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Aging-associated Immune Signature as a Predictor of Mortality in End-stage Renal Disease: Results from the Longitudinal iESRD Study

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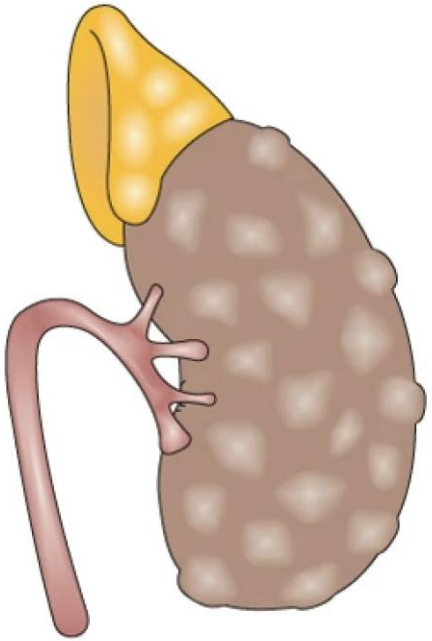
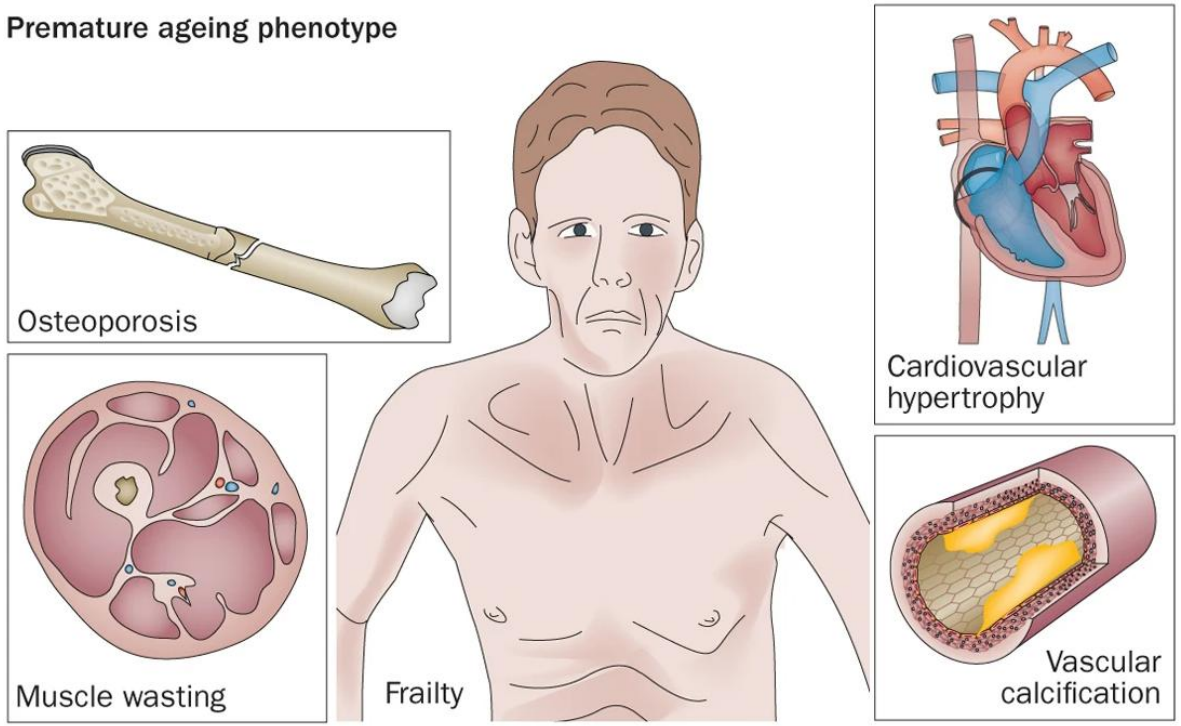
Chronic Kidney Disease

Premature Aging





Nat Rev Nephrol 2014

Shared Immune Features in the Two Diseases

	Aging (in general population)	**End Stage Kidney Disease**
Chronic low-grade **inflammation**	Inflammageing: chronic **inflammation** in ageing, cardiovascular disease, and frailty *(Nat Rev Cardiol 2018)*	Immune cell dysfunction and **inflammation** in end-stage renal disease *(Nat Rev Nephrol 2013)*
Decreased naïve and accumulation of differentiated **T lymphocytes**	**Immune parameters** in a longitudinal study of a very old population of Swedish people: a comparison between survivors and nonsurvivors *(J Gerontol A Biol Sci Med Sci 1995)*	Naïve and central memory **T-cell** lymphopenia in end-stage renal disease *(Kidney Int 2006)* Progressive loss of renal function is associated with activation and depletion of naive **T lymphocytes** *(Clin Immunol 2006)*
Skewing to proinflammatory **monocyte** profiles	Aging is associated with chronic innate immune activation and dysregulation of **monocyte** phenotype and function *(Aging Cell 2012)*	Hemodialysis-related changes in phenotypical features of **monocytes** *(Sci Rep 2018)*
Adverse survival **outcomes** with altered immune composition	An **immune risk phenotype**, cognitive impairment, and **survival** in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans *(J Gerontol A Biol Sci Med Sci 2005)*	**?**

