

Increased plasma levels of donor-derived cell-free DNA correlate with acute rejection in the recipients of living donor-lobar lung transplantation.



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Introduction

➤ Donor-derived cell-free DNA (dd-cf-DNA) has been shown to be an informative biomarker of rejection after lung transplantation from deceased donors.

➤ However, in living-donor lobar lung transplantation (LDLLT), because small grafts are implanted with short ischemic time from blood-relatives, the detection of dd-cf-DNA might be challenging, and the role of dd-cf-DNA in the LDLLT recipients remains unknown.

Methods

➤ Plasma samples were collected daily for the first 14 days after LDLLT. Cell-free (cf-DNA) was extracted from 182 plasma samples from 13 recipients of the LDLLT, including recipients with stable condition (n=5), recipients with pneumonia (n=4), and recipient with acute rejection (AR) (n=4).

➤ Single-nucleotide polymorphisms (SNPs) genotyping was performed to differentiate between DNA from donors and recipients by real-time PCR

➤ After obtaining the informative SNPs assays for each patient, quantification of dd-cf-DNA was measured by using digital droplet PCR.

Objective

Our study was aimed at examining the role of the dd-cf-DNA in the diagnosis of acute rejection after LDLLT.

Results

TABLE 1. Preoperative and postoperative patient characteristics

Characteristics	AR (n= 4)	Infection (n=4)	Stable (n=5)	P-value
Age, years	15 (10-24)	22 (6-55)	7 (2-29)	0.47
Male, sex (%)	3 (23.2)	2 (15.3)	3 (23.2)	0.76
Diagnosis				0.62
Pulmonary graft-versus-host disease (%)	3 (23.1)	1 (7.7)	2 (15.3)	
Interstitial lung disease (%)	0	2 (15.4)	2 (15.4)	
Pulmonary hypertension (%)	1 (7.7)	0	1 (7.7)	
Bronchiectasis (%)	0	1 (7.7)	0	
3D-CT volumetry of the graft (ml)	1074 (652-1259)	776 (465-1185)	991 (790-1380)	0.58
Lung transplant procedure				0.94
Single (%)	2 (15.3)	2 (15.3)	3 (23.2)	
Double (%)	2 (15.3)	2 (15.3)	2 (15.3)	
Ischemic time (min)	78.5 (71-144)	133 (106-198)	120 (98-163)	0.16
Operative time (min)	380 (300-546)	470 (221-785)	454 (239-608)	0.74
Intubation time (day)	2 (2-46)	5 (1-17)	2 (1-12)	0.56
ICU stay (day)	17 (14-101)	17 (5-28)	13 (8-28)	0.55

