Supplementary table 1. The number of enrolled patients from each institution in the derivation and validation cohorts

Derivation cohort (*n* =8,291)		Validation cohort (*n* =2,029)	
Institution	No. of patients	Institution	No. of patients
Shizuoka Cancer Centre	1,180	Fukushima Medical University Hospital	373
Cancer Institute Hospital	1,178	Tonan Hospital	332
Toranomon Hospital	519	Ehime Prefectural Central Hospital	313
Ishikawa Prefectural Central Hospital	397	Hirosaki University Hospital	299
Osaka City University Graduate School of Medicine	374	Tohoku University Graduate School of Medicine	299
The Jikei University School of Medicine	368	Nagasaki University Hospital	268
The University of Tokyo	360	Ehime University Graduate School of Medicine	121
Wakayama Medical University	332	National Hospital Organization Hakodate Hospital	24
Kobe University School of Medicine	331		
Osaka General Medical Centre	309		
Fukui Prefectural Hospital	291		
Yamaguchi University Graduate School of Medicine	283		
Chiba University Graduate School of Medicine	281		
Osaka City General Hospital	279		
Toyonaka Municipal Hospital	270		
Juntendo University School of Medicine	253		
Osaka University Graduate School of Medicine	228		
Shiga University of Medical Science Hospital	201		

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Kansai Rosai Hospital	192
Kohnodai Hospital, National Centre for Global Health and Medicine	129
Saitama Medical Centre	125
University of Tsukuba Hospital	112
Kanazawa University Hospital	110
Gunma University Graduate School of Medicine	103
Shuto General Hospital	86

Supplementary table 2. Univariate analysis of predictive factors for bleeding after ESD for EGC in the derivation cohort

		No. of patients	No. of bleeding	Unadjusted OR	95% CI	*p* value
Age	≥75 years	3,278	172	1.24	1.01–1.52	0.043
	<75 years	5,013	215	1	Reference	
Sex	Male	6,182	314	1.49	1.15–1.94	0.003
	Female	2,109	73	1	Reference	
Ischemic heart	Yes	567	74	3.55	2.72–4.65	<0.001
disease	No	7,724	313	1	Reference	
Liver cirrhosis	Yes	155	9	1.27	0.64–2.50	0.498
	No	8,136	378	1	Reference	
CKD with	Yes	129	29	6.32	4.13–9.69	<0.001
haemodialysis	No	8,162	358	1	Reference	
Endoscopic	Mild/no	632	25	0.83	0.55–1.25	0.373
gastric atrophy¶	Moderate/severe	7,646	362	1	Reference	
Aspirin	Yes	793	85	2.86	2.22–3.68	<0.001
	No	7,498	302	1	Reference	
P2Y12RA	Yes	344	46	3.44	2.48–4.78	< 0.001
	No	7,947	341	1	Reference	
Cilostazol	Yes	168	15	2.04	1.19–3.51	0.010
	No	8,123	372	1	Reference	
Warfarin	Yes	255	53	6.05	4.39–8.35	<0.001
	No	8,036	334	1	Reference	
DOAC	Yes	189	32	4.45	3.00–6.60	<0.001
	No	8,102	355	1	Reference	
Interruption of	Each kind of	1,077	132	2.85	2.41–3.36	<0.001
AT agents¶	agents					
	No	7,211	255	1	Reference	
Heparin bridging	Yes	311	53	4.70	3.43–6.45	<0.001
	No	7,980	334	1	Reference	
Replacement of	Yes	85	11	3.10	1.63–5.88	0.001
APAs¶	No	8,205	376	1	Reference	
The number of	Multiple	1,014	69	1.60	1.22–2.09	0.001
tumours	Single	7,277	318	1	Reference	