Better **Together** Among Cell Subsets: single cell types versus immune cell pattern

frontiers in Immunology

Decreased Peripheral Naïve T Cell Number and Its Role in Predicting Cardiovascular and Infection Events in Hemodialysis Patients

BMC Nephrology

Premature aging of circulating T cells predicts all-cause mortality in hemodialysis patients

SCIENTIFIC REPORTS

Altered monocytic phenotypes are linked with systemic inflammation and may be linked to mortality in dialysis patients

nature medicine

A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring

Hypothesis

- Composite immune profiles independently predict survival outcome in end-stage kidney disease

Specific aims

- Quantification of T lymphocyte differentiation and monocyte subsets by flow cytometry
- Construction of composite immune indexes through Principal Component Analysis (PCA)
- Analyzing the relationship between composite immune indexes and suvival in hemodialysis patients

The "Immunity in ESRD" Cohort

1 Country

2 Hospitals

409 Patients

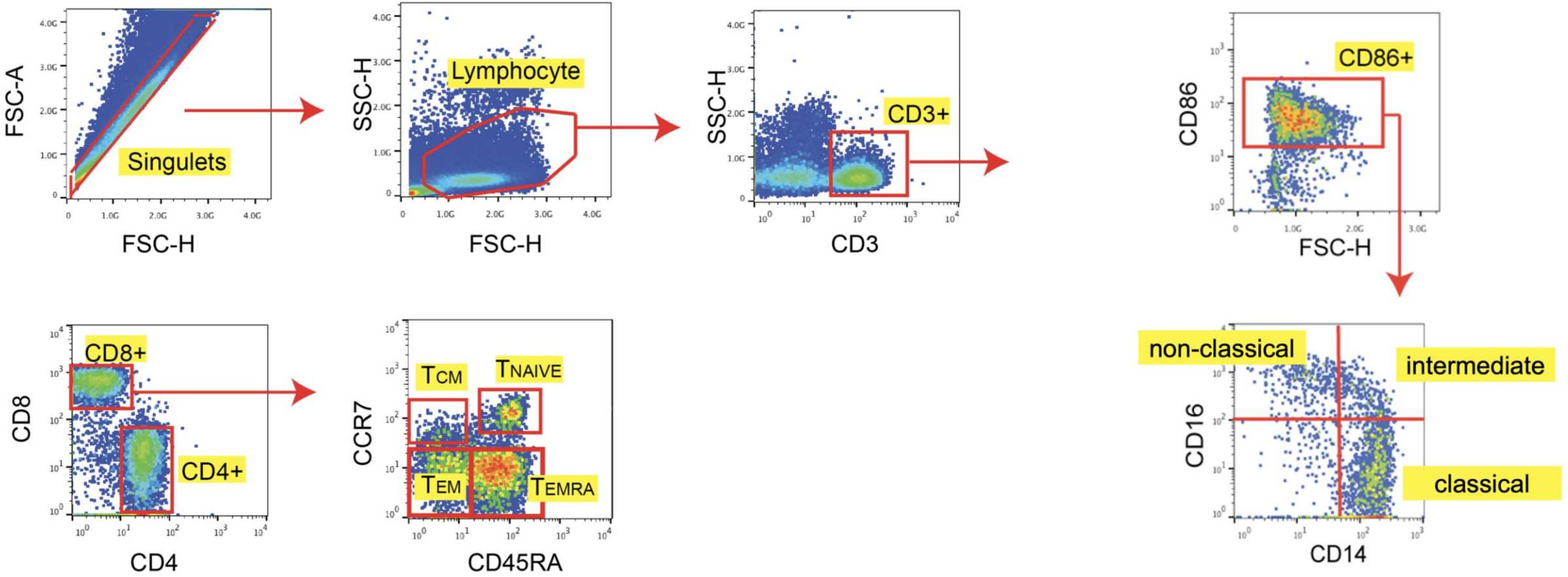
3 Years of follow up
(2014-2017)

