ISHLT JOURNAL WATCH
December 2025 | Pulmonology

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Impact of continuous distribution as the allocation strategy on lung transplantation

Banga A, Harley C, Tulu Z, MacArthur JW, Dhillon G. *Am J Transplant* 2025 Jun;25(6):1218-1225. | DOI: 10.1016/j.ajt.2025.02.001

Study Highlights

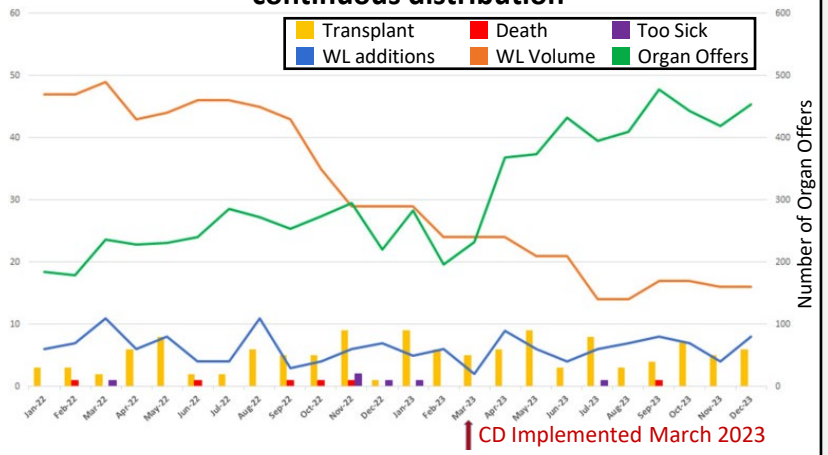
Background:
A new lung allocation system, known as continuous distribution (CD), was implemented in March 2023. CD was intended to prioritize the sickest patients, promote harder-to-match patients, & improve post-transplant survival and procurement efficiency.

Objective:
To understand the impact of CD for lung transplantation on patient characteristics, clinical outcomes, and resource utilization

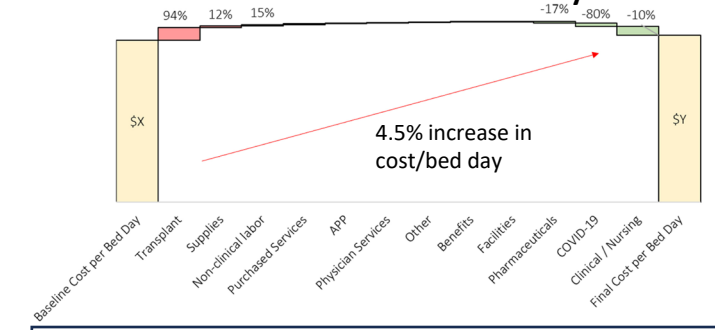
Methods:
- Single-center retrospective study in California, USA
- Data collected and compared for 9 months pre- and post- CD implementation (March-November for 2022 and 2023)

Results:
- The post-CD period was associated with increased donor offers (333 vs 203 offers per month, p=0.002) and a lower median time on waitlist (90 vs 30 days, p<0.001)
- Post-CD noted a small increase in number of transplants (50 vs 45 transplants, p=0.7), and simultaneously a longer procurement distance (153 vs 323.5 miles, p=0.029)
- No significant change in length of stay or 1-year survival found
- ↑ transplant costs, primarily due to transportation costs
  - ↑ 82% organ procurement cost, ↑4.5% cost/bed day

Key transplant metrics before and after implementation of continuous distribution



Cost waterfall for transplant costs per bed day before and after the continuous distribution system



Take Home Message
- Lung allocation via CD is associated with increased donor lung access and shorter waitlist times
- No change in early post-survival with CD, but higher costs primarily due to transportation costs

Reviewer's Comments

- Single center retrospective analysis in similar times of the year, with no change in the listing criteria or donor organ filters before or after CD, which allowed for a case-control study design
- These findings mirror UNOS data on increased access to transplant and decreased death on the waitlist post-CD
- Provides financial comparisons before and after CD implementation, highlighting change in procurement costs, and notes new OPOs for this center post-CD

