

Data-driven subtypes of polycystic ovary syndrome and their association with clinical outcomes

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Supplementary materials for:

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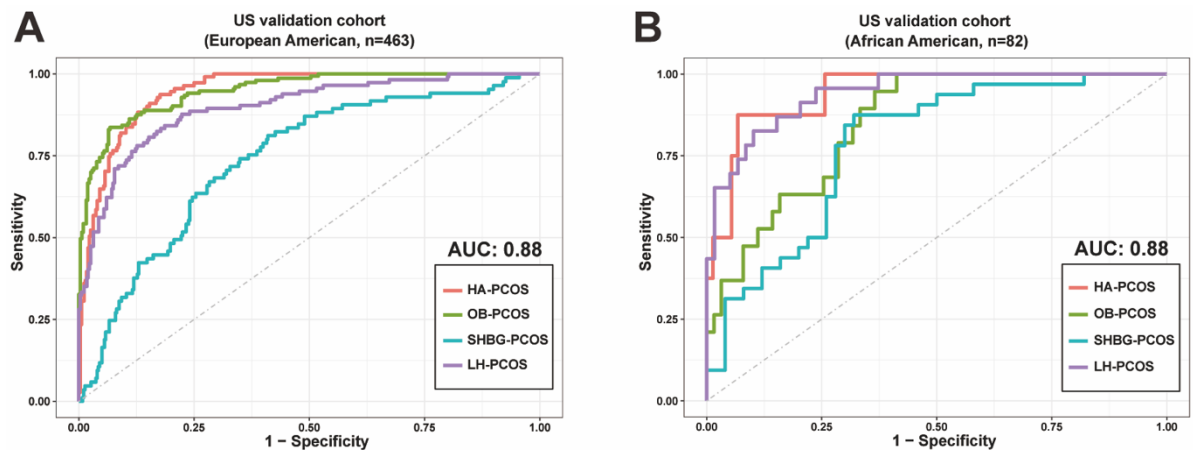
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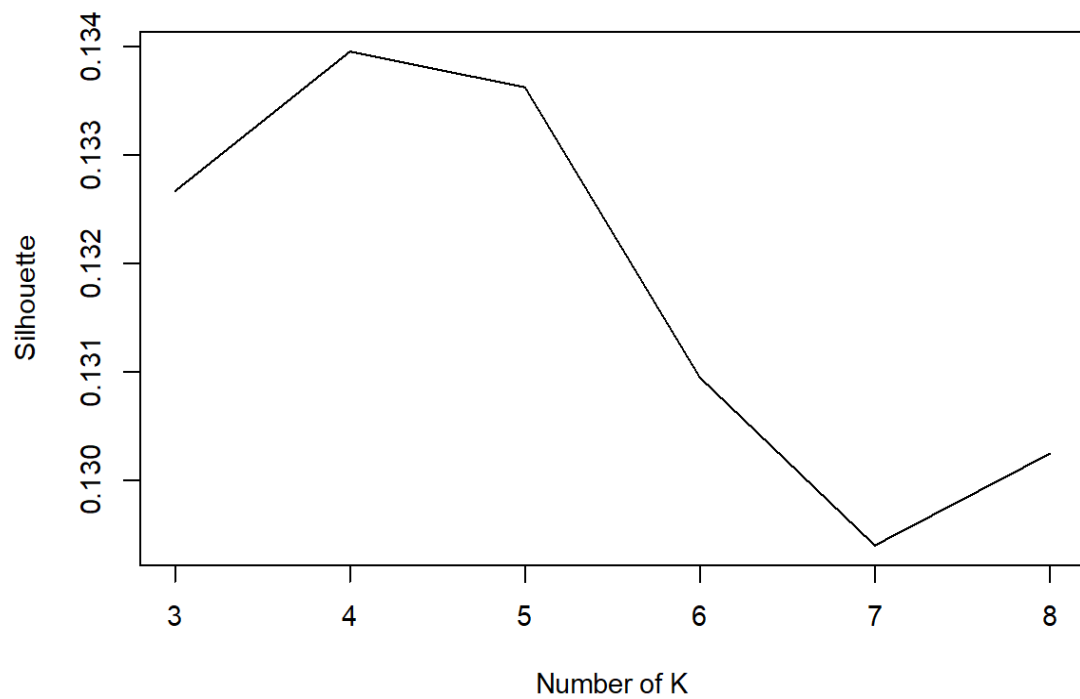
Supplementary Figure 1.



