Supplemental Digital Content (SDC)

Identification of Transfusion Events

Transfusions were identified using the following codes: ICD-9 procedure (99.03-99.04, V58.2), common procedural terminology (CPT-4) (3640), healthcare common procedure coding system (HCPCS; P9010, P9011, P9016, P9021, P9022, P9038-P9040, P9051, P9054, P9056-P9058 and revenue (37) codes.

Analysis of Change in HLA Antibody Levels Over Time

Statistical Analysis

General estimating equations were used to evaluate change in HLA class I and class II antibody values for up to one year following the follow-up HLA measurement among transfused patients who exhibited any antibody response. Within-person correlation was accounted for using an independent correlation structure.

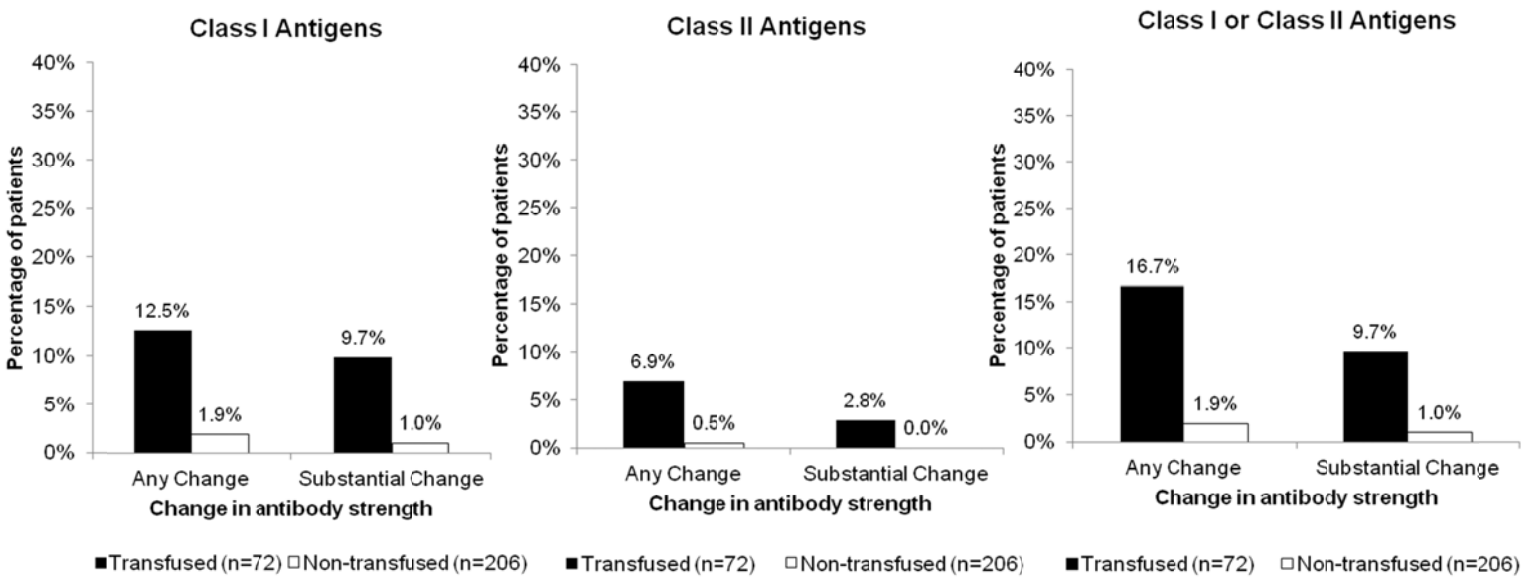
Results

Among the transfused patients who developed any response in HLA class I antibodies (n=17) and class II antigens (n=7), two patients were administratively censored shortly after their peak measurement and therefore were excluded, leaving 15 and 5 patients, respectively, for this analysis. Antibody levels for up to one year after their follow-up antibody measurement were evaluated and any measurements taken on or after a transfusion or pro-inflammatory event were excluded. Patients had, on average, 5 additional measurements (SD 4.1, IQR 1-8) over the following year, separated by average of 34 days between measurements (median 29 days, IQR 21-35 days). The adjusted values for HLA class I antibodies declined over time (β= -0.06 per day, SE = 0.05), as did those for the class II antibodies (β= -0.01 per day, SE=0.06) in **SDC, Figure 5**.

Figure S1. Change in adjusted value for Class I or Class II antibodies identified in all patients with CPRA data included in transfused and matched non-transfused groups (panels a, b, c) and crossover cohort (panels d,e,f). "Substantial change" refers to clinically relevant changes in antibody strength at the higher threshold levels, i.e., increases that could result in positive crossmatch tests.

Matched cohort

a) b) c)



Crossover cohort:

d) e) f)