Limitations

- Study had a smaller sample size from a single center, so limited ability to identify trends in transplant indications and may impact generalizability
- Does not show differences in blood type and wait list time post-CD. Of note, this did prompt modification to lung CD scores based on blood type in September 2023
- Certain organ offer filters for this program may not be applicable to other transplant centers. This may change the number of offers, time on waitlist, procurement distance for donor lungs, and post-transplant outcomes due to higher-risk donor offers
- Follow-up for clinical outcomes was limited to 1 year

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Cell-free DNA in Ex-Vivo Lung Perfusate is Associated With Low-Quality Lungs and Lung Transplant Outcome

Yamamoto H, Wilson GW, Sundby A, Zhu S, et al. *JHLT* 2025 Sep;44(9):1438-1448. | DOI: 10.1016/j.healun.2025.02.1693

Study Highlights

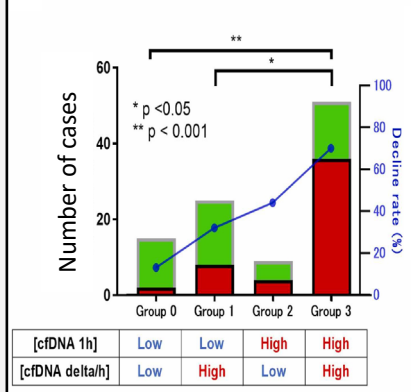
Background:
Cell free DNA(cfDNA) is used as a marker for lung injury following lung transplant (LTx), but studies are more limited for its potential in predicting outcomes during ex-vivo lung perfusion (EVLP).

Objective:
To assess whether cfDNA from EVLP perfusate may reflect lung quality and ultimate decision on whether to utilize donor lungs

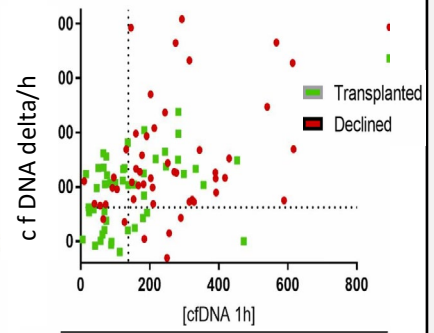
Methods:
- Single-center retrospective study with discovery cohort (n=100) and validation cohort (n=50)
- Perfusate cfDNA collected at 1 hour and final hour of EVLP
- Assessment for donor factors, EVLP data, perfusate cfDNA at 1 hour (1h-cfDNA), and change in perfusate cfDNA/hour (ΔcfDNA)
- ROC analysis determined high vs low for 1h-cfDNA & ΔcfDNA

Results:
- 1h-cfDNA correlated with 1 hour PO2 & perfusate volume loss, but not dynamic compliance.
- Both 1h-cfDNA and ΔcfDNA were higher in declined lungs.
- 1h-cfDNA but not ΔcfDNA significant in multivariate analysis
- 1h-cfDNA showed dose response association with decline rate.
- Validation cohort demonstrated higher 1h-cfDNA but not ΔcfDNA for transplanted vs declined cases
- 1h-cfDNA improved machine learning model predicting EVLP outcomes of extubation within 72h and organ acceptance

EVLP acceptance decisions by quartile status of 1h-cfDNA and ΔcfDNA

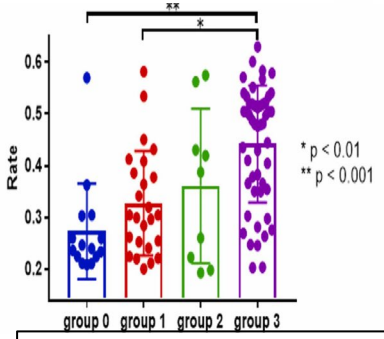


[cfDNA 1h]	Low	Low	High	High
[cfDNA delta/h]	Low	High	Low	High

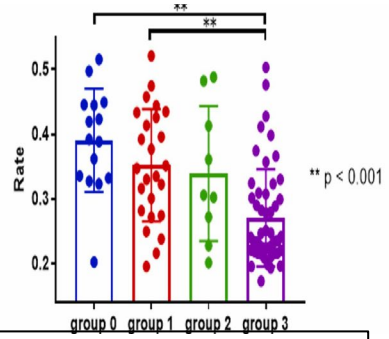


Group	0	1	2	3
Declined	2	8	4	36
Transplanted	13	17	5	15
Declined rate	13%	32%	44%	71%

