TABLE 1. Univariate Analysis for 30-Day Mortality of Right Hemicolectomy

	US/NSQIP (N = 15,863) (Died = 299, Died [%] = 1.88%)			Japan/NCD (N = 34,638) (Died = 264, Died [%] = 0.76%)		
	Total (N [%])	Died (n [%])	*P*	Total (N [%])	Died (n [%])	*P*
Age			<0.001			<0.001
<60	3903 (24.6)	14 (0.4)		3756 (10.8)	13 (0.3)	
60–70	4242 (26.7)	50 (1.2)		8453 (24.4)	33 (0.4)	
70–80	4408 (27.8)	86 (2.0)		12825 (37.0)	73 (0.6)	
80–90	2851(18.0)	114 (4.0)		8616 (24.9)	110 (1.3)	
≥90	459 (2.9)	35 (7.6)		988 (2.9)	35 (3.5)	
Sex			0.113			0.108
Men	7398 (46.6)	153 (2.1)		17596 (50.8)	121 (0.7)	
Women	8465 (53.4)	146 (1.7)		17042 (49.2)	143 (0.8)	
Diabetes			0.015			0.73
Insulin	999 (6.3)	29 (2.9)		1171 (3.4)	10 (0.9)	
Noninsulin	14864 (93.7)	270 (1.8)		33467 (96.6)	254 (0.8)	
COPD			<0.001			<0.001
No	14823 (93.4)	258 (1.7)		33618 (97.1)	244 (0.7)	
Yes	1040 (6.6)	41 (3.9)		1020 (2.9)	20 (2.0)	
Hypertension			<0.001			0.041
No	6371 (40.2)	85 (1.3)		21706 (62.7)	149 (0.7)	
Yes	9492 (59.8)	214 (2.3)		12932 (37.3)	115 (0.9)	
Congestive heart failure			<0.001			<0.001
No	15676 (98.8)	281 (1.8)		34147 (98.6)	241 (0.7)	
Yes	187 (1.2)	18 (9.6)		491 (1.4)	23 (4.7)	
Bleeding disorder			<0.001			<0.001
No	15207 (95.9)	260 (1.7)		33282 (96.1)	228 (0.7)	
Yes	656 (4.1)	39 (6.0)		1356 (3.9)	36 (2.7)	
Emergency status			<0.001			<0.001
No	15153 (95.5)	247 (1.6)		33027 (95.3)	201 (0.6)	
Yes	710 (4.5)	52 (7.3)		1611 (4.7)	63 (3.9)	
Functional status			<0.001			<0.001
Independent	15299 (96.4)	247 (1.6)		31345 (90.5)	138 (0.4)	
Partially dependent	489 (3.1)	41 (8.4)		2536 (7.3)	78 (3.1)	
Totally dependent	75 (0.5)	11 (14.7)		757 (2.2)	48 (6.3)	
ASA class			<0.001			<0.001
1-No disturb	333 (2.1)	0 (0.0)		10660 (30.8)	24 (0.2)	
2-Mild disturb	6205 (39.1)	26 (0.4)		19454 (56.2)	104 (0.5)	
3-Severe disturb	8349 (52.6)	191 (2.3)		4278 (12.4)	107 (2.5)	
4-Life threat	965 (6.1)	78 (8.1)		189 (0.5)	21 (11.1)	
5-Moribund	11 (0.1)	4 (36.4)		57 (0.2)	8 (14.0)	
Dyspnea			<0.001			<0.001
None	14030 (88.4)	231 (1.7)		33707 (97.3)	225 (0.7)	
Moderate	1691 (10.7)	55 (3.3)		789 (2.3)	25 (3.2)	
At rest	142 (0.9)	13 (9.2)		142 (0.4)	14 (9.9)	
Sepsis			<0.001			<0.001
None	15371 (96.9)	251 (1.6)		34323 (99.1)	222 (0.6)	
SIRS/sepsis/septic shock	492 (3.1)	48 (9.8)		315 (0.9)	42 (13.3)	
Weight loss			<0.001			<0.001
No	15129 (95.4)	259 (1.7)		32654 (94.3)	219 (0.7)	
Yes	734 (4.6)	40 (5.5)		1984 (5.7)	45 (2.3)	
Disseminated cancer			<0.001			<0.001
No	14770 (93.1)	235 (1.6)		32539 (93.9)	200 (0.6)	
Yes	1093 (6.9)	64 (5.9)		2099 (6.1)	64 (3.0)	
BMI			<0.001			<0.001
Underweight	390 (2.5)	20 (5.1)		5294 (15.3)	69 (1.3)	
Normal	4718 (29.7)	115 (2.4)		22845 (66.0)	156 (0.7)	
Overweight	5465 (34.5)	85 (1.6)		5640 (16.3)	32 (0.6)	
Obese 1	3077 (19.4)	49 (1.6)		688 (2.0)	5 (0.7)	
Obese 2/3	2213 (13.9)	30 (1.4)		170 (0.5)	2 (1.2)	

	US/NSQIP (N = 15,863) (Died = 299, Died [%] = 1.88%)			Japan/NCD (N = 34,638) (Died = 264, Died [%] = 0.76%)		
	Total (N [%])	**Died (n [%])**	***P***	**Total (N [%])**	**Died (n [%])**	***P***
Steroid			<0.001			0.006
No	15432 (97.3)	281 (1.8)		34276 (99.0)	256 (0.7)	
Yes	431 (2.7)	18 (4.2)		362 (1.0)	8 (2.2)	
Surgical approach			<0.001			<0.001
Lap	9031 (56.9)	82 (0.9)		12664 (36.6)	39 (0.3)	
Open	6832 (43.1)	217 (4.0)		21974 (63.4)	225 (1.0)	
Albumin (g/dL)			<0.001			<0.001
≥3.5	7994 (50.4)	80 (1.0)		23102 (66.7)	69 (0.3)	
2.8–3.5	2095 (13.2)	89 (4.3)		6831 (19.7)	78 (1.1)	
≤2.8	769 (4.9)	76 (9.9)		2824 (8.2)	103 (3.6)	
Missing	5005 (31.5)	54 (1.1)		1881 (5.4)	14 (0.7)	
PT-INR			<0.001			<0.001
≤1.25	7520 (47.4)	163 (2.2)		30576 (88.3)	169 (0.6)	
>1.25	804 (5.1)	52 (6.5)		1474 (4.3)	61 (4.1)	
Missing	7539 (47.5)	84 (1.1)		2588 (7.5)	34 (1.3)	
Chronic kidney stage			<0.001			<0.001
Stage 1 (GFR ≥90)	3928 (24.8)	77 (2.0)		3100 (8.9)	27 (0.9)	
Stage 2 (GFR 60–89)	7598 (47.9)	104 (1.4)		13287 (38.4)	64 (0.5)	
Stage 3 (GFR 30–59)	3017 (19.0)	85 (2.8)		15661 (45.2)	120 (0.8)	
Stage 4 (GFR 15–29)	244 (1.5)	16 (6.6)		1229 (3.5)	29 (2.4)	
Stage 5 (GFR ≤15 or dialysis)	145 (0.9)	12 (8.3)		499 (1.4)	14 (2.8)	
Missing	931 (5.9)	5 (0.5)		862 (2.5)	10 (1.2)	
Platelets (×1000/μL)			<0.001			<0.001
>120	14743 (92.9)	269 (1.8)		30332 (87.6)	165 (0.5)	
≤120	361 (2.3)	25 (6.9)		3843 (11.1)	95 (2.5)	
Missing	759 (4.8)	5 (0.7)		463 (1.3)	4 (0.9)	
Total bilirubin (mg/dL)			<0.001			<0.001
≤2.0	10847(68.4)	241 (2.2)		33607 (97.0)	248 (0.7)	
>2.0	107 (0.7)	6 (5.6)		281 (0.8)	11 (3.9)	
Missing	4909 (30.9)	52 (1.1)		750 (2.2)	5 (0.7)	
AST (U/L)			<0.001			<0.001
≤100	10762(67.9)	242 (2.3)		33914 (97.9)	236 (0.7)	
>100	82 (0.5)	4 (4.9)		212 (0.6)	24 (11.3)	
Missing	5019 (31.6)	53 (1.1)		512 (1.5)	4 (0.8)	
WBC (×1000/μL)			<0.001			<0.001
≥3.5 to ≤9.0	11818 (74.5)	171 (1.5)		28358 (81.8)	144 (0.5)	
<3.5 or >9.0	3289 (20.7)	121 (3.7)		5530 (16.0)	115 (2.1)	
Missing	756 (4.8)	7 (0.9)		750 (2.2)	5 (0.7)	
		Median (IQR)			**Median (IQR)**	
Length of stay (d)						
Total		5 (4–7)			14 (10–20)	
Survived		5 (4–7)			14 (10–20)	
Died		8 (5–13)			15 (6.25–22)	

Data are expressed as mean ± standard deviation or frequency(%).

T test/Wilcoxon Mann–Whitney test applied for continuous variables and chi-square/Fisher exact test applied for categorical variables.

ASA = American Society of Anesthesiologists, AST = aspartate aminotransferase, BMI = body mass index, COPD = chronic obstructive pulmonary disease, GFR = glomerular filtration rate, IQR = interquartile range, NCD = National Clinical Database, NSQIP = National Surgical Quality Improvement Program, PT-INR = prothrombin time–international normalized ratio, SIRS = systemic inflammatory response syndrome, WBC = white blood cell.

More than 2000 hospitals performing gastrointestinal (GI) tract surgery joined NCD, and 95% of surgical cases (949,824 cases in 2011 and 2012) were collected in this database, making NCD a nationally representative sample.[15] Meanwhile, data submitted to ACS-NSQIP from participating hospitals include a considerable proportion of cases (442,149 cases from 315 sites in 2011) sufficient to provide benchmark support to individual hospitals. We identified a number of differences in risk factor prevalence between datasets. Mortality rates reported in this study differed slightly, with lower unadjusted mortality rates for all 3 procedures in Japan than in US. The duration of hospital stay also differed, being longer in Japan compared to the US for all 3 procedures. The Japanese patients were older and had a higher prevalence of CKD. In contrast, US patients were younger and substantially more obese.

