臨床 総論　5. 疫学 (GPA/MPA, MPO/PR3-ANCA)

- GPAとMPAの臨床像の違い
- $PR3^{+}$GPAとMPO^{+}GPAの違い

ANCA-associated vasculitis [Nat Rev Dis Primers. 2020; 6: 71.]

GPAとMPAの比較

Table 1 | **Comparison of the three syndromic presentations of AAV**

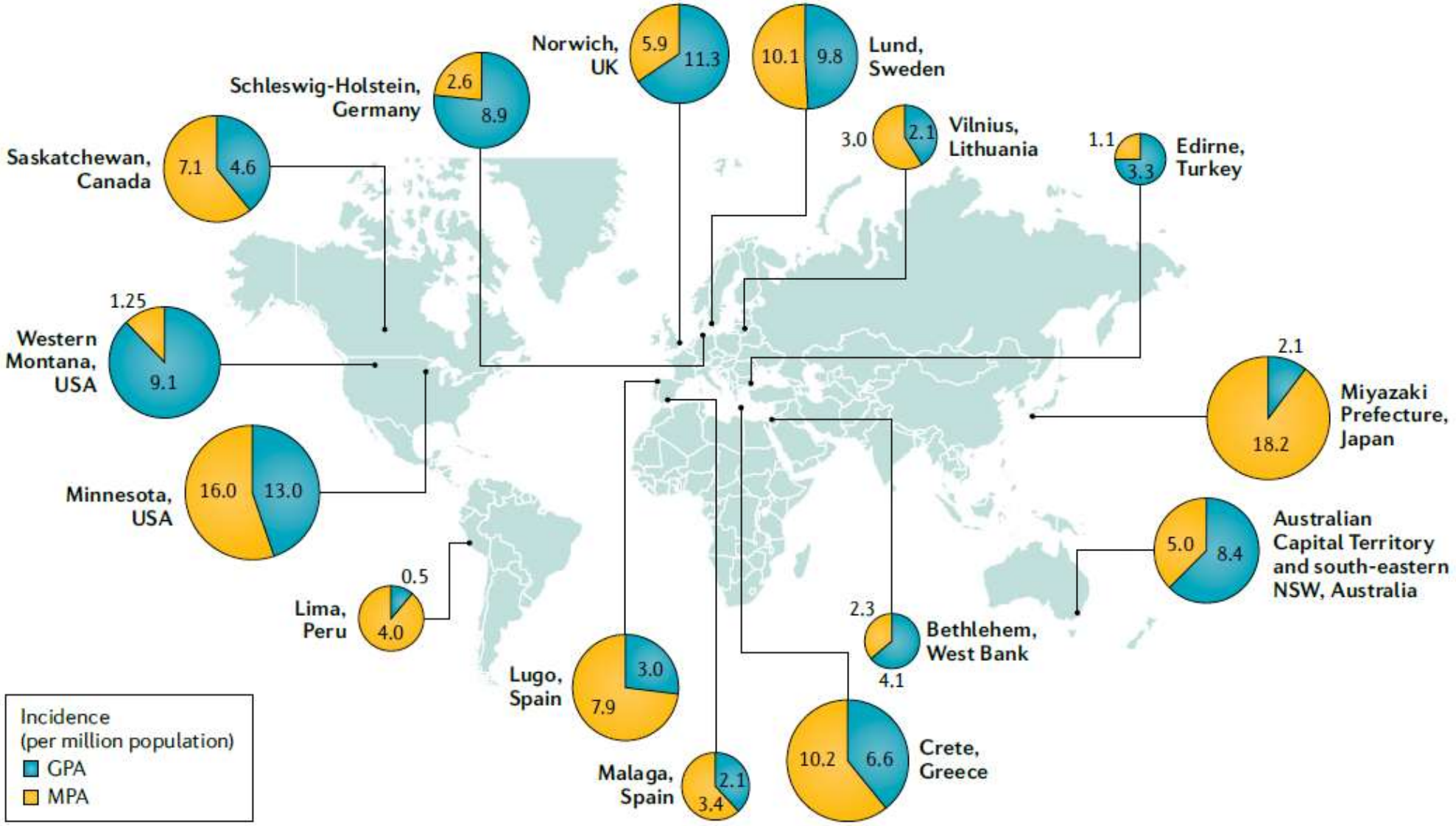
Feature	GPA	MPA	Eosinophilic GPA
Incidence	0.4–11.9 cases per 1 million person-years	0.5–24.0 cases per 1 million person-years	0.5–2.3 cases per 1 million person-years
Prevalence	2.3–146.0 cases per 1 million persons	9.0–94.0 cases per 1 million persons	2.0–22.3 cases per 1 million persons
Typical age of onset (years)	45–65	55–75	38–54
Male: female ratio	1:1	1:1	1:1
2012 revised CHCC definition[145]	Necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract; necrotizing vasculitis affecting predominantly small-to-medium vessels (such as capillaries, venules, arterioles, arteries and veins); necrotizing glomerulonephritis is common	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (such as capillaries, venules or arterioles); necrotizing arteritis involving small and medium arteries may be present; necrotizing glomerulonephritis is very common; pulmonary capillaritis often occurs; granulomatous inflammation is absent	Eosinophil-rich and necrotizing granulomatous inflammation, often involving the respiratory tract; necrotizing vasculitis predominantly affecting small-to-medium vessels; associated with asthma and eosinophilia; ANCA$^+$ is more frequent when glomerulonephritis is present
Frequency of ANCA	PR3-ANCA$^+$: 65–75% MPO-ANCA$^+$: 20–30% ANCA$^-$: 5%	PR3-ANCA$^+$: 20–30% MPO-ANCA$^+$: 55–65% ANCA$^-$: 5–10%	PR3-ANCA$^+$: <5% MPO-ANCA$^+$: 30–40% ANCA$^-$: 55–65%
Key innate immune cell	Neutrophil	Neutrophil	Eosinophil
Relapse rate	Higher than MPA (or MPO-AAV)	Lower than GPA (or PR3-AAV)	Relapse is frequent