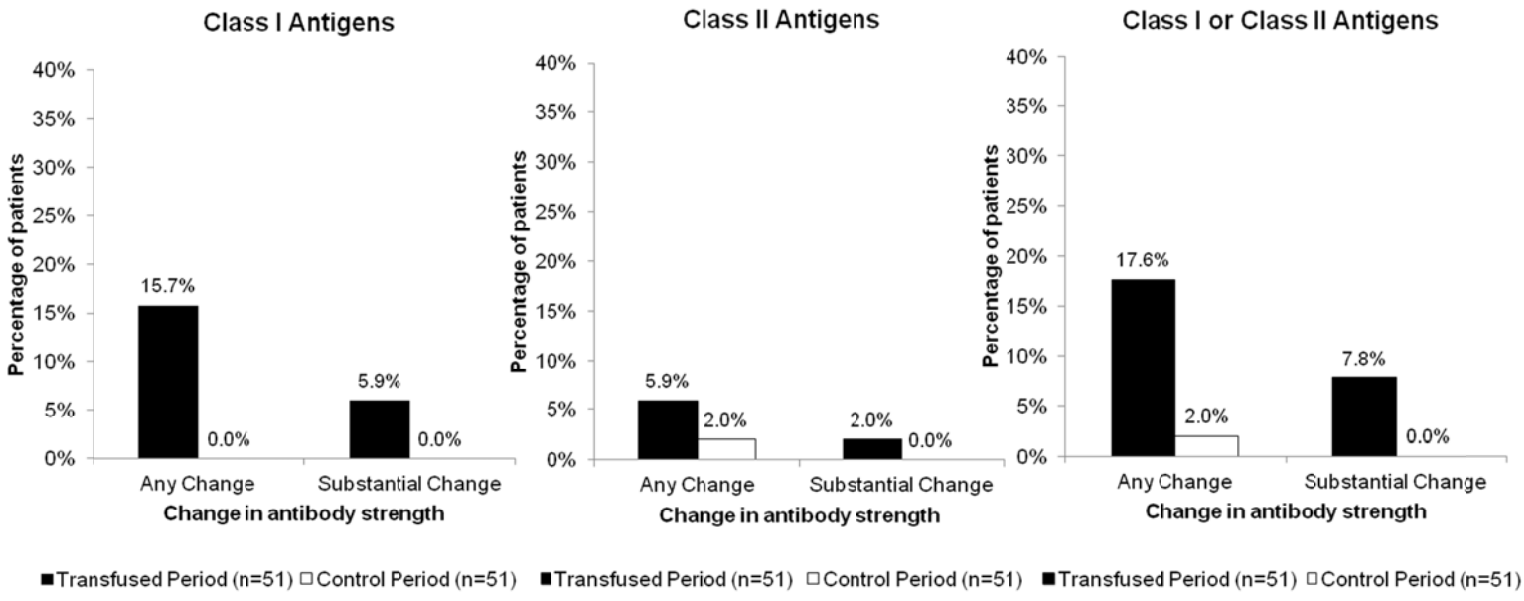
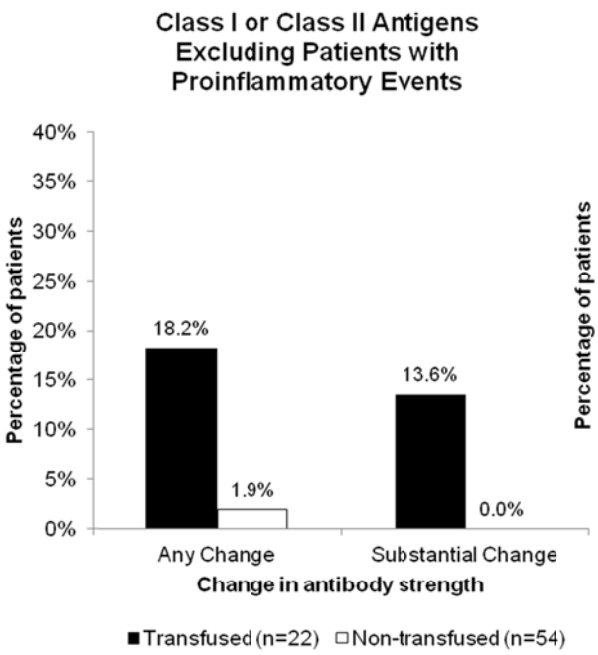

Class I Antigens
Percentage of patients
40%
35%
30%
25%
20%
15%
10%
5%
0%
15.7%
0.0%
5.9%
0.0%
Any Change
Substantial Change
Change in antibody strength
Class II Antigens
Percentage of patients
5.9%
2.0%
2.0%
0.0%
Any Change
Substantial Change
Change in antibody strength
Class I or Class II Antigens
Percentage of patients
17.6%
2.0%
7.8%
0.0%
Any Change
Substantial Change
Change in antibody strength
Transfused Period (n=51)
Control Period (n=51)
Transfused Period (n=51)
Control Period (n=51)
Transfused Period (n=51)
Control Period (n=51)

Figure S2. Change in adjusted value for Class I or Class II antibodies identified in all patients included in transfused and matched non-transfused groups (panels a, b) and crossover cohort (panels c, d) by pro-inflammatory event status. "Substantial change" refers to clinically relevant changes in antibody strength at the higher threshold levels, i.e., increases that could result in positive crossmatch tests.

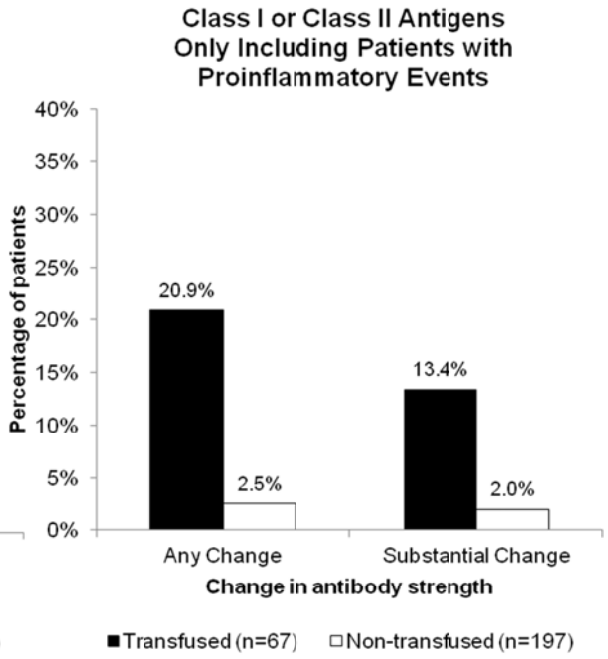
:

Matched cohort

a)



