

# The CD14<sup>+</sup>CD16<sup>+</sup> Monocytes Worsen Glucose Metabolism After Simultaneous Pancreas-Kidney Transplantation

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## OBJECTIVES

To assess the pancreas-graft-censored mortality rate in a retrospective study, followed by a cross-sectional phase evaluating the percentage of CD14<sup>+</sup>CD16<sup>+</sup> monocytes subset after simultaneous SPKT and their influence in glucose metabolism.

## METHODS

We conducted a two phases analysis in which we included all SPKT performed in our hospital from January 1990 to July 2015 for the retrospective phase. Cardiovascular-mortality was defined as death due to stroke, heart failure, fatal arrhythmia or acute coronary syndrome. The cross-sectional analysis assessed the percentage of pro-inflammatory monocytes (CD14<sup>+</sup>CD16<sup>+</sup>) by Flow-Cytometry in SPKT recipients with fasting glucose within the normal range and a GFR >60 ml/min by MDRD4. Correlation analysis of pro-inflammatory monocytes with glucose metabolism parameters was performed.

Table 1. Demographic characteristics of the recipients

Variable	Value
Age (Years, SD)	35.9 ± 5.48
Gender (Male sex, %)	66.7%
HLA class II alleles	
DR3 (n, %)	10 (26.3)
DR4 (n, %)	9 (23.7)
DR3/DR4 (n, %)	10 (26.3)
HLA Mismatch (Mean ± SD)	3.8 ± 1.8
Comorbidities	
Hypertension (n, %)	16 (45.7)
Smoking (n, %)	10 (31.4)
Inducción therapy Basiliximab (n, %)	42 (100)
BMI <sup>a</sup> (mean, SD)	25.9 ± 4.16
Blood Pressure (Mean, SD)	
- Systolic	143 ± 19.32
- Diastolic	87.9 ± 8
Time Since Transplantation (Months, median, IQR)	60.55 (67-88)
Fasting plasma Glucose (mmol/L, mean, SD)	5.15 ± 1.93
<sup>a</sup> Hb1Ac % (Mean,SD)	5.65 ± 0.58
C-peptide (µU/L, mean, SD)	0.71 ± 0.30
LDL (mg/dL, Median, IQR)	91 (20-103)
HDL (mg/dL, Median, IQR)	54.5 (29-79)
Triglycerides (mg/dL, Median, IQR)	83.5 (40-122)
HOMA-β <sup>b</sup> (%., median, IQR)	57 (31-92)
HOMA-IR <sup>c</sup> (Mean, SD)	3.34 ± 1.36
<sup>d</sup> GFR by MDRD4 (ml/min/1.72 m <sup>2</sup> , mean, SD)	77 ± 19.23
<sup>e</sup> Tacrolimus (mean, SD)	7.87 ± 1.86

Table 2. bi-variate analysis showing the factors associated with a higher percentage of CD14<sup>+</sup>CD16<sup>+</sup> monocytes