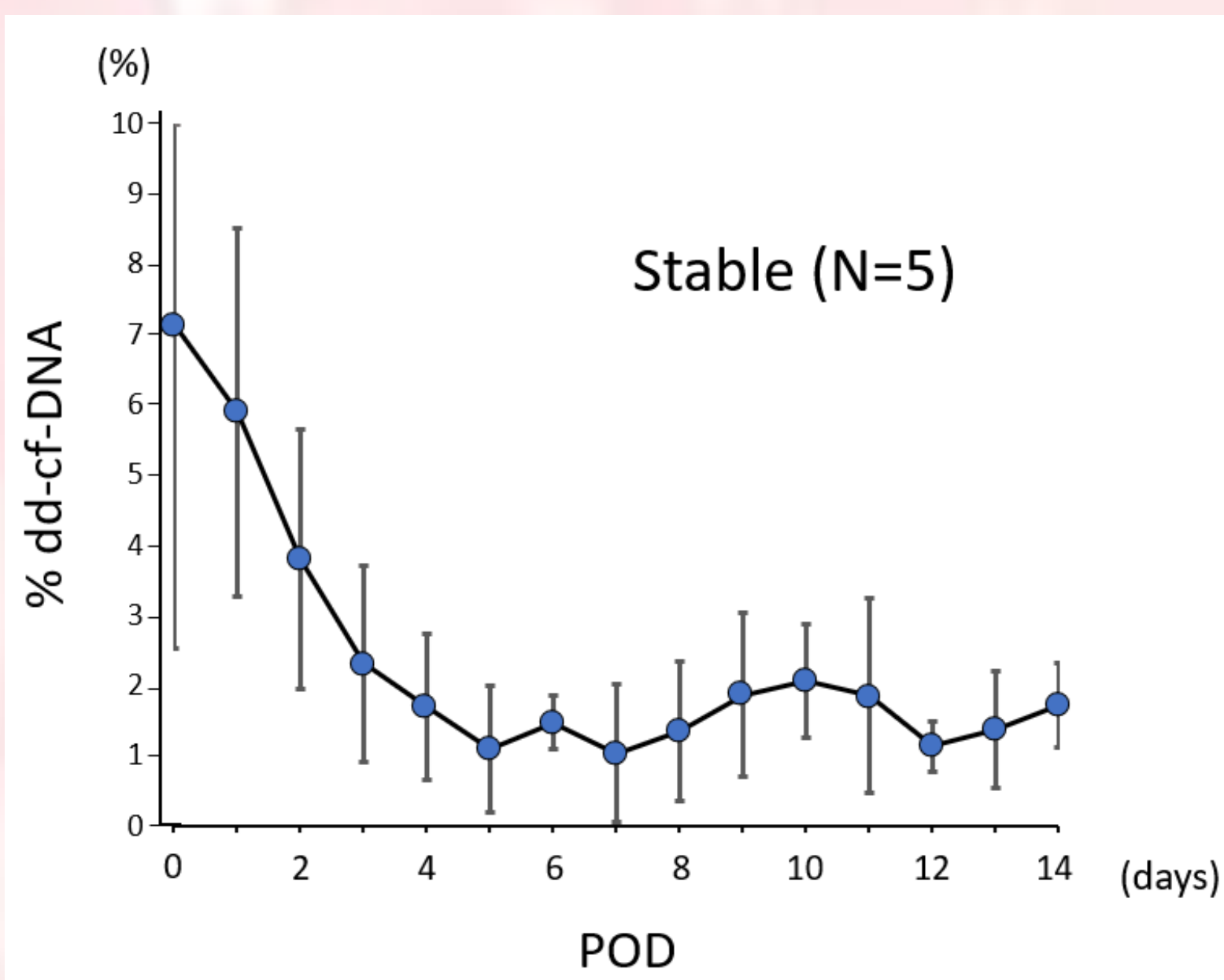


Figure 1. Time course of plasma % dd-cf-DNA (dd-cf-DNA / total cfDNA) without rejection and pneumonia.