Table 1. Patient characteristics at baseline

	All (n=409)		Alive (n=334)		Dead (n=75)		P value	CMV seropositive (n=402)		CMV seronegative (n=7)		P value
Age (years)	61.7	(12.2)	59.9	(11.9)	69.3	(10.3)	**<0.01**	62.0	(12.0)	44.1	(11.9)	**<0.01**
Sex (male%)	50.6		51.2		48.0		0.70	50.8		42.9		0.72
Medical history												
Diabetes mellitus (%)	44.5		41.3		58.7		**<0.01**	45.0		14.3		0.14
Hypertension (%)	76.3		74.9		82.7		0.18	76.9		42.9		0.06
Duration of Dialysis (years)	6.23	(5.09)	6.16	(5.06)	6.55	(5.25)	0.56	6.20	(5.02)	8.27	(8.58)	0.55
Laboratory data												
Hemoglobin (g/dl)	10.9	(1.4)	11.0	(1.2)	10.4	(1.8)	**<0.01**	10.9	(1.38)	10.7	(1.09)	0.62
Platelet (x 10^3/μl)	190.4	(65.9)	191.5	(62.4)	185.5	(80.1)	0.48	190.0	(65.1)	215.0	(109.0)	0.57
WBC (/μl)	6407	(1962)	6403	(1918)	6421	(2160)	0.95	6407	(1960)	6393	(2207)	0.99
Neutrophil (/μl)	4205	(1625)	4195	(1570)	4248	(1863)	0.80	4202	(1626)	4362	(1729)	0.82
Lymphocyte (/μl)	1486	(537)	1492	(514)	1457	(635)	0.61	1488	(538)	1359	(543)	0.56
Monocyte (/μl)	397	(178)	390	(176)	429	(183)	0.09	399	(179)	317	(99)	0.07
Total cholesterol (mg/dl)	152	(36.7)	154	(37.1)	143	(33.5)	**0.02**	152	(36.6)	152	(44.4)	1.00
Triglyceride (mg/dl)	147	(95.1)	147	(94.0)	146	(100.7)	0.95	147	(95.3)	124	(86.0)	0.50
Albumin (g/dl)	4.02	(0.38)	4.08	(0.32)	3.77	(0.52)	**<0.01**	4.02	(0.39)	4.20	(0.26)	0.12
C-reactive protein (mg/dl)	0.290	(0.120-0.768)	0.271	(0.110-0.661)	0.533	(0.190-1.720)	**<0.01**	0.30	(0.120-0.770)	0.190	(0.020-0.74)	0.30
CMV IgG (U/ml)	382.1	(175.3-801.7)	375.8	(167.4-739.0)	469.4	(240.3-1021.0)	**<0.01***	389.5	(181.0-812.8)	0.150	(0-0.150)	**<0.01***

*Log-transformed Welch's t test was performed for CMV IgG. Continuous variables are shown as mean and standard deviation. Dichotomous variables are shown as percentage. CRP and anti-CMV IgG are shown as median with interquartile range. *P* values represent comparisons between surviving and deceased individuals. CMV, cytomegalovirus. To convert hemoglobin, albumin, and CRP g/dl to g/l, times 10. To convert total cholesterol mg/dl to mmol/L, times 0.0259. To convert triglyceride mg/dl to mmol/L, times 0.0113.