Variable	CD14 <sup>+</sup> CD16 <sup>+</sup> <4.67 (%)	CD14 <sup>+</sup> CD16 <sup>+</sup> >4.67(%)	p <sup>1</sup>
Recipients			
Age (Years, SD)	34.53 ± 5.52	38.33 ± 4.73	0.016
Gender, Male (n, %)	13 (76.5)	6 (54.5)	0.320
HLA Class II			
DR3 (n, %)	6 (46.2)	3 (37.5)	0.283
DR4 (n, %)	3 (23.1)	2 (25)	0.146
DR3/DR4 (n, %)	4 (30.8)	3 (37.5)	0.931
HLA Mismatch (Mean, SD)	3.9 ± 1.7	3.5 ± 1.9	0.395
Time since Transplantation (Months, median, IQR)	64 (59)	57.86 (81)	0.876
BMI (mean, SD)	26.40 ± 4.16	25.97 ± 3.64	0.565
Blood Pressure (Mean, SD)			
- Systolic	142 ± 19.2	144 ± 19.7	0.764
- Diastolic	87 ± 9.1	89 ± 6.91	0.566
LDL (mg/dL, Median, IQR)	92 (83-100)	84 (72-105)	0.597
HDL (mg/dL, Median, IQR)	55 (47-67)	48 (41-59)	0.292
Triglycerides (mg/dL, Median, IQR)	90 (70-108)	101 (74-122)	0.435
Fasting Glucose (mmol/L, mean, SD)	4.73 ± 0.53	5.18 ± 1.31	0.208
Hb1Ac % (Mean,SD)	5.45 ± 0.48	5.80 ± 0.65	0.033
C-peptide (µU/L, mean, SD)	0.73 ± 0.41	0.82 ± 0.23	0.180
Albumin (g/L, mean, SD)	4.26 ± 0.42	4.27 ± 0.28	0.585
Ferritin (ng/mL, median, IQR)	60.5 (51.5)	24 (45.5)	0.323
CRP (mean, SD)	2.45 ± 2.33	5.99 ± 6.82	0.379
GFR (ml/min/1.72 m <sup>2</sup> , mean, SD)	67 ± 22	70 ± 18	0.389
HOMA-β (%., median, IQR)	57.5 (38-79)	65.5 (50-86)	0.213
HOMA-IR (Median, IQR)	1.82 (1.21-2.28)	2.42 (1.64-3.41)	0.025
Tacrolimus levels (mean, SD)	7.57 ± 1.70	7.74 ± 2.23	0.361

Table 3. Univariate Linear Regression model

Variable	OR	95% CI	p
Age, (years)	0.18	0.35-0.42	0.172
Sex, n			
Female	1		
Male	0.88	0.20-3.86	0.875
HLA Class II, DR3			
DR4			
DR3/DR4	-0.09	-0.21-0.19	0.926
Time after Transplantation	-0.01	-0.04-0.28	0.573
Fasting Glucose (mmol/ml)	-1.07	-4.44-2.30	0.507
Hb1Ac (%)	0.26	-3.43-3.96	0.879
C-peptide (µU/L)	-1.90	-5.23-1.42	0.253
Albumin (g/L)	1.15	-3.18-5.49	0.577
Ferritin (ng/dL)	0.08	-0.15-0.31	0.470
CRP (mg/dL)	0.02	-0.28-2.77	0.856
BMI (Kg/m <sup>2</sup> )	0.18	-0.82-0.45	0.178
GFR (ml/min/1.72 m <sup>2</sup> )	1.02	0.98-1.05	0.913
HOMA-IR	1.43	0.47-2.39	0.004
HOMA-β	0.98	0.93-1.03	0.240
Tacrolimus (ng/ml)	1.18	0.81-1.71	0.229

## CONCLUSIONS

Recipients with an increased percentage of CD14<sup>+</sup>CD16<sup>+</sup> monocytes showed a worse HOMA-IR index and higher Hb1Ac levels. These pro-inflammatory monocytes could be in part responsible for a higher incidence of CVE and recipients' death despite a normal function for both pancreas and kidney grafts. Further investigation should clarify the long-term impact that these monocytes subset may have on SPKT recipient's outcomes.

## RESULTS

Overall, 191 SPKT were performed. 15.78% (n=30) died over the study period. 13 in 30 (43.3%) died due to a CVE despite a good function for both grafts. The cross-sectional phase included 42 SPKT-recipients and 10 matched for age and sex healthy-controls. SPKT-recipients showed a higher mean percentage of CD14<sup>+</sup>CD16<sup>+</sup> monocytes compared to healthy controls (5.53 ± 3.44% versus 3.44 ± 0.93%; p:0.040; figure 1).

