

Ki-67 Proliferation Index Is Associated With Tumor Grade and Survival in Pleural Epithelioid Mesotheliomas

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背景：胸膜上皮型中皮腫（PEM）は、核異型、有糸分裂、および壊死に基づいて低グレードと高グレードに分類されるが、これらの評価は労力を要し、再現性に限界がある。Ki-67 増殖指数は PEM の予後因子として知られているが、腫瘍グレードや有糸分裂数との直接的な関連性は明確ではない。

目的：Ki-67 指数を腫瘍グレードの代替指標として評価し、有糸分裂数と Ki-67 指数の全生存率（OS）予測力を比較すること。

2000 年から 2021 年に採取された検体 96 症例を使用した。

2 人の病理医がそれぞれに腫瘍グレードを評価し、デジタル画像解析（DIA）を通じて Ki-67 指数を評価した。κ 指数を用いて評価者間の一致度を計算し、Spearman-rank 法を用いて有糸分裂数と Ki-67 指数の相関を評価した。腫瘍グレードの評価は中程度の一一致（Kappa 値=0.47）であった。

Ki-67 指数と腫瘍グレードの関連：Ki-67 指数は高グレードの腫瘍で有意に高く、低グ

レードの腫瘍と比較して有意差があった ($P \leq 0.0001$)。

生存率の予測：Ki-67 指数高値 ($\geq 30\%$) および有糸分裂数 ($\geq 10/2 \text{ mm}^2$) は、低い OS と有意に関連していた ($P=0.03$ および 0.0005)。

結論：Ki-67 指数は腫瘍グレードおよび有糸分裂数と良好に相関し、OS の予測力も有糸分裂数と同等であるため、腫瘍グレードの代替指標として有望である。また、Ki-67 指数は、PEM の治療計画や予後予測において重要な役割を果たす可能性がある。

TABLE 1. Patient Demographics	
Patients (n = 85)	
Age at diagnosis (years)	
Mean (SD)	67.2 (11.2)
Range	(26.6–88.6)
Sex, N (%)	
F	19 (22.4)
M	66 (77.6)
Total specimens per patient, N (%)	
1	74 (87.1)
2	11 (12.0)

TABLE 2. Interobserver Agreement Using WHO Grading Guidelines (N = 96 Specimens)			
WHO parameter	Reviewer 1, N (%)	Reviewer 2, N (%)	Kappa (95% CI)*
Mitotic count			
0–1	24 (25.0)	34 (35.4)	0.53 (0.39, 0.66)
2–4	26 (27.1)	18 (18.8)	—
5+	46 (47.9)	44 (45.8)	—
0–4	50 (52.1)	52 (54.2)	0.52 (0.38, 0.66)
5–9	15 (15.6)	21 (21.9)	—
10+	31 (32.3)	23 (24.0)	—
Nuclear atypia score			
1	5 (5.2)	5 (5.2)	0.37 (0.22, 0.52)
2	30 (31.3)	54 (56.3)	—
3	61 (63.5)	37 (38.5)	—
Nuclear grade			
1	16 (16.7)	23 (24.0)	0.49 (0.35, 0.63)
2	44 (45.8)	53 (55.2)	—
3	36 (37.5)	20 (20.8)	—
Necrosis			
No	73 (76.0)	71 (74.0)	0.56 (0.36, 0.75)
Yes	23 (24.0)	25 (26.0)	—
Tumor grade			
Low	53 (55.2)	60 (62.5)	0.47 (0.29, 0.64)
High	43 (44.8)	36 (37.5)	—

*Weighted kappa presented for mitotic score, nuclear atypia score, and nuclear grade. Kappa values assess the amount of agreement expected above and beyond chance alone.

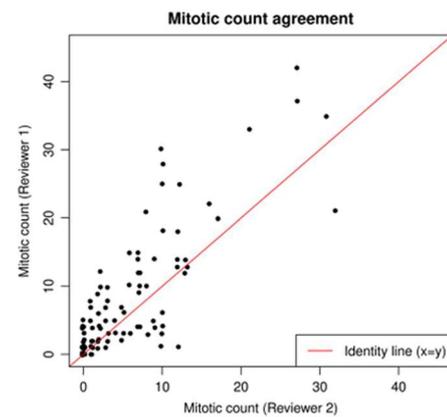


FIGURE 1. Interobserver Agreement for Mitotic Counts. Scatter plot demonstrating interobserver correlation (reviewer 2 x-axis, reviewer 1 y-axis) based on mitotic counts for 96 specimens. The red diagonal line (identity line) demonstrates perfect agreement between reviewers.