Gating Strategy for T Lymphocyte and Monocyte Subsets



T lymphocytes

Monocytes

Table 2. Baseline immune cell subset percentages and numbers

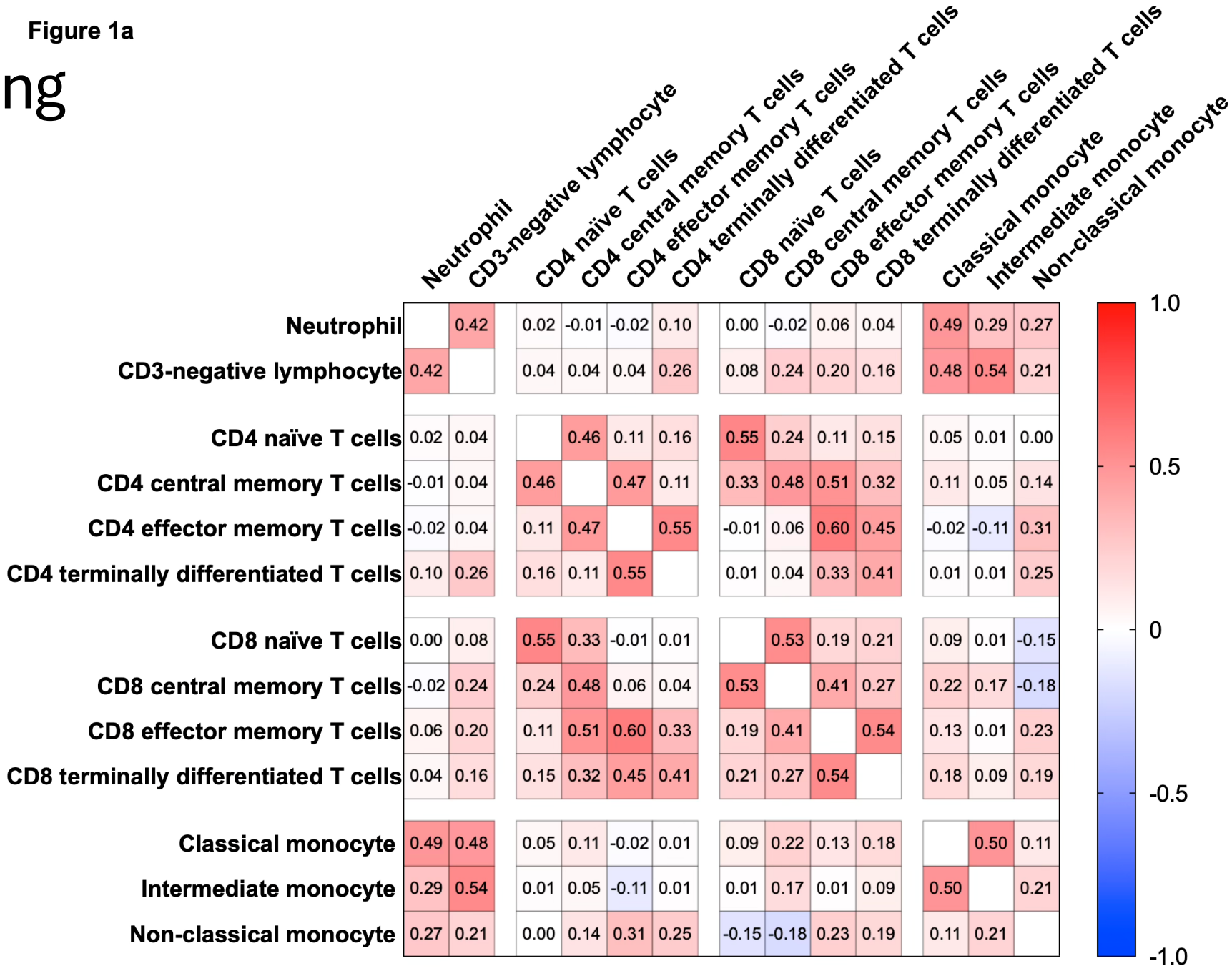
	All (n=409)		Alive (n=334)		Dead (n=75)		P value
Absolute number							
Neutrophil	4205	(1625)	4195	(1570)	4248	(1863)	0.80
CD3	907.4	(414.1)	918.4	(387.8)	858.6	(515.3)	0.26
CD3-negative lymphocyte	578.2	(288.1)	573.6	(287.1)	598.7	(293.7)	0.50
CD4	523	(232.6)	529.8	(218.5)	492.7	(287.2)	0.21
Naïve T cells	164.5	(111.9)	171.6	(110.2)	133.1	(114.3)	**0.01**
Central memory T cells	228.6	(116.2)	233.1	(113.1)	208.4	(127.8)	0.10
Effector memory T cells	120.6	(86.4)	116.4	(74.1)	139.6	(126.6)	**0.04**
Terminally differentiated T cells	9.3	(11.7)	8.7	(9.5)	11.7	(18.6)	**0.04**
CD8	275	(180.2)	277.6	(177.1)	263.6	(194.2)	0.54
Naïve T cells	54.5	(61.9)	59.4	(65.5)	32.7	(35.5)	**<0.01**
Central memory T cells	12.1	(13.9)	12.6	(14.4)	9.9	(11.5)	0.13
Effector memory T cells	102.5	(83.6)	101.2	(76.7)	108.3	(109.5)	0.51
Terminally differentiated T cells	105.8	(95.2)	104.3	(95.0)	112.7	(96.8)	0.49
Monocyte	397.4	(177.9)	390.3	(176.3)	429.1	(182.5)	0.09
Classical monocyte	264.4	(141.6)	259.1	(141.3)	287.9	(141.7)	0.11
Intermediate monocyte	40.4	(33.9)	39.2	(31.7)	45.7	(42.1)	0.13
Non-classical monocyte	56.3	(38.2)	56.1	(37.8)	57.4	(40.3)	0.78