Tumour size	>30 mm	956	68	1.68	1.28–2.21	<0.001
	≤30 mm	7,335	319	1	Reference	
Tumour location	Lower	3,811	221	1.60	1.30–1.97	<0.001
	Upper/middle	4,480	166	1	Reference	
Tumour	Undifferentiated	445	22	1.07	0.69–1.66	0.777
differentiation	Differentiated	7,846	365	1	Reference	
Tumour depth	SM2	528	32	1.35	0.93–1.96	0.118
	M/SM1	7,763	355	1	Reference	
Ulceration¶	Positive	771	40	1.13	0.81–1.58	0.473
	Negative	7,497	346	1	Reference	
ESD procedure	>120 min.	1,447	85	1.36	1.06–1.74	0.016
time¶	≤120 min.	6,821	300	1	Reference	
Resection type	Piecemeal	48	2	0.89	0.22–3.67	0.869
	En bloc	8,243	385	1	Reference	
Second-look	Yes	5,536	270	1.16	0.93–1.44	0.200
endoscopy	No	2,755	117	1	Reference	

¶ There were missing data (13 cases in endoscopic gastric atrophy, 3 cases in interruption of AT agents, 1 case in replacement of APAs, 23 cases in ulceration, and 23 cases in ESD procedure time).

ESD, endoscopic submucosal dissection; EGC, early gastric cancer; OR, odds ratio; CI, confidence interval; CKD, chronic kidney disease; P2Y12RA, P2Y12 receptor antagonist; DOAC, direct oral anticoagulant; AT, antithrombotic; APAs, antiplatelet agents; SM2, submucosal invasion ≥500 μm from the muscularis mucosa; M, confined to the mucosa; SM1, submucosal invasion <500 μm from the muscularis mucosa.

Supplementary table 3. Interaction for bleeding after ESD for EGC between two AT agents

	Aspirin	P2Y12RA	Cilostazol	Warfarin	DOAC
Aspirin	–	0.098	0.087	0.402	0.278
P2Y12RA		–	0.817	0.889	0.588
Cilostazol			–	0.087	0.745
Warfarin				–	–
DOAC					–

ESD, endoscopic submucosal dissection; EGC, early gastric cancer; AT antithrombotic; P2Y12RA, P2Y12 receptor antagonist; DOAC, direct oral anticoagulant.

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Supplementary table 4. Diagnostic accuracy of the prediction model at each cut-off point

Cut-off point	Sensitivity (%)	Specificity (%)	Accuracy (%)	Weighted accuracy (%)
1	85.0	36.3	38.5	60.6
2	54.8	77.1	76.1	65.9
3	38.0	89.7	87.3	63.8
4	26.4	95.1	91.9	60.7
5	15.5	98.2	94.3	56.9
6	8.8	99.4	95.2	54.1
7	3.1	99.8	95.3	51.5
8	1.3	99.9	95.3	50.6

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Supplementary table 5. The predictive model for bleeding after ESD for EGC by the combination of AC and CKD with haemodialysis

	Derivation cohort			Validation cohort		
Combination of risk factors	Patients (*n* = 8,291)	Bleeding (*n* = 387)	Rate of bleeding (%)	Patients (*n* = 2,029)	Bleeding (*n* = 102)	Rate of bleeding (%)
AC (–) and CKD (–)	7,740	284	3.7	1,870	69	3.7
AC (–) and CKD (+)	107	18	16.8	24	7	29.2
AC (+) and CKD (–)	422	74	17.5	133	26	19.5
AC (+) and CKD (+)	22	11	50.0	2	0	0.0
c-statistics (95% CI)		0.61 (0.57–0.64)			0.63 (0.57–0.69)	
Calibration-in-the-large		NA			0.05	
Calibration slope		NA			1.04	

ESD, endoscopic submucosa dissection; EGC, early gastric cancer; ACs, anticoagulants; CKD, chronic kidney disease; CI, confidence interval; NA, not applicable.

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Supplementary table 6. Time of interrupting/resuming AT agents in each agent in the derivation and validation cohorts