Supplementary Figure 1. Receiver operating characteristic curves plots of four subtypes in different ethnics of US validation cohort.

Receiver operating characteristic curves plot of four subtypes in different ethnics, European American (A) and African American (B), of US validation cohort. Abbreviations: AUC, area under the curve.

Supplementary Figure 2.



Supplementary Figure 2. The average silhouette width for each cluster with a range of k values from 3 to 8.

Supplementary Table 1. Jaccard scores of the four subtypes.

	HA-PCOS	OB-PCOS	SHBG-PCOS	LH-PCOS
Jaccard score	0.85	0.79	0.85	0.83

Supplementary Table 2. Sensitivity and specificity of ridge regression compared with k-means in each validation cohort.

Validation cohort	Sensitivity	Specificity
China		
HA-PCOS	0.64	0.89
OB-PCOS	0.68	0.88
SHBG-PCOS	0.75	0.90
LH-PCOS	0.67	0.91
America		
HA-PCOS	0.82	0.93
OB-PCOS	0.78	0.94
SHBG-PCOS	0.54	0.90
LH-PCOS	0.85	0.89
Europe		
HA-PCOS	0.70	0.87
OB-PCOS	0.72	0.90
SHBG-PCOS	0.80	0.96
LH-PCOS	0.50	0.96
Singapore		
HA-PCOS	0.79	0.91
OB-PCOS	0.71	0.98
SHBG-PCOS	0.73	1.00
LH-PCOS	1.00	0.83
Brazil		
HA-PCOS	0.61	0.84
OB-PCOS	0.57	0.87
SHBG-PCOS	0.56	0.85
LH-PCOS	0.67	0.50

Supplementary Table 3. Ovarian hyperstimulation, embryo culture, and transfer.

