



Lupus low disease activity state and remission and risk of mortality in patients with systemic lupus erythematosus: a prospective, multinational, longitudinal cohort study

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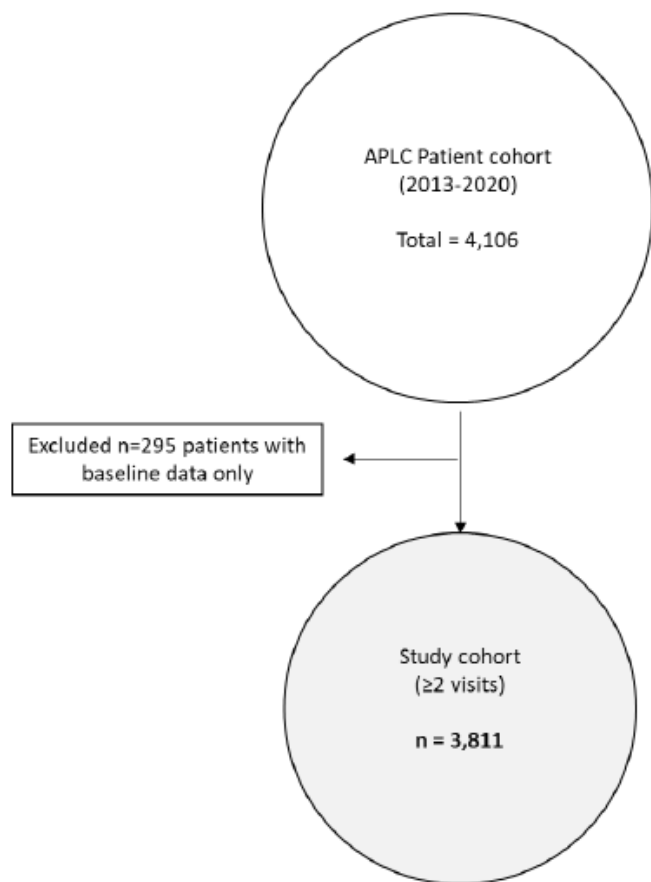
LLDAS達成が死亡率低下とも関連することを示した。
DORIS寛解達成も、死亡率低下と関連するが、
十分な差を出すにはPSL offとしなければならない。

Introduction

- SLEの死亡率は5-64歳女性ではtop20に入っている (2000-2015 in USA)
- LLDASとremissionは臓器障害抑制、再燃・入院数低下、QOL改善と関連
- LLDASと死亡率の関連を示したスタディはsingle cohortの retrospective study | つのみ (Arthritis Care Res 2020; 72: 447)
- LLDASおよびDORIS寛解とそのより厳しいGC量の定義を用いて、死亡率との関連を明らかにすることを目的とする

Methods

Supplementary Figure 1. Study flow diagram



3811名の前向きSLEコホート
2013/5/1～2020/12/31の成人SLE対象
1997 ACR or 2012 SLICC 分類を満たす

- SLEDAI-2K, SELENA-SLEDAI flare index, PGA 薬剤情報を全visitで記録
- LLDASとDORIS寛解、DORIS寛解(PSL<5mg/d)、DORIS寛解(PSL=0)を記録

