

New Prevalence Data

MetS was present in 439/1150 patients (38.2%). The individual MetS criteria met were: MetS WC (686/1334 - 48.4%), MetS BP (491/1150 – 42.7%), MetS triglycerides (508/1099 – 46.2%), MetS HDL (470/792 – 59.3%) and MetS glucose (204/1077 – 18.9%). MetS was more common in men than women (55.3% vs. 36.3%;  $p = 0.03$ ) and those with MetS were older than those without (mean (SD) age 36.9 (13.3) years vs. 34.9 (14.7) years;  $p < 0.04$ ). Patients of Hispanic, Korean and African Ancestry race/ethnicity had the highest prevalence of MetS (41.3% and 48.4% vs. 55.7%)

Table A: New, revised multivariable model of predictors of MetS at enrolment

<b>Variable</b>	<b>Adjusted Odds Ratio (95% CI)</b>
Age (years)	1.05 (1.04, 1.07)
Hispanic race/ethnicity	1.79 (1.13, 2.87)
Korean race/ethnicity	2.07 (1.31, 3.25)
African Ancestry race/ethnicity	2.73 (1.46, 5.12)
Active Renal Disease (yes/no)	2.70 (1.83, 3.99)
Peak CS dose (mg)	1.02 (1.01, 1.03)
Cumulative CS dose (g)	1.07 (1.01, 1.12)
Current Anti-malarial use (yes/no)	0.53 (0.37, 0.75)

**Background:**

The metabolic syndrome (MetS) may contribute to increased cardiovascular risk in SLE. We aimed to examine the association of demographic factors, lupus phenotype and therapy exposure with the presence of metabolic syndrome.

**Methods:**

The Systemic Lupus International Collaborating Clinics Registry for Atherosclerosis inception cohort enrolled recently diagnosed (<15 months) SLE patients from 30 centres across 11 countries since 2000. Clinical, laboratory and therapeutic data were collected according to a standardised protocol. MetS was defined according to the 2009 Consensus Statement from the International Diabetes Federation. Univariate and backward stepwise multivariate logistic regression were used to assess the relationship of individual variables with MetS.

**Results:**

We studied 1686 patients of whom 1150 (68.2%) had sufficient data to determine their MetS status. The mean (SD) age at enrolment and disease duration was 34.8 (13.6) years old and 24.2 (18.0) weeks respectively. MetS was present at the enrollment visit in 439 (38.2%). In backward stepwise multivariable regression analysis, higher peak oral prednisolone dose (mg) (OR [95% CI] 1.02 [1.01, 1.03]), cumulative corticosteroid dose (g) (1.07 [1.01, 1.12]), older age (years) (1.05 [1.04, 1.07]), Korean (2.07 [1.31, 3.25]), Hispanic (1.79 [1.13, 2.87]) and African Ancestry (2.73 [1.46, 5.12]) race/ethnicity, and current renal disease (2.70 [1.83, 3.99]) were associated with MetS. Antimalarial use was associated with a reduced risk of MetS (0.53 [0.37, 0.75]).

**Conclusions:**

Renal lupus, higher corticosteroid doses, Korean, Hispanic and African Ancestry race/ethnicity are associated with MetS in SLE patients whilst antimalarials appear 'protective'. Balancing disease control and minimizing corticosteroid exposure should therefore be at the forefront of personalised treatment decisions in SLE patients.