- MPAはMPO-ANCAと, GPAはPR3-ANCAと強く関連し, EGPAはMPO-ANCA陽性もしくはANCA陰性.
- 遺伝子解析の結果からは, MPO-ANCA/PR3-ANCAの違いの方がMPA/GPAの違いより大きく, 抗原特異性が病態生理に重要と考えられる.
- GPAは再燃率がMPAより高い.

ANCA-associated vasculitis [Nat Rev Dis Primers. 2020; 6: 71.]

GPAとMPAの分布

- MPAとGPAの地理的分布
- GPA (PR3-AAV) はEuropeanが主流の国で多く, 東アジアで少ない.
- MPA (MPO-AAV) は中国や日本などアジアで主流.
- GPAの頻度は緯度とも関係し, 赤道に近くなるほど減少する.



Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK

Shouichi Fujimoto[1], Richard A. Watts[2], Shigeto Kobayashi[3], Kazuo Suzuki[4], David R. W. Jayne[5], David G. I. Scott[6], Hiroshi Hashimoto[7] and Hiroyuki Nunoi[8]

[Rheumatology 2011:50:1916-20.]

Disease spectrum and ANCA status	Japan	UK
Numbers of total AAV	86	50
Male *vs* female	42 *vs* 44	24 *vs* 26
Mean (median) age, years	69.7 (72)*	60.5 (61)
pANCA/MPO, *n* (%)	72 (84)**	15 (30)
cANCA/PR3, *n* (%)	6 (7)**	29 (58)
Negative, *n* (%)	8 (9)	6 (12)
Annual incidence/million		
Adults		
Total AAV	22.6 (19.1, 26.2)	21.8 (12.6, 30.9)
MPA	18.2 (14.3, 22.0)	6.5 (1.9, 11.2)
Granulomatosis with polyangiitis	2.1 (0.6, 3.7)	14.3 (5.8, 23.0)
CSS	2.4 (0.3, 4.4)	0.9 (0, 1.9)
Seniors		
Total AAV	57.0 (53.4, 60.6)	47.9 (25.0, 70.8)
MPA	50.7 (38.3, 63.0)	20.8 (−0.6, 42.2)
Granulomatosis with polyangiitis	2.7 (−0.8, 6.3)	25.0 (14.6, 35.4)

95% CI values are given within parentheses for annual incidence values. *$P < 0.001$ by unpaired *t*-test; **$P < 0.001$ by chi-square test.

- AAVの日本とUKの疫学的比較
- 日本 (n=86)
  AAV 22.6 /million (2005-2009, 宮崎県)
  MPA (83%) >>GPA
  pANCA/MPO (84%)>>cANCA/PR3 (7%)
- UK (n=50)
  AAV 21.8 /million (2005-2009, Norfolk)
  GPA (66%) > MPA
  cANCA/PR3 (58%)>pANCA/MPO (30%)

結論

- AAVの発生率は日本/UK同等
- 腎病変は日本/UKとも同等
- GPA, cANCA/PR3は, 日本では非常に少ない.

