AI-based analyses of trastuzumab deruxtecan-related interstitial lung disease/pneumonitis: TILD-A

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This study was sponsored by: **Daiichi Sankyo**

Conflict of Interest

Conflict of Interest Self-Declaration Form: **Naoya Tanabe**

		Applicability	If applicable, company name, etc
1	Position as an officer or advisor	No	
2	Ownership of stock	No	
3	Royalties fees or licensing fees	No	
4	Honoraria, etc.	No	
5	Manuscript fees, etc.	No	
6	Research funding	No	
7	Donation	No	
8	Consulting fee for litigation, etc.	No	
9	Accept contract researcher	No	
10	Endowed course	No	
11	Other remuneration	No	

Background (1/2)

- Trastuzumab deruxtecan (T-DXd) has been used in Japan for the treatment of HER2-positive and HER2-low unresectable or metastatic breast cancer patients who have previously received chemotherapy in the metastatic setting[1]

- Interstitial lung disease/pneumonitis is defined as the important risk of T-DXd[1,2,3]

- In the nine-trial pooled analysis[4], the independent ILD adjudication committee (AC) detected T-DXd–related ILD/pneumonitis (T-DXd–ILD) onset earlier than the investigators for 53.2% events adjudicated. The median (range) difference in detection between the ILD AC and investigators was 43 (1-499) days.

- Multidisciplinary guidelines for diagnosing and managing T-DXd–ILD recommend proactive patient monitoring[2]

- While computed tomography (CT) is periodically performed during T-DXd treatment, the accuracy and reproducibility of diagnosing T-DXd–ILD to promote early detection remain to be improved.

1. Enhertu (trastuzumab deruxtecan). Package insert. Daiichi Sankyo Co.,Ltd (Japan); 2025., 2. Swain SM, et al. *Cancer Treat Rev*. 2022;106:102378., 3.Rugo HS, et al. *ESMO Open*. 2022;7(4):100553., 4. Powell CA, et al. *ESMO Open*. 2022;7(4):100554

Background (2/2)

- The Artificial intelligence-based quantitative CT analysis software (AIQCT) was co-developed by Kyoto University and FUJIFILM Corporation using deep learning methods for HRCT images of patients with ILD[1]

- AIQCT can consistently and automatically detect, classify and quantify the volume of each lung parenchymal pattern: ground-glass opacities (GGO), consolidation, reticulation, honeycombing, nodules, interlobular septum, bronchi, vessels, and normal lung regions[1]

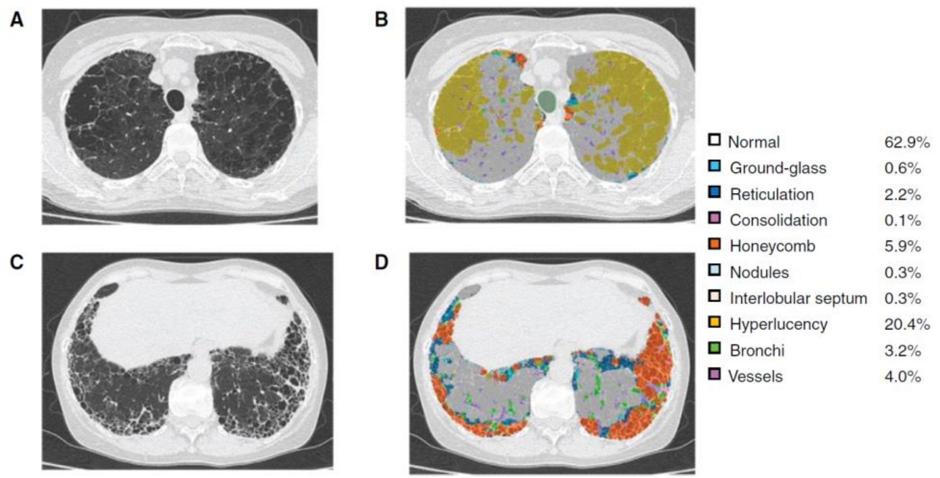


Figure 1. Visualization and quantification of lung parenchymal lesions using the artificial intelligence-based quantitative computed tomographic (CT) system. (*A–D*) Representative high-resolution CT scans (*A* and *C*) and corresponding overlayed images (*B* and *D*) are shown.