TABLE 3. Association Between Ki-67 Index and Tumor Grade in 2 reviewers

	Tumor grade		P
	Low	High	
Ki-67: reviewer 1			
N	53	43	0.0001
Median	13.5	29.5	—
Q1, Q3	8.2, 25.5	19.2, 42.1	—
Range	(1.8–76.6)	(1.1–70.5)	—
Ki-67: reviewer 2			
N	60	36	<0.0001
Median	13.7	31.4	—
Q1, Q3	8.4, 24.5	25.6, 44.3	—
Range	(1.1–76.6)	(6.0–70.5)	—

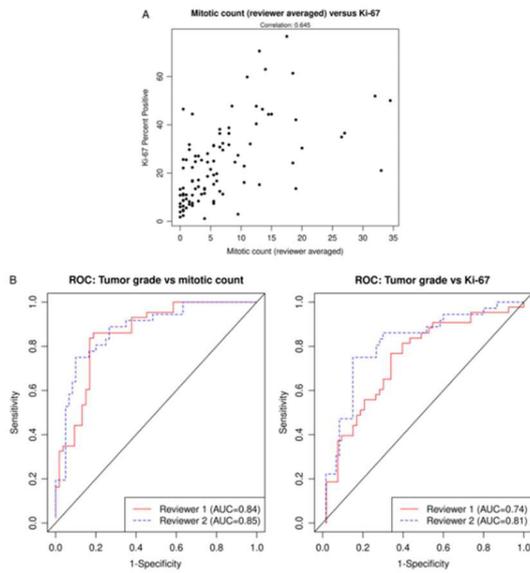


FIGURE 2. A, Correlation between mitotic count (reviewer averaged) with Ki-67%. Scatter plot demonstrating moderate correlation (0.645) between reviewer-averaged mitotic count (x-axis) and Ki-67% positivity (y-axis) for 96 specimens. B, ROC curves predicting tumor grade based on mitotic count or Ki-67%. ROC curve for tumor grade versus mitotic count for each reviewer (left). ROC curve for tumor grade versus Ki-67% for each reviewer (right). AUC indicates area under the curve; ROC, receiver operating characteristic.

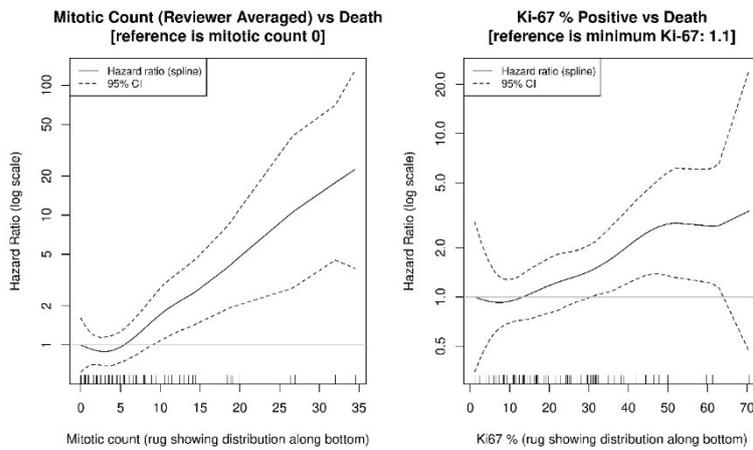


TABLE 4. Overall Survival (OS) by Mitotic Count and Ki-67 Index

Variable	Patients, N	Deaths, N	1-y OS (95% CI)	3-y OS (95% CI)	Hazard ratio (95% CI)	P	C
Mitotic count (reviewer averaged)							
0-4	43	38	76.5 (63.8, 89.3)	26.3 (13.0, 39.6)	Reference	0.001*	0.587
5-9	22	19	81.0 (64.2, 97.7)	15.2 (0.0, 32.5)	1.31 (0.72, 2.30)	—	—
≥ 10	20	16	43.8 (19.4, 68.1)	0.0 (non-Est.†)	3.55 (1.83, 6.66)	—	—
< 10	65	57	78.0 (67.8, 88.2)	23.2 (12.6, 33.8)	Reference	0.0005	0.585
≥ 10	20	16	43.8 (19.4, 68.1)	0.0 (non-Est.†)	3.21 (1.72, 5.72)	—	—
Ki-67 Index							
0- < 10	18	15	77.4 (57.8, 96.9)	23.8 (3.5, 44.1)	Reference	0.14	0.554
10- < 20	25	21	74.1 (56.2, 91.9)	30.5 (11.7, 49.3)	1.05 (0.54, 2.07)	—	—
20- < 30	15	13	78.6 (57.1, 100.0)	10.7 (0.0, 29.0)	1.37 (0.63, 2.97)	—	—
≥ 30	27	24	60.0 (40.8, 79.2)	5.3 (0.0, 15.1)	2.00 (1.03, 4.04)	—	—
< 30	58	49	76.2 (64.9, 87.5)	23.9 (12.4, 35.4)	Reference	0.03	0.556
≥ 30	27	24	60.0 (40.8, 79.2)	5.3 (0.0, 15.1)	1.79 (1.06, 2.96)	—	—