TABLE 2. Univariate Analysis for 30-Day Mortality of Low Anterior Resection

	US/NSQIP (N = 7325) (Died = 79, Died [%] = 1.08%)			Japan/NCD (N = 35,445) (Died = 154, Died [%] = 0.43%)		
	Total (N [%])	Died (n [%])	*P*	Total (N [%])	Died (n [%])	*P*
Age			<0.001			<0.001
<60	3172 (43.3)	10 (0.3)		8329 (23.5)	9 (0.1)	
60–70	1944 (26.6)	19 (1.0)		12300 (34.7)	38 (0.3)	
70–80	1409 (19.2)	25 (1.8)		10541 (29.8)	59 (0.6)	
80–90	720 (9.8)	22 (3.1)		4010 (11.3)	40 (1.0)	
≥90	80 (1.1)	3 (3.8)		265 (0.7)	8 (3.0)	
Sex			0.030			0.015
Men	4126 (56.3)	54 (1.3)		23140 (65.3)	115 (0.5)	
Women	3199 (43.7)	25 (0.8)		12305 (34.7)	39 (0.3)	
Diabetes			0.395			0.109
Insulin	321 (4.4)	5 (1.6)		1194 (3.4)	9 (0.8)	
Noninsulin	7004 (95.6)	74 (1.1)		34251 (96.6)	145 (0.4)	
COPD			<0.001			0.008
No	6994 (95.5)	66 (0.9)		34512 (97.4)	144 (0.4)	
Yes	331 (4.5)	13 (3.9)		933 (2.6)	10 (1.1)	
Hypertension			<0.001			<0.001
No	3775 (51.5)	24 (0.6)		24061 (67.9)	78 (0.3)	
Yes	3550 (48.5)	55 (1.6)		11384 (32.1)	76 (0.7)	
Congestive heart failure			<0.001			0.001
No	7282 (99.4)	75 (1.0)		35190 (99.3)	148 (0.4)	
Yes	43 (0.6)	4 (9.3)		255 (0.7)	6 (2.4)	
Bleeding disorder			<0.001			<0.001
No	7123 (97.2)	70 (1.0)		34441 (97.2)	139 (0.4)	
Yes	202 (2.8)	9 (4.5)		1004 (2.8)	15 (1.5)	
Emergency status			<0.001			0.006
No	7216 (98.5)	72 (1.0)		35077 (99.0)	148 (0.4)	
Yes	109 (1.5)	7 (6.4)		368 (1.0)	6 (1.6)	
Functional status			<0.001			<0.001
Independent	7200 (98.3)	69 (1.0)		33982 (95.9)	124 (0.4)	
Partially dependent	111 (1.5)	9 (8.1)		1242 (3.5)	20 (1.6)	
Totally dependent	14 (0.2)	1 (7.1)		221 (0.6)	10 (4.5)	
ASA class			<0.001			<0.001
1-No disturb	201 (2.7)	0 (0.0)		14205 (40.1)	21 (0.1)	
2-Mild disturb	3402 (46.4)	15 (0.4)		18307 (51.6)	86 (0.5)	
3-Severe disturb	3471 (47.4)	50 (1.4)		2848 (8.0)	42 (1.5)	
4-Life threat	250 (3.4)	14 (5.6)		58 (0.2)	5 (8.6)	
5-Moribund	1 (0.1)	0 (0.0)		27 (0.1)	0 (0.0)	
Dyspnea			<0.001			<0.001
None	6799 (92.8)	62 (0.9)		34909 (98.5)	145 (0.4)	
Moderate	487 (6.7)	11 (2.3)		464 (1.3)	7 (1.5)	
At rest	39 (0.5)	6 (15.4)		72 (0.2)	2 (2.8)	
Sepsis			<0.001			<0.001
None	7232 (98.7)	71 (1.0)		35356 (99.7)	149 (0.4)	
SIRS/sepsis/septic shock	93 (1.3)	8 (8.6)		89 (0.3)	5 (5.6)	
Weight loss			<0.001			<0.001
No	6996 (95.5)	65 (0.9)		34254 (96.6)	137 (0.4)	
Yes	329 (4.5)	14 (4.3)		1191 (3.4)	17 (1.4)	
Disseminated cancer			<0.001			<0.001
No	6690 (91.3)	61 (0.9)		33895 (95.6)	131 (0.4)	
Yes	635 (8.7)	18 (2.8)		1550 (4.4)	23 (1.5)	
BMI			0.849			0.005
Underweight	161 (2.2)	2 (1.2)		4223 (11.9)	29 (0.7)	
Normal	2266 (31.0)	28 (1.2)		23889 (67.4)	94 (0.4)	
Overweight	2520 (34.4)	26 (1.0)		6433 (18.2)	22 (0.3)	
Obese 1	1479 (20.2)	16 (1.1)		755 (2.1)	9 (1.2)	
Obese 2/3	899 (12.2)	7 (0.8)		145 (0.4)	0 (0.0)	

	US/NSQIP (N = 7325) (Died = 79, Died [%] = 1.08%)			Japan/NCD (N = 35,445) (Died = 154, Died [%] = 0.43%)		
	Total (N [%])	**Died (n [%])**	***P***	**Total (N [%])**	**Died (n [%])**	***P***
Steroid			0.231			0.019
No	7171 (97.9)	76 (1.1)		35214 (99.3)	150 (0.4)	
Yes	154 (2.1)	3 (2.0)		231 (0.7)	4 (1.7)	
Surgical approach			0.007			<0.001
Lap	3238 (44.2)	23 (0.7)		15208 (42.9)	42 (0.3)	
Open	4087 (55.8)	56 (1.4)		20237 (57.1)	112 (0.6)	
Albumin			<0.001			<0.001
≥3.5	4437 (60.6)	28 (0.6)		28807 (81.3)	91 (0.3)	
2.8–3.5	631 (8.6)	15 (2.4)		3804 (10.7)	45 (1.2)	
≤2.8	190 (2.6)	16 (8.4)		946 (2.7)	13 (1.4)	
Missing	2067 (28.2)	20 (1.0)		1888 (5.3)	5 (0.3)	
INR			<0.001			<0.001
≤1.25	3704 (50.6)	42 (1.1)		32069 (90.5)	122 (0.4)	
>1.25	167 (2.3)	10 (6.0)		872 (2.5)	18 (2.1)	
Missing	3454 (47.1)	27 (0.8)		2504 (7.0)	14 (0.6)	
Chronic kidney stage			0.002			<0.001
Stage 1 (GFR ≥90)	2441 (33.3)	26 (1.1)		2808 (7.9)	11 (0.4)	
Stage 2 (GFR 60–89)	3575 (48.8)	31 (0.9)		13958 (39.4)	35 (0.3)	
Stage 3 (GFR 30–59)	893 (12.2)	20 (2.2)		16678 (47.1)	87 (0.5)	
Stage 4 (GFR 15–29)	49 (0.7)	2 (4.1)		815 (2.3)	16 (2.0)	
Stage 5 (GFR <15 or dialysis)	36 (0.5)	0 (0.0)		334 (0.9)	4 (1.2)	
Missing	331 (4.5)	0 (0.0)		852 (2.4)	1 (0.1)	
Platelets (× 1000/μL)			0.160			<0.001
>120	6879 (93.9)	77 (1.1)		31408 (88.6)	112 (0.4)	
≤120	172 (2.4)	2 (1.2)		3599 (10.2)	41 (1.1)	
Missing	274 (3.7)	0 (0.0)		438 (1.2)	1 (0.2)	
Total bilirubin (mg/dL)			0.776			0.603
≤2.0	5290 (72.2)	58 (1.1)		34445 (97.2)	150 (0.4)	
>2.0	50 (0.7)	1 (2.0)		271 (0.8)	2 (0.7)	
Missing	1985 (27.1)	20 (1.0)		729 (2.0)	2 (0.3)	
AST (U/L)			0.463			0.188
≤100	5193 (70.9)	59 (1.1)		34811 (98.2)	151 (0.4)	
>100	39 (0.5)	1 (2.7)		151 (0.4)	2 (1.3)	
Missing	2093 (28.6)	19 (0.9)		483 (1.4)	1 (0.2)	
WBC (× 1000/μL)			0.004			0.003
≥3.5 to ≤9.0	5890 (80.4)	55 (0.9)		30481 (86.0)	120 (0.4)	
<3.5 or >9.0	1167 (15.9)	23 (2.0)		4235 (11.9)	32 (0.8)	
Missing	268 (3.7)	1 (0.4)		729 (2.1)	2 (0.3)	
		Median (IQR)				**Median (IQR)**
Length of stay						
Total		6 (4–8)				16 (12–25)
Survived		6 (4–8)				16 (12–25)
Died		6 (4–10)				10 (6–20)

Data are expressed as mean ± standard deviation or frequency (%).

T test/Wilcoxon Mann–Whitney test applied for continuous variables and chi-square/Fisher exact test applied for categorical variables.

ASA = American Society of Anesthesiologists, AST = aspartate aminotransferase, BMI = body mass index, COPD = chronic obstructive pulmonary disease, GFR = glomerular filtration rate, IQR = interquartile range, NCD = National Clinical Database, NSQIP = National Surgical Quality Improvement Program, PT-INR = prothrombin time–international normalized ratio, SIRS = systemic inflammatory response syndrome, WBC = white blood cell.

The NCD and ACS-NSQIP data have been used in prediction tools to facilitate risk stratification before surgery in a procedure-targeted manner.[16–24] More specifically, the ACS-NSQIP risk calculator works by utilizing information regarding the patient's risk factors related to the planned surgical procedure. The calculator then provides a predicted risk of complications after surgery.[25] However, the ability of risk models created using nationwide databases to predict the surgical risk for patients undergoing the same procedure in other countries has yet to be evaluated. In this study, we used the NCD and NSQIP databases to develop independent 30-day mortality risk models, and identified significant variables

