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Reply to: comment on “Early cancer detection by serum biomolecular fingerprinting spectroscopy with machine learning”

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Dear Editor,

In the accompanying Comment, Bratchenko et al. raised two concerns about the spectral data analysis pipeline employed for the Surface-enhanced Raman scattering and Artificial Intelligence for Cancer Screening (SERS-AICS) technique in our original paper¹: (1) inappropriate accuracy presentation and (2) the use of a single data split for model evaluation. As a promising technique for molecular fingerprinting, SERS-based early cancer detection approaches using biofluids and liquid biopsy are typically evaluated based strictly on their accuracy and reliability^{2–8}.

Regarding their first concern, the commenters stated that the accuracy was presented for the entire dataset instead of separating the training and test sets, leading to potential misinterpretation of the model's performance. They provided hypothetical examples to illustrate how combining training and test data can lead to an overestimation of the model's accuracy for early cancer prediction. In our study, we did separate training and test groups from cancer patients and healthy controls initially, using the training set to establish the AI model, which then generated the predictive values such as accuracy, sensitivity, and specificity. Adhering to the fundamental principles of building an algorithmic classification model, the training set was not subsequently used to evaluate performance. This approach avoids the high risk of

overfitting, which could lead readers to misjudge the accuracy of the SERS-AICS method for pan-cancer universal screening in real-world clinical samples.

We firmly believe that obtaining reliable predictions requires using the test cohort exclusively, without incorporating data from the training cohort. In our original paper, we adhered to a strict workflow, as detailed in the ‘Model training’ section of the ‘Materials and Methods’ in the supporting materials, which provides more comprehensive insights than the main-text part¹. We, however, used the term “internal” to represent “test” when referring to the real test sets in our supplementary Table S1, main-text (paragraph 2, line 25–30, page 5), and the figure legend of Fig. 3 in the original paper. This may have resulted in a misunderstanding for some readers, including the commenters (Fig. 1). In fact, our “training” set plus the “internal” set (referring to the “test” set) are equivalent to the actual internal set as typically used. We admit that the sample size and related descriptions in the original Fig. 3 may have caused some ambiguity. In the original Fig. 3a–e, the ‘*n*’ denoted the total number of samples of both the training and test cohorts. However, it is crucial to clarify here that the AUC values in Fig. 3a–e in the original paper were calculated based solely on the “internal/test” dataset. Additionally, we clearly indicated in both the figure and the corresponding figure legend, to highlight the contrast in sample sizes between the internal and external cohorts (Supplementary Fig. S9A–E in the original paper). Similarly, the calculations of accuracy, sensitivity, and specificity in Fig. 3g–i in the original paper were based exclusively on the “internal/test” cohort.

We have rechecked all our original data again and corrected some ambiguously split sample numbers in the

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a**Table S1 Summary of cancer patient and normal control clinical characteristic.**

Patient type	Cohort	Number	Gender		Age	AJCC stage			
			M	F		I	II	III	IV
Lung cancer (LC)	Training	195	146	49	59.08 ± 8.32 (30–79)	29	23	48	95
	Internal	49	39	10	62.49 ± 6.85 (35–81)	10	5	12	22
	External	57	42	15	59.24 ± 7.06 (32–78)	6	4	20	27
Colorectal carcinoma (CRC)	Training	172	94	78	58.49 ± 8.37 (33–84)	8	31	82	51
	Internal	44	22	22	57.11 ± 9.54 (29–78)	5	10	18	11
	External	63	38	25	56.78 ± 8.46 (27–76)	1	7	22	33
Gastric cancer (GC)	Training	156	88	68	56.64 ± 9.03 (28–80)	13	11	34	98
	Internal	39	21	18	58.46 ± 9.55 (36–79)	1	2	12	24
	External	52	36	16	60.77 ± 8.81 (35–82)	2	7	21	22
Hepatocellular carcinoma (HCC)	Training	163	105	58	56.23 ± 10.55 (26–79)	12	4	15	19
	Internal	40	25	15	57.21 ± 10.58 (33–78)	8	8	16	8
	External	38	30	8	57.63 ± 8.11 (23–83)	2	5	19	12
Esophageal carcinoma (ESCA)	Training	155	126	29	62.75 ± 6.20 (47–76)	18	24	68	45
	Internal	38	31	7	63.30 ± 6.75 (36–78)	2	5	23	8
	External	27	21	6	65.63 ± 6.57 (52–83)	1	2	13	11
Healthy control (HC)	Training	259	142	117	44.37 ± 10.43 (29–71)	/	/	/	/
	Internal	65	39	26	41.29 ± 11.65 (26–70)	/	/	/	/
	External	58	25	33	39.47 ± 10.55 (25–65)	/	/	/	/

LC lung cancer, CRC colorectal carcinoma, GC gastric cancer, HCC hepatocellular carcinoma, ESCA esophageal carcinoma, HC healthy control, Training and Internal The patients and healthy controls for the training set and internal validation set from Zhongnan Hospital, Hubei Cancer Hospital and Wuhan Hospital of Traditional Chinese and Western Medicine, Hubei, China (blue background), External The patients and healthy controls for the external validation set from the Tianjin Medical University General Hospital, Tianjin, China (marked in red), M male, F female, AJCC American Joint Committee on Cancer.