Predicted probability organ decline by 1h-cfDNA and ΔcfDNA quartiles



Predicted probability of extubation in < 72h by 1h-cfDNA and ΔcfDNA quartiles



Take-home message
- 1h-cfDNA from EVLP perfusate was higher in declined organs, and associated with key EVLP parameters
- Including EVLP cfDNA may support acceptance decisions, especially for non-veteran usage of EVLP systems

Reviewer's Comments

- Future studies including a larger contemporary validation cohort with multiple centers would further support these findings
- Future studies assessing time to accept/decline decisions may be informative
- The lack of enzymatic degradation of cfDNA in an ex vivo circuit may decrease the variability seen in vivo

Limitations

- Retrospective, single center cohort study
- The discovery cohort excluded transplanted cases that resulted in post-graft dysfunction (PGD) 3 at 72 hours, which may confound results
- The validation cohort was comprised of more recent cases confounded by greater confidence in accepting lungs off EVLP, perhaps driving a higher 1h-cfDNA for the validation cohort's transplanted lungs than the discovery cohort's declined lungs
- The validation cohort had significantly higher cold ischemic time than discovery cohort
- There were fewer CVAs as cause of death among declined cases in discovery cohort, otherwise characteristics well matched

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Outcomes of Lung Transplantation for end stage lung disease with connective tissue disease: a systematic review and meta-analysis

Liu J, Zhou R, Li Z, Li Y, et al. *BMC Pulm Med* 2025 May;27;25(1):264. | DOI: 10.1186/s12890-025-03640-x

Study Highlights

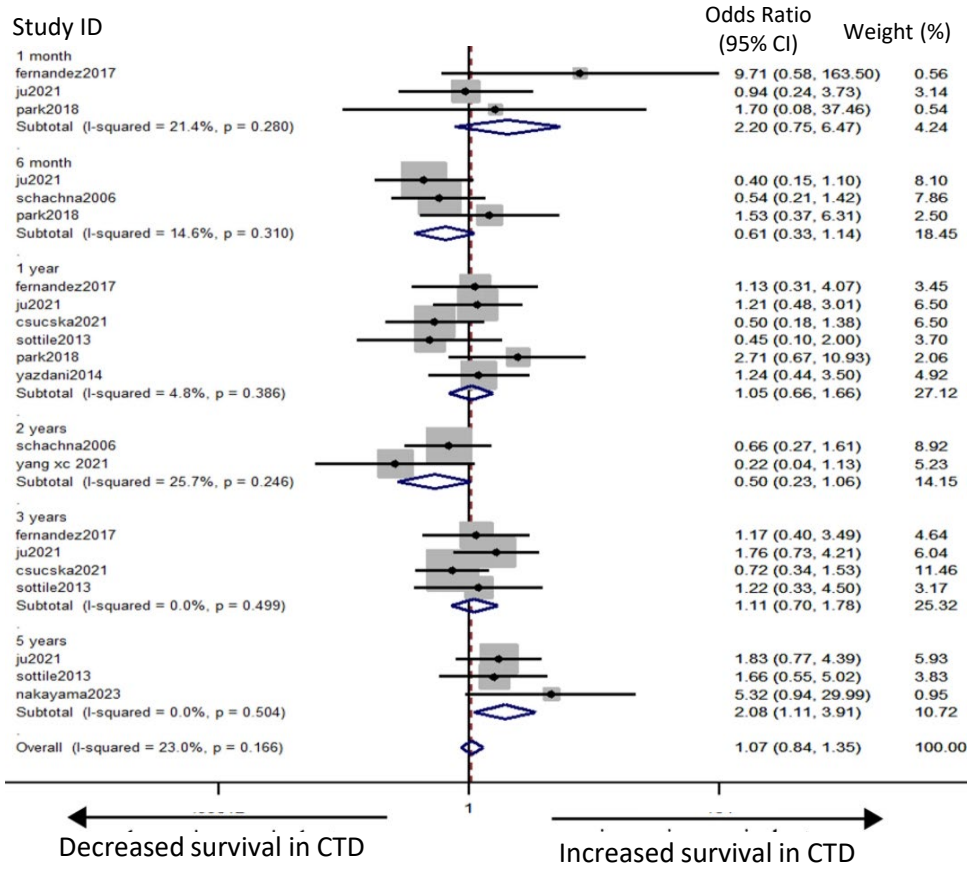
Background:
Connective tissue diseases (CTD) such as systemic sclerosis (SSc), lupus, & myositis may manifest with interstitial lung disease which, when severe, may lead to referral for lung transplant. Some CTD transplant outcomes (ex: PGD / primary graft dysfunction) are inconsistent across studies.