- Quantitative Evaluation Support Program for ILD has been approved in Japan this April[2]

1. Handa, T. et al. Ann Am Thorac Soc. 2022:19:399., 2. Quantitative Evaluation Support Program for ILD FS-AI694, package insert. FUJIFILM Corporation, 2025.

Objectives

The AIQCT software was evaluated for its potential to assist in the imaging diagnosis of T-DXd-related ILD/pneumonitis (T-DXd–ILD)

1. To determine whether AIQCT can detect, classify and quantify the abnormal lung lesions of T-DXd–ILD on chest CT images

2. To assess the diagnostic performance of AIQCT by performing receiver operating characteristic (ROC) analysis based on the quantified proportion of abnormal lesions on chest CT images.

3. To compare the diagnostic accuracy of the readers for T-DXd–ILD with and without the assistance of AIQCT.

T-DXd : trastuzumab deruxtecan, ILD: Interstitial lung disease, CT: computed tomography, ROC: receiver operating characterstic,

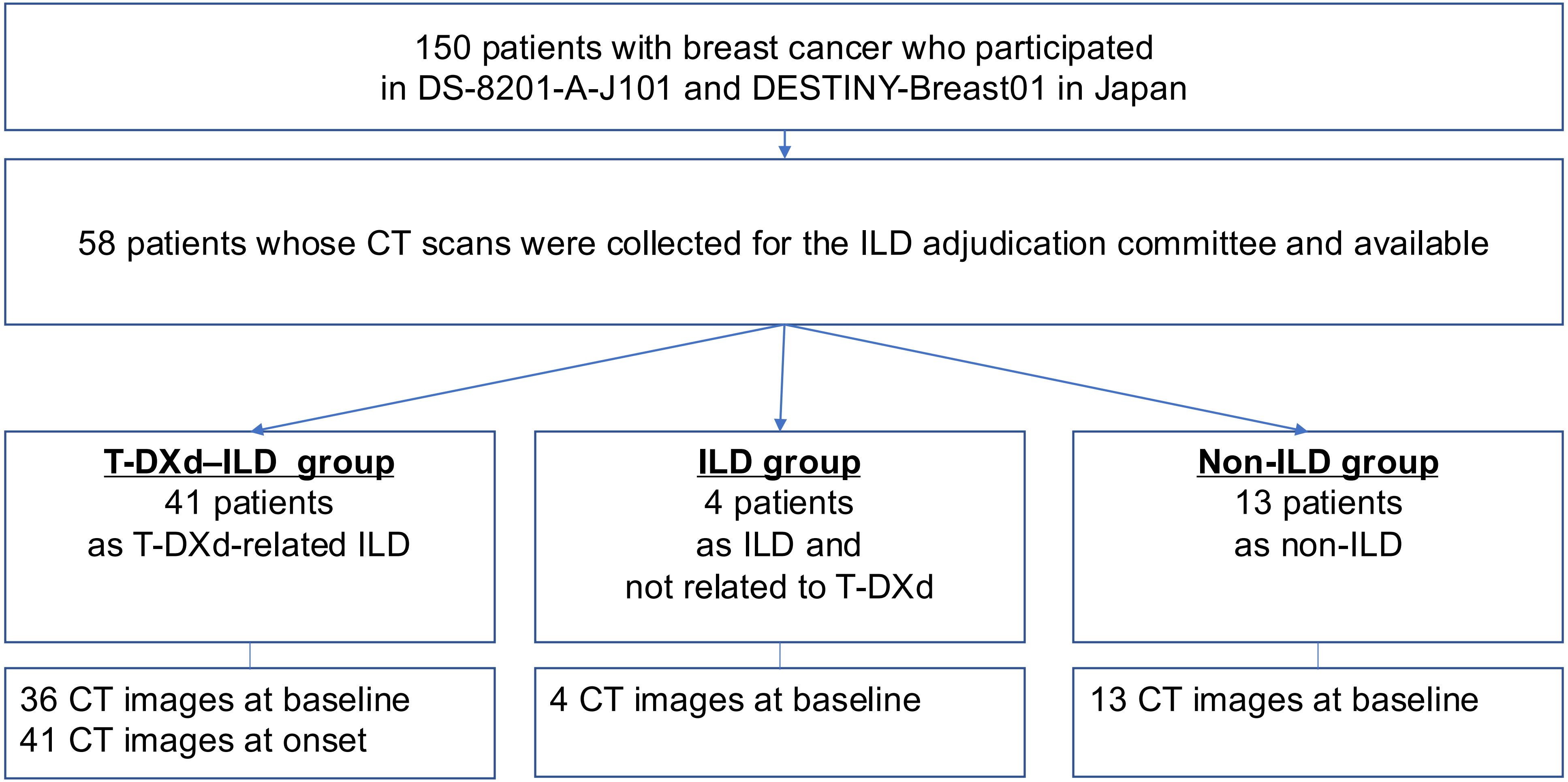
Methods

- This was a single-center retrospective study (UMIN000047612).
- Chest CT images which were collected for the ILD adjudication committee (AC) assessment from breast cancer patients who participated in phase I DS8201-A-J101 and phase II DESTINY-Breast01 (DB01) trials in Japan and received at least one dose of T-DXd were used*.
- The judgement of ILD AC is used as the reference standard.
- Chest CT images at baseline and at the T-DXd–ILD onset were evaluated with AIQCT
- The volumes as percentage of the abnormal lesion to the total lung volume on chest CT images were calculated.
- In the reading test, four independent respiratory physicians – two with more than 20 years of experience and two with less than 10 years – interpreted chest CT images with or without AIQCT-assistance.

*Data Cut-Off date are Feb 1, 2019 in J101, and Mar 21, 2019 in DB01

UMIN: University hospital medical information network, CT: computed tomography, ILD: Interstitial lung disease, T-DXd : trastuzumab deruxtecan, CT: computed tomography, ROC: receiver operating characterstic,