Are PR3 positive and MPO positive GPA the same disease?

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[Int J Rheum Dis. 2019; 22 Suppl 1:86-89.]

PR3⁺ GPAとMPO⁺GPAは同じ疾患か?

- 大部分PR3-ANCA⁺, 少数がMPO-ANCA⁺
- N=321 GPA cohort (WGETとRAVEのpooled study)では PR3 85%, MPO 10%, ANCA negative 5%でPR3⁺GPAとMPO⁺GPAに臨床phenotypeの差はなかった [Arthritis Rheumatol 2016; 68: 2945-52.]

Table 1 Identified SNPs found to have opposite associations for PR3 and MPO serotypes

SNP	PR3 ANCA	MPO ANCA	GPA	MPA
HLA-DPB2 rs3130215	Protective	Increased risk		
TLR9 rs352162	Increased risk	Protective	Increased risk	Protective
TLR9 rs352140	Increased risk	Protective	Increased risk	Protective
TLR9 rs352139	Increased risk	Protective	Increased risk	Protective

[Ann Rheum Dis 2016; 75: 1687-92.]からのtable

- 両者は違うというのが本論文の主張.
- MPO⁺GPAはより”limited”で軽症と報告されている.
- 日本人GPAでは61%がPR3⁺, UKでは85%がPR3⁺ [J Rheumatol 2016; 44: 216-22.]
- AAVのmeta-analysisでは 25, PR3/MPO共通では7 genetic variant
- PR3とMPOで異なるgenetic variance は4 variantで, TLR9の同一SNPがPR3-ANCA risk↑/MPO-ANCA risk↓と逆の作用がある [Ann Rheum Dis 2016; 75: 1687-92.].
- Genotype → Serotype → Phenotype に違いがあると思われるがまだ解明されてはいない.
- ドイツCase-control study 59人MPO⁺GPAとPR3⁺GPA(118人)比較 [Arthritis Rheumatol 2016; 68: 2953-63.] . MPO⁺GPAに軽症(37% vs 74%; P <0.001), MPO⁺GPAがlimited (声門下狭窄など)が多い(29% vs 11%; P=0.003), 重症例はPR3⁺GPAに多い; 肺(67% vs 46%; P=0.007), 腎(52% vs 27%; P=0.002)
- 治療反応性は違うという報告はあるがcontroversial (PR3がRTX>IVCY有効だが再燃する)

Myeloperoxidase–Antineutrophil Cytoplasmic Antibody (ANCA)–Positive Granulomatosis With Polyangiitis (Wegener's) Is a Clinically Distinct Subset of ANCA-Associated Vasculitis

A Retrospective Analysis of 315 Patients From a German Vasculitis Referral Center

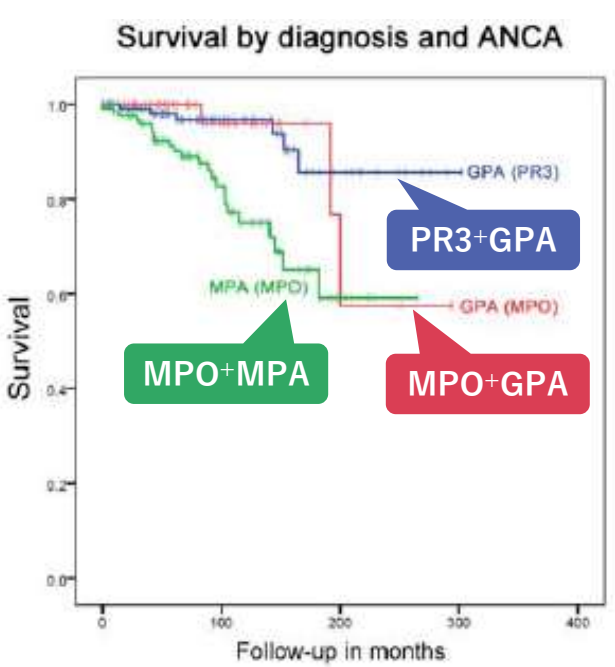
[Arthritis Rheumatol 2016; 68: 2953-63.]