死亡症例80例と非死亡症例3731例の背景を比較

患者背景 I

	All patients (n=3811)	Patients alive at end of study period (n=3731)	Patients who died during study period (n=80)	p value*
Demographics				
Age at enrolment, years	39 (30-50)	39 (30-50)	41 (28-54)	0.60
Age at diagnosis, years	29 (21-39)	29 (21-39)	31 (22-39)	0.38
Disease duration at enrolment, years	8 (3-15)	8 (3-15)	7 (3-13)	0.64
Study duration, years	2.8 (1.0-5.3)	2.9 (1.0-5.1)	2.2 (1.1-3.6)	0.030
Sex				
Female	3509 (92.1%)	3438 (92.1%)	71 (88.8%)	0.27
Male	302 (7.9%)	293 (7.9%)	9 (11.3%)	..
Ethnicity				
Asian	3385 (89.1%)	3314 (89.1%)	71 (88.8%)	0.92
Other	415 (10.9%)	406 (10.9%)	9 (11.3%)	..
Missing data	11 (0.3%)	11 (0.3%)	0	..
Family history of SLE				
Family history of SLE	303 (8.1%)	299 (8.1%)	4 (5.1%)	0.32
Missing data	62 (1.6%)	61 (1.6%)	1 (1.3%)	..
Current smoker at enrolment				
Current smoker at enrolment	194 (5.1%)	185 (5.0%)	9 (11.3%)	0.012
Missing data	33 (0.9%)	33 (0.9%)	0	..
Highest attained educational level				
Primary	481 (13.4%)	468 (13.3%)	13 (17.8%)	0.0080
Secondary	1185 (33.1%)	1151 (32.8%)	34 (46.6%)	..
Tertiary	1918 (53.5%)	1892 (53.9%)	26 (35.6%)	..
Missing data	227 (6.0%)	220 (5.9%)	7 (8.8%)	..
GDP (purchasing power parity) per capita, INT\$				
<20 000	1346 (35.3%)	1306 (35.0%)	40 (50.0%)	0.020
20 000-49 999	559 (14.7%)	549 (14.7%)	10 (12.5%)	..
≥50 000	1906 (50.0%)	1876 (50.3%)	30 (37.5%)	..

罹病期間8年
平均39歳
観察期間 2.8年
アジア人89%
Smoker 5.1%
GDP<\$20,000が35%

死亡群で差があるのは

- current smoker
- 低学歴
- 低所得

患者背景2 & QOL

	All patients (n=3811)	Patients alive at end of study period (n=3731)	Patients who died during study period (n=80)	p value*
Medication use				
Prednisolone	3277 (86.0%)	3199 (85.7%)	78 (97.5%)	0.0030
Time-adjusted mean prednisolone dose, mg/day	5.0 (2.5-8.9)	5.0 (2.4-8.7)	8.9 (5.7-5.5)	<0.0001
Cumulative prednisolone dose, g	3.9 (1.1-10.0)	3.9 (1.1-9.9)	7.2 (3.5-12.9)	<0.0001
Antimalarials†	3012 (79.0%)	2964 (79.4%)	48 (60.0%)	<0.0001
Immunosuppressants‡	2725 (71.5%)	2663 (71.4%)	62 (77.5%)	0.23
Biologics§	138 (3.6%)	134 (3.6%)	4 (5.0%)	0.50
Health-related quality of life (36-item Short Form Health Survey data)				
Time-adjusted mean physical component summary score	49.7 (44.0-54.0)	49.8 (44.1-54.0)	45.5 (37.4-51.7)	<0.0001
Time-adjusted mean mental component summary score	48.6 (42.0-53.4)	48.5 (42.0-53.3)	50.7 (43.8-54.3)	0.39
Missing data	1228 (32.2%)	1194 (32.0%)	34 (42.5%)	..

PSL 内服は 86%
 平均PSL 5.0mg/d
 累積PSL量 3.9 g
 HCQ 使用率 79%
 IS 使用率 71%
 バイオ使用率 3.6%

死亡群で差がみられたのは
 ・ PSL内服率
 ・ PSL量
 ・ 累積PSL量
 ・ HCQ使用率
 ・ SF-36 physical component summary score

