributed to a greater proportion of EMB complications in more recent literature, consistent with our study findings.[6,7,9,22] We hypothesize that vascular complications and tricuspid valve injury have decreased because of improved techniques utilizing ultrasound for vascular access and increased attention to avoiding tricuspid valve injury, respectively.[23] In contrast, the incidence of pericardial effusions as an EMB complication is likely unchanged because of the fact that the majority of studies, including this study, continue to report the practice of fluoroscopy-guided EMBs.[6,7,9] However, despite the theoretical benefit of echo-guided EMBs, no studies have demonstrated a significant decrease in EMB complications with the use of echo-guided compared with fluoroscopy-guided EMBs.[24,25] At our institution, fluoroscopy-guided EMBs are solely performed because of provider preference and lack of sonographers with the expertise to guide HTx cardiologists in performing echo-guided EMBs. These reasons also likely explain why fluoroscopy guidance will continue to remain the predominant method for EMBs for most institutions.[6,10] Compared with other studies, our patients more frequently prompted intervention for the pericardial effusion, which likely reflect differences in practice patterns. Furthermore, we did not find that donor heart size contributed to the development of incidental pericardial effusion.

Our study showed a novel finding that earlier time from HTx was associated with a higher rate of EMB complications, with the rate significantly increased within the first month after HTx compared with after 1 mo from HTx. This finding was driven by a significantly increased rate of EMB-related pericardial effusions. We hypothesize that myocyte necrosis from ischemia-reperfusion injury and its persistence related to immunosuppression predisposes patients to EMB-related pericardial effusions within 1 mo after HTx.[26,27] This hypothesis is also supported by greater levels donor-derived cell-free DNA (dd-cfDNA) early in the post-HTx period, indicating a vulnerable period because of allograft injury in the early post-HTx period.[2] Although prior studies have described the rate of EMB complications, this is the first study to identify a potential risk factor associated with EMB complications. This finding has significant clinical relevance, and future studies should further evaluate this high-risk time period to identify potential strategies to reduce the risk of EMB complications.

Our study findings also corroborated a reduced incidence of ACR in the contemporary era compared with prior eras, attributed to modern immunosuppression regimens, and

improved post-HTx care.[12,13,28] However, in contrast to earlier eras,[7,28] our findings showed that time from HTx was not independently associated with treated ACR.[22] In addition to other literature,[9,28] our study findings suggest sufficient equipoise for future randomized controlled trials that include clinical vigilance as a study arm to determine whether surveillance EMBs are better than clinical assessment alone, a fact that has not yet been established in the contemporary era.[29]

In contrast to our study findings with respect to ACR, we observed an increased incidence of AMR, likely because of increasing awareness of AMR.[30,31] Although a large proportion of AMR (42.7%) were not treated, the absolute number of treated AMR was greater than ACR in our study. However, despite the increase in treated AMR, the total number and rate of treated AR remained low. The inconsistency in treatment of AMR reflects the current uncertainty of benefit with treatment.[32] Until there is consensus in the HTx field for treating AMR, the utility of surveillance EMBs for asymptomatic AMR patients will likely remain uncertain.

Our study demonstrates that for-cause EMB still detects treated AR at a high rate and remains an important tool in the clinical armamentarium for HTx patients with signs or symptoms concerning for AR. In our study, we also demonstrated a trend toward reduced EMB complications in the for-cause group as the utilization of for-cause compared with surveillance EMBs was significantly decreased within 1 mo after HTx. Thus, prioritizing for-cause EMBs could potentially reduce EMBs performed within 1 mo after HTx, a high-risk time period for EMB complications.

With the improvement of HTx care, AR rates have significantly decreased to the point, where noninvasive biomarker tests have demonstrated both safety and noninferiority to surveillance EMBs.[33] IMAGE was the first and largest clinical trial that demonstrated the use of gene-expression profiling could safely replace surveillance EMB as early as 6 mo after HTx in low-risk patients. The eIMAGE trial expanded on this result to show that gene-expression profiling could be safely used as early as 55 d after HTx, again in low-risk patients.[34] However, a recurring critique for both studies was the lack of an appropriate "control" arm of clinical vigilance, given the low rate of prespecified outcome events for both studies.[35] Our study suggests that, in a real world setting that includes both low and high-risk HTx patients in the contemporary era, surveillance EMBs may incur a greater risk of cardiac injury than detect AR in the early post-HTx period. Currently, the leading candidate for noninvasive AR surveillance, dd-cfDNA, has limited accuracy in this high-risk time period.[2,19] Further efforts to improve dd-cfDNA testing[3] and cardiovascular magnetic resonance–based AR surveillance[5] could be potential solutions to reduce the risk of cardiac injury while increasing the potential benefit by identifying HTx patients more likely to have AR. Benefit/risk of EMBs could be also improved by coming to a consensus for when to treat AMR and thus limiting EMBs to scenarios where the results can potentially change treatment. In addition, knowledge of this high-risk time period (within 1 mo of HTx) for EMB complications may itself be useful in reducing EMB complications. Clinicians can use this important information to be more cautious during these higher risk EMBs to possibly reduce the rate of complications, similar to the reductions seen in vascular complications and tricuspid valve injuries. HTx programs may also reevaluate the necessity of surveillance EMB during this time period. Finally, our study findings contribute to prior literature to suggest sufficient clinical equipoise for future randomized controlled trials to compare surveillance EMBs with "standardized clinical and functional allograft vigilance."[9,28,35-37] We believe these trials are necessary in the contemporary era because of the decreasing treated AR versus EMB complications incidence ratio and would also complement the growing research in noninvasive biomarkers, including dd-cfDNA testing.

Limitations

This study should be interpreted within the context of several important limitations. First, this was a retrospective study from a single center and may not necessarily represent the experience of other centers with different patient demographics, procedural characteristics, and variations in post-HTx management. Second, UC San Diego Health does not consistently perform echocardiograms after every EMB, as reported in some other studies.[6,7] However, the incidence of pericardial effusions in this study is similar to recent studies.[6,22] Third, all EMBs in this study were performed with fluoroscopic guidance. Increased use of echo-guidance could potentially further reduce EMB complications. Finally, we give equal weight to EMB complications, including some that may be considered minor, and treatment of AR. Because the benefit of treating certain ARs, including asymptomatic 2R ACR and AMR episodes, is uncertain,[9,37,38] we simply calculated the treated AR versus EMB complications incidence ratio using the N of AR versus N of EMB complications for consistency and objectivity.

CONCLUSION

Detection of treated AR by surveillance EMBs in adult HTx patients has declined in the contemporary era, resulting in a higher incidence of EMB complications compared with detected AR. Future randomized controlled trials that compare surveillance EMBs to clinical assessment alone are necessary to evaluate whether our current practice of surveillance EMBs should be continued in the contemporary era.

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