Table 3. Association between immune cell subset numbers and age

	ρ	95% CI	P value
Absolute number			
Neutrophil	0.05	-0.05 to 0.14	0.36
CD3-negative lymphocyte	0.11	0.01 to 0.21	**0.03**
CD4	-0.11	-0.21 to -0.01	**0.02**
Naïve T cells	-0.26	-0.35 to -0.16	**<0.01**
Central memory T cells	-0.11	-0.20 to -0.01	**0.03**
Effector memory T cells	0.12	0.02 to 0.22	**0.01**
Terminally differentiated T cells	0.12	0.02 to 0.21	**0.02**
CD8	-0.07	-0.17 to 0.03	0.14
Naïve T cells	-0.49	-0.56 to -0.41	**<0.01**
Central memory T cells	-0.09	-0.19 to 0.01	0.08
Effector memory T cells	0.01	-0.09 to 0.11	0.89
Terminally differentiated T cells	0.14	0.04 to 0.24	**<0.01**
Monocyte	0.17	0.07 to 0.26	**<0.01**
Classical monocyte	0.13	0.03 to 0.23	**0.01**
Intermediate monocyte	0.14	0.04 to 0.23	**0.01**
Non-classical monocyte	0.11	0.01 to 0.21	**0.02**

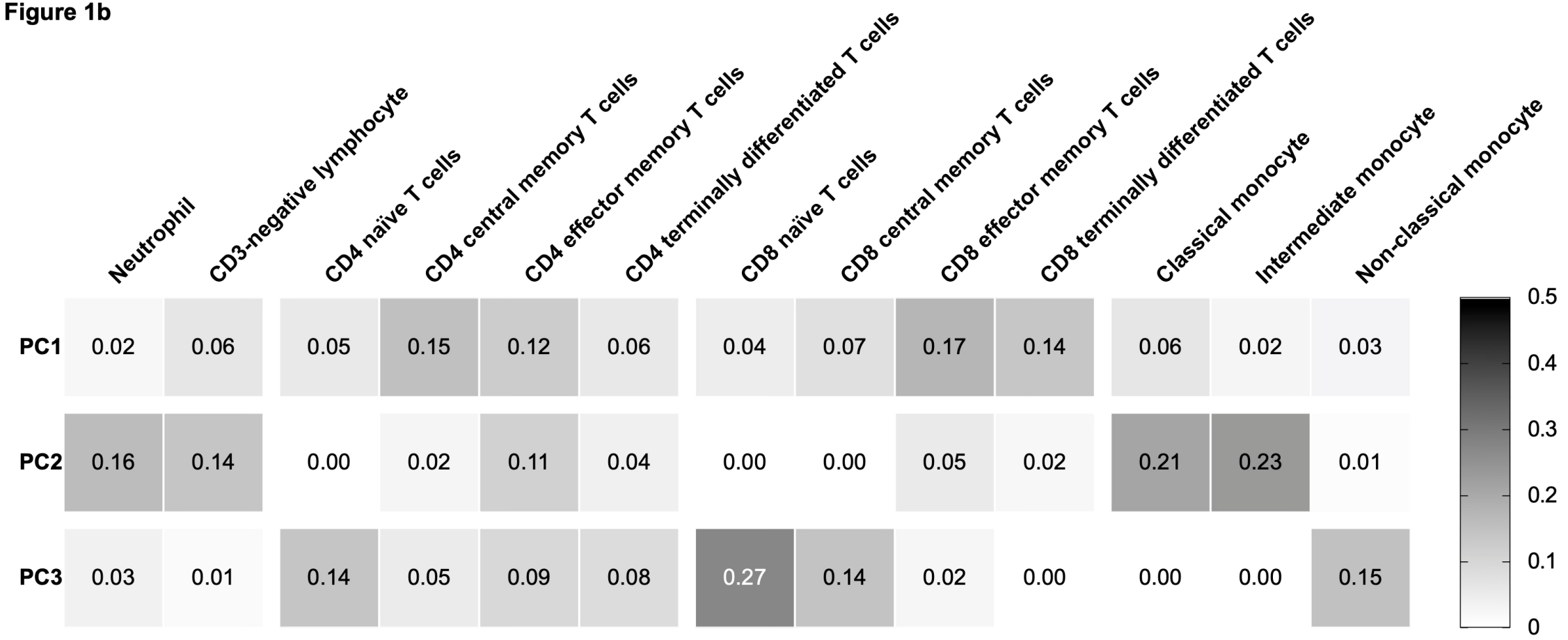
Figure 1a

Correlogram Among Immune Cell Subsets



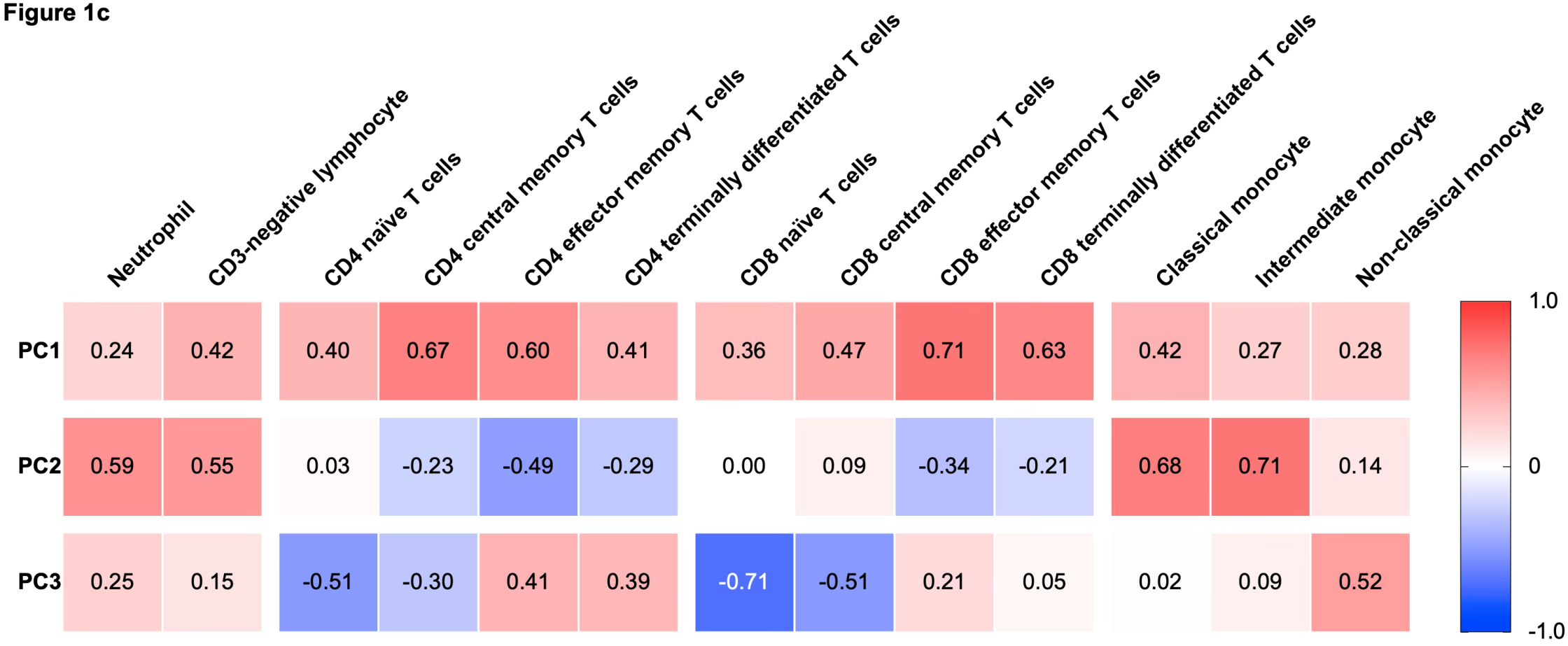
Composition of Each Principal Component (PC)

Figure 1b



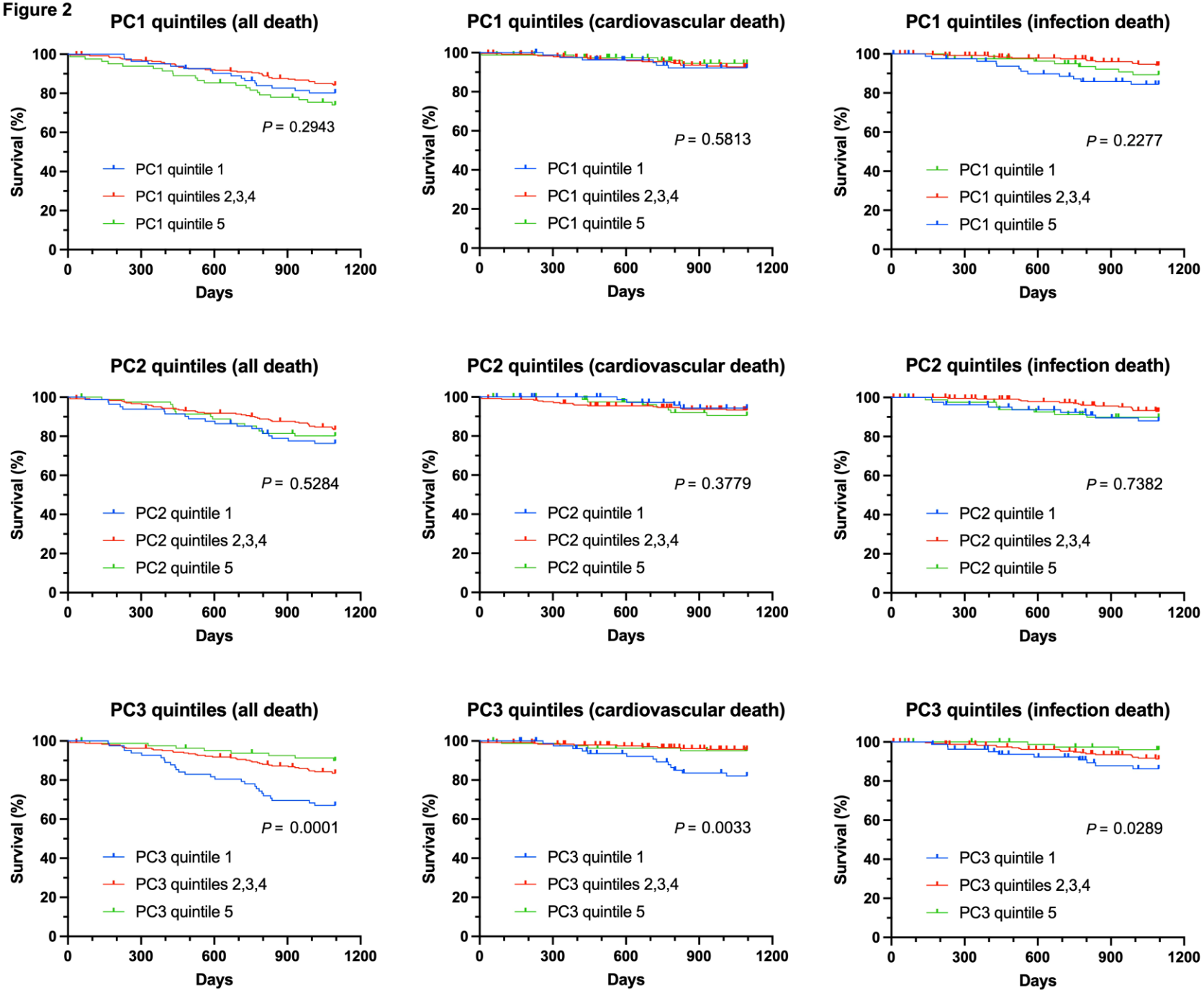
Correlation Between PCs and Cell Subsets