患者特徴 I

	All patients (n=3811)	Patients alive at end of study period (n=3731)	Patients who died during study period (n=80)	p value*
Clinical profile across follow-up period				
Time-adjusted mean SLEDAI-2K score	2.9 (1.3-4.7)	2.9 (1.3-4.7)	5.2 (2.7-7.1)	<0.0001
Time-adjusted mean PGA score	0.4 (0.2-0.7)	0.4 (0.2-0.7)	0.9 (0.5-1.4)	<0.0001
Any flare (mild, moderate, or severe)	2142 (56.2%)	2080 (55.7%)	62 (77.5%)	<0.0001
Number of flares	1 (0-2)	1 (0-2)	2 (1-3)	<0.0001
Organ damage present at enrolment (SDI score >0)	1319 (38.2%)	1269 (37.6%)	50 (68.5%)	<0.0001
Missing data	362 (9.5%)	355 (9.5%)	7 (8.8%)	..
Organ damage accrued during study period (SDI score >0)	717 (20.8%)	690 (20.4%)	27 (37.0%)	<0.0001
Missing data	362 (9.5%)	355 (9.5%)	7 (8.8%)	..
SDI score at last visit	0 (0-2)	0 (0-1)	2 (0-3)	<0.0001
Missing data	362 (9.5%)	355 (9.5%)	7 (8.8%)	..
Organ-specific damage at last visit				
Ocular¶¶	457 (13.3%)	440 (13.0%)	17 (23.3%)	0.0050
Neuropsychiatric	341 (9.9%)	324 (9.6%)	17 (23.3%)	<0.0001
Renal**	394 (11.4%)	382 (11.3%)	12 (16.4%)	0.12
Pulmonary††	147 (4.3%)	140 (4.1%)	7 (9.6%)	0.015
Cardiovascular‡‡	168 (4.9%)	156 (4.6%)	12 (16.4%)	<0.0001
Perivascular§§	122 (3.5%)	119 (3.5%)	3 (4.1%)	0.71
Gastrointestinal¶¶¶	25 (0.7%)	22 (0.7%)	3 (4.1%)	<0.0001
Musculoskeletal	616 (17.9%)	601 (17.8%)	15 (20.5%)	0.40
Skin***	148 (4.3%)	141 (4.2%)	7 (9.6%)	0.016
Other	315 (9.1%)	294 (8.7%)	21 (28.8%)	<0.0001
Premature gonadal failure	70 (2.0%)	64 (1.9%)	6 (8.2%)	<0.0001
Diabetes	145 (4.2%)	136 (4.0%)	9 (12.3%)	<0.0001
Malignancy	123 (3.6%)	115 (3.4%)	8 (11.0%)	0.0001
Missing data	362 (9.5%)	355 (9.5%)	7 (8.8%)	..

SLEDAI 平均 2.9
 PGA平均 0.4
 flare率 56.2%
 SDI(+) at entry 38%
 SDI ↑ 20.8%

死亡群で差のあった点

- ・ SLEDAI平均値
- ・ PGA平均値
- ・ フレア率
- ・ SDI陽性率
- ・ SDI上昇率
- ・ SDI項目の中では
 目、脳神経、肺、心
 腸、皮膚、早期閉経
 糖尿、悪性腫瘍