**Amended Table 1: Characteristics of patients at enrolment into SLICC-RAS**

No. of patients	1150
Age (years) (mean (SD))	34.8 (13.6)
Gender (%)	
Female	1036 (90.1)
Male	114 (9.9)
Ethnicity (%)	
Caucasian	516/1148 (44.9)
African Ancestry	153/1148 (13.3)
SE Asian	237/1148 (20.6)
Hispanic	182/1148 (15.9)
Other	59/1148 (5.1)
Region (%)	
Canada	358/1134 (27.1)
Mexico	194/1134 (13.5)
USA	374/1134 (22.6)
Asia	168/1134 (13.4)
Europe	383/1134 (23.5)
CHD Risk Factors (mean (SD))	
BP systolic (mmHg)	118.5 (16.4)
BP diastolic (mmHg)	74.7 (10.7)
On AHT medication (%)	328 (28.5)
Total cholesterol (mmol/l)	4.89 (1.50)
Triglyceride (mmol/l)	1.78 (1.21)
HDL-cholesterol (mmol/l)	1.39 (0.60)
On lipid-lowering medication (%)	168 (14.6)
Glucose (mmol/l)	5.02 (1.71)
Diabetes (%)	43 (3.7)
Smoker current (%)	169 (14.7)
Pre-menopausal (%)	813 (78.3)
BMI	24.9 (5.9)
WC (cm)	82.0 (14.0)
5 year % Framingham Risk	
Females	0.57
Males	5.03
Disease duration (weeks) (mean (SD))	24.2 (18.0)
SLEDAI (mean (SD))	5.4 (5.2)
SLICC/ACR-DI = 0	407/504 (80.8%)
Disease Phenotype (%)	
Active renal disease	243/1115 (21.1)
Anti-dsDNA positive	427/1034 (41.3)
Low Complement	419/1038 (40.4)
Thrombocytopenia	34/1313 (3.4)
Oral CS use (median (IQR))	796 (69.2)
Average CS dose(mg)	20 (10, 35)
Highest CS dose(mg)	40 (20, 60)
Cumulative CS dose (g)	2.5 (1.1, 5.0)
Pulse IV CS (%)	52/1095 (4.8)
Immunosuppressant use (%)	464/1147 (40.5)
Azathioprine	196 (42.2)
Methotrexate	84 (18.1)
Mycophenolate Mofetil	77 (16.6)
IV cyclophosphamide	78 (16.8)
Cyclosporin	17 (3.7)
Other	12 (2.6)
Antimalarial use (%)	759(66.0)

SD standard deviation; CHD coronary heart disease; BP blood pressure; AHT anti-hypertensive; HDL high density lipoprotein; BMI body mass index; WC waist circumference; SLEDAI Systemic Lupus Erythematosus Disease Activity index; SLICC Systemic Lupus Erythematosus; ACR American College of Rheumatology; CS corticosteroid; IV intravenous.

**Amended Table 2: Significant factors associated with MetS at enrolment into SLICC-RAS in age, ethnicity and gender adjusted analyses**

	<u>MetS</u> <u>Yes</u>	<u>Mets</u> <u>No</u>	<u>p</u>	<u>Odds Ratio</u> <u>(95% CI)</u>
Current CS (%)	340/439 (77.4)	456/711 (64.1)	<0.001	2.01 (1.47, 2.74)
Average CS dose (mg) (median (IQR))	25 (15, 40)	16.9 (10, 30)	<0.001	1.03 (1.02, 1.04)
Highest CS dose (mg) (median (IQR))	50 (30, 60)	30 (15, 50)	<0.001	1.03(1.02, 1.04)
Cumulative CS dose (g) (median (IQR))	3.24 (1.5, 5.9)	1.98 (0.8, 4.0)	<0.001	1.13 (1.07, 1.18)
Past IV CS (%)	14/439 (3.2)	6/711 (0.8)	0.03	4.33 (1.60, 11.74)
Antimalarial (%)	239/439 (54.5)	520/711 (73.1)	<0.001	0.43 (0.33, 0.56)
Immunosuppressant (%)	232/437 (53.1)	232/710 (32.7)	<0.001	2.55 (1.94, 3.34)
SLICC-DI $\geq$ 1 (%)	57/198 (28.8)	40/306 (13.1)	<0.001	2.35 (1.46, 3.79)
SLEDAI-2K (mean (SD))	6.29 (5.76)	4.91 (4.82)	0.001	1.07 (1.04, 1.10)
SLEDAI $\geq$ 10 (%)	110/439 (25.1)	107/708 (15.1)	<0.001	2.26 (1.64, 3.13)
Thrombocytopenia (%)	19/389 (4.9)	15/615 (2.4)	0.003	1.95 (0.93, 4.11)
Leucopenia (%)	14/383 (3.7)	57/619 (9.2)	0.001	0.35 (0.19, 0.67)
Active renal disease (%)	152/439 (34.6)	91/711 (12.8)	<0.001	4.60 (3.29, 6.43)
Past renal disease (%)	39/439 (8.9)	29/711 (4.1)	0.001	2.43 (1.43, 4.13)