	Derivation cohort	Validation cohort	*p* value
Time of interrupting AT agents before ESD (day), median (P25–P75)			
Aspirin	5 (3–7)	5 (3–6)	0.003
P2Y12RA	7 (5–7)	6 (5–7)	0.605
Cilostazol	1.5 (1–3)	1 (1–5.5)	0.578
Warfarin	5 (3–5)	4 (3–5)	0.385
DOAC	1 (1–2)	1 (1–2)	0.050
Time of resuming AT agents after ESD (day), median (P25–P75)			
Aspirin	3 (2–5)	2 (1–4)	0.001
P2Y12RA	2 (2–5)	2 (1–7)	0.984
Cilostazol	3 (2–5)	2 (1–3)	0.014
Warfarin	2 (1–3)	1 (1–2)	0.051
DOAC	1 (1–2)	1 (1–2)	0.462
Duration of interrupting AT agents (day), median (P25–P75)			
Aspirin	8 (6–12)	7 (4–10)	<0.001
P2Y12RA	9 (7–14)	9.5 (7–14)	0.730
Cilostazol	5 (3–8)	3 (2–8)	0.136
Warfarin	7 (5–9)	6 (5–8)	0.095
DOAC	3 (3–4)	2 (2–4.5)	0.003

AT, antithrombotic; ESD, endoscopic submucosal dissection; P2Y12RA, P2Y12 receptor antagonist; DOAC, direct oral anticoagulant.

Supplementary table 7. Association between time of interrupting and resuming AT agents after ESD and bleeding in each agent

Agent	Time of interrupting AT agents (before ESD)	Adjusted OR¶	95% CI	*p* value	Time of resuming AT agents (after ESD)	Adjusted OR¶	95% CI	*p* value
Aspirin†								
	≥3 days	0.78	0.47–1.28	0.317	≥1 day	0.77	0.46–1.29	0.320
	≥4 days	0.59	0.33–1.04	0.069	≥2 days	0.75	0.44–1.27	0.288
	≥5 days	0.57	0.31–1.03	0.061	≥3 days	0.60	0.32–1.13	0.112
	≥6 days	0.39	0.18–0.86	0.020	≥4 days	0.75	0.39–1.44	0.387
P2Y12RA‡								
	≥4 days	0.79	0.35–1.79	0.571	≥1 day	0.89	0.40–1.99	0.784
	≥5 days	0.75	0.30–1.84	0.527	≥2 days	0.81	0.33–2.01	0.655
	≥6 days	0.75	0.29–1.92	0.549	≥3 days	1.08	0.42–2.76	0.874
	≥7 days	0.68	0.26–1.76	0.422	≥4 days	0.87	0.33–2.34	0.789
Cilostazol§								
	≥1 day	1.40	0.40–4.96	0.598	≥1 day	1.30	0.37–4.58	0.680
	≥2 days	1.10	0.27–4.45	0.892	≥2 days	1.19	0.32–4.36	0.799
	≥3 days	0.91	0.20–4.18	0.906	≥3 days	2.03	0.53–7.84	0.304
	≥4 days	1.06	0.20–5.63	0.950	≥4 days	1.27	0.27–6.03	0.768
Warfarin*								
	≥3 days	0.61	0.19–2.01	0.420	≥1 day	0.61	0.20–1.86	0.383
	≥4 days	0.61	0.18–2.02	0.419	≥2 days	0.60	0.18–2.00	0.408
	≥5 days	0.55	0.16–1.86	0.332	≥3 days	0.69	0.20–2.45	0.570
	≥6 days	0.31	0.07–1.34	0.117	≥4 days	0.77	0.21–2.85	0.699
DOAC**								
	≥1 day	1.63	0.36–7.33	0.525	≥1 day	0.77	0.30–1.96	0.578
	≥2 days	1.61	0.37–7.03	0.527	≥2 days	0.97	0.23–4.16	0.965
	≥3 days	1.09	0.19–6.26	0.924	≥3 days	0.48	0.08–2.88	0.419
	≥4 days	0.54	0.05–6.41	0.622	≥4 days	0.95	0.15–6.20	0.958

¶ Adjusted by all variables in table 2 except a variable of interruption of AT agents, interruption of AT agent other than the evaluated agent, and time of interrupting/resuming AT agents smaller than the assessed days (e.g., when the variable of ≥3 days of interruption of warfarin before ESD was assessed, the variable of ≤2 days of interruption

of warfarin before ESD was also included in the multivariate model).

† Twenty-four and 41 cases were excluded from the analyses of time of interrupting and resuming aspirin, respectively, due to the missing data.

‡ Seven and 13 cases were excluded from the analyses of time of interrupting and resuming P2Y12RA, respectively, due to the missing data.