死亡原因

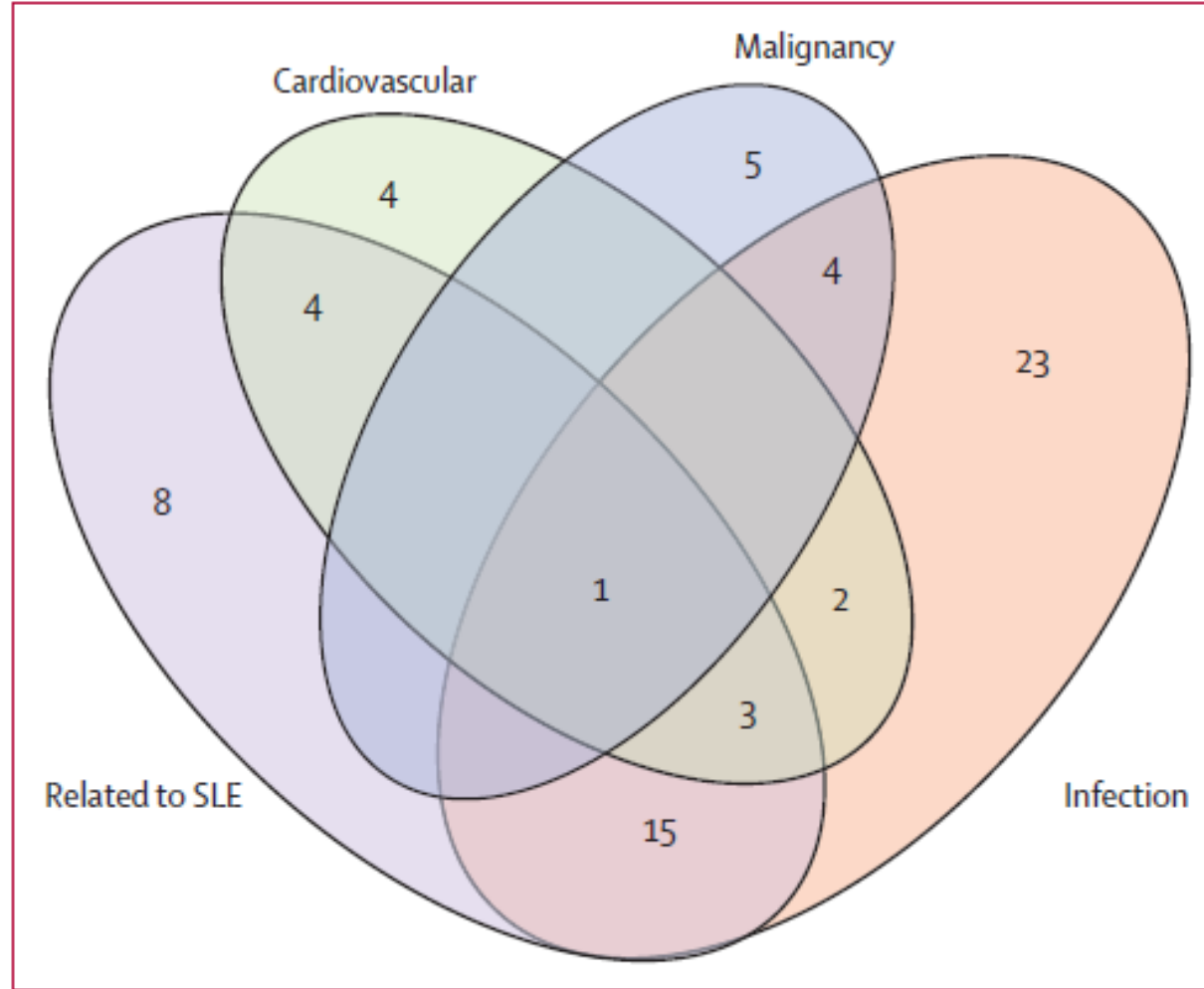
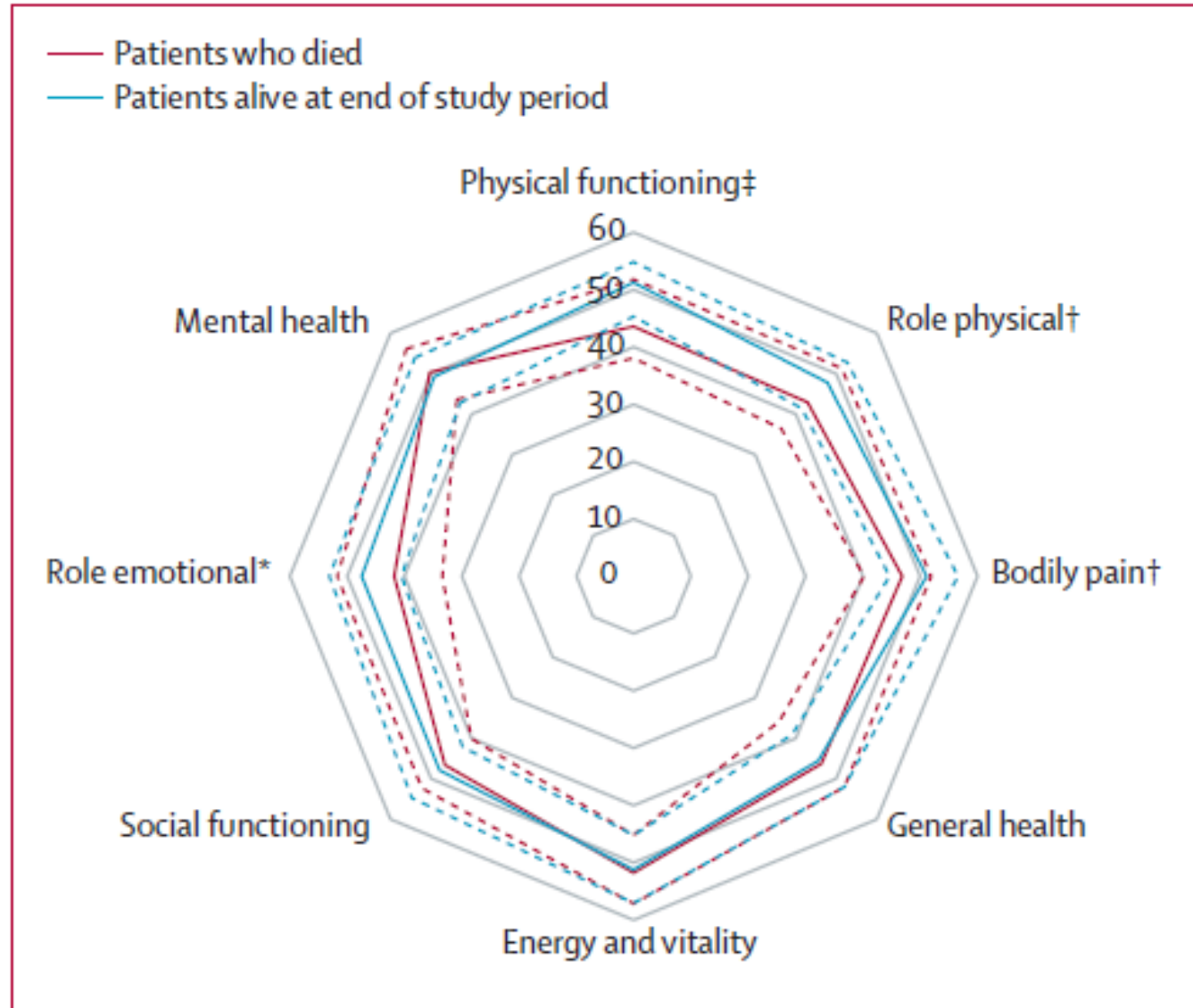