*Pairwise P-values: 5 to 9 versus 0 to 4 ($P=0.37$), ≥ 10 versus 0 to 4 ($P=0.0003$), ≥ 10 versus 5-9 (HR 2.72, 95% CI: 1.35-5.39, $P=0.006$). Of note, OS did not differ significantly when comparing 2 to 4 versus 0 to 1 mitotic count (HR = 0.83, 95% CI: 0.44-1.59).
 †CI nonestimable due to low or no variability.

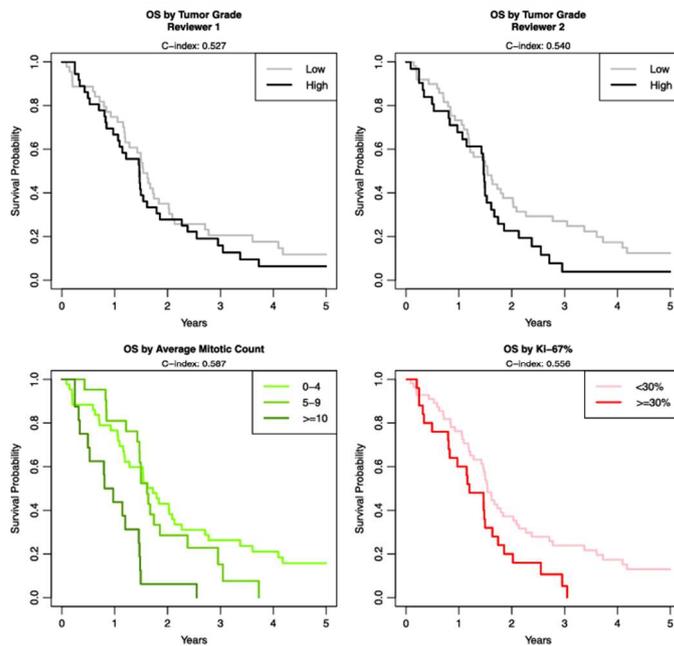


FIGURE 3. Overall survival by WHO tumor grade, mitotic count, and Ki-67 proliferation index. Kaplan-Meier plots illustrating overall survival for 85 patients with diffuse pleural epithelioid mesothelioma. Proposed mitotic count categorizations of 0 to 4, 5 to 9, and > 10 mitoses show poorer survival probability with higher mitotic counts (lower left). Ki-67 proliferation index with a delineation of 30% positivity (lower right), showing similar performance to the tumor grade by reviewer 2.

TABLE 5. Mitotic count, Ki-67 Index, and Overall Tumor Grade in the Cases With 2 Procedures

Patients with 2 biopsies (n = 11)	Specimens	Days after the		Mitotic count (average by 2 reviewers)	Ki-67 index (%)	Overall tumor grade (reviewer 1)	Overall tumor grade (reviewer 2)
		first biopsy	Procedure type				
1	1	0	Biopsy	0.5	8.6	Low	Low
	2	118	Resection	0.0	1.8	Low	Low
2	1	0	Biopsy	6.5	38.1	High	High
	2	145	Pneumonectomy	2.0	22.3	Low	Low
3	1	0	Biopsy	6.5	36.4	Low	High
	2	157	Excision	17.5	76.6	Low	Low
4	1	0	Biopsy	5.5	31.3	Low	High
	2	89	Excision	1.5	7.0	Low	Low
5	1	0	Excision	20.0	30.3	High	High
	2	212	Biopsy	0.5	8.7	Low	Low
6	1	0	Biopsy	1.5	8.2	Low	Low
	2	100	Resection	0.5	25.6	Low	Low
7	1	0	Biopsy	6.5	30.8	High	High
	2	329	Biopsy	33.0	21.1	High	High
8	1	0	Biopsy	5.5	7.4	Low	High
	2	496	Resection	15.0	44.4	High	High
9	1	0	Biopsy	12.5	47.7	High	High
	2	112	Pneumonectomy	0.5	22.1	High	High
10	1	0	Resection	8.0	31.7	High	Low
	2	79	Resection	8.5	47.8	High	High
11	1	0	Biopsy	4.0	13.2	High	Low
	2	155	Biopsy	5.5	15.4	Low	Low