§ Ten and 13 cases were excluded from the analyses of time of interrupting and resuming cilostazol, respectively, due to the missing data.

* One and 2 cases were excluded from the analyses of time of interrupting and resuming warfarin, respectively, due to the missing data.

** One and 12 cases were excluded from the analyses of time of interrupting and resuming DOAC, respectively, due to the missing data.

AT, antithrombotic; ESD, endoscopic submucosal dissection; OR, odds ratio; CI, confidence interval; P2Y12RA, P2Y12 receptor antagonist; DOAC, direct oral anticoagulant.

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Supplementary table 8. The rate of bleeding after ESD for EGC in patients with and without SLE in the whole cohort

Risk category	SLE	Patients (n =10,319)	Bleeding (n =489)	Rate of bleeding (%)	p value
Low-risk	Yes	5,403	144	2.7	0.329
	No	2,345	72	3.1	
Intermediate-risk	Yes	1,003	57	5.7	0.891
	No	324	19	5.9	
High-risk	Yes	766	99	12.9	0.240
	No	218	21	9.6	
Very high-risk	Yes	210	61	29.0	0.601
	No	48	16	33.3	

ESD, endoscopic submucosal dissection; EGC, early gastric cancer; SLE, second-look endoscopy.

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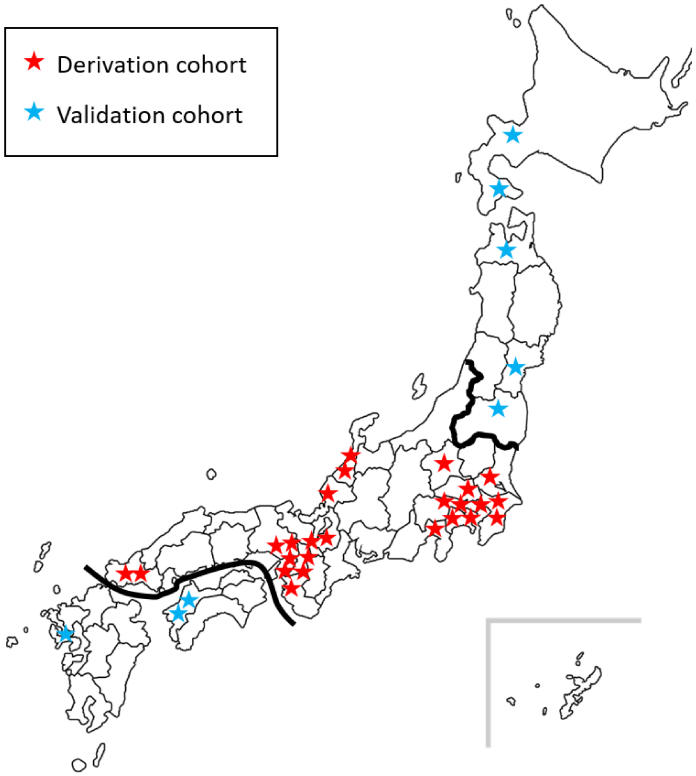
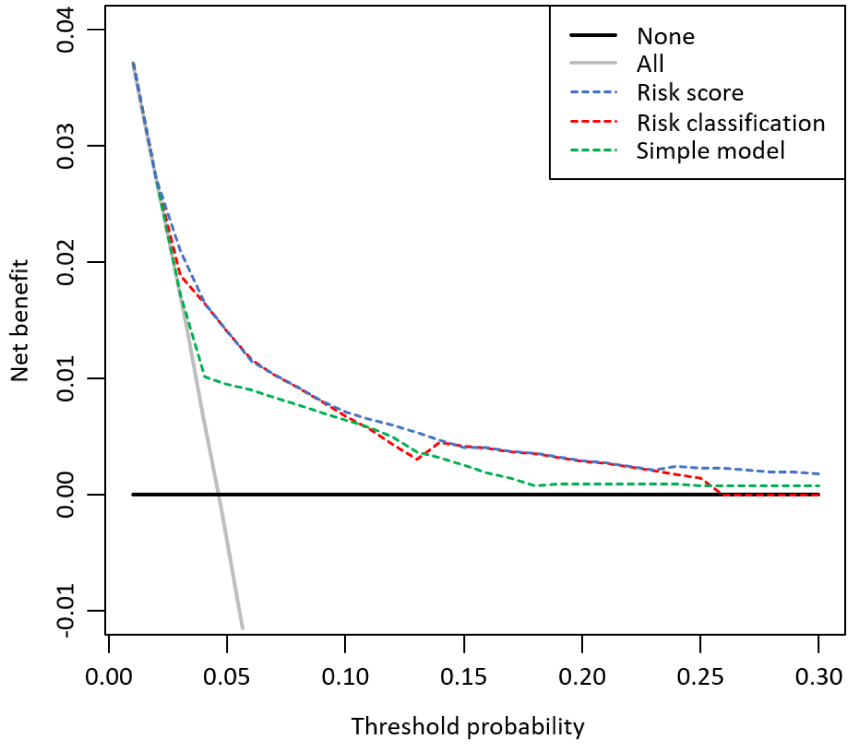