Figure 1: Causes of death among patients who died during the study period
SLE=systemic lupus erythematosus.

SF-36によるQOLカテゴリー別スコア



中央値が実線、
4分位点が破線

Figure 2: Domain scores from the 36-item Short Form Health Survey

LLDAS/寛解の割合

	All patients (n=3811)	Patients alive at end of study period (n=3731)	Patients who died during study period (n=80)	p value
LLDAS				
Never	730 (19.2%)	694 (18.6%)	36 (45.6%)	..
At least once	3078 (80.8%)	3035 (81.4%)	43 (54.4%)	<0.0001
LLDAS for ≥50% of observed time	1988 (52.2%)	1966 (52.7%)	22 (27.8%)	<0.0001
Missing data	3 (0.1%)	2 (0.1%)	1 (1.3%)	..
Time in LLDAS, %	50.0% (12.8–77.6)	50.0% (13.7–78.1)	7.3% (0.0–51.6)	<0.0001
Remission				
Never	1373 (36.1%)	1326 (35.6%)	47 (59.5%)	..
At least once	2435 (63.9%)	2403 (64.4%)	32 (40.5%)	<0.0001
Remission for ≥50% of observed time	1403 (36.8%)	1389 (37.2%)	14 (17.7%)	<0.0001
Missing data	3 (0.1%)	2 (0.1%)	1 (1.3%)	..
Time in remission, %	25.9% (0.0–66.5)	26.9% (0.0–67.1)	0.0% (0.0–27.6)	<0.0001

1度はLLDAS 80.8%
LLDAS >50%の割合 52.2%

1度は寛解63.9%
寛解>50%の割合 36.8%

死亡群で差のあった点
・ LLDASの割合
・ 寛解の割合

Modified DORIS寛解の割合

	All patients (n=3811)	Patients alive at end of study period (n=3731)	Patients who died during study period (n=80)	p value
Remission on <5 mg/day of prednisolone				
Never	1969 (51.7%)	1912 (51.3%)	57 (72.2%)	..
At least once	1839 (48.3%)	1817 (48.7%)	22 (27.8%)	<0.0001
Remission for $\geq 50\%$ of observed time	921 (24.2%)	916 (24.6%)	5 (6.3%)	<0.0001
Missing data	3 (0.1%)	2 (0.1%)	1 (1.3%)	..
Time in remission, %	0.0 (0.0–47.7)	0.0 (0.0–48.8)	0.0 (0.0–8.6)	<0.0001
Glucocorticoid-free remission				
Never	2801 (73.6%)	2730 (73.2%)	71 (89.9%)	..
At least once	1007 (26.4%)	999 (26.8%)	8 (10.1%)	<0.0001
Remission for $\geq 50\%$ of observed time	525 (13.8%)	524 (14.1%)	1 (1.3%)	<0.0001
Missing data	3 (0.1%)	2 (0.1%)	1 (1.3%)	..
Time in remission, %	0.0 (0.0–4.9)	0.0 (0.0–6.3)	0.0 (0.0–0.0)	<0.0001

Data are n (%) or median (IQR). LLDAS was defined as SLEDAI-2K score ≤ 4 with no major organ or new activity, PGA score ≤ 1 , and prednisolone ≤ 7.5 mg/day. Remission was defined as clinical SLEDAI-2K score 0, PGA score < 0.5 , and prednisolone ≤ 5.0 mg/day. LLDAS=lupus low disease activity state. SLE=systemic lupus erythematosus. SLEDAI-2K=SLE Disease Activity Index-2K. PGA=Physician Global Assessment.