TABLE 3. Univariate Analysis for 30-Day Mortality of Pancreaticoduodenectomy

	US/NSQIP (N = 5182) (Died = 133, Died [%] = 2.57%)			Japan/NCD (N = 15,527) (Died = 210, Died [%] = 1.35%)		
	Total (N [%])	Died (n [%])	*P*	Total (N [%])	Died (n [%])	*P*
Age			<0.001			<0.001
<60	1466 (28.3)	17 (1.2)		2186 (14.0)	14 (0.6)	
60–70	1732 (33.4)	44 (2.5)		5181 (33.4)	62 (1.2)	
70–80	1456 (28.1)	50 (3.4)		6394 (41.2)	99 (1.6)	
80–90	508 (9.8)	19 (3.7)		1755 (11.3)	35 (2.0)	
≥90	20 (0.4)	3 (15.0)		11 (0.1)	0 (0.0)	
Sex			0.029			0.004
Male	2749 (53.1)	83 (3.0)		9604 (61.8)	150 (1.6)	
Female	2433 (46.5)	50 (2.1)		5923 (38.2)	60 (1.0)	
Diabetes			0.842			0.425
Insulin	613 (11.8)	15 (2.5)		1637 (10.5)	18 (1.1)	
Noninsulin	4569 (88.2)	118 (2.6)		13890 (89.5)	192 (1.4)	
COPD			<0.001			0.028
No	4935 (95.2)	117 (2.4)		15115 (97.3)	199 (1.3)	
Yes	247 (4.8)	16 (6.5)		412 (2.7)	11 (2.7)	
Hypertension			<0.001			0.028
No	2314 (44.6)	34 (1.5)		10009 (64.5)	199 (2.0)	
Yes	2868 (55.4)	99 (3.5)		5518 (35.5)	11 (0.2)	
Congestive heart failure			1.000			0.058
No	5174 (99.8)	133 (2.6)		15462 (99.6)	207 (1.3)	
Yes	8 (0.2)	0 (0.0)		65 (0.4)	3 (4.6)	
Bleeding disorder			0.415			0.001
No	5040 (97.3)	128 (2.5)		15044 (96.9)	194 (1.3)	
Yes	142 (2.7)	5 (3.5)		483 (3.1)	16 (3.3)	
Emergency status			0.577			0.002
No	5149 (99.4)	132 (2.6)		15429 (99.4)	204 (1.3)	
Yes	33 (0.6)	1 (3.0)		98 (0.6)	6 (6.1)	
Functional status			0.304			<0.001
Independent	5118 (98.8)	130 (2.5)		15007 (96.7)	189 (1.3)	
Partially dependent	58 (1.1)	3 (5.2)		472 (3.0)	18 (3.8)	
Totally dependent	6 (0.1)	0 (0.0)		48 (0.3)	3 (6.3)	
ASA class			<0.001			<0.001
1-No disturb	37 (0.7)	0 (0.0)		4696 (30.2)	35 (0.8)	
2-Mild disturb	1341 (25.9)	15 (1.1)		9368 (60.3)	136 (1.5)	
3-Severe disturb	3502 (67.5)	100 (2.9)		1421 (9.2)	35 (2.5)	
4-Life threat	300 (5.8)	18 (6.0)		28 (0.2)	3 (10.7)	
5-Moribund	2 (0.1)	0 (0.0)		14 (0.1)	1 (7.1)	
Dyspnea			<0.001			<0.001
None	4794 (92.5)	110 (2.3)		15349 (98.8)	202 (1.3)	
Moderate	377 (7.3)	20 (5.3)		165 (1.1)	8 (4.9)	
At rest	11 (0.2)	3 (27.3)		13 (0.1)	0 (0.0)	
Sepsis			0.297			0.043
None	5091 (98.2)	129 (2.5)		15452 (99.5)	208 (1.4)	
SIRS/sepsis/septic shock	91 (1.8)	4 (4.4)		75 (0.5)	2 (2.7)	
Weight loss			0.960			0.105
No	4333 (83.6)	111 (2.6)		14422 (92.9)	189 (1.3)	
Yes	849 (16.4)	22 (2.6)		1105 (7.1)	21 (1.9)	
Disseminated cancer			0.014			0.294
No	5021 (96.9)	124 (2.5)		15455 (99.5)	208 (1.4)	
Yes	161 (3.1)	9 (5.6)		72 (0.5)	2 (2.8)	
BMI			0.016			<0.001
Underweight	140 (2.7)	5 (3.6)		2293 (14.8)	21 (0.9)	
Normal	1864 (36.0)	39 (2.1)		10938 (70.4)	137 (1.3)	
Overweight	1842 (35.5)	39 (2.1)		2068 (13.3)	47 (2.3)	
Obese 1	850 (16.4)	29 (3.4)		187 (1.2)	3 (1.6)	
Obese 2/3	486 (9.4)	21 (4.3)		41 (0.3)	3 (7.3)	

	US/NSQIP (N = 5182) (Died = 133, Died [%] = 2.57%)			Japan/NCD (N = 15,527) (Died = 210, Died [%] = 1.35%)		
	Total (N [%])	**Died (n [%])**	***P***	**Total (N [%])**	**Died (n [%])**	***P***
Steroid			0.237			0.323
No	5062 (97.7)	128 (2.5)		15350 (98.9)	208 (1.4)	
Yes	120 (2.3)	5 (4.2)		177 (1.1)	2 (1.1)	
Surgical complexity			0.009			0.020
PD alone	4444 (85.8)	104 (2.3)		12975 (83.6)	161 (1.2)	
With adjacent organ	240 (4.6)	13 (5.4)		623 (4.0)	14 (2.3)	
Vascular ± other organ	498 (9.6)	16 (3.2)		1929 (12.4)	35 (1.8)	
Albumin			0.003			0.012
≥3.5	3303 (63.7)	69 (2.1)		10963 (70.6)	129 (1.2)	
2.8–3.5	1030 (19.9)	34 (3.3)		3391 (21.8)	55 (1.6)	
≤2.8	414 (8.0)	20 (4.8)		706 (4.6)	16 (2.3)	
Missing	435 (8.4)	10 (2.3)		467 (3.0)	10 (2.1)	
INR			0.004			<0.001
≤1.25	4277 (82.5)	99 (2.3)		14086 (90.7)	175 (1.2)	
>1.25	272 (5.3)	15 (5.5)		627 (4.0)	21 (3.4)	
Missing	633 (12.2)	19 (3.0)		814 (5.3)	14 (1.7)	
Chronic kidney stage			0.002			<0.001
Stage 1 (GFR ≥90)	2139 (41.3)	39 (1.8)		1627 (10.5)	13 (0.8)	
Stage 2 (GFR 60–89)	2255 (43.5)	62 (2.8)		6857 (44.1)	69 (1.0)	
Stage 3 (GFR 30–59)	641 (12.4)	24 (3.7)		6382 (41.1)	110 (1.7)	
Stage 4 (GFR 15–29)	30 (0.6)	2 (6.7)		281 (1.8)	6 (2.1)	
Stage 5 (GFR <15 or dialysis)	25 (0.5)	3 (12.0)		149 (1.0)	7 (4.7)	
Missing	92 (1.8)	3 (3.3)		231 (1.5)	5 (2.2)	
Platelets (× 1000/μL)			0.045			<0.001
>120	4982 (96.1)	123 (2.5)		9602 (61.8)	73 (0.8)	
≤120	104 (2.0)	6 (5.8)		5795 (37.3)	134 (2.3)	
Missing	96 (1.9)	4 (4.2)		130 (0.9)	3 (2.3)	
Total bilirubin (mg/dL)			0.576			0.156
≤2.0	3482 (67.2)	86 (2.5)		11578 (74.5)	147 (1.3)	
>2.0	1211 (23.4)	31 (2.6)		3800 (24.5)	59 (1.6)	
Missing	489 (9.4)	16 (3.3)		149 (1.0)	4 (2.7)	
AST (U/L)			0.260			0.612
≤100	3993 (77.1)	97 (2.4)		13510 (87.0)	183 (1.4)	
>100	757 (14.6)	26 (3.4)		1887 (12.2)	24 (1.3)	
Missing	432 (8.3)	10 (2.3)		130 (0.8)	3 (2.3)	
WBC (× 1000/μL)			0.169			0.303
≥3.5 to ≤9.0	3966 (76.5)	96 (2.4)		13434 (86.5)	177 (1.3)	
<3.5 or >9.0	1122 (21.7)	32 (2.9)		1944 (12.5)	29 (1.5)	
Missing	94 (1.8)	5 (5.3)		149 (1.0)	4 (2.7)	
		Median (IQR)				**Median (IQR)**
Length of stay						
Total		9 (7–14)				31 (22–43)
Survived		9 (7–14)				31 (22–43)
Died		11 (6–17)				15 (7–24)

Data are expressed as mean ± standard deviation or frequency (%).

T test/Wilcoxon Mann–Whitney test applied for continuous variables and chi-square/Fisher exact test applied for categorical variables.

ASA = American Society of Anesthesiologists, AST = aspartate aminotransferase, BMI = body mass index, COPD = chronic obstructive pulmonary disease, GFR = glomerular filtration rate, INR = international normalized ratio, IQR = interquartile range, NCD = National Clinical Database, NSQIP = National Surgical Quality Improvement Program, PD = pancreaticoduodenectomy, SIRS = systemic inflammatory response syndrome, WBC = white blood cell.

from both datasets to create NCD/ACS-NSQIP risk models using a common set of variables. For the purpose of estimating risk, the 2 models based on the 2 country's own dataset were able to adequately predict mortality with a good c-index and similar ORs observed for each variable (Table 4).

We found that discrimination decreased when we ran each risk model using the other country's data. When we focused on a measure of calibration (the Hosmer–Lemeshow plot), we found that both NCD and ACS-NSQIP models accurately predicted the number of deaths in their respective datasets. However, calibration diminished when data from the other country were

TABLE 4. Risk Models of Preoperative Factors for 30-Day Mortality Rates After RH, LAR, and PD

	US/NSQIP			Japan/NCD		
		95% CI			95% CI	
RH Variables	**Odds Ratio**	**Lower CI**	**Upper CI**	**Odds Ratio**	**Lower CI**	**Upper CI**
Age 60–70	3.641	1.984	6.682	1.068	0.563	2.147
Age 70–80	5.427	3.028	9.726	1.426	0.796	2.761
Age ≥80	10.473	5.890	18.623	2.23	1.249	4.309
Sex (male)	1.615	1.267	2.059	1.332	1.006	1.766
Bleeding disorder (yes)	1.826	1.249	2.668	1.721	1.134	2.534
Emergency status (yes)	1.653	1.146	2.384	1.873	1.304	2.644
Functional status (partially dependent)	1.923	1.317	2.810	2.767	1.994	3.815
Functional status (totally dependent)	3.429	1.644	7.153	4.241	2.83	6.263
Dyspnea at rest	2.697	1.414	5.144	2.519	1.22	4.844
Dyspnea moderate exertion	1.404	1.026	1.923	1.485	0.909	2.327
Sepsis (yes)	2.113	1.424	3.135	2.899	1.829	4.524
Weight loss (yes)	1.678	1.149	2.451	1.244	0.854	1.774
Disseminated cancer (yes)	3.045	2.233	4.151	3.385	2.452	4.616
Albumin (g/dL) 2.8–3.5	2.315	1.674	3.200	2.022	1.432	2.856
Albumin (g/dL) ≤2.8	3.991	2.777	5.736	3.447	2.385	4.989
Albumin (g/dL) missing	1.162	0.808	1.670	1.571	0.767	2.943
CKD missing	0.617	0.225	1.691	4.115	1.69	8.835
CKD stage 3	1.242	0.940	1.642	1.352	0.994	1.845
CKD stage 4/5	2.699	1.730	4.211	2.123	1.383	3.21
WBC (×1000/μL) <3.5 or >9.0	1.572	1.210	2.043	1.885	1.423	2.487
WBC (×1000/μL) missing	1.490	0.628	3.534	0.475	0.133	1.422
C-statistic	0.840			0.857		
Hosmer–Lemeshow chi-square	5.866 ($P=0.662$)			11.243 ($P=0.188$)		