Figure 1c

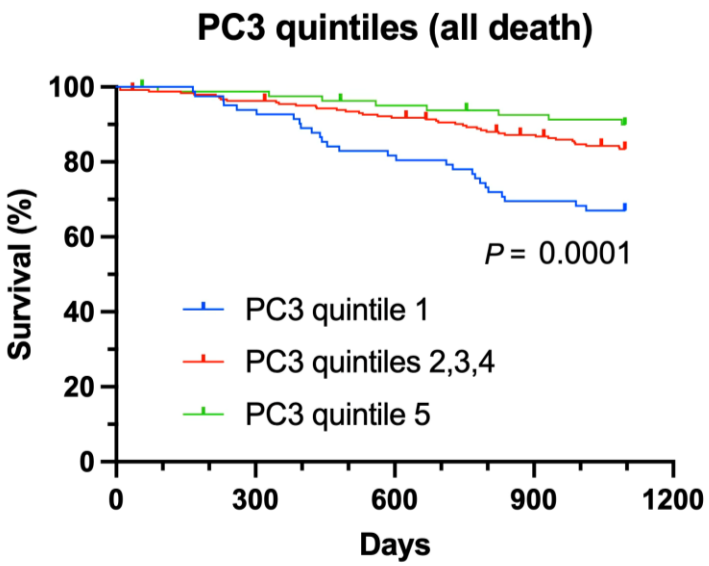


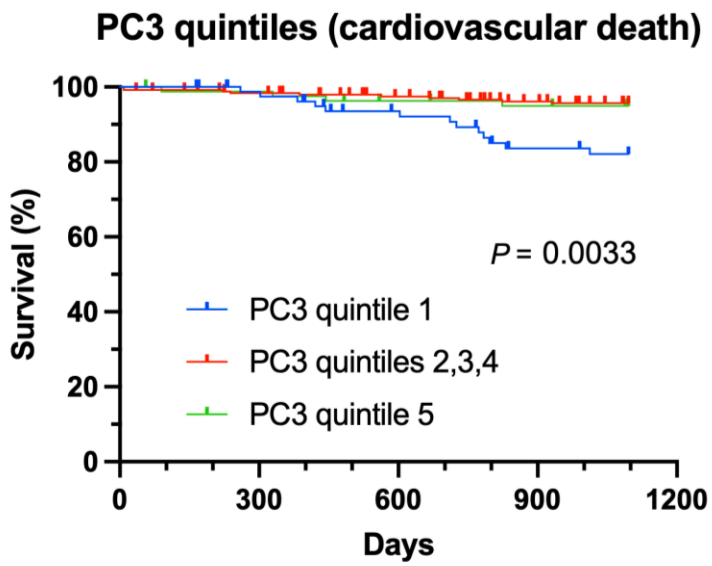
Survival Curves Among Quintiles of Principal Components