Table 2: LLDAS or remission in patients with SLE

寛解 (PSL<5mg/d)の場合

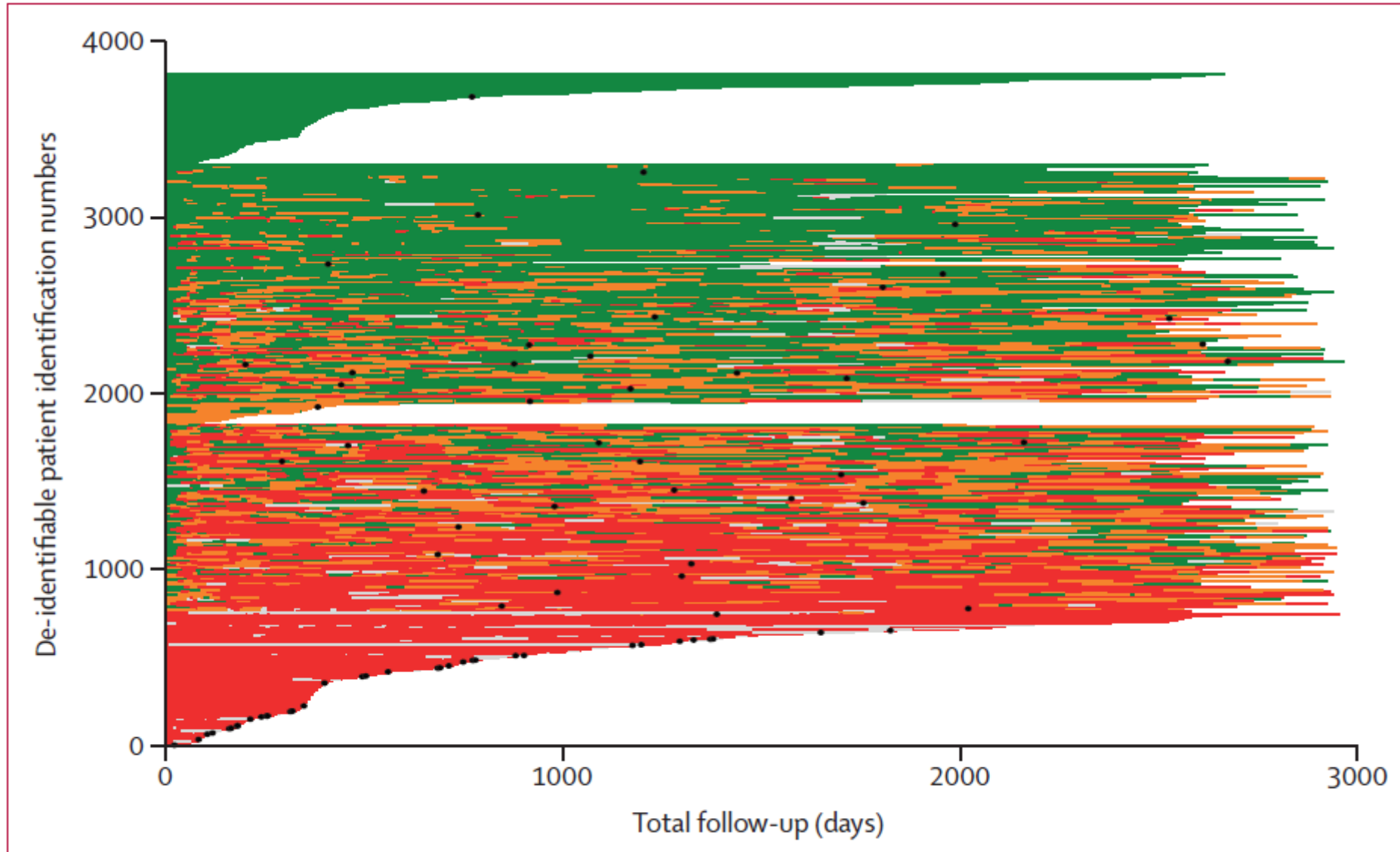
1度は寛解 48.3%
寛解>50%の割合 24.2%

寛解 (PSL free)の場合

1度は寛解 26.4%
寛解>50%の割合 13.8%

死亡群で差のあった点
・いずれの寛解でも

個々の患者のLLDAS達成状態



緑はin LLDAS
赤はnot in LLDAS
オレンジは移行期
黒点は死亡者

Figure 3: Heat map of study participants

様々な寛解/LLDASの死亡リスク

	Univariable model*		Multivariable model†	
	HR (95% CI)	p value	HR‡ (95% CI)	p value
LLDAS for ≥50% of observed time	0.39 (0.24–0.64)	<0.0001	0.51 (0.31–0.85)	0.010
Remission on ≤5 mg/day prednisolone for ≥50% of observed time	0.40 (0.22–0.72)	0.0020	0.52 (0.29–0.93)	0.027
Remission on <5 mg/day prednisolone for ≥50% of observed time	0.22 (0.09–0.55)	0.0010	0.31 (0.12–0.77)	0.012
Glucocorticoid-free remission for ≥50% of observed time	0.09 (0.01–0.61)	0.015	0.13 (0.02–0.96)	0.046

多変量解析は喫煙、GDP、SDIで調整

LLDAS>50%とDORIS寛解>50%はともにHR 0.5で変わらない。寛解(PSL<5mg/d)でHR 0.31となり寛解(PSL free)でHR 0.13となる