Objective:
Compare survival and outcomes following lung transplant for patients with vs without CTD, via a systematic review & meta-analysis

Methods:
- Search of multiple databases including PubMed, Embase, Web of Science, Cochrane, and Chinese databases (Wanfang, VIP, CNKI, CBM)
- Studies included through October 18, 2023
- Of 6,184 deduplicated studies, 12 met inclusion criteria- 369 CTD and 2165 non-CTD transplant recipients

Results:
Survival was higher for CTD compared to non-CTD at 5 years (OR 2.08, p=.027), but not different at 1 month – 3 years. 5-year survival was lower for SSc vs non-SSc
- ↑ PGD1 & PGD2 in CTD, but no difference for PGD3
- Similar post-LTx rejection in CTD and non-CTD
- ↑ time to extubation and hospital length of stay in CTD

Pooled survival for transplant recipients with CTD vs without CTD



Take-home message
CTD patients may have a higher risk of immediate complications (PGD, hospital length of stay, and time to extubation), but long-term survival outcomes are more favorable on pooled analysis. Multidisciplinary planning is encouraged to prevent perioperative complications

Reviewer's Comments

- Increased early post-transplant complications in CTD highlights the need for close attention & pre-transplant optimization in this patient population
- Greater long-term survival in CTD recipients is unexpected. A younger age for CTD patients that undergo transplant may provide one explanation; alternatively, selective publication of disproportionately favorable outcomes in CTD by high-volume centers may drive publication bias
- Lung transplant candidates with CTD often carry additional medical complexity. This meta-analysis found similar survival for patients with and without CTD, which is helpful for transplant centers and referring physicians in considering lung transplant candidacy for CTD patients

Limitations

- Most CTD patients in this analysis had SSc, resulting in limited representation for other sub-types of CTD
- 7/12 studies used patients with idiopathic pulmonary fibrosis (IPF) for their control group, limiting outcome comparisons from other LTx indications
- Cut-off date of October 2023 excludes more recent data from the past two years
- Bias analysis performed by the authors was suggestive of possible publication bias
- All studies included were observational, which may introduce confounders that cannot be addressed

ISHLT JOURNAL WATCH
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CD26/DPP-IV inhibitors and associations with chronic lung allograft dysfunction in a multicenter cohort

Graham AR, Grau-Sepulveda MV, Buckley EJB, Dilling DF, et al. *JHLT* 2025 Apr 27;44(9):1493-1503. | DOI: 10.1016/j.healun.2025.04.010

Study Highlights

Background:

- Chronic lung allograft dysfunction (CLAD) significantly impacts long-term survival after lung transplantation
- CD26/DPP-IV inhibitors (gliptins) may modulate immune responses via TH-17 cells and IL-17, which link to CLAD and ACR.
- Animal studies suggest gliptins may reduce CLAD risk by decreasing T-cell infiltration and improving allograft function.

Objective:

To assess whether post-transplant exposure to gliptins reduces the risk of CLAD by leveraging their anti-inflammatory/ immunomodulatory effects.

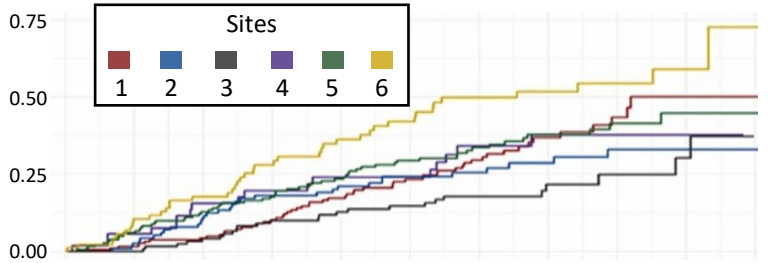
Methods:

- N = 779 lung transplants performed 12/2015–8/2018
- Prospective and retrospective cohort across 6 lung transplant centers in North America
- Gliptin exposure defined as any use of gliptins post-transplant, with data on timing (early vs. late) used in statistical models.