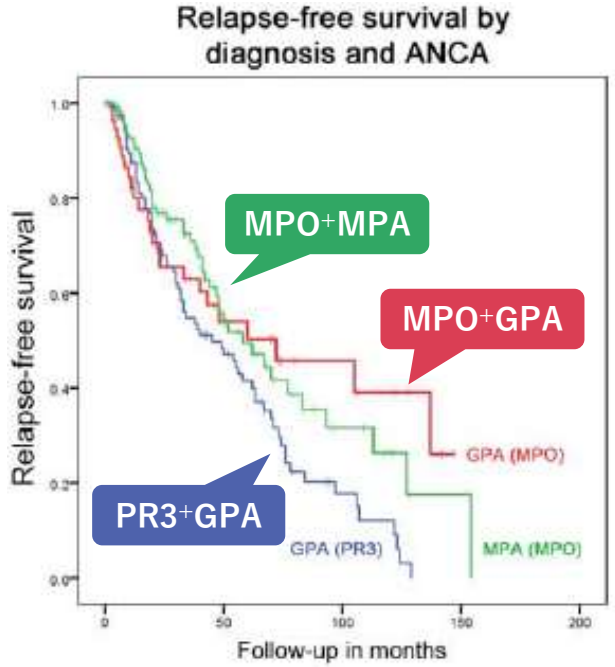
	PR3-ANCA–positive GPA	P†	MPO-ANCA–positive GPA	P‡	MPO-ANCA–positive MPA	All cohorts
Demographic characteristic						
No. of patients	118 (100.0)	NC	59 (100.0)	NC	138 (100.0)	315 (100.0)
Women	90 (76.3)	NC	45 (76.3)	0.007§	77 (55.8)	212 (67.3)
MPO-ANCA	0 (0.0)	NC	59 (100.0)	NC	138 (100.0)	197 (62.5)
PR3-ANCA	118 (100.0)	NC	0 (0.0)	NC	0 (0.0)	118 (37.5)
Age, mean ± SD (range) years	48.5 ± 15.4 (18–75)	NC	48.7 ± 15.5 (20–75)	<0.001§	59.3 ± 14.7 (18–86)	53.3 ± 15.9 (18–86)
Disease stage						
Limited	31 (26.3)	<0.001§	37 (62.7)	<0.001§	7 (5.1)	75 (23.8)
Severe	87 (73.7)	<0.001§	22 (37.3)	<0.001§	131 (94.9)	240 (76.2)

Table 4. Cox regression analysis of survival and relapse in each of the cohorts analyzed*

	Death†		Relapse‡	
	HR (95% CI)	P	HR (95% CI)	P
Analyzed by diagnosis and ANCA status				
MPO-ANCA–positive GPA; reference PR3-ANCA–positive GPA	NC§	–	0.63 (0.39–1.01)	0.057
MPO-ANCA–positive GPA; reference MPO-ANCA–positive MPA	NC§	–	NC§	–
PR3-ANCA–positive GPA; reference MPO-ANCA–positive MPA	0.38 (0.15–0.98)	0.045¶	1.41 (0.95–2.12)	0.092
Analyzed by diagnosis				
GPA; reference MPA	0.40 (0.17–0.91)	0.028#	1.10 (0.91–1.34)	0.308
Analyzed by ANCA status				
PR3-ANCA; reference MPO-ANCA	0.46 (0.18–1.14)	0.092	1.48 (1.04–2.10)	0.029

- **MPO⁺ GPA** (59人)と**PR3⁺ GPA** (118人; age-gender-matched)と**MPO⁺ MPA** (138人) の比較 (ドイツ)
- **MPO⁺ GPA**が有意に軽症(37% vs 74%; $P<0.001$)
- **PR3⁺ GPA**はSevereに多い; 肺(67% vs 46%; P=0.007), 腎(52% vs 27%; P=0.002)
- **MPO⁺ GPA**はlimited (声門下狭窄など)に多く(29% vs 11%; $P=0.003$), RTX/CYなど積極的な治療を要さない
- **MPO⁺ GPA**は**MPA**より若く女性が多い
- GPAはMPAより予後が良い(MPAはILDのため悪い), MPO-ANCAはPR3-ANCAより再燃率は有意に低い.





Comparison of the Phenotype and Outcome of Granulomatosis with Polyangiitis Between UK and Japanese Cohorts

[J Rheumatol 2016; 44: 216-22.]