	US/NSQIP			Japan/NCD		
		95% CI			95% CI	
LAR Variables	**Odds Ratio**	**Lower CI**	**Upper CI**	**Odds Ratio**	**Lower CI**	**Upper CI**
Age 60–70	2.833	1.299	6.180	2.725	1.372	6.033
Age 70–80	4.976	2.332	10.619	4.584	2.372	9.984
Age ≥80	7.220	3.265	15.967	7.988	4.009	17.757
Sex (male)	1.880	1.140	3.100	1.742	1.212	2.558
Bleeding disorder (yes)	2.250	1.028	4.925	1.987	1.091	3.366
Emergency status (yes)	2.433	0.924	6.403	1.768	0.608	4.227
Functional status (partially dependent)	1.931	0.810	4.603	1.91	1.111	3.132
Functional status (totally dependent)	5.118	0.608	43.110	3.798	1.734	7.534
Dyspnea at rest	5.606	1.816	17.307	2.21	0.346	7.743
Dyspnea moderate exertion	1.370	0.688	2.728	1.1	0.446	2.313
Sepsis (yes)	2.020	0.765	5.333	3.79	1.132	10.471
Weight loss (yes)	2.585	1.315	5.082	1.798	1.003	3.036
Disseminated cancer (yes)	2.736	1.520	4.925	3.087	1.887	4.835
BMI class (obese)	1.118	0.662	1.888	3.723	1.728	7.069
BMI class (underweight)	0.721	0.162	3.199	1.16	0.74	1.761
Steroid use (yes)	0.934	0.273	3.190	3.102	0.936	7.584
Albumin (g/dL) 2.8–3.5	2.190	1.127	4.254	2.091	1.406	3.066
Albumin (g/dL) ≤2.8	5.425	2.547	11.557	1.887	0.952	3.464
Albumin (g/dl) missing	1.533	0.854	2.752	0.775	0.272	1.729
C-statistic	0.822			0.782		
Hosmer–Lemeshow chi-square	10.946 ($P=0.205$)			5.236 ($P=0.631$)		

PD Variables	US/NSQIP			Japan/NCD		
		95% CI			95% CI	
	Odds Ratio	Lower CI	Upper CI	Odds Ratio	Lower CI	Upper CI
Age 60–70	1.933	1.085	3.442	1.706	0.977	3.193
Age 70–80	2.591	1.447	4.638	1.989	1.157	3.688
Age ≥80	3.280	1.656	6.498	2.462	1.317	4.844
Sex (male)	1.519	1.059	2.181	1.325	0.949	1.866
Bleeding disorder (yes)	1.013	0.401	2.556	1.829	1.033	3.025
Emergency status (yes)	0.651	0.084	5.056	4.389	1.666	9.566
Functional status (dependent)	1.378	0.415	4.572	2.394	1.44	3.789
Disseminated cancer (yes)	2.161	1.044	4.471	1.854	0.3	6.113
Hypertension (yes)	1.738	1.145	2.639	1.393	1.048	1.85
Albumin (g/dL) 2.8–3.5	1.520	0.994	2.324	1.233	0.885	1.696
Albumin (g/dL) ≤2.8	1.985	1.174	3.357	1.515	0.846	2.54
Albumin (g/dL) missing	1.030	0.486	2.182	1.643	0.747	3.209
CKD missing	1.665	0.448	6.192	2.148	0.69	5.471
CKD stage 3	1.183	0.736	1.903	1.421	1.031	1.969
CKD stage 4/5	3.020	1.133	8.044	2.054	1.057	3.704
Surgical complexity (adjacent organ)	2.281	1.234	4.214	1.796	0.986	3.018
Surgical complexity (vascular)	1.524	0.881	2.633	1.701	1.154	2.44
COPD (yes)	2.382	1.371	4.137	1.541	0.775	2.758
BMI class (obese)	1.905	1.306	2.779	1.53	0.535	3.434
BMI class (underweight)	1.823	0.712	4.668	0.659	0.404	1.023
C-statistic	0.719			0.782		
Hosmer–Lemeshow chi-square	8.619 ($P = 0.375$)			9.908 ($P = 0.272$)		

BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, LAR = low anterior resection, NCD = National Clinical Database, NSQIP = National Surgical Quality Improvement Program, PD = pancreaticoduodenectomy, RH = right hemicolectomy, US = United States, WBC = white blood cell.

TABLE 5. Observed and Expected Mortality after RH, LAR, and PD

Mortality	US/NSQIP Model	Japan/NCD Model	Difference in Mortality Rate (%)
RH			
US/NSQIP mortality	(Observed)	(Expected)	
%	1.88	0.60	−68
C-statistic	0.840	0.789	
Hosmer–Lemeshow chi-square	5.866 ($P = 0.662$)	171.01 ($P < 0.001$)	
Japan/NCD mortality	(Expected)	(Observed)	
%	3.83	0.76	404
C-statistic	0.828	0.857	
Hosmer–Lemeshow chi-square	955.233($P < 0.001$)	11.243 ($P = 0.188$)	
LAR			
US/NSQIP mortality	(Observed)	(Expected)	
%	1.08	0.60	−44
C-statistic	0.822	0.786	
Hosmer–Lemeshow chi-square	10.946 ($P = 0.205$)	49.54 ($P < 0.001$)	
Japan/NCD mortality	(Expected)	(Observed)	
%	1.08	0.43	151
C-statistic	0.778	0.782	
Hosmer–Lemeshow chi-square	145.375 ($P < 0.001$)	5.236 ($P = 0.631$)	
PD			
US/NSQIP mortality	(Observed)	(Expected)	
%	2.57	2.41	−6
C-statistic	0.719	0.674	
Hosmer–Lemeshow chi-square	8.619 ($P = 0.375$)	8.817 ($P = 0.358$)	
Japan/NCD mortality	(Expected)	(Observed)	
%	4.23	1.35	213
C-statistic	0.540	0.782	
Hosmer–Lemeshow chi-square	366.217 ($P < 0.001$)	9.908 ($P = 0.272$)	

LAR = low anterior resection, NCD = National Clinical Database, NSQIP = National Surgical Quality Improvement Program, PD = pancreaticoduodenectomy, RH = right hemicolectomy, US = United States.

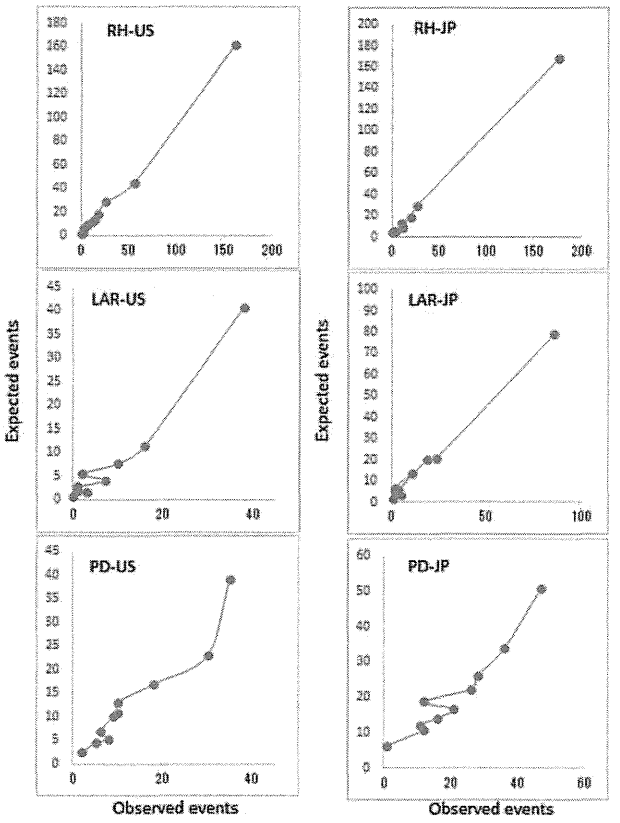

FIGURE 1. Calibration for 30-day mortality models for RH, LAR, and PD based on the US data using the US/ACS-NSQIP model (US) and the Japanese data using the Japan/NCD model (JP). ACS-NSQIP = American College of Surgeons National Surgical Quality Improvement Program, JP = Japan, LAR = low anterior resection, PD = pancreaticoduodenectomy, RH = right hemicolectomy, US = United States.

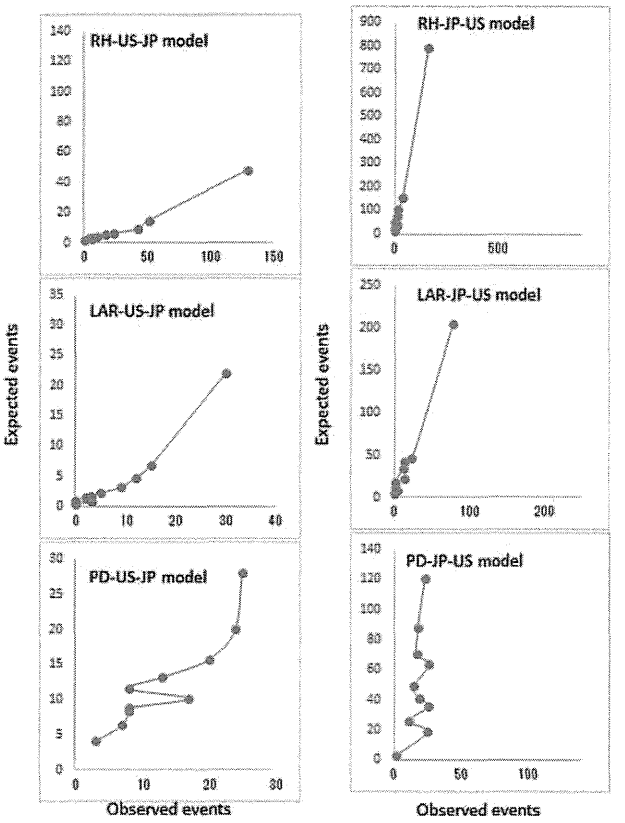

FIGURE 2. Calibration for 30-day mortality models for RH, LAR, and PD based on the US data using the Japan/NCD model (US-JP model) and the Japanese data using the US/ACS-NSQIP model (JP-US model). ACS-NSQIP = American College of Surgeons National Surgical Quality Improvement Program, JP = Japan, LAR = low anterior resection, PD = pancreaticoduodenectomy, RH = right hemicolectomy, US = United States.

used. These results indicate that risk models based on local data accurately predict mortality rate; however, risk models based on data from other countries are unable to accurately predict mortality rate. When evaluating the performance of a prediction model in adherence to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis guideline,[26] investigators should pay attention to the discrepancy, involving the use of participant data collected by another country for external validation.

We considered reasons for this discrepancy. Differences in the prevalence of risk factors are unlikely to have a significant impact on model performance since we conducted a risk-adjusted analysis. However, there may be several risk factors not included in our model. These are likely to be ethnicity; operative information (operation time, amount of bleeding, and transfusion amount); and incidence and management of postoperative complications. Cytokine response has been shown to differ between races[27,28]; it is reasonably assumed that this difference may lead to different outcomes. Because the incidence of severe morbidity affects mortality, successful prophylactic management as a team may reduce the incidence of morbidity and decrease mortality rates.[10,29] Relatively longer hospital stays after surgery due to the insurance system in Japan[30] may protect patients with high morbidity after surgery, but this assumption needs to be fully assessed in future comparative studies.