Patient selection



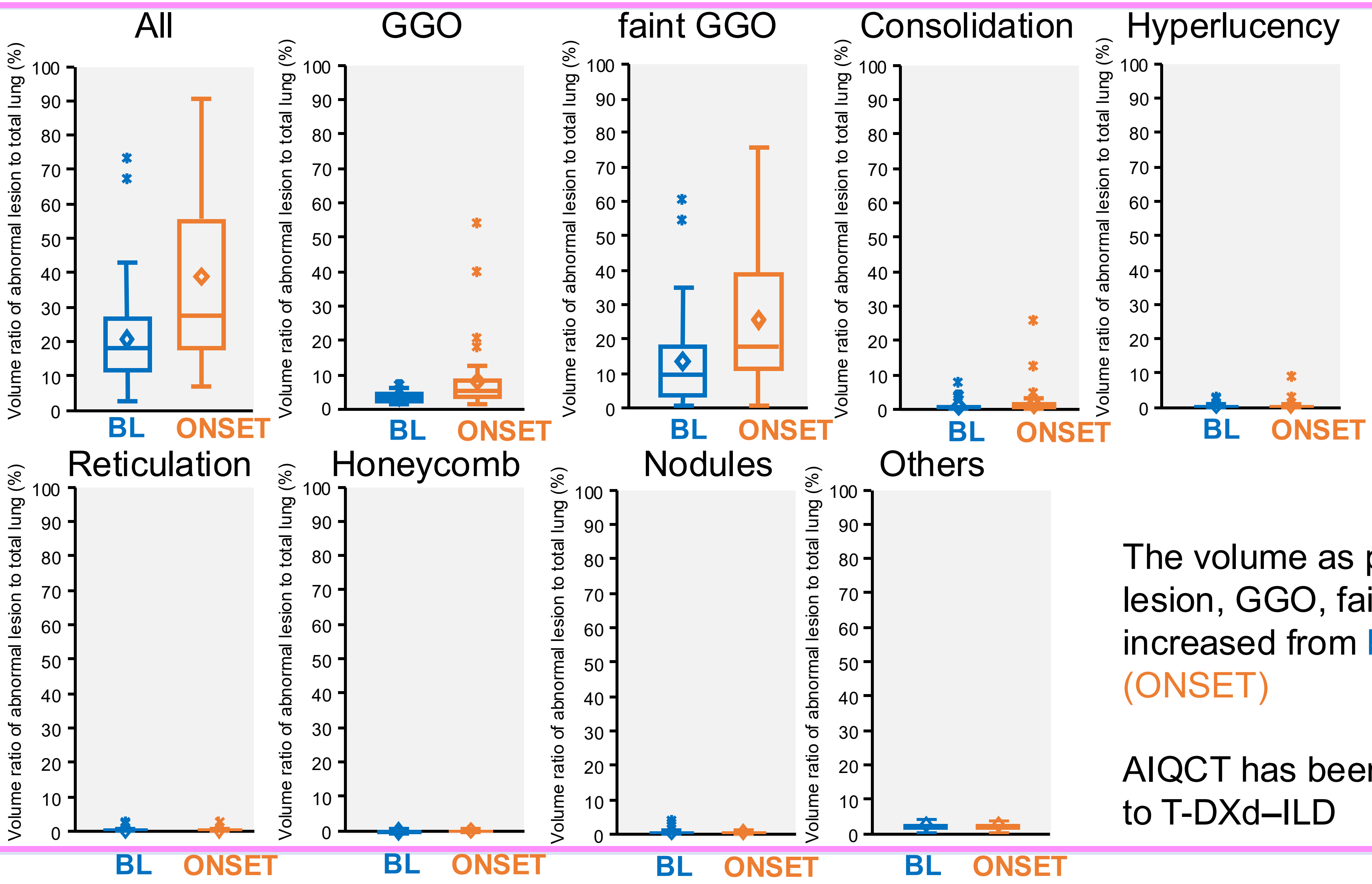
CT: computed tomography, T-DXd : trastuzumab deruxtecan, ILD: Interstitial lung disease

Patient characteristics

	Total N=58	T-DXd–ILD group N=41
Age (years)		
Median	57.5	57.0
(Min, Max)	(33, 79)	(33, 79)
Female, n (%)	57 (98.3)	40 (97.6)
ECOG PS, n (%)		
0	43 (74.1)	33 (80.5)
1	15 (25.9)	8 (19.5)
Initial dose of T-DXd, n (%)		
5.4 mg/kg	20 (34.5)	11 (26.8)
6.4 mg/kg	31 (53.4)	24 (58.5)
> 6.4 mg/kg	7 (12.1)	6 (14.6)

T-DXd : trastuzumab deruxtecan, ILD: Interstitial lung disease, ECOG PS: Eastern Cooperative Oncology Group Performance Status

Classification and Quantification of T-DXd–ILD by AIQCT



BL (n=36)
ONSET (n=41)

The volume as percentage of all abnormal lesion, GGO, faint GGO and consolidation increased from baseline (BL) to ILD onset (ONSET)

AIQCT has been shown to be applicable to T-DXd–ILD

T-DXd : trastuzumab deruxtecan, ILD: Interstitial lung disease, GGO: Grand-glass opacity

Clinical performance of AIQCT- ROC analysis

ROC analysis: ROC curves were plotted using the percentage of All, GGO, faint GGO, and consolidation to the total lung volume. Cutoff values in which both sensitivity and specificity were better were selected using Youden's index.