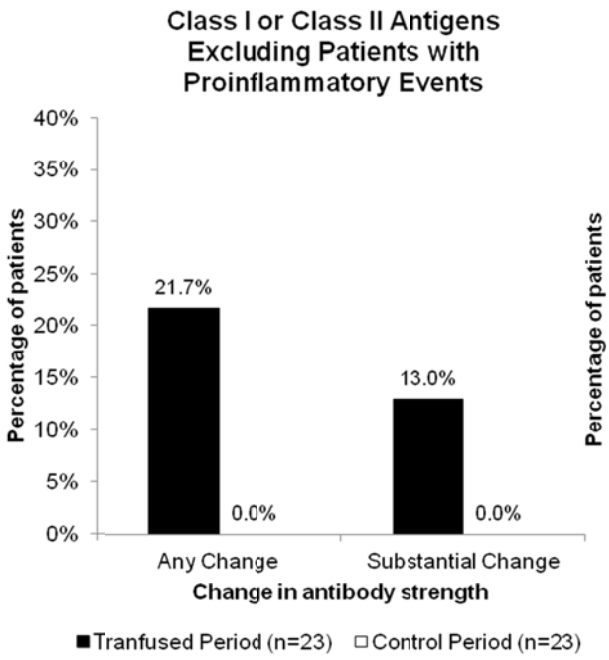
b)



Crossover cohort:

c)

d)


Class I or Class II Antigens
Excluding Patients with
Proinflammatory Events
40%
35%
30%
25%
20%
15%
10%
5%
0%
Percentage of patients
21.7%
0.0%
13.0%
0.0%
Any Change
Substantial Change
Change in antibody strength
Tranfused Period (n=23)
Control Period (n=23)

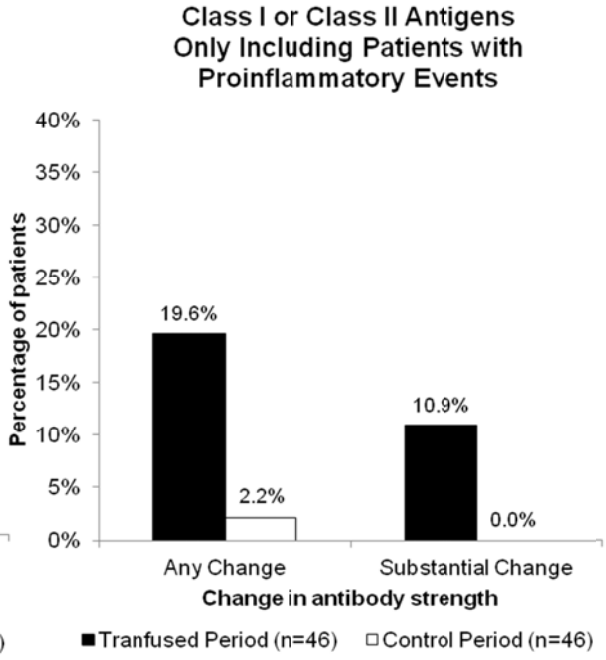

Class I or Class II Antigens
Only Including Patients with
Proinflammatory Events
40%
35%
30%
25%
20%
15%
10%
5%
0%
Percentage of patients
19.6%
2.2%
10.9%
0.0%
Any Change
Substantial Change
Change in antibody strength
Tranfused Period (n=46)
Control Period (n=46)

Figure S3. Change in adjusted value for Class I or Class II antibodies identified in all patients included in transfused and matched non-transfused groups according to time between transfusion and follow-up HLA measurement (<30 [panel a], 30-<90 [panel b], ≥ 90 days [panel c]). "Substantial change" refers to clinically relevant changes in antibody strength at the higher threshold levels, i.e., increases that could result in positive crossmatch tests.

a) b) c)

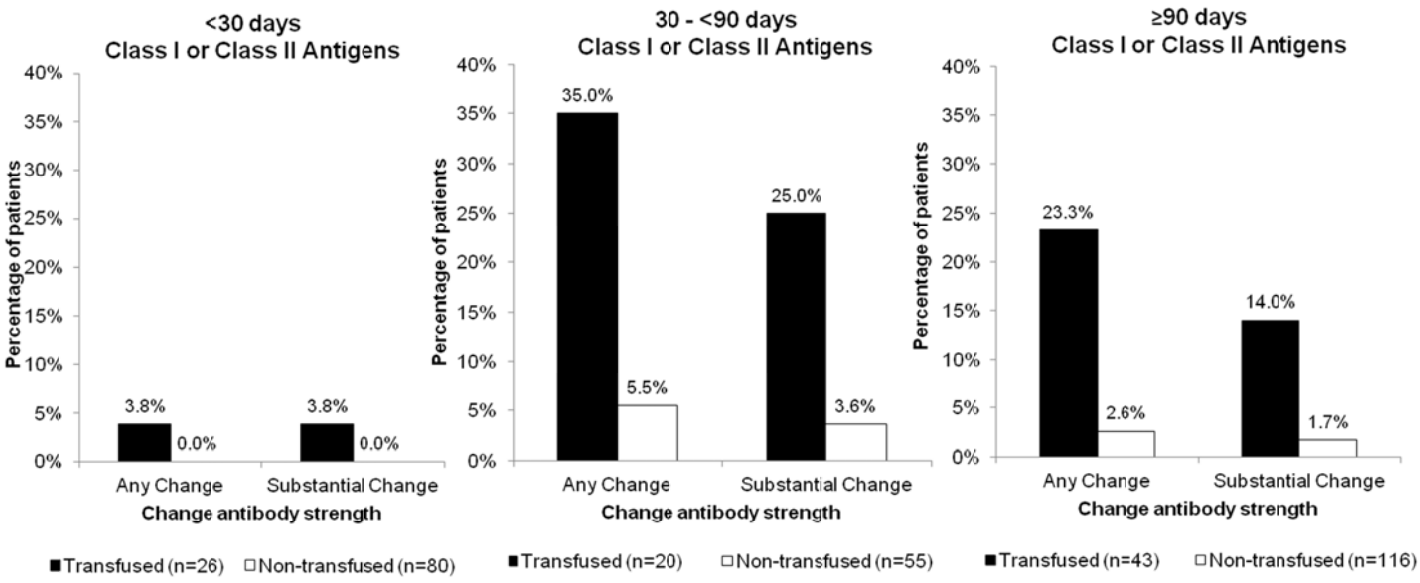
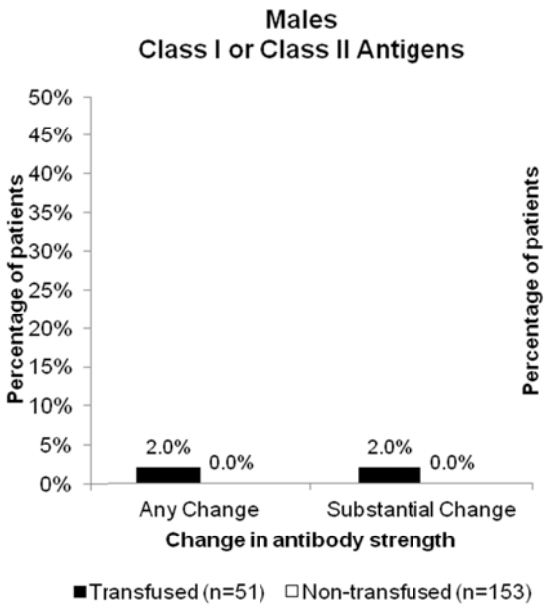
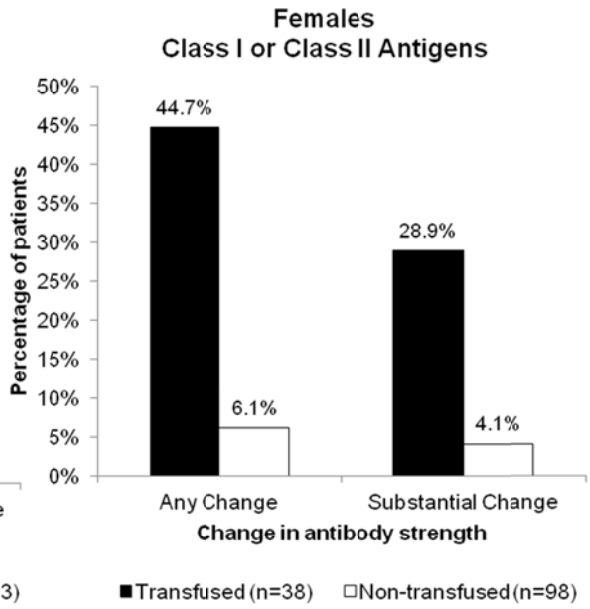