SLE=systemic lupus erythematosus. LLDAS=lupus low disease activity state. HR=hazard ratio. *Included 3811 patients: 3731 patients alive at the end of the study period and 80 who died. †Included 3204 patients, of whom 70 patients had complete data for all follow-up visits. ‡HRs adjusted for current smoking status, gross domestic product, and Systemic Lupus International Collaborating Clinics–American College of Rheumatology Damage Index score (appendix p 2).

Table 3: Risk of mortality among patients with SLE in LLDAS or remission

Discussion (I)

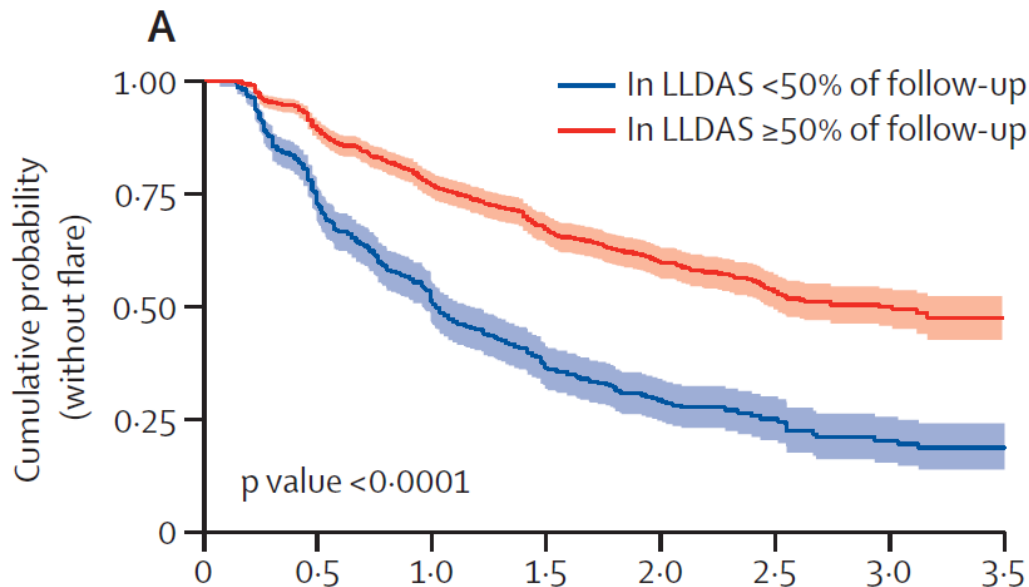
- 過去に低疾患活動性や寛解と死亡率の関連を示したものは複数ある
- 206名のSLE inception cohortでは低疾患活動性と低死亡率の関連が示されたが(Arthritis Care Res 2020)、そうでないという報告もある(ARD 2017)。ともにPGAは用いていない。PGAはSLEDAIの欠点を補っており、PGA 10%上昇は死亡率50%上昇に相当する。
- 疾患活動性で調整して、GC量と死亡率の関連を示した。
DORIS寛解のみではLLDASと比較して死亡率を下げないが、GC量を下げたmodified DORIS寛解だとLLDASより死亡率は低く、GC freeだと87%死亡率を低下させた
- 経済力やsmokingも重要な死亡率関連因子であったことは従来同様