This study should be interpreted with the appreciation of several limitations. We were unable to combine data from the 2 datasets due to the prohibition by NCD for security reasons. The backgrounds of the databases may be different. Although the NCD/Japan contains nearly 95% of surgical cases from all hospitals in Japan, ACS-NSQIP contains samples from selected hospitals in US only. This may be a source of bias if there was a difference in surgical practice or hospital procedural volume. Other differences in patient factors, including social, economic, and racial differences, have not been considered. Secondly, 30-day mortality was the only outcome studied. The 30-day mortality likely underestimates treatment-associated mortality by not including mortality occurring 30 days after operations. Thirdly, the impact of perioperative and postoperative complications that potentially affects surgical mortality are unknown due to a lack of data regarding these variables.

In conclusion, we found significantly different mortality rates, comorbidity prevalences, and procedural practices between Japan and the US. Risk-prediction models that can be reasonably used for both patient groups should be developed while recognizing that some risk predictors may be population-specific. This study demonstrates the feasibility and utility of

international collaborative research between Japan and the US, but risk models based on local data remain essential for quality assessment and improvement.

ACKNOWLEDGMENTS

We wish to thank all of the data managers and hospitals that participated in the NCD project and the ACS-NSQIP for their great efforts in data entry. In addition, we wish to express appreciation to all the people and academies that cooperated in this project.

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This problem is well illustrated in the study by Mangurian et al[1] in this issue of *JAMA Internal Medicine*. The authors used California Medicaid data to identify patients who were prescribed an antipsychotic medication. They then assessed what percentage of the patients had some form of glucose screening, a recommendation by the American Diabetes Association[2] for persons taking antipsychotic medications, in a yearlong period. Overall, 30.1% of individuals were screened. It would be fair to point out that the efficacy of screening for diabetes has not been well established. However, that less than one-third had such screening for a known adverse effect of antipsychotic medication use suggests opportunities for improvement in integrated health care. Among those who had at least 1 primary care visit during the year, the proportion screened was significantly higher at 35.6% vs 19.8% for those who had no primary care visit.

To improve care for persons with serious mental illness, it will be necessary to break down the silos that separate the mental health and physical health care systems. Integrated care (care provided by a team of physical and mental health clinicians)—or at least colocated care (care provided by physical and mental health clinicians in the same place)—offers the promise of improving the physical health of individuals with mental illness, as well as the mental health of those seeking physical health services.

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Conflict of Interest Disclosures: None reported.

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LESS IS MORE

Use of Intra-aortic Balloon Pump in a Japanese Multicenter Percutaneous Coronary Intervention Registry

We read with interest the recent meta-analysis by Ahmad et al,[1] demonstrating a negative association between intra-aortic balloon pump (IABP) therapy and mortality among patients experiencing acute myocardial infarction. We agree that efforts are needed to clarify the role of IABP therapy and to examine its effect on care in other regions and countries. In Japan, IABP therapy is frequently used in patients with guideline-based indications and in patients with less established indications, and the judicious use of invasive procedures has been highlighted.[2,3] Our objective herein was to investigate the prognostic effect of IABP use in patients undergoing percutaneous coronary intervention (PCI) for nonacute and acute indications registered in a contemporary multicenter Japanese PCI registry (Japan Cardiovascular Database-Keio Interhospital Cardiovascular Studies[4]).

Invited Commentary
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Methods | We analyzed data from 14 378 consecutive patients treated between September 2, 2008, and May 19, 2014. Of those, 1124 patients were excluded because of missing baseline information (n = 192), registration for staged PCI during the same hospitalization (n = 801), or PCI performed under percutaneous cardiopulmonary support (n = 132). The remaining 13 253 patients were included herein, and logistic regression models for in-hospital mortality were used to correct for differences in variables. We included in the logistic regression model all variables exhibiting a significant ($P < .10$) bivariate association with IABP use. Baseline inequality between patients with and without IABPs was evaluated with the baseline inequality index, the same method used by Ahmad et al.[1] Because our study focused on the effect of IABP on in-hospital mortality for all PCIs, we redefined a list of baseline characteristics recognized as markers of mortality risk based on a previous study.[5] Data analyses were performed using statistical software (SPSS, version 22.0; SPSS Inc). This study was approved by each participating hospital's ethics review board (Keio University School of Medicine, Saiseikai Utsunomiya Hospital, Ashikaga Red Cross Hospital, Saitama City Hospital, Saitama National Hospital, Hino Municipal Hospital, Tokyo Dental College Ichikawa General Hospital, Tokyo Saiseikai Central Hospital, Tokyo Medical Center, St Luke's International Hospital, Kawasaki Municipal Hospital, and Yokohama Municipal Citizen's Hospital), and written informed consent was obtained from each patient.

Results | Baseline demographics in patients with and without IABPs are summarized in the **Table**. Overall, PCIs after ST-segment elevation myocardial infarctions and PCIs after non-ST-segment elevation myocardial infarctions or unstable angina accounted for 23.9% and 24.2% of the procedures, respectively. Before PCI, 486 patients (3.7%) and 900 patients (6.8%) manifested complications of cardiogenic shock and serious heart failure (New York Heart Association functional classification ≥3), respectively. The proportions of interventions for left main trunk and 3-vessel disease were 3.7% and 0.9%, respectively. Intra-aortic balloon pumps were inserted in 885 patients (6.7%). There were 134 in-hospital deaths (15.1%) among the patients receiving an IABP and 111 in-hospital deaths (0.9%) among the patients not receiving an IABP. In the crude analysis, the use of IABP was associated with an increased risk of in-hospital mortality (**Figure**, A).

Intra-aortic balloon pump use remained an independent predictor of in-hospital mortality after adjusting for baseline differences (odds ratio, 3.87; 95% CI, 2.71-5.52; $P < .001$). Among several subgroups thought to potentially have indications for IABP use, the use of IABPs was consistently associated with risk of in-hospital death (Figure, B), and IABP recipients had a worse baseline risk profile than nonrecipients (Figure, C). Notably, the risk of death appeared to be higher (with higher odds ratios) as the indications for IABP use became less established.

Discussion | Among a cohort of Japanese patients undergoing PCI in whom IABP use was frequent, we found that the use of IABP was associated with a higher risk of in-hospital death. This

Table. Baseline Characteristics of Patients With and Without Intra-aortic Balloon Pump Use in the Entire Cohort[a]

Variable	Patients Without IABP (n = 12 368)	Patients With IABP (n = 885)	*P* Value
Age, mean (SD), y	67.9 (10.9)	69.0 (11.7)	.004
Male sex, No. (%)	9807 (79.3)	695 (78.5)	.59
History of heart failure, No. (%)	1050 (8.5)	121 (13.7)	<.001
NYHA functional classification ≥3, No. (%)[b]	645 (5.2)	255 (28.8)	<.001
Diabetes mellitus, No. (%)	5201 (42.1)	388 (43.8)	.28
Previous myocardial infarction, No. (%)	3050 (24.7)	183 (20.7)	.008
Previous PCI, No. (%)	4723 (38.2)	183 (20.7)	<.001
Previous coronary artery bypass graft, No. (%)	680 (5.5)	49 (5.5)	.96
Cerebrovascular disease, No. (%)	1078 (8.7)	114 (12.9)	<.001
Peripheral vascular disease, No. (%)	1059 (8.6)	58 (6.6)	.04
Chronic lung disease, No. (%)	376 (3.0)	30 (3.4)	.55
Hypertension, No./total No. (%)	9330/12 363 (75.5)	624/883 (70.7)	.001
Current or recent smoker, No./total No. (%)	4150/12 347 (33.6)	332/880 (37.7)	.01
Dyslipidemia, No./total No. (%)	8298/12 359 (67.1)	500/883 (56.6)	<.001
Renal dysfunction, No./total No. (%)[c]	4772/11 368 (42.0)	475/863 (55.0)	<.001
Urgent or emergent PCI, No. (%)	5130 (41.5)	773 (87.3)	<.001
Presentation, No. (%)	(n = 12 369)		
STEMI	2612 (21.1)	551 (62.3)	
NSTEMI	941 (7.6)	113 (12.8)	
Unstable angina	2068 (16.7)	102 (11.5)	<.001
Stable angina or silent ischemia	6663 (53.9)	95 (10.7)	
Other indication	84 (0.7)	24 (2.7)	
No. of target vessels, No. (%)	(n = 12 358)	(n = 884)	
1	11 226 (90.8)	715 (80.8)	
2	1036 (8.4)	145 (16.4)	
3	96 (0.8)	24 (2.7)	<.001
Unknown	10 (0.1)	1 (0.1)	
LMT lesion, No. (%)	1006 (8.1)	203 (22.9)	<.001
Proximal left anterior descending intervention, No. (%)	2886 (23.3)	298 (33.7)	<.001
Cardiogenic shock, No. (%)	206 (1.7)	280 (31.6)	<.001

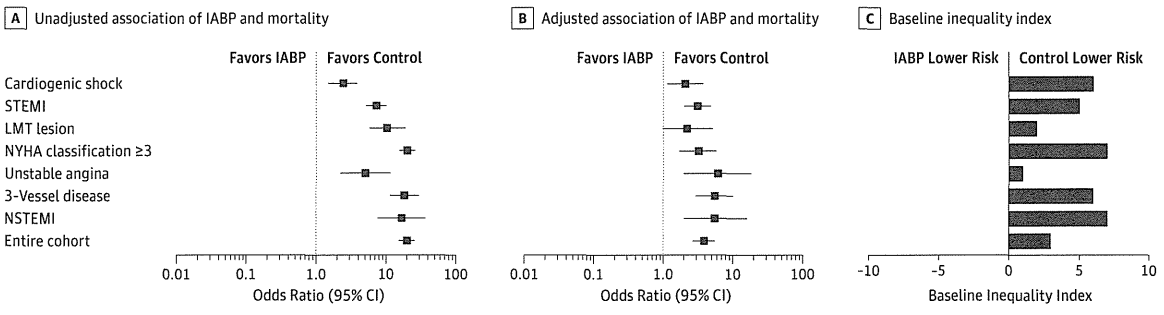
Abbreviations: IABP, intra-aortic balloon pump; LMT, left main trunk; NSTEMI, non-ST-segment elevation myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

[a] Differences in each variable between the patients with and without IABP use were evaluated using the χ^2 test for categorical variables and the unpaired *t* test for continuous variables.

[b] At the time of the procedure.

[c] Defined as an estimated glomerular filtration rate exceeding 60 mL/min/1.73 m^2.