Figure S4. Change in adjusted value for Class I or Class II antibodies identified in all patients included in transfused and matched non-transfused groups according to gender (panels a, b), race (panels c, d), and age (panels e, f, g, h) sub-groups. "Substantial change" refers to clinically relevant changes in antibody strength at the higher threshold levels, i.e., increases that could result in positive crossmatch tests.

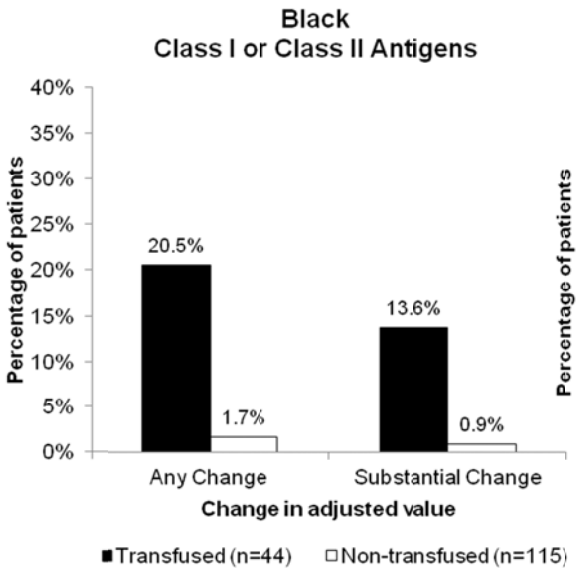
a)



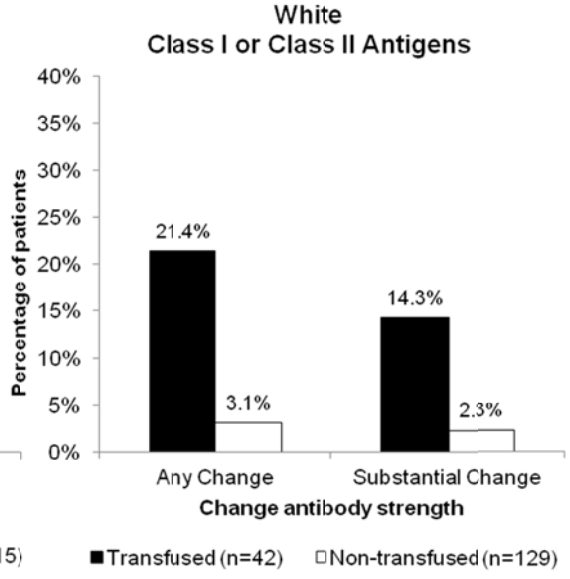
b)



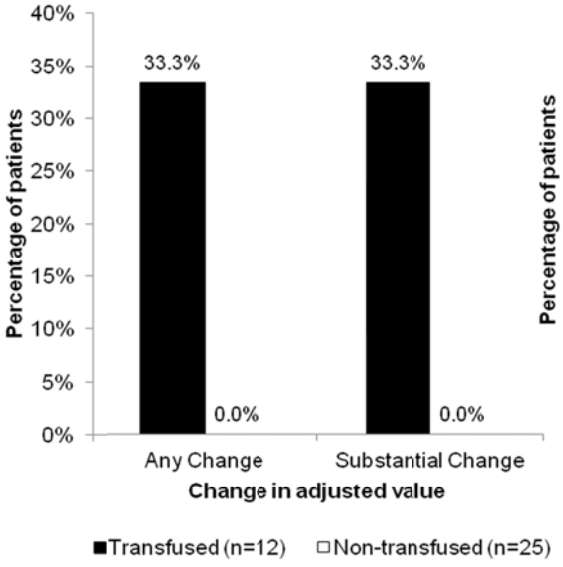
c)