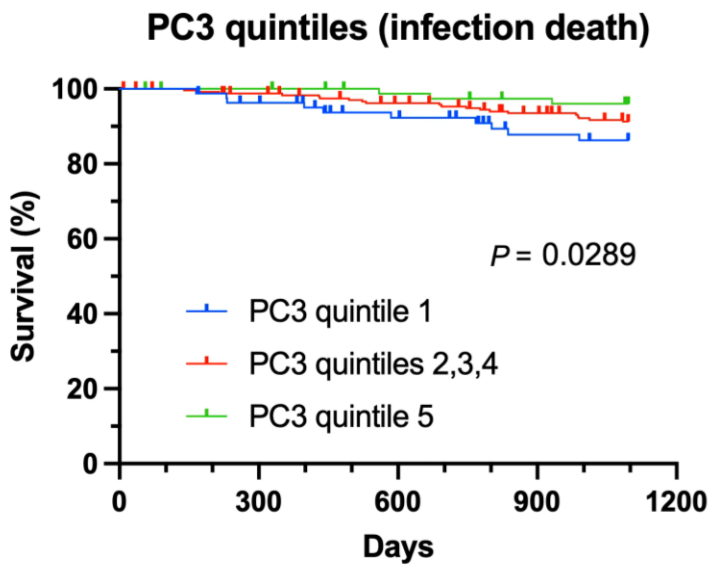
Figure 2



Higher PC3 is Associated with Worse Survival







Higher PC3 is Associated with Worse Survival, Independent of Age

Table 4. Association between Principal Components and CMV IgG Titers with All-Cause Mortality, Cardiovascular Death, and Infection-Related Death.

	Univariable			Model 1			Model 2			Model 3*		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
All-cause death												
Principal Component 1	1.00	0.87 to 1.14	0.95	0.99	0.86 to 1.12	0.84	1.02	0.89 to 1.16	0.79	1.01	0.88 to 1.15	0.87
Principal Component 2	1.04	0.89 to 1.21	0.62	0.99	0.83 to 1.17	0.87	0.89	0.74 to 1.06	0.20	0.89	0.75 to 1.06	0.21
Principal Component 3	1.49	1.23 to 1.79	**<0.01**	1.43	1.15 to 1.78	**<0.01**	1.33	1.06 to 1.66	**0.01**	1.31	1.05 to 1.66	**0.02**
Log CMV IgG*	1.55	0.97 to 2.51	0.07	1.29	0.80 to 2.11	0.30	1.24	0.76 to 2.05	0.39			
Cardiovascular death												
Principal Component 1	1.19	0.97 to 1.43	0.08	1.18	0.96 to 1.42	0.09	1.17	0.95 to 1.40	0.11	1.17	0.96 to 1.41	0.10
Principal Component 2	0.82	0.62 to 1.08	0.17	0.82	0.61 to 1.10	0.18	0.73	0.55 to 0.99	**0.04**	0.73	0.54 to 0.98	**0.04**
Principal Component 3	1.61	1.18 to 2.19	**<0.01**	1.51	1.05 to 2.20	**0.03**	1.45	1.01 to 2.11	0.05	1.50	1.03 to 2.21	**0.04**
Log CMV IgG*	1.06	0.50 to 2.31	0.88	0.88	0.40 to 1.97	0.75	0.91	0.42 to 2.02	0.82			
Infection death												
Principal Component 1	0.90	0.72 to 1.11	0.35	0.88	0.70 to 1.08	0.26	0.93	0.74 to 1.14	0.51	0.89	0.70 to 1.11	0.33
Principal Component 2	0.98	0.76 to 1.24	0.87	0.90	0.68 to 1.17	0.46	0.86	0.65 to 1.12	0.28	0.86	0.65 to 1.13	0.28
Principal Component 3	1.51	1.14 to 2.01	**<0.01**	1.38	1.01 to 1.92	0.05	1.31	0.95 to 1.82	0.10	1.23	0.90 to 1.73	0.21
Log CMV IgG*	2.55	1.23 to 5.39	**0.01**	2.05	0.97 to 4.38	0.06	1.99	0.90 to 4.44	0.09			

*CMV seronegative subjects excluded. Univariable and multivariable Cox regression. Model 1 was adjusted for age, sex, and patient source. Model 2 was adjusted for age, sex, patient source, hemoglobin, diabetes mellitus, albumin, and C-reactive protein. Model 3 included all parameters from Model 2, with addition of log-transformed CMV IgG titers.

Conclusion

- Aging-associated immune cell patterns, characterized by loss of **naïve T cells** and accumulation of **differentiated T cells** and **non-classical monocytes**, independently predict mortality in hemodialysis patients.

Future Directions

- Evaluation of aging-associated immune cell pattern in **other chronic diseases**
- Further delineation of **mechanism** for immune cell pattern alterations, with possible **intervention**

Your Attention is Appreciated