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BACKGROUND

Breast cancer subtype¹
HR+/HER2-
 Most common in Japan

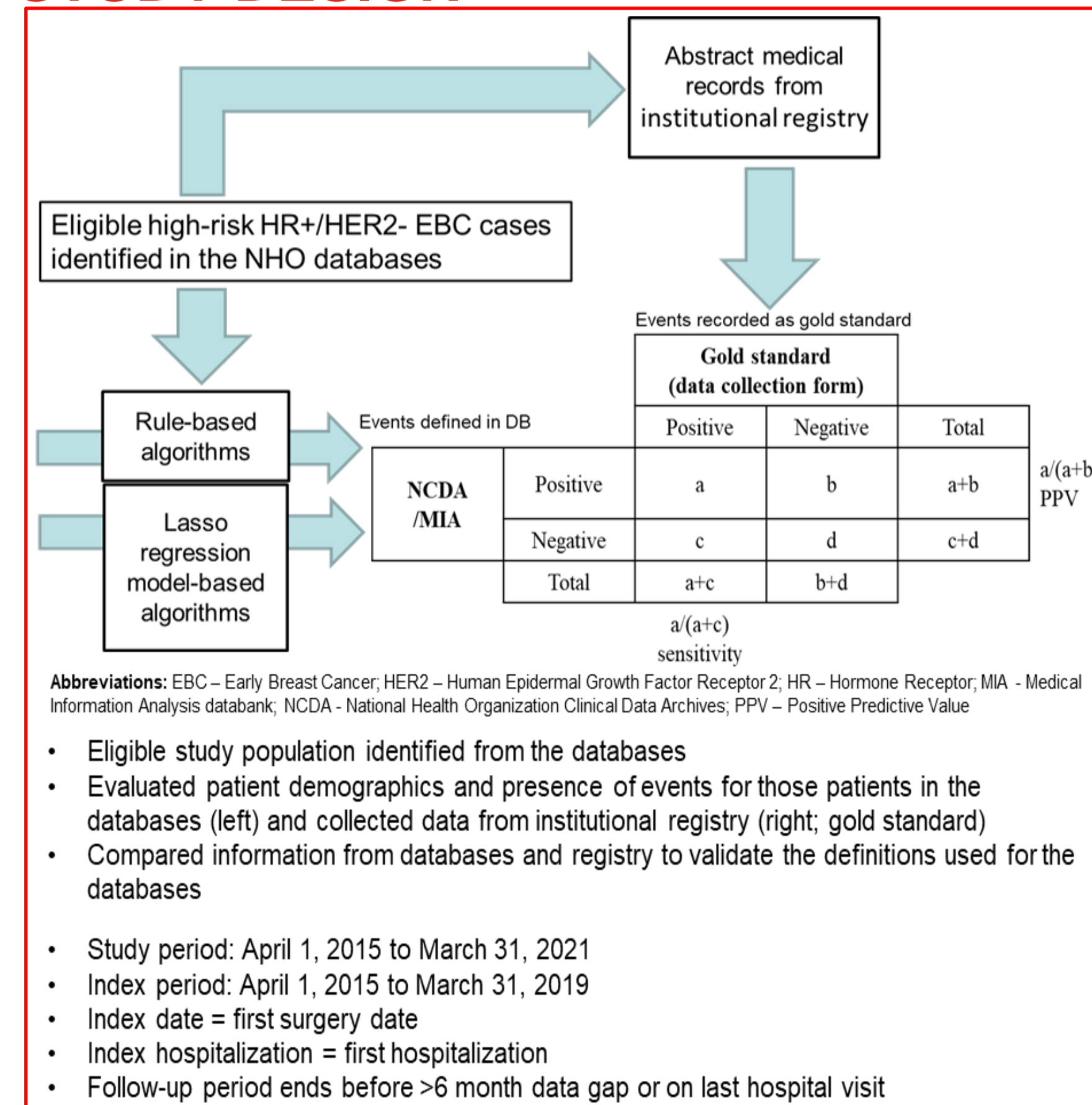
Breast cancer recurrence^{2,3}
30%–37%
 Among high-risk patients