	HA-PCOS (n=1295)	OB-PCOS (n=1203)	SHBG-PCOS (n=1650)	LH-PCOS (n=1270)	Control (n=4165)	p (P vs C) ^{††}	p (overall P) ^{§§}
Controlled ovarian hyperstimulation protocols						<0.001	<0.001
Antagonist	629 (48.6%) ^{d,e}	555 (46.1%) ^{d,e}	770 (46.7%) ^{d,e}	720 (56.7%) [#]	821 (19.7%)		
Non-antagonist	666 (51.4%)	648 (53.9%)	880 (53.3%)	550 (43.3%)	3344 (80.3%)		
Days of ovarian stimulation	11.17±3.01 ^{c,d,e}	11.48±2.96 ^{c,d,e}	10.17±2.33 ^{a,b,d}	10.49±2.74 [#]	10.02±2.12	<0.001	<0.001
Total gonadotropin dose (IU)	2022±953 [#]	2318±1073 [#]	1552±662 ^{a,b,e}	1594±960 ^{a,b,e}	1887±868	0.023	<0.001
Total hCG dose (IU)	6293±1879 [#]	6751±1851 [#]	5939±1785 ^{a,b,e}	5832±1864 ^{a,b,e}	7105±1615	<0.001	<0.001
Number of oocytes retrieved	15.62±8.31 ^{b,e}	13.9±7.84 [#]	16.24±7.48 ^{b,e}	16.35±8.78 ^{b,e}	11.38±5.41	<0.001	<0.001
Number of day3 high-score embryo	4.60±3.43 ^{b,e}	4.19±3.15 ^{a,c,d}	4.86±3.49 ^{b,e}	4.99±3.53 ^{a,b,e}	3.96±2.94	<0.001	<0.001
Ratio of high-score embryo	52.92±28.92	52.71±29.95	52.91±28.39	54.56±28.46	54.55±29.78	0.033	0.323
Regimen of endometrial preparation for frozen embryo transfer						<0.001	<0.001
Artificial	640/685 (93.4%) ^{c,e}	512/556 (92.1%) ^{c,d,e}	856/983 (87.1%) [#]	764/798 (95.7%) ^{b,c,e}	477/1270 (37.6%)		
Natural	45/685 (6.57%)	44/556 (7.91%)	127/983 (12.9%)	34/798 (4.26%)	793/1270 (62.4%)		
Transferred embryo						<0.001	<0.001
Fresh	510/1195 (42.7%) [#]	554/1110 (49.9%) [#]	541/1524 (35.5%) ^{a,b,e}	378/1176 (32.1%) ^{a,b,e}	2601/3871 (67.2%)		
Frozen	685/1195 (57.3%)	556/1110 (50.1%)	983/1524 (64.5%)	798/1176 (67.9%)	1270/3871 (32.8%)		
Mean number of embryos transferred							
Fresh	1.74±0.44	1.72±0.45	1.77±0.42	1.72±0.45	1.72±0.45	0.223	0.147
Frozen	1.06±0.24 ^e	1.06±0.25 ^e	1.07±0.25 ^e	1.06±0.24 ^e	1.11±0.31	<0.001	0.972
Stage of fresh embryo transferred							
Fresh						0.102	0.487
Blastocyst transfer	101/510 (19.8%)	113/554 (20.4%)	111/541 (20.5%)	90/378 (23.8%)	597/2601 (23.0%)		
Cleavage-stage embryo transfer	409/510 (80.2%)	441/554 (79.6%)	430/541 (79.5%)	288/378 (76.2%)	2004/2601 (77.0%)		
Frozen						<0.001	0.088
Blastocyst transfer	683/685 (99.7%) ^e	549/556 (98.7%) ^e	980/983 (99.7%) ^e	795/798 (99.6%) ^e	1206/1270 (95.0%)		
Cleavage-stage embryo transfer	2/685 (0.29%)	7/556 (1.26%)	3/983 (0.30%)	3/798 (0.38%)	64/1270 (5.04%)		

Abbreviations: hCG, human chorionic gonadotropin.

Data are means ± SD, n (%), or n/N (%). Statistical tests used are two-sided paired t-test or ANOVA test for continuous variables, and Chi-squared test Categorical variables. For multiple comparisons, post-hoc test among four subtypes were performed using either Bonferroni or Dunnett T3 correction.

a p<0.05 compared with HA-PCOS.

b p<0.05 compared with OB-PCOS.

c p<0.05 compared with SHBG-PCOS.

d p<0.05 compared with LH-PCOS.

e p<0.05 compared with control.

p<0.05 compared with any other four groups.

†† p value compared between PCOS versus controls

§§ p value compared among four PCOS subtypes.

Supplementary Table 4. Odds ratios of IVF outcomes.