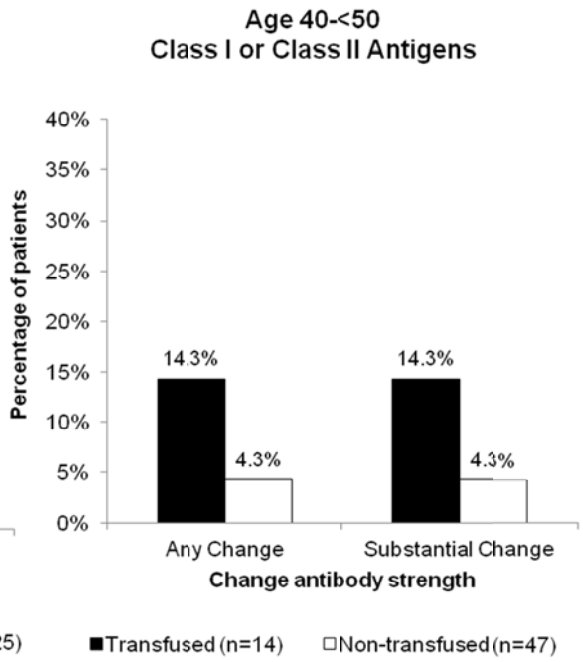
d)



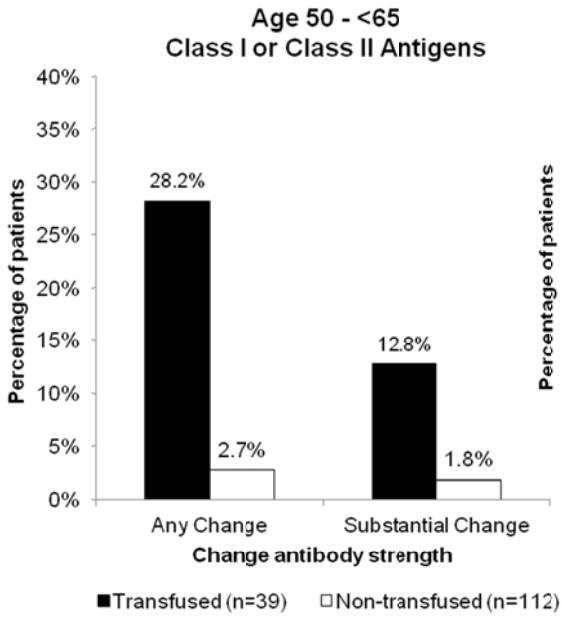
e)


Age <40
Class I or Class II Antigens
40%
35%
30%
25%
20%
15%
10%
5%
0%
Percentage of patients
33.3%
33.3%
0.0%
0.0%
Any Change
Substantial Change
Change in adjusted value
Transfused (n=12)
Non-transfused (n=25)

f)


Age 40-<50
Class I or Class II Antigens
40%
35%
30%
25%
20%
15%
10%
5%
0%
Percentage of patients
14.3%
14.3%
4.3%
4.3%
Any Change
Substantial Change
Change antibody strength
Transfused (n=14)
Non-transfused (n=47)

g)


Age 50 - <65
Class I or Class II Antigens
40%
35%
30%
25%
20%
15%
10%
5%
0%
Percentage of patients
28.2%
2.7%
12.8%
1.8%
Any Change
Substantial Change
Change antibody strength
Transfused (n=39)
Non-transfused (n=112)

h)

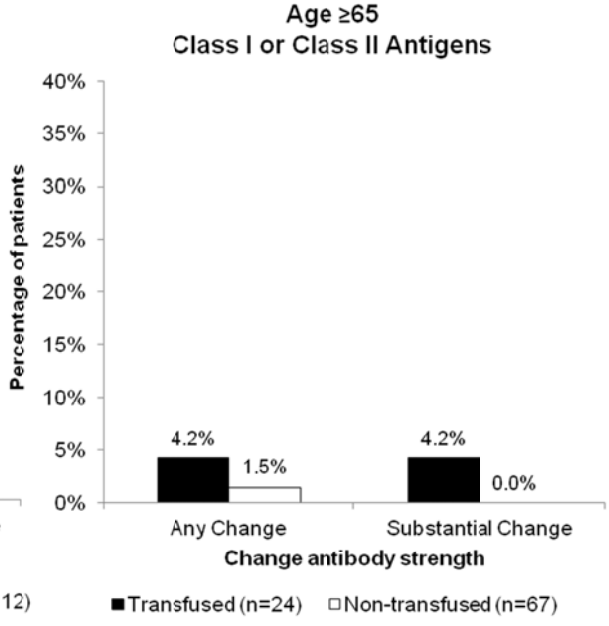

Age ≥65
Class I or Class II Antigens
40%
35%
30%
25%
20%
15%
10%
5%
0%
Percentage of patients
4.2%
1.5%
4.2%
0.0%
Any Change
Substantial Change
Change antibody strength
Transfused (n=24)
Non-transfused (n=67)

Table S1: Odds ratios (OR) and 95% confidence intervals (CI) for the association between receiving a transfusion and the risk of any antibody response (change in adjusted value ≥25 HLA class I or ≥30 class II pooled antigen assays) or a substantial antibody response (change in adjusted value ≥50 class I or ≥60 class II pooled antigen assays) in the matched cohort. Estimates are provided for the population overall and within patient sub-groups.