- The monarchE⁴ study assessed a new treatment option in patients with hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) early breast cancer (EBC), who
 - had surgery ± radiotherapy and/or (neo) adjuvant chemotherapy, and
 - were at high risk of recurrence (≥4 positive nodes, OR 1-3 positive nodes AND [Grade 3, tumor ≥5 cm, or centrally assessed Ki-67 ≥20%])
- Population-level breast cancer recurrence data is unavailable but claims data may be used as a proxy to detect recurrence.⁵
- Models to estimate breast cancer recurrence using real-world data have been reported from Denmark, Canada, and the United States.⁵
- Limited real-world evidence for clinical outcomes and lack of validated algorithms to define such outcomes in Japan, especially in high-risk patients.

OBJECTIVE

- To develop and validate algorithms for identifying metastasis/recurrence events in high-risk patients with HR+/HER2- EBC using hospital-based databases.

STUDY DESIGN



KEY RESULT

Validation of Rule-based and Lasso-based Definitions for Metastasis/Recurrence

Algorithm	Rule-based 1	Rule-based 2	Lasso-based
Sensitivity (95% CI)	93.8 (71.7-98.9)	68.8 (44.4-85.8)	87.5 (64.0-96.5)
PPV (95% CI)	62.5 (42.7-78.8)	68.8 (44.4-85.8)	73.7 (51.2-88.2)
Registry (+) AND Database (+)	15	11	14
Registry (-) AND Database (+)	9	5	5
Registry (+) AND Database (-)	1	5	2
Registry (-) AND Database (-)	141	145	145
Registry (+)	16	16	16
Registry (-)	150	150	150
Database (+)	24	16	19
Database (-)	142	150	147
Total	166	166	166

The + and - symbols denote presence and absence of the event. **Abbreviations:** CI – Confidence Interval; PPV – Positive Predictive Value

- Sixteen metastasis/recurrence events identified as true outcomes from the registry
- Lasso-model had high sensitivity (87.5%) and highest positive predictive value (PPV; 73.7%)

CONCLUSIONS

- Algorithm developed with the Lasso method resulted in relatively high sensitivity (87.5%) and PPV (73.7%).
- Observed sensitivity and PPV were comparable to previous validation studies for breast cancer recurrence (sensitivity range 43.9–97.3%, PPV range 20.0–94.2% among 17 studies)⁵.
- Outcome validation studies in Japan are still quite scarce; this study contributes to establishing the basis for administrative database studies with higher credibility. However, more validation studies are warranted.

Limitations

- Patients were lost to follow-up if they moved to other hospitals in or outside the NHO network. Care provided outside the NHO network, if any, could not be detected in these databases.
- We used gold standard data from 2 NHO hospitals only. Generalizability of these results to other NHO hospitals or beyond the NHO hospitals needs further confirmation.

DISCLOSURES

- NI, TT, NK, and HH are employees of the National Hospital Organization, which received joint research fees from Eli Lilly and Company. The authors report no other competing interest in this work. ET received personal fees as honoraria from Chugai Pharmaceutical, AstraZeneca, Daiichi Sankyo, and Eli Lilly Japan K.K. KA received personal fees as honoraria from Chugai Pharmaceutical, Eisai, AstraZeneca, Taiho Pharmaceutical, Novartis Pharma, Daiichi Sankyo, Mochida Pharmaceutical, Ono Pharmaceutical, Pfizer and Eli Lilly Japan K.K., and his institution received research funds from Chugai Pharmaceutical, Eisai, and Takeda Pharmaceutical. ZC, SO, TK, and YT are employees of Eli Lilly Japan K.K. and minor stockholders of Eli Lilly and Company.
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REFERENCES

- Ushimado K et al. Fujita Med J. 2019;5:92–7. 2) Cheng L et al. Cancer Epidemiol Biomarkers Prev. 2012;21:800–9. 3) Sheffield KM et al. Future Oncol. 2022;18:2667–82. 4) Johnston SRD et al. J Clin Oncol. 2020;38:3987–98. 5) Izci H et al. J Natl Cancer Inst. 2020;112:979–88.