Supplementary figure 1. The distribution of patients in the derivation and validation cohorts with respect to the institutions from which they were derived.



Supplementary figure 2. Decision curve analysis for net benefits of the prediction model.¶

Use of the risk score for predicting bleeding after ESD achieved the highest net benefit. The net benefit of the risk classification was higher than that of the simple model consisting of ACs and CKD with haemodialysis for most threshold probabilities.

¶ Threshold probabilities that achieve a net benefit greater than the "All" and "None" curves identify the segment of threshold probabilities where the model provides clinical utility, and at any given threshold, the model with the higher net benefit is the preferred model.

ESD, endoscopic submucosal dissection; ACs, anticoagulants; CKD, chronic kidney

disease.

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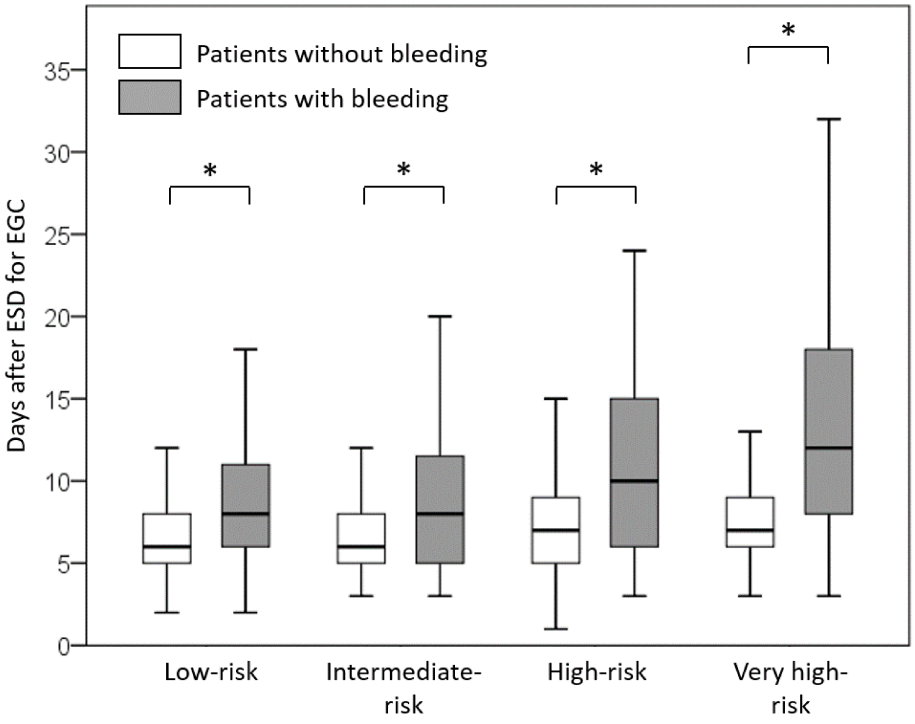

Supplementary figure 3. The period of hospital stay after ESD for EGC for the four risk categories in the whole cohort.

The differences of the periods of hospital stay between patients with and without bleeding after ESD for EGC were significant in all risk categories (p <0.001).

* p <0.001

ESD, endoscopic submucosal dissection; EGC, early gastric cancer.