Group	No. of Transfused	Non-transfused	Any Change OR (95% CI)	Substantial Change OR (95% CI)
Overall	89	251	10.4 (4.0, 27.1)	9.6 (3.0,30.7)
Adjusted*	89	251	11.1 (4.1, 29.7)	9.3 (2.8, 30.6)
Excluding Proinflammatory events	22	54	NA	11.8 (1.2, 112.4)
Including Proinflammatory events only	67	197	10.1 (3.5, 29.4)	7.5 (2.2, 25.2)
Females Only	38	98	12.4 (4.4, 35.3)	9.57 (2.8, 32.5)
Males Only	51	153	NA	NA
Age <40	12	25	NA	NA
Age 40->50	14	47	3.7 (0.5, 29.5)	3.8 (0.5, 29.4)
Age ≥50	63	179	9.3 (1.8, 47.5)	7.6 (1.4, 40.4)
Blacks Only	44	115	14.5 (3.0, 70.4)	18 (1.7, 154.2)
Whites Only	42	129	8.5 (2.5, 29.4)	7.0 (1.7,29.4)

*Adjusted for heart failure, atherosclerotic heart disease, and duration on dialysis.NA – We were not able to calculate OR due to zero patients with an antibody response in the non-transfused group

Figure S5. Plots showing changes in HLA class I (a) and class II (b) antibodies over one year following the peak antibody measurement for each individual who exhibited an antibody response following a transfusion. Each line represents one patient (n=15 for class I and n=5 for class II). Plots for the same patients showing the mean and 95% CI (shaded area) change in HLA class I (c) and class II (d) antibodies over the one year following the peak antibody measurement.

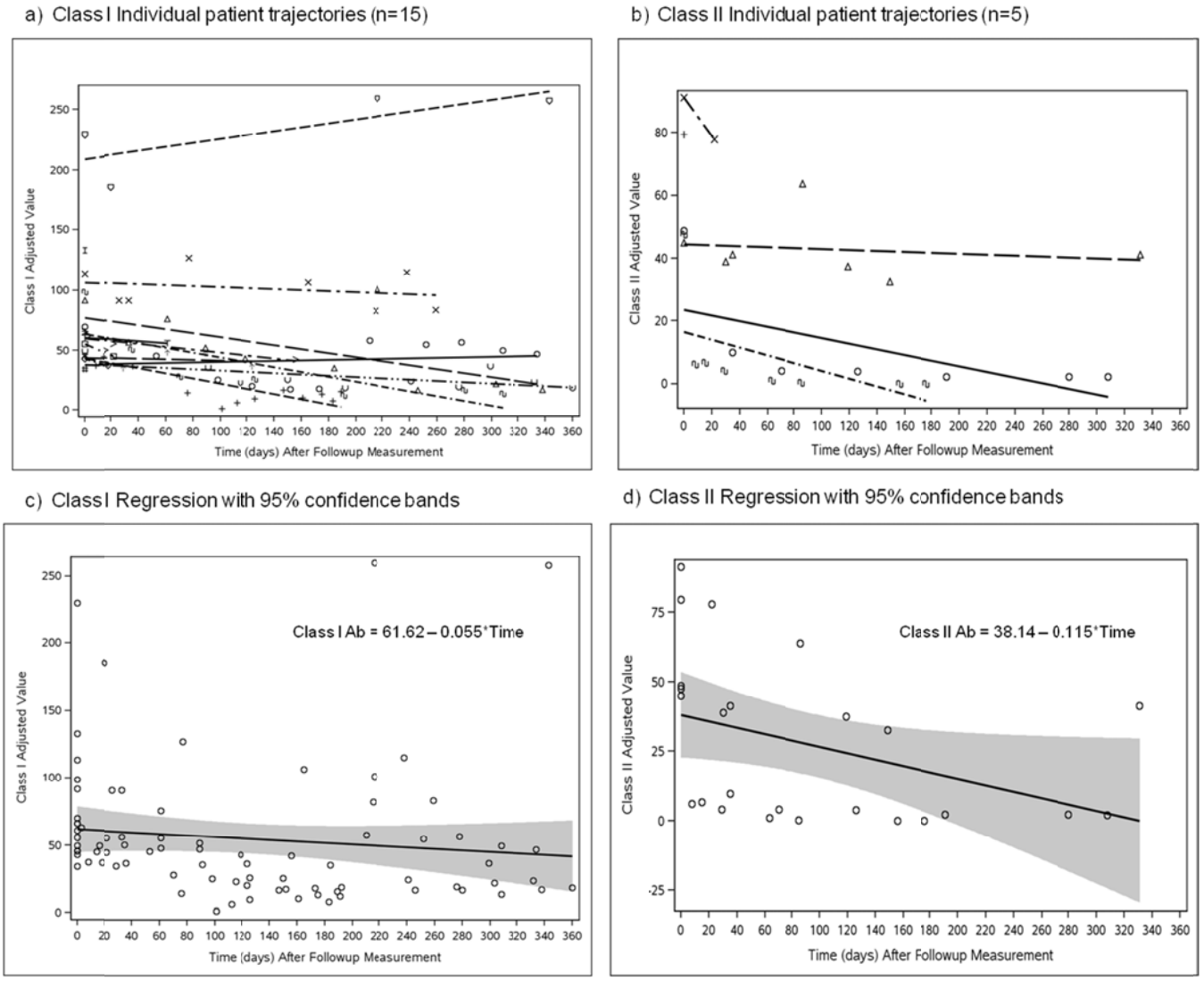
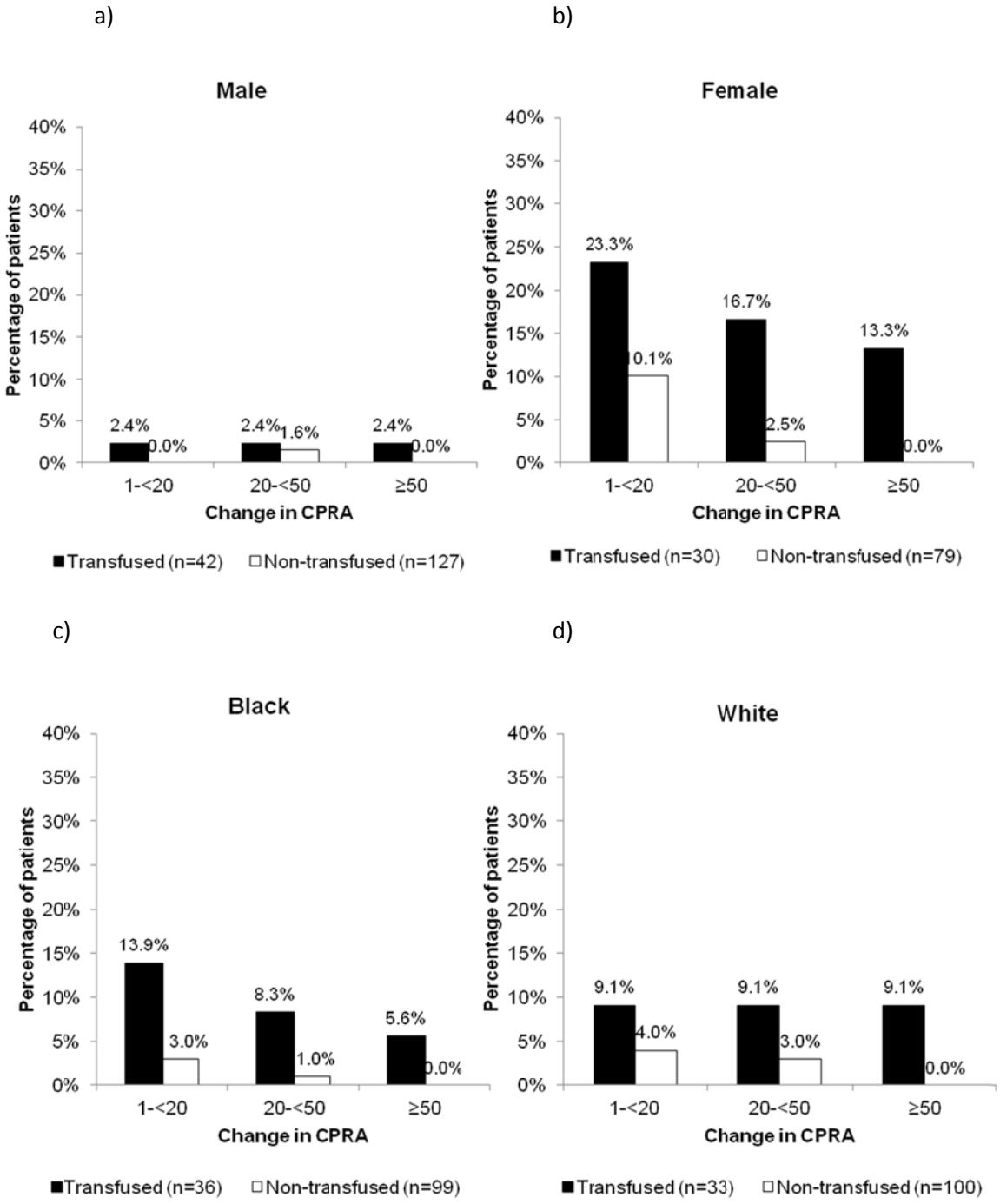
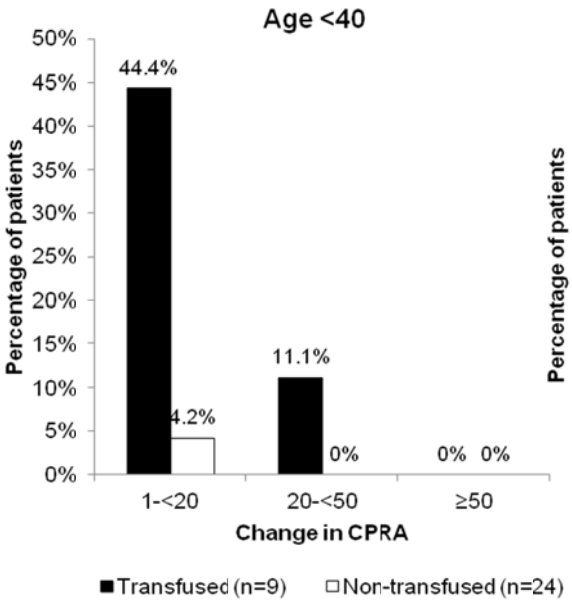