Figure. Unadjusted and Adjusted Effects of Intra-aortic Balloon Pump (IABP) Use on In-Hospital Mortality in Various Situations



A and B, Intra-aortic balloon pump use was adversely associated with patient outcome, regardless of situation, in crude (A) and multivariable (B) analyses. In the logistic regression model, adjustments were made using all variables exhibiting a bivariate association with the use of IABP with $P < .001$ in the Table, which included all variables except the following: diabetes mellitus, previous coronary artery bypass graft, chronic lung disease, stable angina or silent ischemia, and 1-vessel disease. C, For evaluating the baseline inequality index, we redefined a list of the following baseline characteristics that are recognized markers of mortality risk: age, cardiogenic shock, prior heart failure, peripheral vascular disease, chronic lung disease, renal dysfunction, NYHA functional classification of at least 3 at the time of percutaneous coronary intervention, and clinical presentation (STEMI or NSTEMI). LMT indicates left main trunk; NSTEMI, non-ST-segment elevation myocardial infarction; NYHA, New York Heart Association; and STEMI, ST-segment elevation myocardial infarction.

unfavorable association was consistent across clinical settings and was more pronounced as the indications for IABP use became less established.

Several limitations need to be acknowledged. Because of the observational design, we cannot assume a causal relationship between IABP use and mortality. Despite rigorous risk adjustment, the possibility of confounding by unmeasured covariates remains. However, the consistency of the association between IABP use and mortality in various subgroups is notable. Our registry does not capture reasons for IABP insertion. Some physicians or patients may have declined IABP based on institutional or personal preferences.

Using a contemporary multicenter Japanese PCI registry, we have shown a negative association between IABP use and mortality. Our findings are consistent with the meta-analysis by Ahmad et al[1] and suggest that it is time to reconsider the appropriate use of IABP therapy, a potentially life-saving but extremely costly and high-risk intervention for patients.

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Published Online: November 2, 2015. doi:10.1001/jamainternmed.2015.5119.

Author Contributions: Dr Inohara had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Inohara, Kohsaka.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Inohara, Kohsaka.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Inohara, Miyata.
Obtained funding: Inohara, Ueda, Fukuda, Kohsaka.
Administrative, technical, or material support: Miyata, Ueda, Maekawa, Fukuda, Kohsaka.
Study supervision: Miyata, Ueda, Maekawa, Fukuda, Kohsaka.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was funded by grants 25460630 and 80571398 from the Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research and by the Pfizer Health Research Foundation.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Invited Commentary | LESS IS MORE

Is Increased Use of Mechanical Circulatory Support Devices Justified? A Cause for Concern

There has been a significant increase in the use of mechanical circulatory support devices in recent years.[1] This increase has been largely due to the availability of several new percutaneous ventricular assist devices (PVADs). Khera et al[1] documented in this journal a 30-fold increase in the use of PVADs based on National Inpatient Sample data from 2007 through 2012. In this issue of *JAMA Internal Medicine*, Inohara et al[2] identify frequent use of the intra-aortic balloon pump (IABP) in Japan among patients with guideline-based indications and other less established indications. However, increased implantation of IABPs or PVADs is not supported by any evidence of clinical benefit or by professional guidelines.

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Both Khera et al[1] and Inohara et al[2] demonstrate that the use of mechanical circulatory support devices is associated with increased mortality. The latter is an observational study[2] from a multicenter Japanese registry of 13 253 patients undergoing angioplasty for various indications, with substantial heterogeneity among subgroups of the patients. Similar to some previous reports, the study by Inohara et al[2] also showed that the use of IABPs is associated with higher in-hospital mortality overall and among various subgroups, including those with less severe disease. These data are consistent with several randomized clinical trials that have not shown benefit from IABP implantation. For example, IABP use has been found to have no survival benefit in patients with myocardial infarction-related heart failure or shock who receive thrombolysis or angioplasty.[3] In hemodynamically stable patients undergoing high-risk angioplasty, there was no demonstrable difference in clinical outcomes or infarct size associated with the use of IABPs.[4] A recent meta-analysis by Ahmad et al[5] summarized data from major clinical trials and observational studies and concluded that IABP use did not improve mortality after myocardial infarction in patients with or without cardiogenic shock. Furthermore, IABP outcomes in those observational studies were better compared with controls only among lower-risk patients, questioning whether IABP use was ever indicated in those patients.[5]

With increasing evidence showing no benefit in hard outcomes, enthusiasm for IABP use in guidelines seems to be waning. Recent European Society of Cardiology guidelines[6] recommend against regular use of IABPs in patients with cardiogenic shock (class III). The guidelines also cite no mortality benefit of PVADs over IABPs in these patients and provide no definite

recommendation for their use. Despite the lack of guideline-based recommendations and little evidence to support IABP use, the study by Inohara et al[2] finds that IABPs continue to be used frequently and that their use is associated with increased in-hospital mortality.

Although there has been enthusiasm about newer PVADs (eg, Impella LP2.5 [Abiomed Europe GmbH] and TandemHeart [Cardiac Assist]), initial studies regarding their use to treat cardiogenic shock have not shown any significant survival benefit compared with IABPs and observed increased bleeding and a tendency toward more limb ischemia from the use of larger sheaths with PVADs.[7] Similar to IABPs, no net benefit was demonstrated in hemodynamically stable patients with an implanted PVAD undergoing high-risk angioplasty, another common clinical scenario for the use of PVADs.[8]

Why is there reluctance to abandon these invasive, expensive, and seemingly ineffective therapies? The answer might be multifactorial. Cardiogenic shock complicating myocardial infarction remains a formidable foe and is associated with 40% to 50% in-hospital mortality.[9] In this setting, only early revascularization has shown improved survival. In some of these critically ill patients, it may seem reasonable to use mechanical circulatory support devices as salvage therapy. However, they offer little benefit in reducing clinical events, and have high costs and significant complication rates. Inohara et al[2] confirm previous findings that IABPs and PVADs are being increasingly used in patients without indications for their use. Although the precise reasons for such excessive use remain to be established, misaligned financial incentives might have a role. Furthermore, continued use of IABPs may be due to established routines or treatment protocols, with commission bias tending toward action rather than inaction.[10]

Based on available data, the use of these invasive and expensive mechanical circulatory support devices should be critically appraised and limited because of significant complication rates associated with their use and a lack of evidence demonstrating any benefit. In the use of IABPs and PVADs, it seems appropriate to conclude that perhaps less is more.

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Published Online: November 2, 2015. doi:10.1001/jamainternmed.2015.6093.

Conflict of Interest Disclosures: None reported.

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Disparities in Time Spent Seeking Medical Care in the United States

The Institute of Medicine identifies timeliness of care as a key aspect of quality. Racial and socioeconomic disparities exist in receipt of timely appointments and interventions.[1]

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Patient time burden (ie, time spent traveling to, waiting for, and receiving ambulatory medical care) is a separate domain of timeliness. Disparities in this domain have received less attention, although prior work has described inequalities in pediatric emergency department wait time[2] and racial disparities in the time adults spend seeking medical care.[3] In prior work, using survey data on time associated with medical visits, we estimated that patients incurred $52 billion in opportunity costs obtaining medical care in 2010.[4] In this article, we assessed how time associated with medical visits varied across socioeconomic variables and visit characteristics.

Methods | The American Time Use Survey data from 2005 to 2013 includes coded single-day 24-hour time diaries for 108 486 respondents 18 years and older.[5] We identified respondents reporting *clinic time*, or time waiting for or obtaining medical care, on their interview day. We excluded respondents reporting more than 6 hours of clinic time as extreme outliers (n = 99), and we also excluded respondents receiving care for multiple individuals on their interview day (n = 101). For the remaining respondents with clinic time (n = 3787), we determined associated *travel time*, or time spent traveling for care, and *total time*, or the sum of clinic time and travel time. We compared these time estimates with *face-to-face time*, or time spent with a physician, collected from 2006 to 2010 by the National Ambulatory Medical Care Survey, a nationally representative survey of office-based physician visits (n = 150 022).

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Annals of Oncology 27: 480–487, 2016
doi:10.1093/annonc/mdv611
Published online 23 December 2015

Changes in tumor expression of HER2 and hormone receptors status after neoadjuvant chemotherapy in 21 755 patients from the Japanese breast cancer registry

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Received 21 August 2015; revised 28 October 2015; accepted 28 November 2015

Background: We investigate rates of pathologic complete response (pCR) and tumor expression of ER, PgR, HER2 discordance after neoadjuvant chemotherapy using Japanese breast cancer registry data.

Patients and methods: Records of more than 300 000 breast cancer cases treated at 800 hospitals from 2004 to 2013 were retrieved from the breast cancer registry. After data cleanup, we included 21 755 patients who received neoadjuvant chemotherapy and had no distant metastases. pCR was defined as no invasive tumor in the breast detected during surgery after neoadjuvant chemotherapy. HER2 overexpression was determined immunohistochemically and/or using fluorescence *in situ* hybridization.

Results: pCR was achieved in 5.7% of luminal tumors ($n = 8730$), 24.6% of HER2-positive tumors ($n = 4403$), and 18.9% of triple-negative tumors ($n = 3660$). Among HER2-positive tumors, pCR was achieved in 31.6% of ER-negative tumors ($n = 2252$), 17.0% of ER-positive ones ($n = 2132$), 31.4% of patients who received trastuzumab as neoadjuvant chemotherapy ($n = 2437$), and 16.2% of patients who did not receive trastuzumab ($n = 1966$). Of the 2811 patients who were HER2-positive before treatment, 601 (21.4%) had HER2-negative tumors after neoadjuvant chemotherapy, whereas 340 (3.4%) of the 9947 patients with HER2-negative tumors before treatment had HER2-positive tumors afterward. Of the 10 973 patients with ER-positive tumors before treatment, 499 (4.6%) had ER-negative tumors after neoadjuvant chemotherapy, whereas 519 (9.3%) of the 5607 patients who were ER-negative before treatment had ER-positive tumors afterward.

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Conclusion: We confirmed that loss of HER2-positive status can occur after neoadjuvant treatment in patients with primary HER2-positive breast cancer. We also confirmed that in practice, differences in pCR rates between breast cancer subtypes are the same as in clinical trials. Our data strongly support the need for retest ER, PgR, HER2 of surgical sample after neoadjuvant therapy in order to accurately determine appropriate use of targeted therapy.

Key words: breast cancer, chemotherapy, HER2, *in situ* hybridization, neoadjuvant therapy

introduction

In breast cancer patients, neoadjuvant chemotherapy (i.e. presurgical systemic chemotherapy) is associated with rates of disease-free survival and overall survival comparable with those for adjuvant (post-surgical) chemotherapy [1]. It is standard in locally advanced and operable breast cancer, being intended to shrink the tumor and improve the chance for breast-conserving surgery [2]. Pathologic complete response (pCR) is the best predictor of patient outcome after neoadjuvant chemotherapy [2–4]; it is generally defined as the absence of residual invasive cancer in the breast [5]. Clinical trials have found that different breast cancer subtypes have different rates of pCR and that patients who show pCR have a different prognosis in each subtype. However, in an attempt to improve pCR, clinical trial investigators may use more frequent or standard doses of chemotherapeutic agents than would be used in a routine clinical setting.