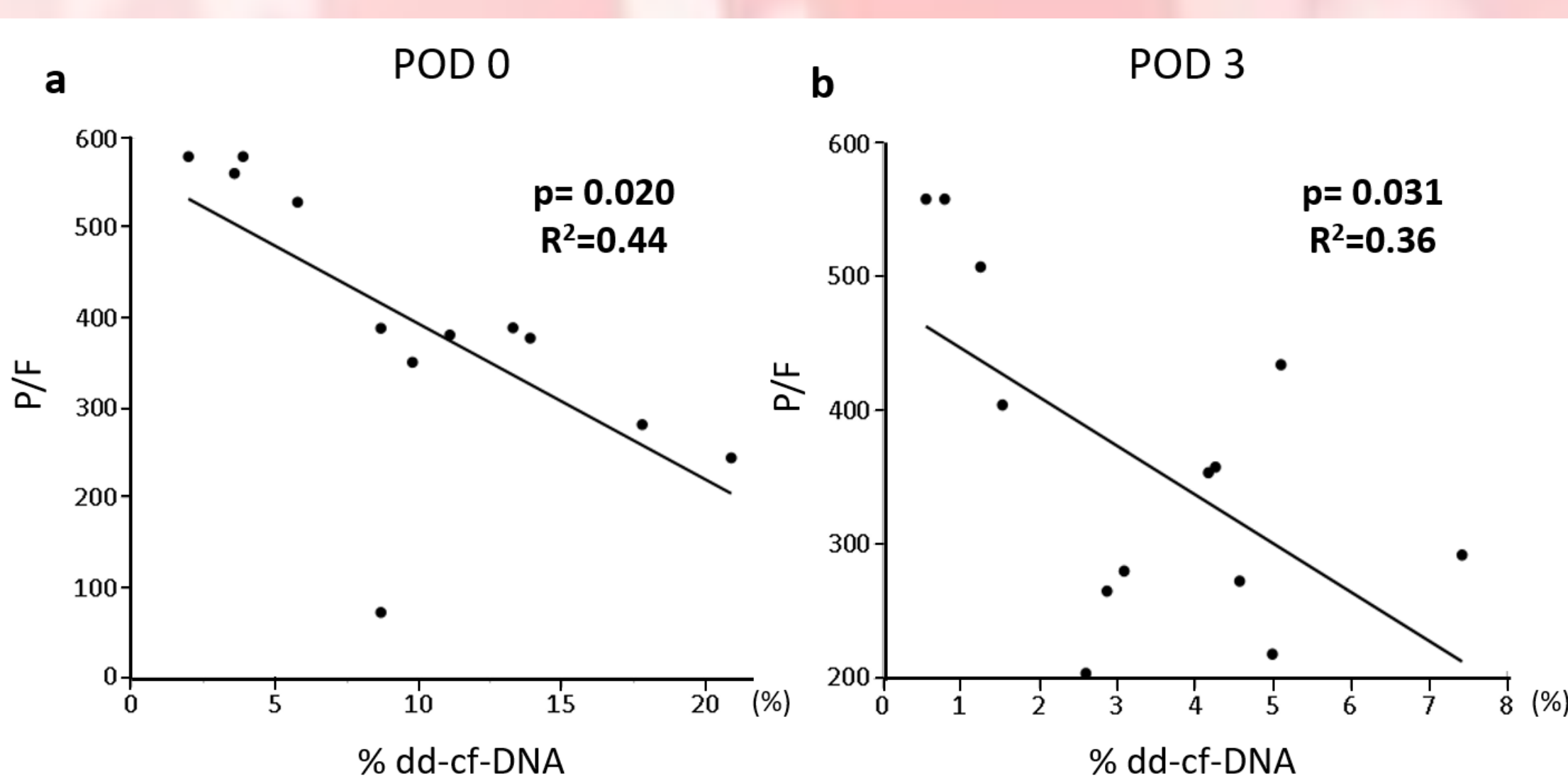


Figure 2. Regression analyses between % dd-cf-DNA and P/F ratio at (a) 0 and (b) 72 hours after LDLLT.