CS corticosteroid; IV intravenous;

Variables reflect current exposures, recorded at enrolment

**Amended Table 3: Multivariable Model of predictors of MetS at enrolment**

Variable	Adjusted Odds Ratio (95% CI)
Age (years)	1.05 (1.04, 1.07)
Hispanic race/ethnicity	1.79 (1.13, 2.87)
Korean race/ethnicity	2.07 (1.31, 3.25)
<del>Black African</del> race/ethnicity	2.73 (1.46, 5.12)
Active Renal Disease (yes/no)	2.70 (1.83, 3.99)
Peak CS dose (mg)	1.02 (1.01, 1.03)
Cumulative CS dose (g)	1.07 (1.01, 1.12)
Current Anti-malarial use (yes/no)	0.53 (0.37, 0.75)

\* includes azathioprine, mycophenolate mofetil, cyclophosphamide, ciclosporin, methotrexate

Variables reflect current exposures, recorded at enrolment

**Amended Table 4: Characteristics of patients of Korean and Hispanic ethnicity compared to all other ethnicities**

	<u>Korean</u>	<u>p *</u>	<u>Hispanic</u>	<u>p **</u>	<u>Other ethnicities</u>
No. of patients	151		182		738
Age (years) (mean (SD))	29.3 (14.5)	<0.0001	28.9(10.3)	<0.0001	37.5 (14.5)
Gender (%)					
Female	134 (88.7)	0.47	162 (89.0)	0.5	669 (90.7)
Male	17 (11.3)	0.47	20 (11.0)	0.5	69 (9.4)
MetS (%)	63 (41.7)	<0.0001	88 (48.4)	<0.0001	244 (33.1)
MetS Phenotype (%)					
MetS WC	32/149 (21.5)	<0.0001	92/178 (51.7)	0.14	303/666 (45.5)
MetS BP	63 (41.7)	0.63	89/182 (48.9)	0.02	289 (39.2)
MetS TG	94/146 (64.4)	<0.0001	99/156 (63.5)	<0.0001	275/722 (38.1)
MetS HDL	107/141 (75.9)	<0.0001	94/146 (64.4)	0.01	246/468 (52.6)
MetS Glu	37/150(24.7)	0.07	27/179 (15.1)	0.33	124/681 (18.2)
BMI (mean(SD))	21.7 (4.5)	<0.0001	24.3 (4.8)	0.02	25.4 (5.9)
WC (cm) (mean (SD))	75.0 (8.1)	<0.0001	82.0 (11.0)	0.56	82.7 (14.9)
Disease duration (wks) (mean SD))	18.0 (15.7)	<0.0001	23.4 (16.5)	0.27	25.1 (18.4)
SLEDAI (mean SD))	7.23 (6.32)	<0.0001	6.41 (5.75)	<0.0001	4.93 (5.2)
SLICC/ACR-DI (mean(SD))	0.19 (0.44)	0.31	0.29 (0.72)	0.95	0.28 (0.68)
Disease Phenotype (%)					
Active renal disease	45 (29.8)	<0.0001	78 (42.9)	<0.0001	99 (13.4)
Anti-dsDNA positive	92/141 (65.3)	<0.0001	62/164 (37.8)	0.89	245/658 (37.2)
Low Complement	109/143 (76.2)	<0.0001	54/163 (33.1)	0.57	234/659 (33.1)
Thrombocytopenia	15/125 (12.0)	<0.0001	2/164 (1.2)	0.29	17/646 (2.6)
Medication (median (IQR))					
Oral CS (%)*	146 (96.7)	<0.0001	159 (87.4)	<0.0001	425 (57.6)
Average CS dose(mg)	20 (10, 35)	0.03	30 (15, 42.5)	<0.0001	15.9 (10, 30)
Highest CS dose(mg)	30 (15, 55)	0.50	50 (30, 60)	<0.0001	30 (20, 50)
Cumulative CS dose (g)	1.4 (0.4, 3.1)	<0.0001	3.9 (1.8, 6.2)	<0.0001	2.27 (1.1, 4.6)
Pulse intravenous CS (%)	22 (14.5)	<0.0001	5/169 (3.0)	0.90	22/700 (3.1)
Immunosuppressant (%)	78 (51.7)	<0.0001	114 (52.2)	<0.0001	236 (32.0)
Antimalarial (%)	107 (71.0)	0.69	95 (62.6)	<0.0001	511 (69.0)