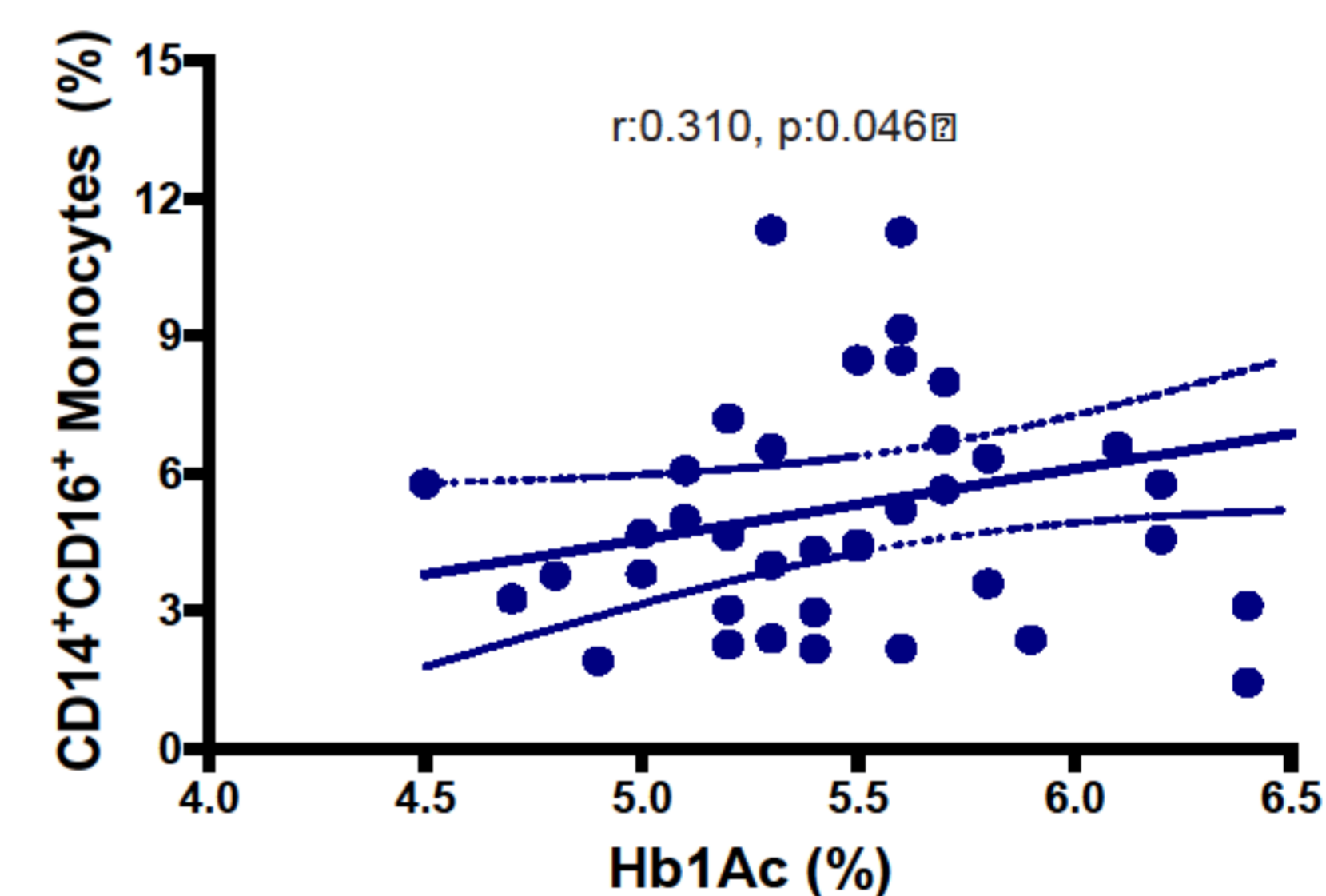
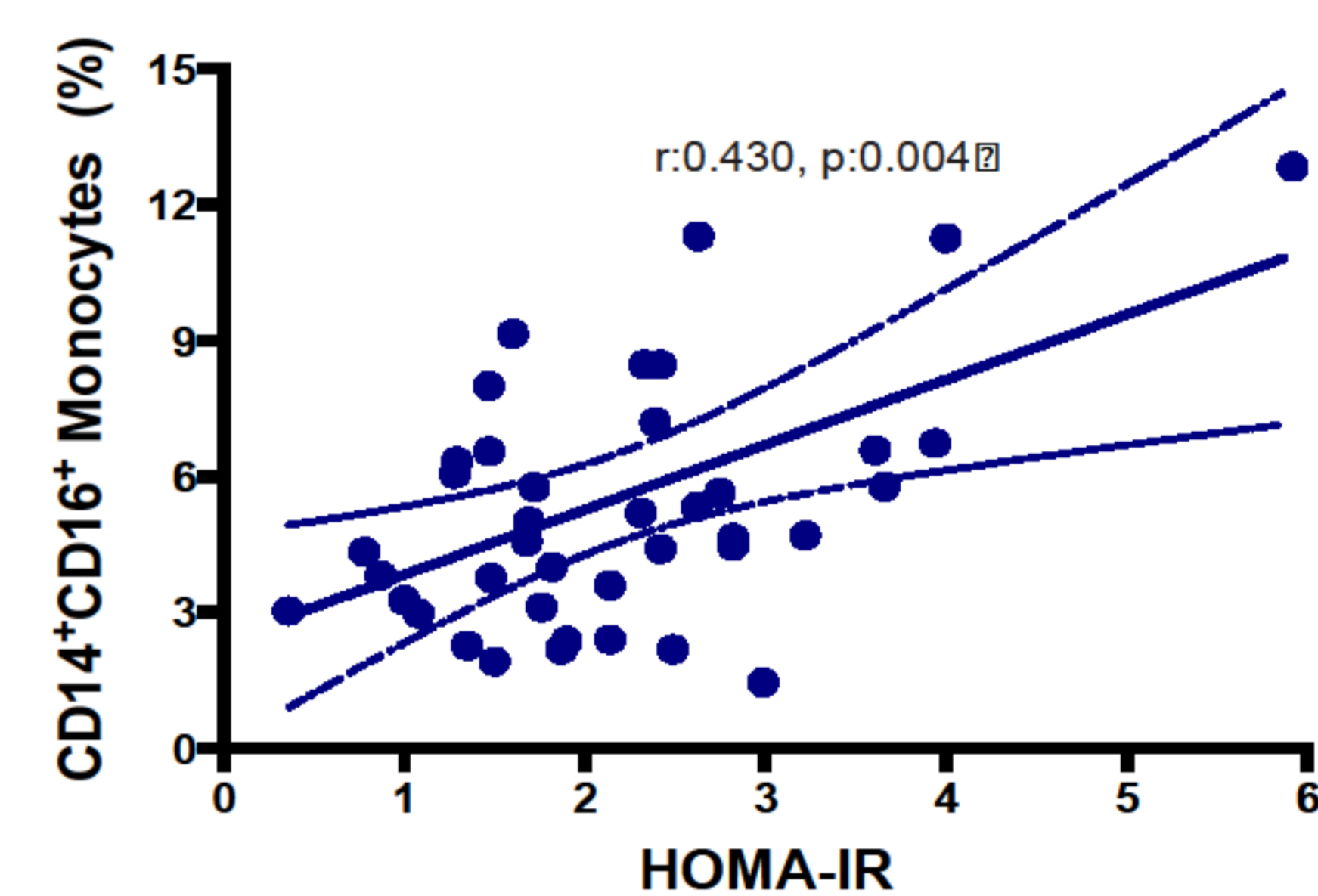
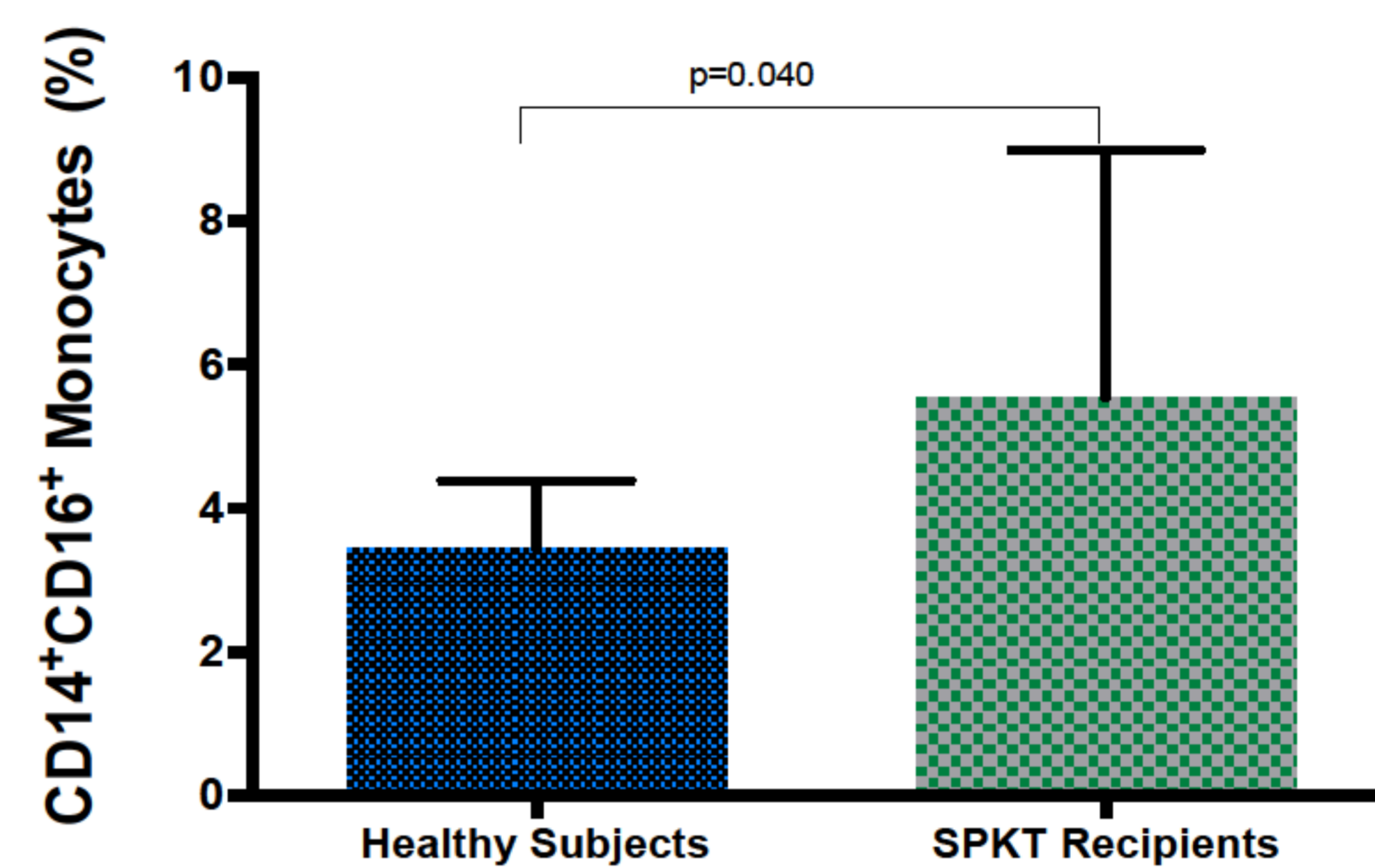


Table 4. Multivariate logistic regression model	Adjusted OR	95% CI	p <sup>*</sup>
Age (years)	0.78	0.59-1.04	0.356
CRP (mg/dL)	-0.17	-0.22-0.19	0.349
Tacrolimus (ng/ml)	-0.19	0.67-3.75	0.852
Time after Transplantation (months)	1	0.97-1.03	0.090
BMI (Kg/m <sup>2</sup> )	-0.22	-0.47-0.02	0.065
HOMA-IR	1.83	0.74-2.92	0.005

## REFERENCES:

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