METHODS

Outcomes

- At each hospital, two independent specialists confirmed the outcomes and classification in the registry.
- Two models were used to develop algorithms to define metastasis/recurrence events in the NHO databases
 - Rule-based models:** 1) Metastasis/recurrence diagnosis codes, 2) Metastasis/recurrence diagnosis codes + drugs indicated for metastatic breast cancer (MBC) ≥6 months after index date
 - Lasso-based model:** Selected variables to identify metastasis/recurrence events from diagnosis codes, medication, and procedure as candidates of independent variables
- Event dates were defined as:
 - Rule-based 1: earliest date of the metastasis/recurrence diagnosis (>0 days)
 - Rule-based 2: earliest date of the metastasis/recurrence diagnosis (>0 days) or first date of MBC drug prescription (≥183 days)
 - Lasso-based: earliest date of the metastasis/recurrence diagnosis (>0 days) among selected variables by Lasso model with odds ratio >1.

RESULTS

Patient Demographics

Database	Registry
Mean ± SD age	Mean ± SD follow-up
55 ± 13 y	1341 ± 421 days
T1 – 32	N0 – 9
T2 – 93	N1 – 129
T3 – 26	N2 – 10
T4 – 15	N3 – 18
T stage, n	N stage, n
IIA – 30 (18.1)	IIB – 86 (51.8)
IIIB – 9 (5.4)	IIIC – 18 (10.8)
IIIC – 18 (10.8)	
Breast cancer stage, n (%)	

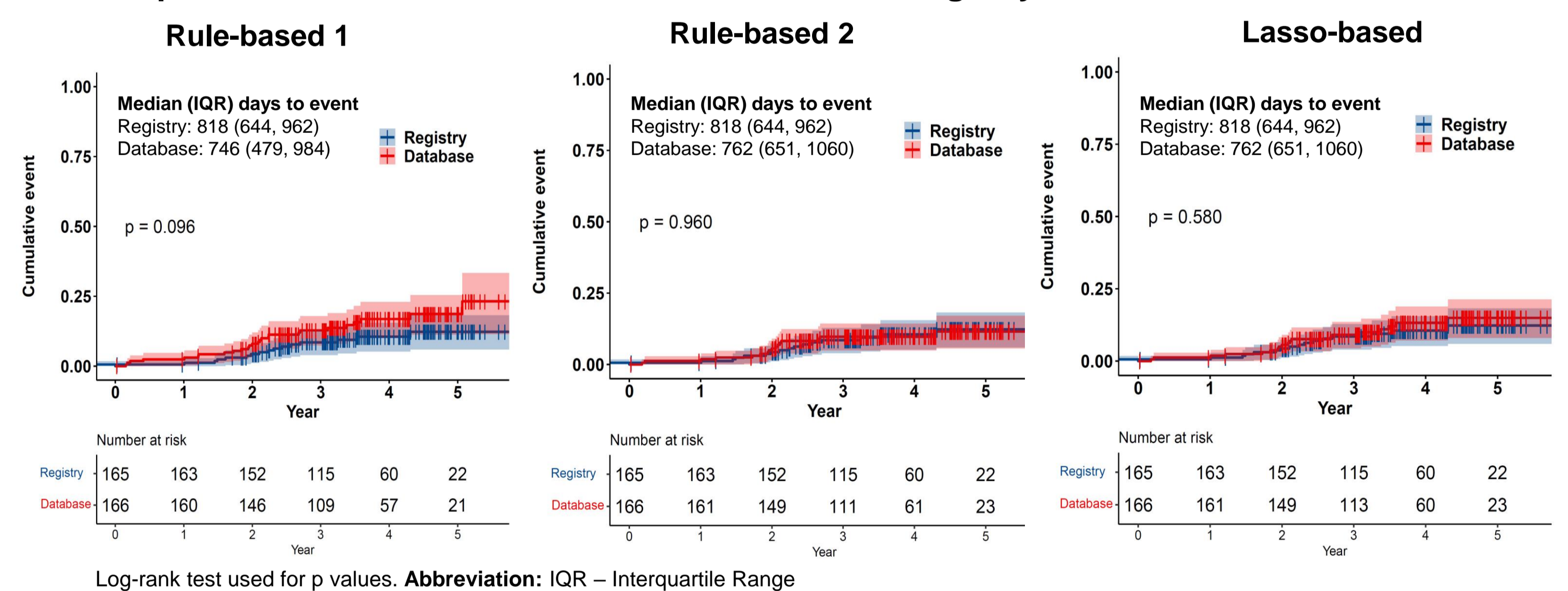
Parameter	Registry (n = 166)
Clinical T stage; n - T1/T2/T3/T4/Tis/unknown	32/93/26/15/11
Pathological T stage; n - T1/T2/T3/T4/Tis/unknown	47/87/22/6/2/2
Clinical N stage; n - N0/N1/N2/N3/unknown	52/86/10/17/1
Pathological N stage; n - N0/N1/N2/N3/unknown	31/85/33/17/0
Clinical diagnosis stage IIA, n (%)	42 (28.8)
Clinical diagnosis stage IIB, n (%)	59 (40.4)
Clinical diagnosis stage IIIA, n (%)	20 (13.7)
Clinical diagnosis stage IIIB, n (%)	8 (5.5)
Clinical diagnosis stage IIIC, n (%)	17 (11.6)
Pathological stage IIA, n (%)	30 (20.8)
Pathological stage IIB, n (%)	55 (38.2)
Pathological stage IIIA, n (%)	36 (25.0)
Pathological stage IIIB, n (%)	6 (4.2)
Pathological stage IIIC, n (%)	17 (11.8)
Histological grade 1, n (%)	40 (24.1)
Histological grade 2, n (%)	72 (43.4)
Histological grade 3, n (%)	45 (27.1)
Histological grade unknown, n (%)	9 (5.4)
Ki67 <20%, n (%)	36 (21.7)
Ki67 ≥20%, n (%)	69 (41.6)
Ki67 unknown, n (%)	61 (36.7)