Lupus low disease activity state as a treatment endpoint for systemic lupus erythematosus: a prospective validation study

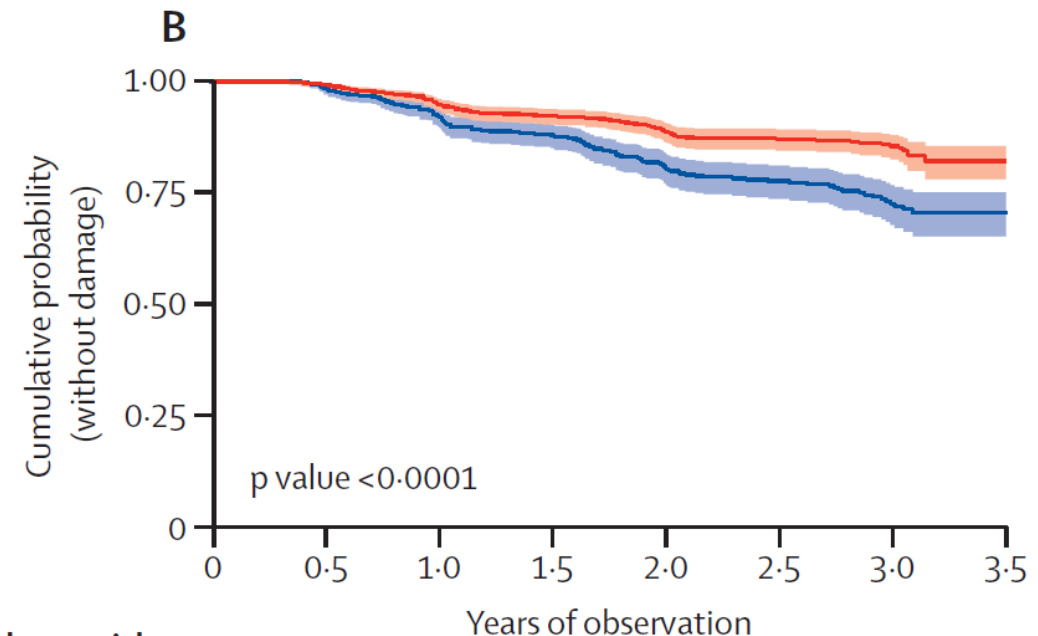


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Number at risk (number censored)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
In LLDAS <50% of follow-up	563 (0)	352 (46)	208 (45)	125 (30)	78 (25)	38 (32)	30 (1)	6 (22)
In LLDAS ≥50% of follow-up	900 (0)	815 (13)	662 (42)	495 (89)	356 (88)	176 (155)	92 (74)	16 (73)



Number at risk (number censored)	0	0.5	1.0	1.5	2.0	2.5	3.0	3.5
In LLDAS <50% of follow-up	735 (0)	657 (67)	543 (76)	423 (96)	326 (66)	230 (84)	129 (89)	27 (99)
In LLDAS ≥50% of follow-up	967 (0)	962 (2)	864 (55)	737 (104)	569 (143)	369 (196)	212 (152)	35 (171)

Discussion (2)

Limitationとして

- 観察期間が中央値3年以下と短い
- アジア人が中心でhealth careへのアクセスが多様
- バイオ使用率が低い
- 比較的重症度の低い患者が多かったかもしれない

まとめ

- LLDAS/寛解達成により死亡リスクを下げる事が明らかになった
- よりPSL量の少ない寛解が通常DORIS寛解より死亡リスクを下げ、PSL freeが最もリスクが低いことが明らかとなった
- 以上はLLDASをclinical trialのEndpointにすることを支持する
- PSL free 寛解が治療のゴールと考えるべきである