Results

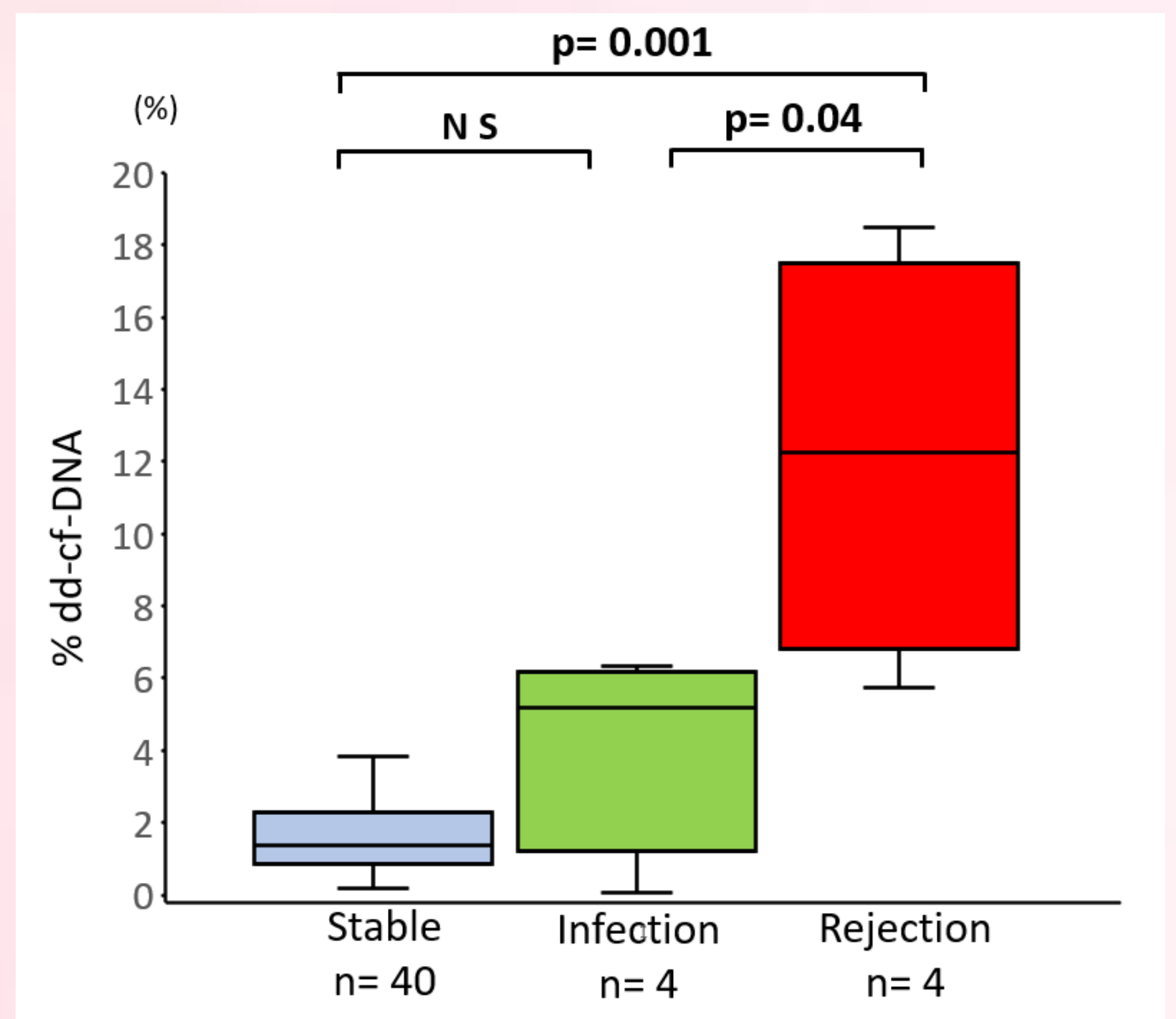


Figure 3. Plasma % dd-cf-DNA during between the first 5 and 14 days.

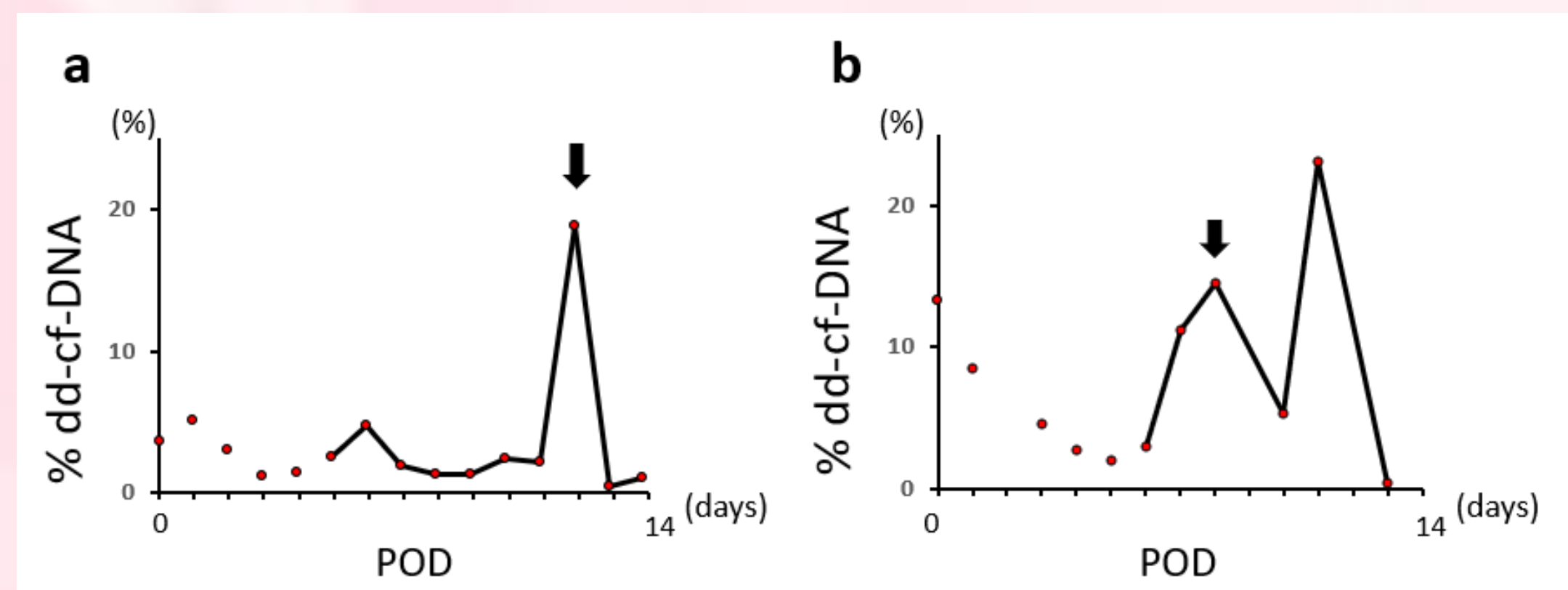


Figure 4. Donor derived cell free DNA at rejection. (a) acute rejection and (b) antibody mediated rejection event. black arrow= the onset of rejection.