Clinical diagnosis and pathological stage percentages are not based on n=166

Validation of Event Date for Metastasis/Recurrence

- Rule-based 2 and Lasso-based models showed the most similarity between registry and database events.
- However, Rule-based 2 model predicted fewer correct events than Lasso-based model.

Comparison of Event Dates between Database and Registry – Survival Plots



Variables to Identify Metastasis/Recurrence Events, Ranked by Coefficients of Lasso-based Model

- Top two variables were
 - secondary malignant neoplasm of other and unspecified sites, and
 - secondary malignant neoplasm of respiratory and digestive organs.

Variables to Identify Metastasis/Recurrence

Variable	Definition	Estimate	Coefficient
Secondary malignant neoplasm of other and unspecified sites	C79, except for "metastatic breast cancer" in C79.8	0.85	2.34
Secondary malignant neoplasm of respiratory and digestive organs	C78	0.71	2.03
Breast cancer recurrence	Recurrence disease codes in C50**	0.55	1.73
Drug for metastatic breast cancer	Prescription of drug indicated for metastatic breast cancer ≥6 months after the index date or later	0.50	1.65
Secondary and unspecified malignant neoplasm of lymph nodes	C77, except for C77.3 (axillary lymph node metastasis)	0.44	1.56

*Japanese disease name claims code 8848981, that is mapped to C79.8 in Japan claims system. **Japanese disease name claims codes that are mapped to C50.9 in Japan claims system are 8849815 - breast cancer local recurrence; 8849816 - breast cancer postoperative recurrence on chest wall; 1749009 - breast cancer recrudescence

Cancer Staging Consistency between Database and Registry

- Cancer stages for 166 patients observed in the database were compared with either the clinical or pathological stage reported in the registry. Comparisons were also performed for T and N staging.
- The count and proportion of patients with the same stage in the database and the registry are reported.

Clinical staging	T staging	N staging
n (%)	n (%)	n (%)
139 (83.7%)	159 (95.8%)	149 (89.8%)

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