Results:

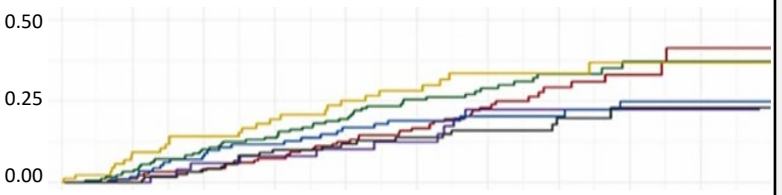
- Median gliptin exposure was 360.5 days, with the highest usage seen in older patients (>65 years: 44.4%)
- Gliptin exposure at any time-point not associated with probable or definite CLAD in this cohort
- Gliptin exposure for >6 months, when started within the first 90 days after transplant, was associated with a decreased risk of definite CLAD (HR = 0.25, CI 0.07-0.83, p < 0.05)

Cumulative Probable CLAD across sites (30.3%-72.6% at 5 years)



Months since CLAD eligibilitiy

Cumulative Definite CLAD across sites (24.8%-41.2% at 5 years)



Months since CLAD eligibilitiy

Gliptin Exposure and Its Relationship With CLAD in Centers With Median Exposures Greater Than 6 Months

	Definite CLAD			
	Unadjusted HR (95% CI)	Unadjusted *p*-value	Adjusted HR[a] (95% CI)	Adjusted *p*-value
Model 3: Any gliptin exposure in the first 6 months post-transplant (N = 670)				
Any gliptin use	0.27 (0.08-0.86)	0.027	0.25 (0.08-0.81)	0.021

Take-home message

Early exposure to gliptins may associate with reduced definite CLAD, but further prospective studies are necessary to validate these findings

Reviewer's Comments

- CLAD remains a significant cause of morbidity and mortality in lung transplant recipients, with limited therapeutic options beyond re-transplantation
- This is a timely large-sized multi-center study on CLAD prevention addressing a well tolerated therapeutic target The association aligns with experimental animal and human data, suggesting that CD26/DPP-IV inhibition may impact rejection after human lung transplantation
- A hazard ratio of 0.24 suggests that Gliptins could have a clinically significant impact on CLAD, with early and substantial enough use of gliptins

Limitations

- The retrospective, observational design limits causality
- Site 6 was excluded post-hoc as an outlier, given disproportionately shorter median gliptin exposure and greater incidence of probable CLAD at 5 years post-transplant, which had an impact on repeat analysis
- Prescription patterns for DPP-IV inhibitors may introduce selection bias given cohort was partially retrospective
- Later-enrolled patients had less total follow-up time, limiting longer-term CLAD data
- Inclusion criteria of >90 day survival and >4 collected PFTs may inadvertently exclude the positive or negative impact of gliptins in sicker patients
- Defining 'early gliptin use' within 90 days may introduce immortal time bias, impacting result validity

ISHLT JOURNAL WATCH
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Thrombotic Microangiopathy After Lung Transplantation: A Retrospective Observational Multicenter Cohort Study

Gazengel P, Bunel V, El-Husseini K, Zaidan M, et al. *JHLT Open* 2025 Aug;9:100335. | DOI: 10.1016/j.jhlto.2025.100335

Study Highlights

Background:

Thrombotic microangiopathy (TMA) is a rare but serious post-transplant complication, often linked to calcineurin inhibitor (CNI) use. Data on TMA after lung transplant (LTx) remains limited.

Objective:

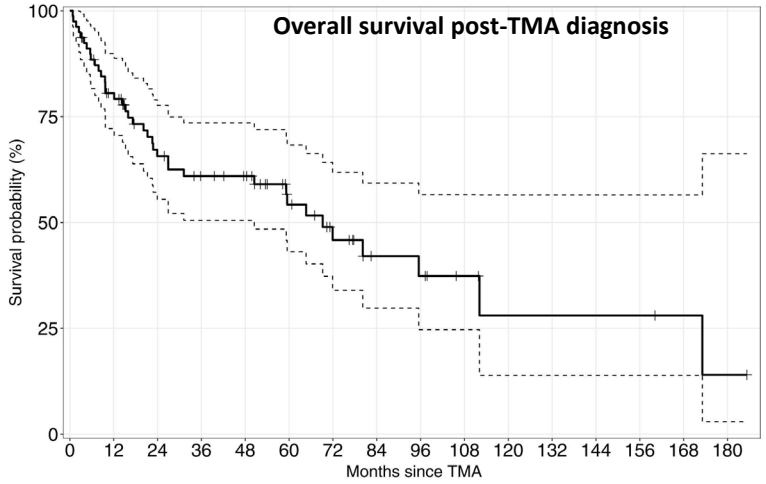
To determine clinical features, outcomes, and survival for TMA after lung transplant in a multi-center cohort, with subset analysis for patients managed with a switch from a CNI to belatacept.

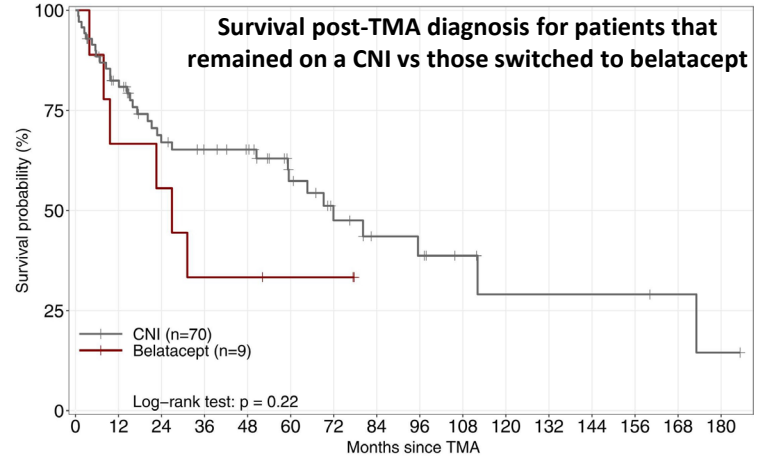
Methods:

- Retrospective multi-center cohort in France
- Lung transplants between January 2006 and December 2023
- n=82 LTx recipients diagnosed with TMA; 3 excluded for co-use of CNI and belatacept at time of TMA

Results:

- TMA incidence of 1.8%; 67 TMA cases (85%) linked to CNI use
- 32 patients (40%) switched CNI, 26 (33%) reduced CNI dose, 9 (11%) switched to belatacept, & 22 (28%) received other therapy
- Univariate risk factors for worse outcomes after TMA included older age, transplant for pulmonary fibrosis, and use of cardiopulmonary bypass; only pulmonary fibrosis remained significant on multivariate analysis (HR 6.92, p=0.01)
- Patients switched to belatacept had greater frequency of bacterial pneumonia (p=0.01) and invasive Aspergillosis (p=0.04)
- There was a trend for higher frequency of graft-infection-related-death in patients switched to belatacept (42% vs 11%, p=0.09), with a median follow-up after TMA episode of 31 months (11-66)





Take-Home Message

TMA after lung transplant is rare and commonly associated with CNI use. Switching CNI to belatacept associates with more infections, which could result in higher mortality.

Reviewer's Comments

- Previous work exploring TMA in transplant chiefly focused on renal transplant. This study fills a critical gap by focusing on LTx recipients, where TMA diagnosis is more scarce (incidence in this study of 1.8%)
- Nearly half of patients that developed TMA were reported to have CNI levels above goal, supporting CNI use as the major risk factor for TMA after lung transplant
- A regimen including belatacept after lung transplant has previously been associated with severe infection risk. This study provides additional evidence for an increased risk for infection after lung transplant with belatacept

Limitations

- Only 9 patients were transitioned from CNI to belatacept after a diagnosis of TMA. Such a small sample size limits the power for TMA outcome comparisons between a switch to belatacept and other management options
- Belatacept is a more recent immunosuppression option, with approval granted in 2011 for kidney transplant rejection. TMA cases that were switched to belatacept were thus generally more recent cases, when other aspects of transplant management may have also differed. This may lead to time period as a confounder
- Because this study was retrospective, the association between belatacept use and outcomes may be confounded. For example, clinicians may have selected belatacept for more severe TMA cases, which could explain worse observed outcomes.