The *HER2/neu* gene is amplified in 10%–20% of primary breast cancer cases. In HER2-positive patients, HER2-targeting therapies such as neoadjuvant trastuzumab result in better rates of pCR than non-HER2-targeting therapies [6, 7], as might be expected, HER2-positive patients who show pCR have a better prognosis than those who do not. In the latter, HER2 status may be discordant between the primary breast tumor and those remaining after chemotherapy [8–12]. Some studies suggest that trastuzumab in particular can convert disease status from HER2-positive in a primary tumor to HER2-negative in residual tumors [13–15]. Mittendorf et al. found that according to fluorescence *in situ* hybridization (FISH) analysis, approximately one-third of their patients with sufficient residual disease to warrant repeat HER2 testing had lost *HER2* gene amplification. Furthermore, patients who have lost *HER2* gene amplification have significantly lower relapse-free survival than those whose tumors retain *HER2* gene amplification [15]. Patients with such HER2 status discordance between primary tumors and residual or metastatic ones may also have shorter survival than those without [15, 16]. However, the prevalence of such discordance in patients who have undergone neoadjuvant chemotherapy has not been conclusively established, and it is unclear if trastuzumab increases its likelihood; if so, the treatment may not be suitable for such patients. Using data from the Japanese national breast cancer registry, we aimed to investigate pCR and discordance rates after neoadjuvant chemotherapy in relation to positivity for estrogen receptor (ER), progesterone receptor (PgR), and HER2.

materials and methods

data collection

The Breast Cancer Registry (BCR) in Japan's National Clinical Database (NCD) contains records on more than 300 000 cases of breast cancer from more than 800 hospitals. Affiliated institutes voluntarily provide the BCR with data on newly diagnosed primary breast cancer patients through a Web-based system, covering more than 50 demographic and clinicopathological categories. TNM classification is registered according to the 6th edition of the Unio Internationalis Contra Cancrum (UICC) staging system [17].

The BCR was originally maintained by the Registration Committee of the Japanese Breast Cancer Society (JBCS) and supported by the Public Health Research Foundation (Tokyo). Until 2012, annual reports on this registry were published in Japanese and made accessible to active JBCS members through the JBCS homepage (http://www.jbcs.gr.jp/Member/tourokusyukei.html). Since 2012, this dataset has been part of the NCD, a nationwide project managed in cooperation with the certification board of the Japan Surgical Society [18]. For the year 2011 alone, data from more than 1.2 million surgical cases were collected from more than 3500 hospitals. The NCD is continuously updated by the data management departments of participating institutions and is evaluated annually using a Web-based data management system to ensure data traceability. All variables, definitions, and inclusion criteria for the NCD are accessible to participating institutions on its web site (http://www.ncd.or.jp); the database administrators also provide e-learning systems to teach participants how to input data consistently [18]. The administrators answer all inquiries regarding data entry, having taken ~80 000 inquiries in 2011, and a list of frequently asked questions is displayed on the web site.

For our study, we used the BCR to review 238 840 breast cancer cases treated between 2004 and 2011 and selected 21 755 patients who received neoadjuvant chemotherapy and had no distant metastases (Figure 1). Male patients, those with bilateral tumors, those who did not undergo surgery, and those with tumor stages of Tis or T0, were excluded. pCR was defined as no invasive tumor in the breast found during surgery after neoadjuvant chemotherapy. HER2 overexpression was defined as immunohistochemically 3+ and/or a positive FISH result. Hormone receptor positivity (ER or PgR positivity) was diagnosed if at least 1% of nuclei in the tumor were stained on immunohistochemical tests for ER or PgR. Immunohistochemical tests for ER, PgR, and HER on core biopsies were carried out before neoadjuvant therapy. Cases were categorized on the basis of their immunohistochemical status as follows: luminal (ER+ and HER2−); HER2-overexpressing (HER2+, regardless of ER status); and triple-negative (ER− and HER2−).

statistical analysis

The median and standard deviations were calculated for age at diagnosis. Associations between clinical categorical variables and HER2 status were analyzed using Pearson's χ^2. Fisher's exact test was also used to determine differences between patients who showed HER2 status discordance and those who did not. All analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC).

results

A total of 21 755 patients who received neoadjuvant chemotherapy and developed no distant metastases were listed in Table 1. More than 80% of patients had a tumor of stage T2 or worse, and more than 60% were node-positive. Almost 70% received anthracyclines and taxanes as neoadjuvant chemotherapy.

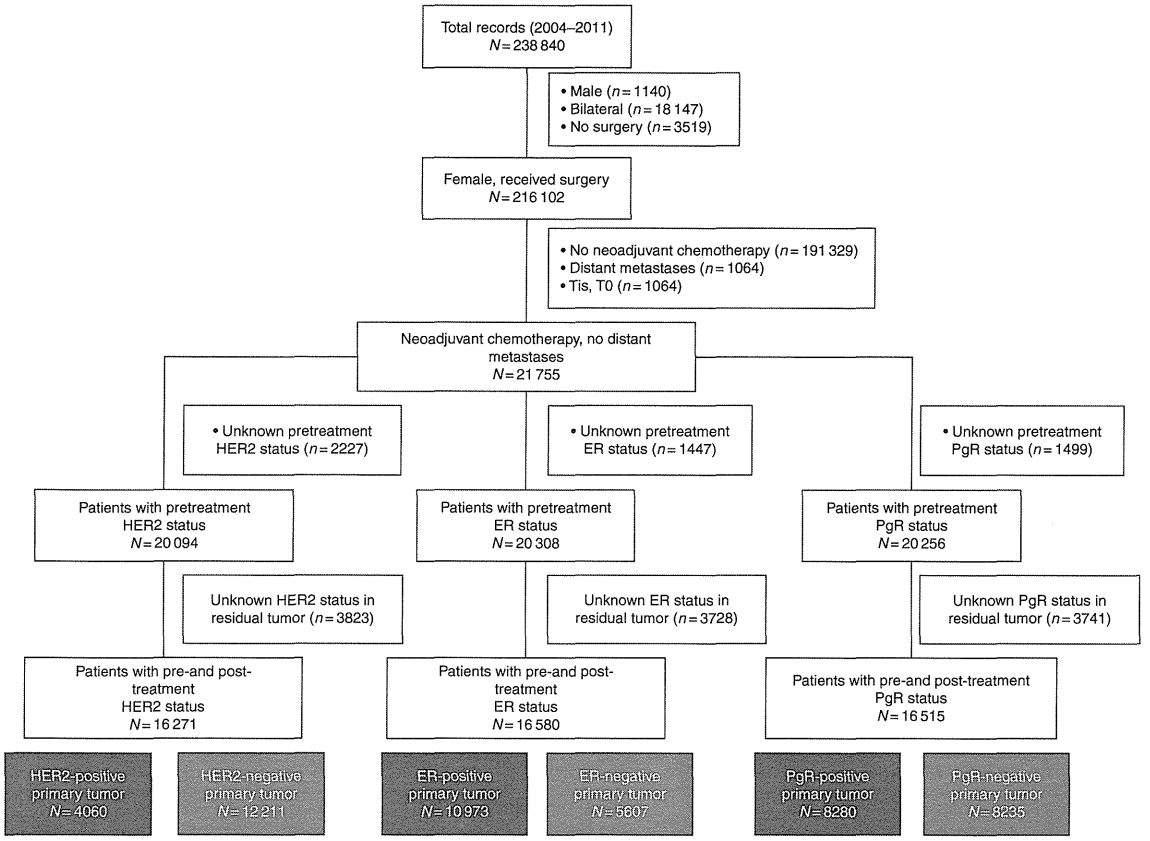

Figure 1. Study flow.

rate of pCR

The rate of pCR was 5.7% for luminal cancer ($n = 8730$), 24.6% for HER2-positive ($n = 4403$), and 18.9% for triple-negative ($n = 3660$) (Figure 2). Thus, HER2-overexpressing tumors had a higher rate of pCR than triple-negative or luminal ones; however, within this category, the rate was 31.6% for ER-negative tumors ($n = 2252$), 17.0% for ER-positive ones ($n = 2132$), 31.4% for those who received trastuzumab as neoadjuvant chemotherapy ($n = 2437$), and 16.2% for those who did not receive trastuzumab ($n = 1966$) (Figure 2). In addition, HER2-positive patients who were ER-negative had a higher rate of pCR than those who were ER-positive ($P < 0.0001$), and those treated with trastuzumab had a higher rate of pCR than those not so treated ($P < 0.0001$).

rate of discordance after chemotherapy

Of the 2811 patients who were HER2-positive before treatment, 601 (21.4%) had tumors that showed HER2 negativity after neoadjuvant chemotherapy, whereas only 340 (3.4%) of the 9947 patients with HER2-negative pretreatment tumors developed HER2-positive tumors after neoadjuvant chemotherapy (Table 2). According to immunohistochemical testing, 499 (20.4%) of the 2447 patients with HER2-positive tumors lost HER2 positivity after neoadjuvant chemotherapy; with FISH, the rate was 8.4% (17/203). Of 342 patients whose tumors converted from HER2-positive to HER2-negative, who received neoadjuvant trastuzumab, 96 (28%) did not receive adjuvant trastuzumab therapy. Conversely, of 340 patients whose tumors converted from HER2-negative to HER2-positive, 206 (60%) received adjuvant trastuzumab therapy.

Of the 10 973 patients with ER-positive tumors before treatment, 499 (4.6%) had ER-negative tumors after neoadjuvant chemotherapy, whereas 519 (9.3%) of the 5607 patients with ER-negative tumors before treatment had ER-positive ones after neoadjuvant chemotherapy. Of the 499 patients whose tumors converted from ER-positive to ER-negative, 280 (56%) did not receive adjuvant endocrine therapy. Conversely, of 519 patients whose tumors converted from ER-negative to ER-positive, 333 (64%) received adjuvant endocrine therapy.