	HA-PCOS (n=1295)		OB-PCOS (n=1203)		SHBG-PCOS (n=1650)		LH-PCOS (n=1270)		Control (n=4165)
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	reference
Total livebirth, pregnancy, and pregnancy loss									
Primary outcome: livebirth per pregnancy	0.81 (0.71-0.93)	0.004	0.83 (0.72-0.95)	0.009	1.07 (0.94-1.22)	0.313	0.96 (0.83-1.11)	0.57	1.00
Singleton	0.93 (0.81-1.08)	0.349	0.91 (0.79-1.05)	0.195	1.08 (0.95-1.23)	0.252	1.04 (0.90-1.21)	0.546	1.00
Twin/Triplet	0.64 (0.50-0.83)	0.001	0.75 (0.58-0.96)	0.022	0.96 (0.77-1.20)	0.719	0.75 (0.57-0.97)	0.032	1.00
Secondary outcomes									
Conception per woman †,	1.20 (1.02-1.39)	0.023	1.21 (1.04-1.42)	0.016	1.30 (1.13-1.50)	<0.001	1.30 (1.10-1.53)	0.020	1.00
Clinical pregnancy per woman ‡,	1.17 (1.01-1.35)	0.037	1.10 (0.96-1.27)	0.176	1.28 (1.12-1.46)	<0.001	1.18 (1.02-1.37)	0.027	1.00
Total pregnancy loss among conception	1.93 (1.61-2.31)	<0.001	1.90 (1.58-2.29)	<0.001	1.32 (1.11-1.57)	0.002	1.58 (1.30-1.91)	<0.001	1.00
Clinical pregnancy loss	2.51 (2.01-3.13)	<0.001	2.19 (1.74-2.76)	<0.001	1.58 (1.22-1.91)	<0.001	1.72 (1.35-2.19)	<0.001	1.00
First trimester pregnancy loss	1.73 (1.31-2.29)	<0.001	1.77 (1.33-2.34)	<0.001	1.47 (1.12-1.92)	0.005	1.47 (1.09-1.98)	0.01	1.00
Second trimester pregnancy loss	7.32 (4.94-10.85)	<0.001	5.73 (3.76-8.73)	<0.001	3.22 (2.07-5.01)	<0.001	4.14 (2.65-6.48)	<0.001	1.00
Maternal and neonatal complications									
Maternal complications									
Moderate or severe ovarian hyperstimulation syndrome¶	5.45 (3.38-8.80)	<0.001	4.58 (2.73-7.67)	<0.001	5.11 (3.21-8.12)	<0.001	7.44 (4.63-11.96)	<0.001	1.00
Gestational diabetes	1.17 (0.81-1.70)	0.394	1.70 (1.20-2.39)	0.003	0.83 (0.57-1.19)	0.312	0.93 (0.64-1.37)	0.730	1.00
Gestational hypertension	2.63 (1.78-3.89)	<0.001	2.83 (1.89-4.23)	<0.001	0.89 (0.54-1.45)	0.636	1.02 (0.61-1.71)	0.944	1.00
Preterm delivery	1.70 (1.20-2.41)	0.003	1.63 (1.12-2.36)	0.010	1.08 (0.74-1.57)	0.689	1.33 (0.91-1.93)	0.142	1.00
Iatrogenic preterm delivery	1.78 (1.22-2.59)	0.003	1.62 (1.08-2.42)	0.019	1.25 (0.85-1.84)	0.264	1.45 (0.97-2.15)	0.068	1.00
Spontaneous preterm delivery	1.25 (0.51-3.06)	0.634	1.57 (0.64-3.86)	0.322	0.16 (0.02-1.22)	0.077	0.62 (0.18-2.18)	0.455	1.00
Premature rupture of membrane	2.91 (1.56-5.43)	0.001	2.16 (1.40-4.47)	0.038	0.23 (0.05-1.00)	0.050	1.27 (0.56-2.88)	0.569	1.00
Neonatal complications									
Small for gestational age	1.00 (0.58-1.70)	0.987	0.46 (0.22-0.97)	0.041	0.51 (0.28-0.93)	0.028	0.58 (0.31-1.08)	0.087	1.00
Large for gestational age	1.40 (1.09-1.79)	0.008	2.14 (1.65-2.73)	<0.001	1.00 (0.79-1.26)	0.983	0.93 (0.72-1.21)	0.588	1.00

Data are odds ratios (95% confidence interval). For each outcome, binary logistic regression was used to calculate odds ratio with 95% CI for each subtype comparing with control. Statistical P value was adjusted by the models of potential confounders.

† Conception: serum human chorionic gonadotropin ≥ 10 mIU/mL.

‡ Clinical pregnancy: detection of a gestational sac in the uterine cavity.

¶|| odds ratio was adjusted by age and ovarian stimulation protocol.

|| odds ratio was adjusted by age and fresh/frozen embryos.