	AUC (95%CI)	Cutoff (%)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Accuracy (95%CI)
All	0.71 (0.60-0.83)	33	0.49 (0.33-0.65)	0.86 (0.71-0.95)	0.80 (0.59-0.93)	0.60 (0.45-0.73)	0.66 (0.55-0.77)
GGO	0.75 (0.65-0.86)	4	0.63 (0.47-0.78)	0.81 (0.64-0.92)	0.79 (0.61-0.91)	0.66 (0.50-0.80)	0.71 (0.60-0.81)
Faint GGO	0.69 (0.57-0.81)	10	0.78 (0.62-0.89)	0.58 (0.41-0.74)	0.68 (0.53-0.81)	0.70 (0.51-0.85)	0.69 (0.57-0.79)
Consolidation	0.52 (0.39-0.65)	1	0.37 (0.22-0.53)	0.83 (0.67-0.94)	0.71 (0.48-0.89)	0.54 (0.40-0.67)	0.58 (0.47-0.70)

The AIQCT's performance using the volume ratio of GGO as an indicator resulted in better accuracy with an AUC of 0.75 (95%CI: 0.65-0.86).

T-DXd : trastuzumab deruxtecan, ILD: Interstitial lung disease, GGO: Grand-glass opacity, AUC: Area under the curve

Sensitivity, specificity and accuracy of the 4 pulmonologists' independent and AIQCT-assisted diagnosis

The slice images were randomly selected from one chest CT image with or without AIQCT-assistance for each patient (either at baseline or at onset) and shuffled in random order.
Four pulmonologists interpreted the slice images with and without AIQCT-assistance: two with more than 20 years of experienced (#1 and #2) and two with less than10 years of experienced (#3 and #4).

		Sensitivity		Specificity		Accuracy	
	AIQCT-assisted	-	+	-	+	-	+
#1	>20-years	0.82	0.80	0.73	0.87	0.76	0.85
	95%CI	(0.57, 0.96)	(0.52, 0.96)	(0.54, 0.87)	(0.73, 0.96)	(0.62, 0.87)	(0.73, 0.93)
#2	>20-years	0.71	0.93	0.91	0.72	0.84	0.78
	95%CI	(0.44, 0.90)	(0.68, 1.00)	(0.76, 0.98)	(0.55, 0.85)	(0.71, 0.93)	(0.64, 0.88)
#3	<10-years	0.65	0.87	0.97	0.90	0.86	0.89
	95%CI	(0.38, 0.86)	(0.60, 0.98)	(0.84, 1.00)	(0.76, 0.97)	(0.73, 0.94)	(0.77, 0.96)
#4	<10-years	0.82	0.80	0.79	0.90	0.80	0.87
	95%CI	(0.57, 0.96)	(0.52, 0.96)	(0.61, 0.91)	(0.76, 0.97)	(0.66, 0.90)	(0.75, 0.95)

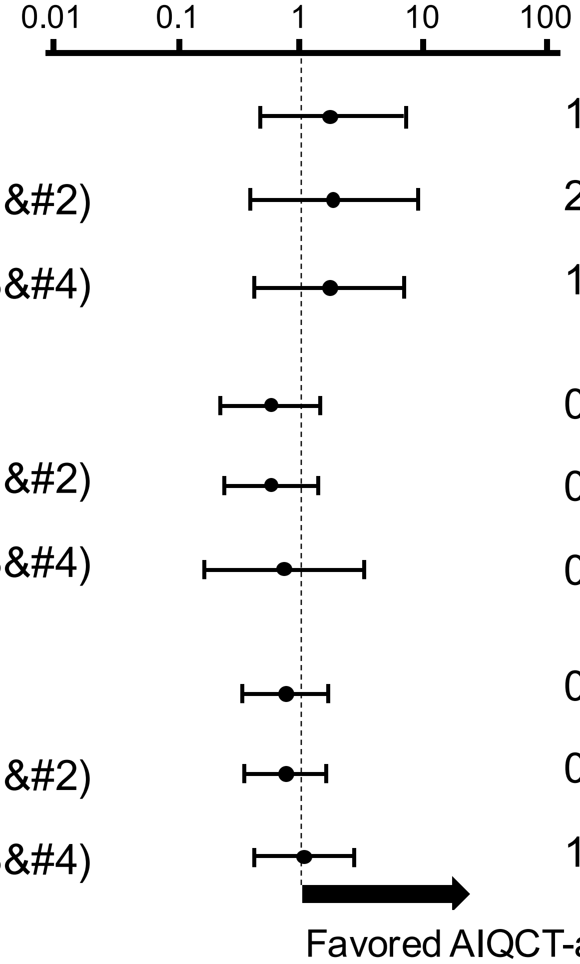
The use of AIQCT resulted in an increase in sensitivity for two pulmonologists and an increase in specificity for another two, while a trade-off between sensitivity and specificity was observed. An increase in accuracy was observed in three out of four. However, no statistically significant differences were observed.