\* Korean vs. all other (non-Hispanic) ethnicities; \*\* Hispanic vs. all other (non-Korean) ethnicities

**Amended Supplemental Table S1: Characteristics of patients with missing MetS status**

	<u>MetS assigned</u>	<u>MetS missing</u>	<u>p</u>
No. of patients	1150	537	-
Age (years) (mean (SD))	34.9 (13.6)	35.9 (12.9)	1.00
Gender (%)			
Female	1036 (90.1)	469 (87.3)	0.013
Male	114 (9.9)	66 (12.7)	
Ethnicity (%)			
Caucasian	516 (44.9)	244 (45.6)	<0.001
African Ancestry	154 (13.4)	118 (22.1)	<0.001
SE Asian	251 (21.9)	76 (14.2)	<0.001
Hispanic	182 (15.9)	75 (14.0)	<0.001
Other	45 (3.9)	22 (4.1)	0.9
Region (%)			
Canada	307/1134 (21.1)	78/521 (15.0)	<0.001
Mexico	153/1134 (13.5)	50/521 (9.6)	<0.001
USA	256/1134 (22.6)	215/521 (41.3)	<0.001
Asia	152/1134 (13.4)	17/521 (3.3)	<0.001
Europe	266/1134 (23.5)	161/521 (30.9)	0.9
CHD Risk Factors (mean (SD))			
BP systolic (mmHg)	118.5 (16.4)	121.4 (17.2)	0.001
BP diastolic (mmHg)	74.7 (10.7)	75.7 (11.6)	0.08
On AHT medication (%)	328 (28.5)	156 (29.1)	0.82
Triglyceride (mmol/l)	1.78 (1.21)	1.81 (1.09)	0.72
HDL-cholesterol (mmol/l)	1.39 (0.61)	1.35 (0.52)	0.72
On lipid-lowering medication (%)	168 (14.6)	3 (0.6)	<0.001
Glucose (mmol/l)	5.02 (1.71)	5.10 (1.31)	0.44
Diabetes (%)	43/1138 (3.8)	13/521 (2.5)	0.18
Smoker current (%)	169/1147 (14.7)	83/535 (15.5)	0.70
BMI	25.1 (5.9)	26.0 (6.0)	0.004
WC (cm)	82.0 (14.0)	85.7 (13.6)	<0.001
Disease duration weeks (mean SD))	24.2 (18.0)	25.0 (18.6)	0.38
SLEDAI (mean SD))	5.4 (5.2)	5.05 (5.58)	0.17
SLICC/ACR-DI (mean(SD))	0.30 (0.74)	0.21 (0.60)	0.09
Disease Phenotype (%)			
Active renal disease	243 (21.1)	92 (17.1)	0.06
Anti-dsDNA positive	427/1034 (41.3)	152/474 (32.1)	0.001
Low Complement	419/1038 (40.4)	150/475 (31.5)	0.001
Thrombocytopenia	34/1004 (3.4)	12/467 (2.6)	0.40
Medication (median (IQR))			
Oral CS (%)	796 (69.2)	369 (68.7)	0.84
Average CS dose(mg)	20 (10, 30)	15 (10, 30)	0.16
Highest CS dose(mg)	40 (20, 60)	40 (20, 60)	0.27
Cumulative CS dose (g)	2.6 (1.0, 5.0)	2.4 (1.1, 4.7)	0.74
Pulse intravenous CS (%)	52/1095 (4.8)	22/512 (4.3)	0.69
Immunosuppressant (%)	464/1147 (40.5)	193/531 (36.4)	0.11
Antimalarial (%)	759 (66.0)	356 (66.3)	0.91

CHD coronary heart disease; BP blood pressure; AHT anti-hypertensive; WC waist circumference; SLEDAI Systemic Lupus Erythematosus Disease Activity index; SLICC Systemic Lupus Erythematosus; ACR American College of Rheumatology; CS corticosteroid.