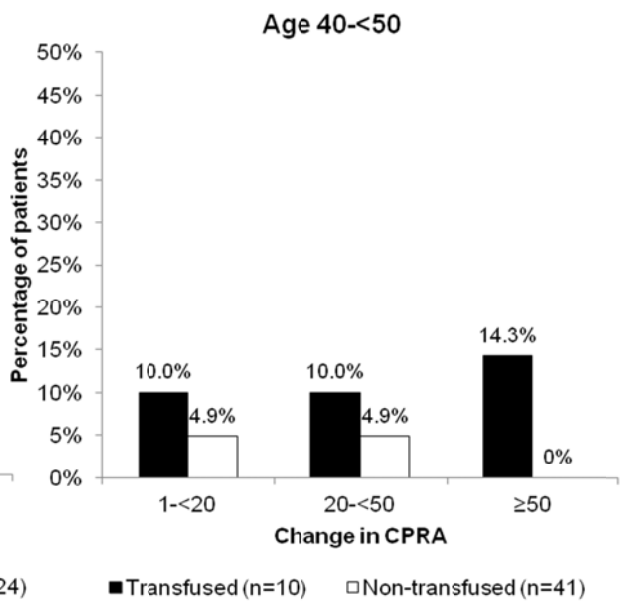
Figure S6. Change in calculated panel reactive antibody (CPRA) levels for patients in transfused and matched non-transfused groups within gender (panels a, b), race (panels c, d), and age (panels e, f, g, h) sub-groups.