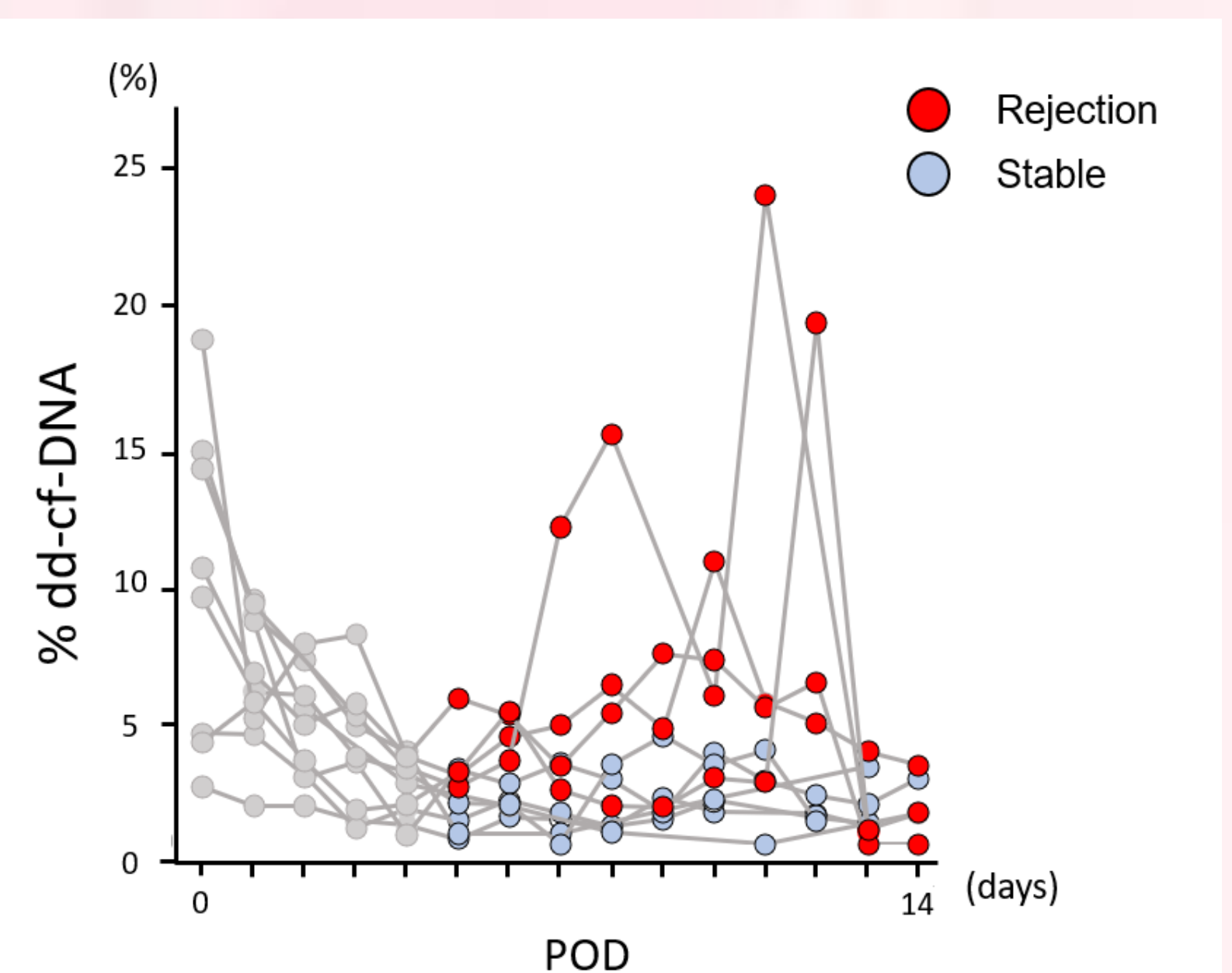


Figure 5. Overview of the first 14 days monitoring data collected for acute rejection group and stable group.