CT: computed tomograp hy, CI: Confidence interval

Sensitivity, specificity and accuracy of the 4 pulmonologists

A generalized linear model was used to investigate the impact of AIQCT-assistance on diagnostic sensitivity, specificity, and accuracy among all pulmonologists collectively. Additionally, we examined whether there were differences in the effects of AIQCT-assistance based on the years of experience of the pulmonologists.

Odds ratio of with AIQCT-assistance vs without AIQCT (95%CI)



Sensitivity		
All	1.89	(0.47, 7.56)
>20 year (#1&#2)	2.00	(0.40, 10.12)
<10 year (#3&#4)	1.80	(0.43, 7.61)
Specificity		
All	0.59	(0.24, 1.47)
>20 year (#1&#2)	0.76	(0.17, 3.43)
<10 year (#3&#4)	0.59	(0.23, 1.54)
Accuracy		
All	0.77	(0.35, 1.73)
>20 year (#1&#2)	0.78	(0.36, 1.70)
<10 year (#3&#4)	1.09	(0.41, 2.90)

The odds ratio exceeded one for sensitivity in all pulmonologists, regardless of the years of experience, and accuracy in <10-year. However, no statistically significant differences were observed in any of the results.

Comparison of accuracy between pulmonologists and AIQCT

The number and proportion of discrepancies between pulmonologists' accuracy (without AIQCT-assistance) and AIQCT's accuracy for T-DXd–ILD were calculated.

	ALL N=41		
	Total number of disagreement with judgement of ILD AC	Difference in proportions of disagreement with judgement of ILD AC	
Pulmonologist	n (%)	(%)	95% CI
#1 (>20-years)	13 (31.7)	7.3	[-9.8, 24.4]
#2 (>20-years)	10 (24.4)	9.8	[-5.1, 24.6]
#3 (<10-years)	7 (17.1)	7.3	[-5.1, 19.8]
#4 (<10-years)	10 (24.4)	9.8	[-5.1, 24.6]

The differences in proportions of disagreement with judgement of ILD AC were all greater than zero.

These results indicated that AIQCT had a higher tendency to agree with the judgment of ILD AC compared to pulmonologist #1 to #4, although no statistically significant difference was observed.

CT: computed tomography, CI: Confidence interval, ILD: Interstitial lung disease, ILD AC: ILD adjudication committee

Summary

1. AIQCT could detect, categorize and quantify lung shadows in chest CT images of patients with adjudicated T-DXd-related ILD

2. The AIQCT's performance using the volume of Grand-glass opacity as an indicator resulted in better accuracy with an AUC of 0.75

3. The assistance of AIQCT had an impact on the pulmonologists' diagnostic sensitivity, specificity, or accuracy

4. AIQCT had a higher tendency to agree with the judgment of ILD AC compared to pulmonologists

These results suggest that AIQCT has the potential to be applied for detecting and monitoring T-DXd–ILD and assisting physicians in their diagnosis

T-DXd : trastuzumab deruxtecan, ILD: Interstitial lung disease

Risks/Limitations

- Like any retrospective observational study, we relied on accurate record-keeping from clinical trials, DS8201-A-J101 and DESTINY-Breast01
- This study only included data from patients enrolled in Japan, so the results may not fully represent the general population, potentially limiting their generalizability
- Additionally, the sample size was small
- Conducting larger studies would be useful to validate these findings