Of the 8280 patients with PgR-positive tumors before treatment, 1545 (18.7%) had PgR-negative ones after neoadjuvant chemotherapy, whereas 766 (9.3%) of the 8235 patients with PgR-negative tumors before treatment had PgR-positive tumors after neoadjuvant chemotherapy (Table 3).

clinicopathologic features associated with discordance

We evaluated HER2 concordance and discordance rates in relation to various clinical factors (Table 4). There were statistically significant differences in HER2 discordance rates between patients

Table 1. Patients Characteristic

		With pretreatment HER2 status ($n = 20\,094$)				With pretreatment ER status ($n = 20\,308$)				With pretreatment PgR status ($n = 20\,256$)			
		Positive ($n = 5535$)		Negative ($n = 14\,559$)		Positive ($n = 12\,938$)		Negative ($n = 7370$)		Positive ($n = 9720$)		Negative ($n = 10\,536$)	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Age	Median		54		51		51		55		49		55
Menopausal status													
	Premenopausal	2079	37.6	6928	47.6	6429	49.7	2679	36.4	5302	54.6	3779	35.9
	Post-menopausal	3289	59.4	7260	49.9	6183	47.8	4468	60.6	4152	42.7	6472	61.4
	Unknown	167	3.0	371	2.6	326	2.5	223	3.0	266	2.7	285	2.7
T stage													
	T1	587	10.6	1772	12.2	1578	12.2	804	10.9	1222	12.6	1157	11.0
	T2	3197	57.8	8288	56.9	7472	57.8	4112	55.8	5673	58.4	5876	55.8
	T3	893	16.1	2071	14.2	1837	14.2	1173	15.9	1346	13.9	1660	15.8
	T4	858	15.5	2428	16.7	2051	15.9	1281	17.4	1479	15.2	1843	17.5
N stage													
	N0	1725	31.2	4793	32.9	4304	33.3	2288	31.0	3353	34.5	3217	30.5
	N1	2807	50.7	7513	51.6	6805	52.6	3631	49.3	5116	52.6	5296	50.3
	N2	582	10.5	1356	9.3	1100	8.5	849	11.5	779	8.0	1169	11.1
	N3	411	7.4	859	5.9	699	5.4	583	7.9	452	4.7	825	7.8
	Unknown	10	0.2	38	0.3	30	0.2	19	0.3	20	0.2	29	0.3
Neoadjuvant chemotherapy													
	CMF alone	2	0.0	12	0.1	9	0.1	5	0.1	7	0.1	7	0.1
	Anthracycline regimen alone	547	9.9	1765	12.1	1502	11.6	851	11.6	1106	11.4	1235	11.7
	TC alone	81	1.5	265	1.8	265	2.1	82	1.1	219	2.3	127	1.2
	Taxane alone	532	9.6	586	4.0	634	4.9	510	6.9	464	4.8	681	6.5
	Anthracycline regimen and taxane	3891	70.3	10 191	70.0	9118	70.5	5097	69.2	6856	70.5	7316	69.4
	Others	482	8.71	1740	11.95	1410	10.90	825	11.19	1068	10.99	1170	11.10

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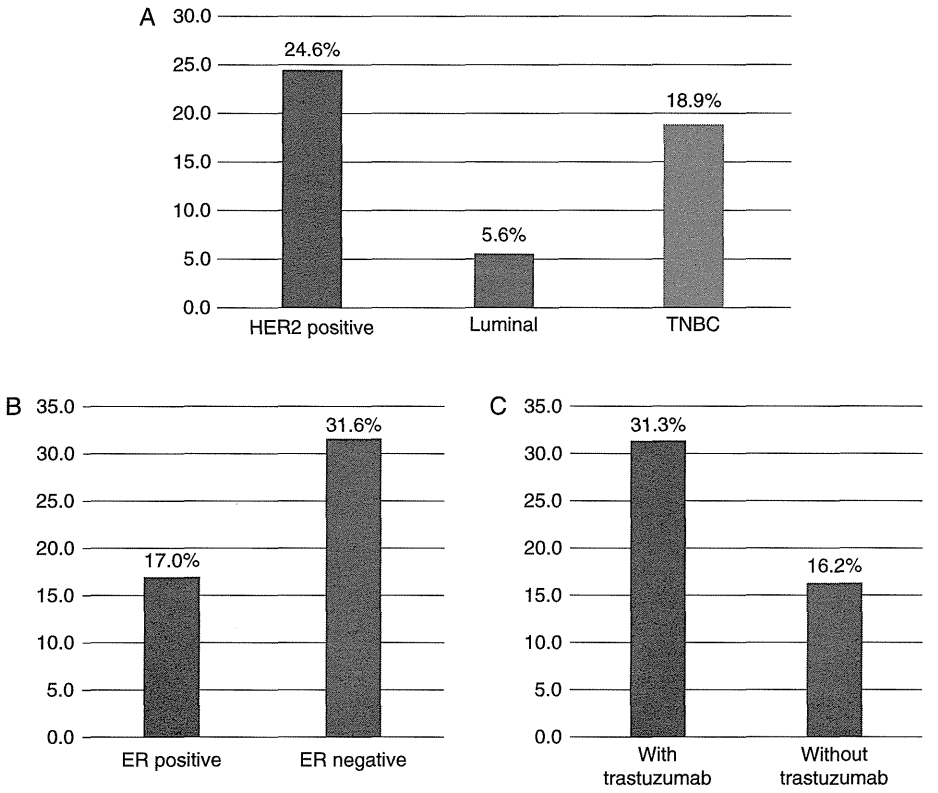

Figure 2. Rates of pathologic complete in response by (A) subtype (HER2-positive, luminal, triple-negative), (B) ER status (for HER2-positive tumors), and (C) treatment with trastuzumab as neoadjuvant therapy (HER2-positive tumors).

Table 2. Change in HER2 status of the primary tumor after neoadjuvant therapy

Primary tumor		Residual tumor	
HER2 status	n	HER2 status	n
Positive	2811	Positive	2210 (78.6%)
		Negative	601 (21.4%)
Negative	9947	Positive	340 (3.4%)
		Negative	9607 (96.6%)
Immunohistochemical analysis			
HER2 3+	2447	HER2 3+	1948 (79.6%)
		HER2 2+	203 (8.3%)
		HER2 1+	163 (6.6%)
		HER2 0	133 (5.4%)
HER2 2+	2077	HER2 3+	128 (6.2%)
		HER2 0, 1+, 2+	1949 (93.8%)
HER2 1+	3741	HER2 3+	68 (1.8%)
		HER2 0, 1+, 2+	3673 (98.2%)
HER2 0	4196	HER2 3+	45 (1.1%)
		HER2 0, 1+, 2+	4151 (98.9%)
FISH analysis			
Positive	203	Positive	186 (91.6%)
		Negative	17 (8.4%)
Negative	572	Positive	28 (4.9%)
		Negative	544 (95.1%)

who received trastuzumab and those who did not ($P < 0.0001$). Of the 1385 patients who received trastuzumab as neoadjuvant therapy, 342 (24.7%) showed HER2 discordance. Similarly, of the 1426 patients who did not receive trastuzumab as neoadjuvant therapy, 259 (18.2%) showed HER2 discordance. Furthermore, there were statistically significant differences in discordance rates in relation to pretreatment ER status ($P < 0.0001$) and PgR status ($P < 0.0001$). In contrast, there were no statistically significant differences in HER2 discordance rates between premenopausal and menopausal women ($P = 0.440$) or among patients with residual tumors of different volumes ($P = 0.345$).

discussion

To the best of our knowledge, we use largest dataset to compare tumor expression of ER, PgR, HER2 discordance after neoadjuvant chemotherapy. Our pCR rates, obtained in a setting of clinical practice, were lower than those reported in clinical trials. One reason may be that in our study, almost 70% of patients were treated with anthracyclines and taxanes, whereas in clinical trials with a focus on pCR, investigators often test new agents and higher doses, patients in the real world have higher age, and poor performance status than in clinical trials. Another may be that 44% of HER-positive patients did not receive trastuzumab as neoadjuvant therapy; it was not until 2008 that trastuzumab was approved as an adjuvant therapy by the Ministry of Health, Labour and Welfare in Japan. However, differences in pCR rates in our study with regard to cancer subtype and trastuzumab treatment were similar to those reported in clinical trials. For

instance, patients with luminal tumors had lower pCR rates than those with HER2-positive or triple-negative tumors. Among HER2-positive tumors, tumors negative for hormonal receptors had higher pCR rates after neoadjuvant chemotherapy than those positive for hormonal receptors. HER2-positive, tumors that are negative for hormonal receptors are highly dependent on the *HER2* gene and respond well to therapies targeted against HER2 such as trastuzumab and pertuzumab [19]. As might be expected, HER2-positive, ER-negative patients who show pCR have better prognosis than those who do not [3, 4]. A previous study found that the use of trastuzumab as a neoadjuvant increased pCR rate (43% with trastuzumab, 26% without) in HER2-positive cancer [6]. Our data also showed this.

Table 3. Change in ER and PgR status of the primary tumor after neoadjuvant therapy

Primary tumor		Residual tumor	
ER status	*n*	ER status	*n*
Positive	10 973	Positive	10 474 (95.5%)
		Negative	499 (4.5%)
Negative	5607	Positive	519 (9.3%)
		Negative	5088 (90.7%)
PgR status			
Positive	8280	Positive	6735 (81.3%)
		Negative	1545 (18.7%)
Negative	8235	Positive	766 (9.3%)
		Negative	7469 (90.7%)

Our results also showed that HER2 status does not necessarily carry over between the original tumor and residual tumors. In 21.4% of HER2-positive patients, the tumor converted to HER2-negative; further, according to immunohistochemistry, 635 (17.9%) of the 3548 patients with HER2-positive tumors before neoadjuvant chemotherapy had HER2-negative tumors afterward. However, inconsistencies in immunohistochemical testing, for example, in antigen retrieval methods, fixation, and observer analysis, may affect the results [20]. Another study [14, 15] using FISH found a loss of HER2 amplification in paired pre- and post-treatment specimens from patients treated with neoadjuvant trastuzumab. FISH data are more easily reproducible than immunohistochemical data [21, 22], and in our study, although the sample size for FISH analysis was small, FISH data were less likely to show discordance than immunohistochemical data.

We previously reported that trastuzumab therapy is not associated with an increased chance of loss of HER2 positivity in metastases, whereas chemotherapy is associated with an increase in the loss of such positivity [16]. Likewise, in a previous study of patients with residual disease treated with either chemotherapy alone or chemotherapy plus an anti-HER2 agent, HER2 expression loss was observed in 40% of the former group and 14.7% of the latter group [23]. We demonstrated that trastuzumab therapy is associated with increased odds of loss of HER2 positivity in residual tumors.

Nevertheless, it is unclear whether loss of HER2 amplification reflects response to therapy or a resistance mechanism and

Table 4. Discordance rates by clinical factors

	Post-treatment HER2 status ($N = 2811$)				*P*-value
	Negative (discordance)		Positive (concordance)		
	n	%	*n*	%	Pearson's χ^2
Pretreatment ER status					
Negative	169	13.0	1130	87.0	<0.0001
Positive	427	28.4	1075	71.6	
Pretreatment PgR status					
Negative	263	14.9	1501	85.1	<0.0001
Positive	330	32.0	701	68.0	
Menopausal status					
Pre	245	22.5	846	77.5	0.4626
Post	337	20.6	1301	79.4	
Unknown	19	23.2	63	76.8	
Neoadjuvant trastuzumab					
No	259	18.2	1167	81.8	<0.0001
Yes	342	24.7	1043	75.3	
Volume of residual tumor					
<50%	265	22.3	923	77.7	0.3436
>50%	313	20.8	1192	79.2	
Year of registration					
2004–2007	159	18.95	680	81.05	0.0405
2008–2011	442	22.41	1530	77.59	
Surgical cases at institution					
>100 cases/year	277	19.74	1126	80.26	0.0346
<100 cases/year	324	23.01	1084	76.99	

Volume of residual tumor: size of residual tumor divided by size of primary tumor.