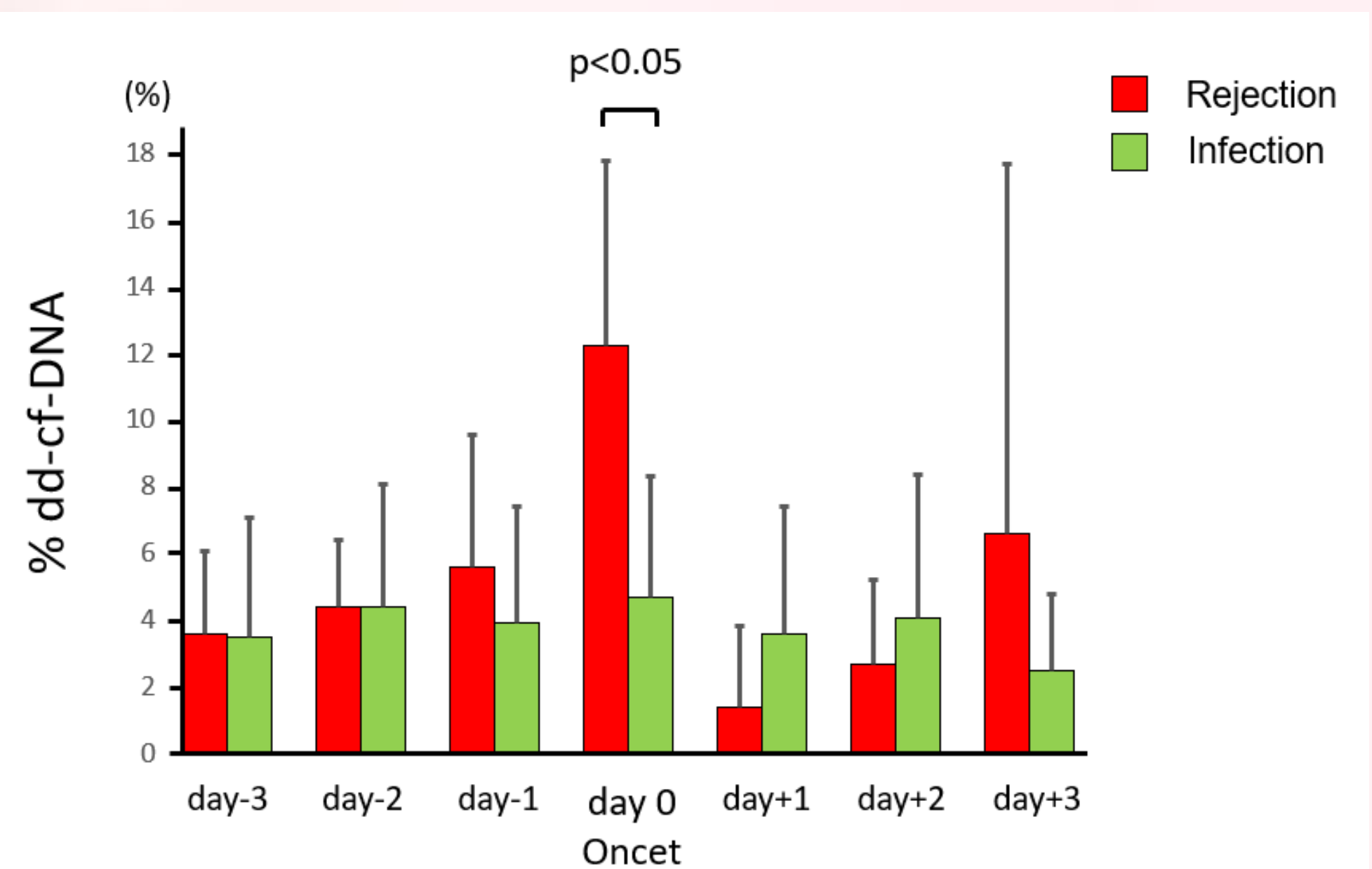


Figure 6. Plasma % dd-cf-DNA around the acute rejection episode and pneumonia episode

Discussion

➤ Cell-free DNA consists mainly of 166 base pair double-stranded DNA fragments resulting from apoptosis, necrosis or the release of nuclear DNA into the circulation.

➤ In the circulation, these fragments have a short half-life of 1.5 hours due to their rapid hepatic and renal clearance .

➤ Therefore, dd-cf-DNA reflects a real-time genomic signature of the graft tissue damage after solid organ transplantation.

Conclusion

In this study, we have shown that the quantification of dd-cf-DNA could be a potential noninvasive biomarker to identify acute rejection in the early phase after LDLLT.



Relevant Financial Relationship Disclosure Statement

No relationships to disclose