**Amended Supplemental Table S2: Characteristics of patients of by immunosuppressant use**

	<u>Not On Immunosuppressive</u>	<u>On Immunosuppressive</u>	<u>p</u>
No. of patients	683	464	
Age (years) (mean (SD))	36.3 (13.6)	32.6 (13.4)	<0.001
Gender (%)			
Female	629 (92.1)	524 (87.1)	0.005
Male	54 (7.9)	75 (12.9)	0.005
MetS (%)	205 (30.0)	232 (50.0)	<0.001
MetS Phenotype (%)			
MetS WC	266/628 (42.4)	209/438 (47.7)	0.08
MetS BP	221/683 (32.4)	267/464 (57.5)	<0.001
MetS TG	247/651 (37.9)	257/445 (58.0)	<0.001
MetS HDL	251/435 (57.7)	218/354 (61.6)	0.27
MetS Glu	104/635 (16.4)	99/435 (22.6)	0.01
BMI (mean(SD))	25.0 (6.0)	24.7 (5.6)	0.41
WC (cm) (mean (SD))	81.7 (14.2)	82.5 (13.6)	0.38
Disease duration (wks) (mean SD))	22.8 (17.8)	26.0 (18.0)	0.003
SLEDAI (mean SD))	4.68 (4.65)	6.57 (5.85)	<0.001
SLICC/ACR-DI (mean(SD))	0.21 (0.62)	0.43 (0.85)	0.006
Medication (median (IQR))			
Oral CS (%)*	369 (54.0)	424 (91.4)	<0.001
Average CS dose(mg)	15 (10, 30)	25 (15, 40)	<0.001
Highest CS dose(mg)	30 (15, 50)	50 (30, 60)	<0.001
Cumulative CS dose (g)	1.5 (0.6, 3.2)	3.4 (1.8, 6.0)	<0.001
Pulse intravenous CS (%)	19/640 (3.0)	33/453 (7.3)	<0.001
Antimalarial (%)	510 (74.7)	248 (53.4)	<0.001



**Table S3: Characteristics of patients of with and without active renal disease**

	<u>No Active Renal Disease</u>	<u>Active Renal Disease</u>	<u>p</u>
No. of patients	907	243	
Age (years) (mean (SD))	36.2 (13.8)	29.9 (11.8)	<0.001
Gender (%)			
Female	836 (92.2)	200 (82.3)	<0.001
Male	71 (7.8)	43 (17.7)	<0.001
MetS (%)	287 (31.6)	152 (62.6)	<0.001
MetS Phenotype (%)			
MetS WC	380/842 (45.1)	96/226 (42.5)	0.48
MetS BP	318/907 (35.1)	173/243 (71.2)	<0.001
MetS TG	329/863 (38.1)	179/236 (75.9)	<0.001
MetS HDL	339/590 (57.5)	131/202 (64.9)	0.07
MetS Glu	154/846 (18.2)	50/231 (21.7)	0.24
BMI (mean(SD))	25.2 (6.1)	23.8 (4.5)	0.001
WC (cm) (mean (SD))	82.2 (14.5)	81.4 (12.0)	0.43
Disease duration (wks) (mean SD))	25.2 (18.1)	20.4 (17.1)	0.002
SLEDAI (mean SD))	4.1 (3.9)	10.6 (6.3)	<0.001
SLICC/ACR-DI (mean(SD))	0.27 (0.71)	0.45 (0.86)	0.04
Medication (median (IQR))			
Oral CS (%)*	570 (62.8)	226 (93.30)	<0.001
Average CS dose(mg)	15 (10, 27.5)	31 (23.5, 50)	<0.001
Highest CS dose(mg)	30 (15, 50)	50 (40, 60)	<0.001
Cumulative CS dose (g)	2.2 (0.8, 4.6)	3.2 (1.6, 5.7)	<0.001
Pulse intravenous CS (%)	23/861 (2.7)	29/234 (12.4)	<0.001
Immunosuppressant (%)	285/905 (31.5)	179/242 (74.0)	<0.001
Antimalarial (%)	653/907 (72.0)	106/243 (43.6)	<0.001