Shunsuke Furuta, Afzal N. Chaudhry, Yoshihiro Arimura, Hiroaki Dobashi, Shouichi Fujimoto, Sakae Homma, Niels Rasmussen, and David R. Jayne

Table 1. Baseline characteristics. Data are n (%) unless otherwise indicated.

Characteristics	UK, n = 128	Japan, n = 82	p
Male:female (female rate)	65:63 (49.2)	34:48 (58.5)	0.19
Age at onset, yrs (IQR)	57.5 (42.5–66.8)	62.2 (56.9–70.3)	< 0.01
PR3-(c-) ANCA–positive	109 (85.2)	50 (61.0)	< 0.01
MPO-(p-) ANCA–positive	11 (8.6)	28 (34.1)	< 0.01
ANCA–double-positive	1 (0.8)	4 (4.9)	0.08
ANCA-negative	9 (7.0)	8 (9.8)	0.48
Granuloma on biopsy–positive	40 (31.2)	31 (37.8)	0.33
DEI (IQR)	7 (5–7)	7 (4–9)	0.43
Creatinine, μmol/l (IQR)	101.0 (74.5–257.3)	68.1 (48.6–122.9)	< 0.01
CRP, mg/l (IQR)	70 (15–187)	80 (15–153)	0.75
Followup, months (IQR)	59.6 (24.6–93.4)	36.4 (8.5–72.8)	

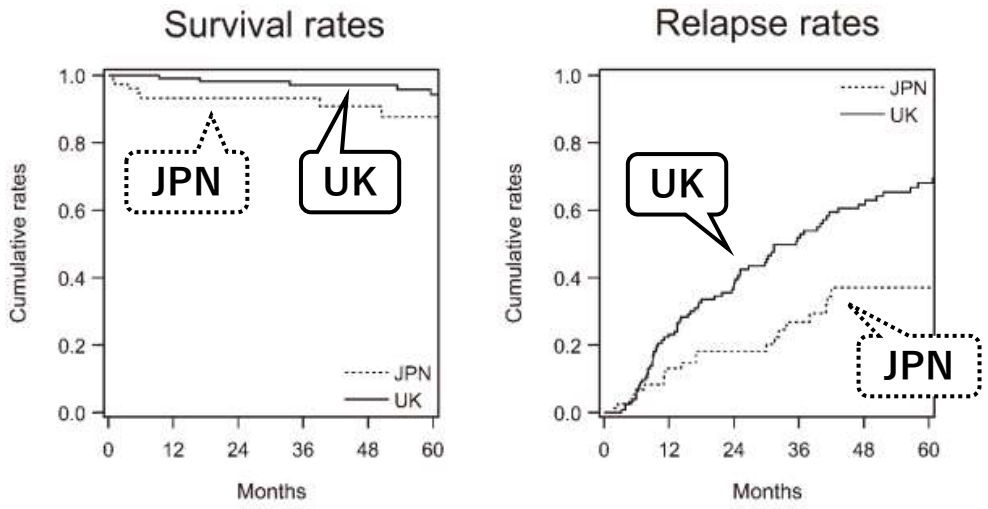


Table 4. Multivariate analysis for relapse.

	Univariate Analysis sHR (95% CI)	p	Multivariate Analysis sHR (95% CI)	p
Creatinine ≤ 100 μmol/l	1	NA	1	NA
100 < Creatinine ≤ 300	0.79 (0.50–1.25)	0.32	0.71 (0.44–1.14)	0.16
Creatinine > 300 μmol/l	0.42 (0.22–0.82)	0.01	0.33 (0.17–0.65)	< 0.01
Skin involvement	1.81 (1.04–3.15)	0.03		
Kidney involvement	0.65 (0.44–0.95)	0.03		
Country: Japan	0.49 (0.32–0.76)	< 0.01	0.39 (0.24–0.64)	< 0.01

- 日本人GPA 82人とUK GPA 128人の比較.
- 日本人GPAが発症時年齢が高い
  (62.2 歳 vs 57.5 歳, p<0.01).
- 日本人GPAがMPO-ANCA陽性が多い
  (34.1% vs 8.6%, p<0.01).
- 日本人GPAが診断時腎機能が良い
  (Cr 68.1 μmol/l vs 101.0 μmol/l, p<0.01)
- 日本人GPAが呼吸器合併症が多い
  (69.5% vs 40.6%, p<0.01)
- 日本人GPAが60週の再発率が低い
  (37.1% vs 68.1%, p < 0.01)