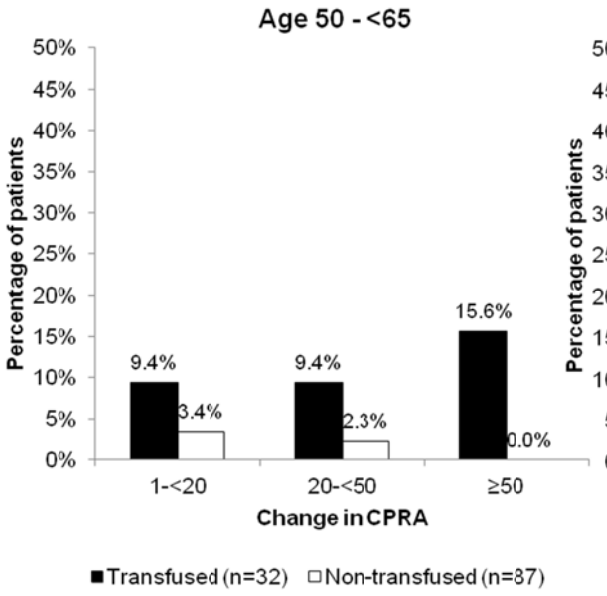
e)


Age <40
Percentage of patients
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
44.4%
4.2%
11.1%
0%
0% 0%
1-<20
20-<50
≥50
Change in CPRA
Transfused (n=9)
Non-transfused (n=24)

f)


Age 40-<50
Percentage of patients
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
10.0%
4.9%
10.0%
4.9%
14.3%
0%
1-<20
20-<50
≥50
Change in CPRA
Transfused (n=10)
Non-transfused (n=41)

g)


Age 50 - <65
Percentage of patients
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
9.4%
3.4%
9.4%
2.3%
15.6%
0.0%
1-<20
20-<50
≥50
Change in CPRA
Transfused (n=32)
Non-transfused (n=87)

h)

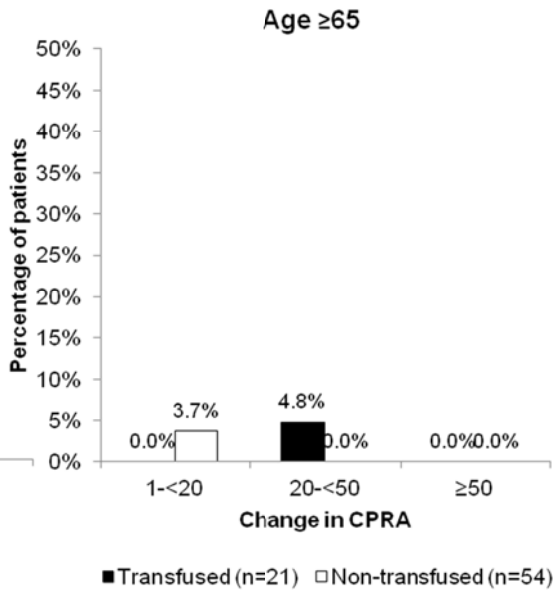

Age ≥65
Percentage of patients
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
0.0%
3.7%
4.8%
0.0%
0.0% 0.0%
1-<20
20-<50
≥50
Change in CPRA
Transfused (n=21)
Non-transfused (n=54)

Figure S7: Change in calculated panel reactive antibody (CPRA) levels for patients in transfused and matched non-transfused groups according to baseline level of sensitization (CPRA=0 [panel a], CPRA > 0 [panel b]).a) b)

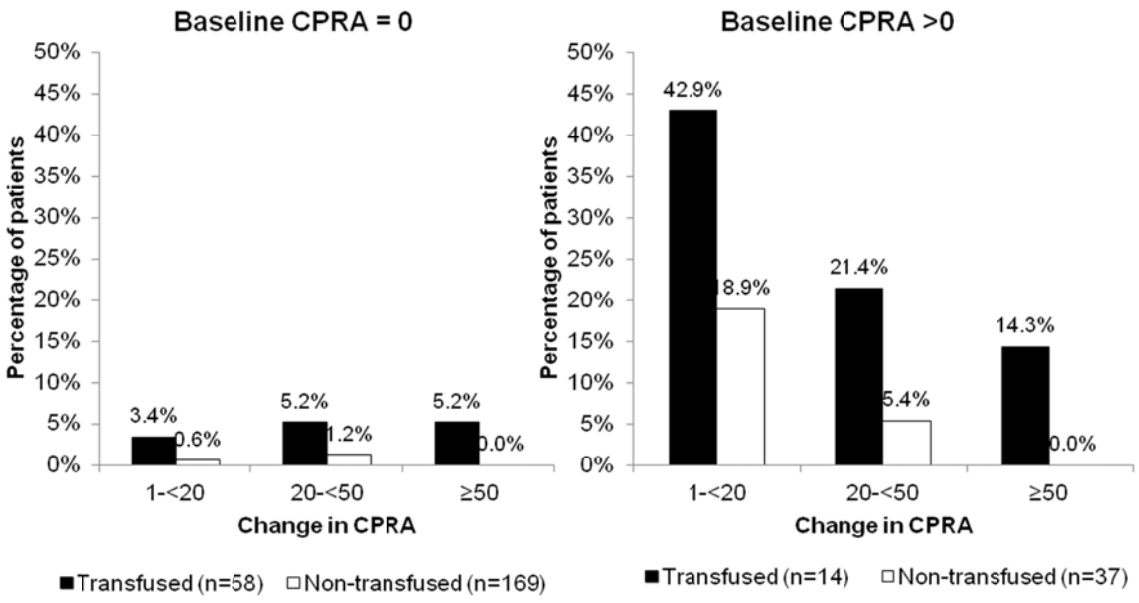


Figure S8. Change in calculated panel reactive antibody (CPRA) levels for patients in transfused and matched non-transfused groups according to time between transfusion and follow-up HLA measurement (<30 [panel a], 30-<90 [panel b], ≥ 90 days [panel c]).

a) b) c)