b

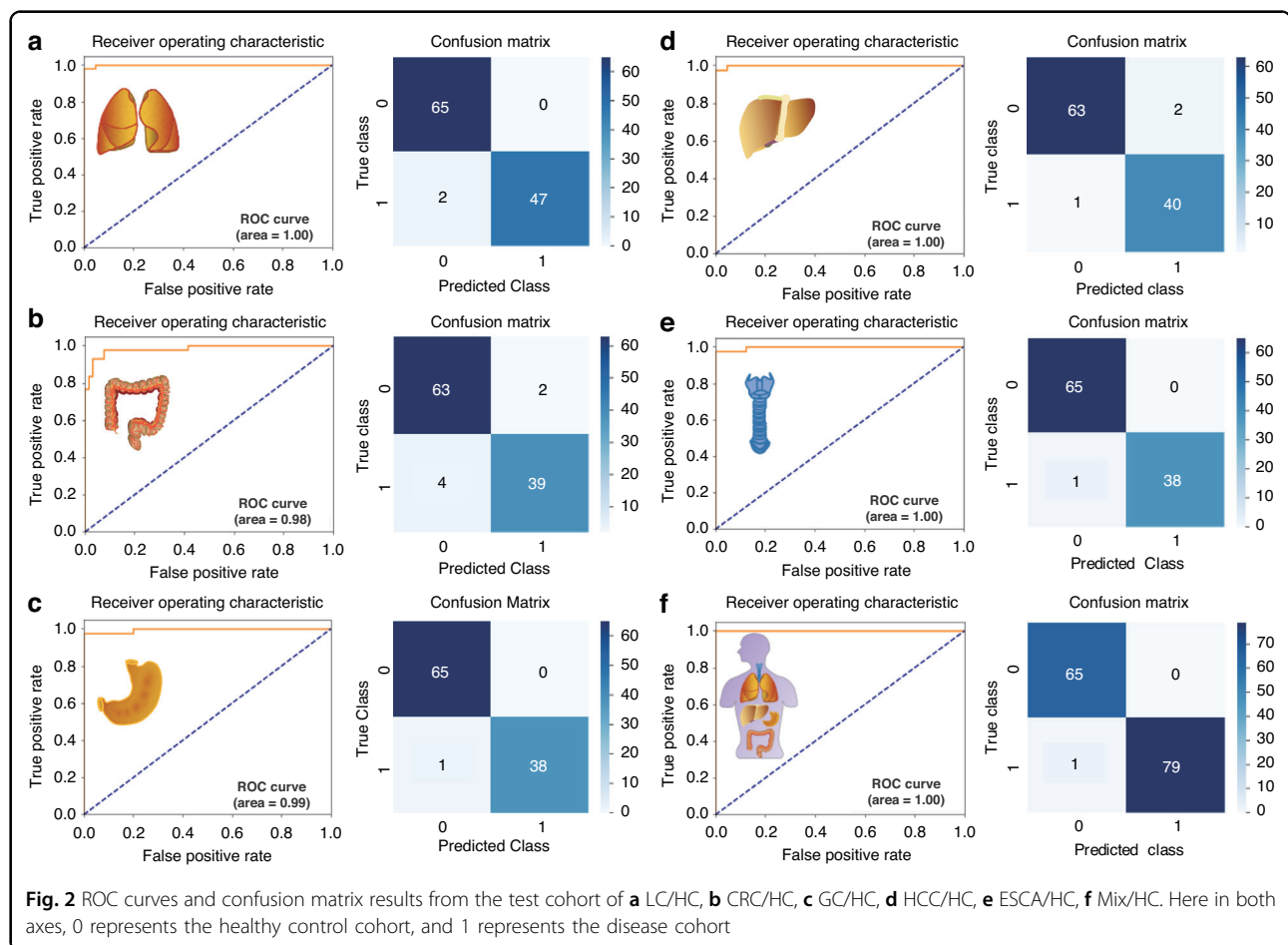
In order to evaluate the performance of the SERS-AICS system based on training data, we further analyzed the internal cohort of LC, which includes 49 patients and 65 healthy controls, for dimension reduction to 60 dimensions with the greatest differences in Raman spectrum for lung cancer (Additional file 1: Fig S3 and Additional file 1: Table S2). The dichotomies SVM classifier separated the 244 LC samples and 324 HC samples from both training and internal cohorts. As shown in Receiver Operating Characteristic (ROC) curve [31, 32], the area under the curve (AUC) [33] of the LC/HC model was 0.90 for discriminating lung cancer patients against healthy controls (Fig. 3A)

c

Fig. 3 SERS-AICS characterization of five cancers with high mortality. ROC curves with covariance matrices-assisted SVM model for distinguishing **A** 244 lung cancer patients, **B** 216 colorectal carcinoma patients, **C** 195 gastric cancer patients, **D** 203 hepatocellular carcinoma patients, **E** 193 esophageal carcinoma patients, **F** 400 mixture cancer patients from 324 healthy controls in the internal cohort. The **G** accuracy, **H** sensitivity and **I** specificity of single or multiple cancers/healthy control, the overall accuracy, sensitivity and specificity of all cancers could reach at 95.81%, 95.87%, 95.40%. The 400 mixed cancer patients were obtained by randomly selecting 80 samples from the five types of cancer each

Fig. 1 The original usage of the term “internal” to mean “test” in various parts of the paper **a** Supplementary Table S1. **b** Main-text (paragraph 2, lines 23–35, page 5). **c** Figure legend Fig. 3. The term “internal” and related information are highlighted in red



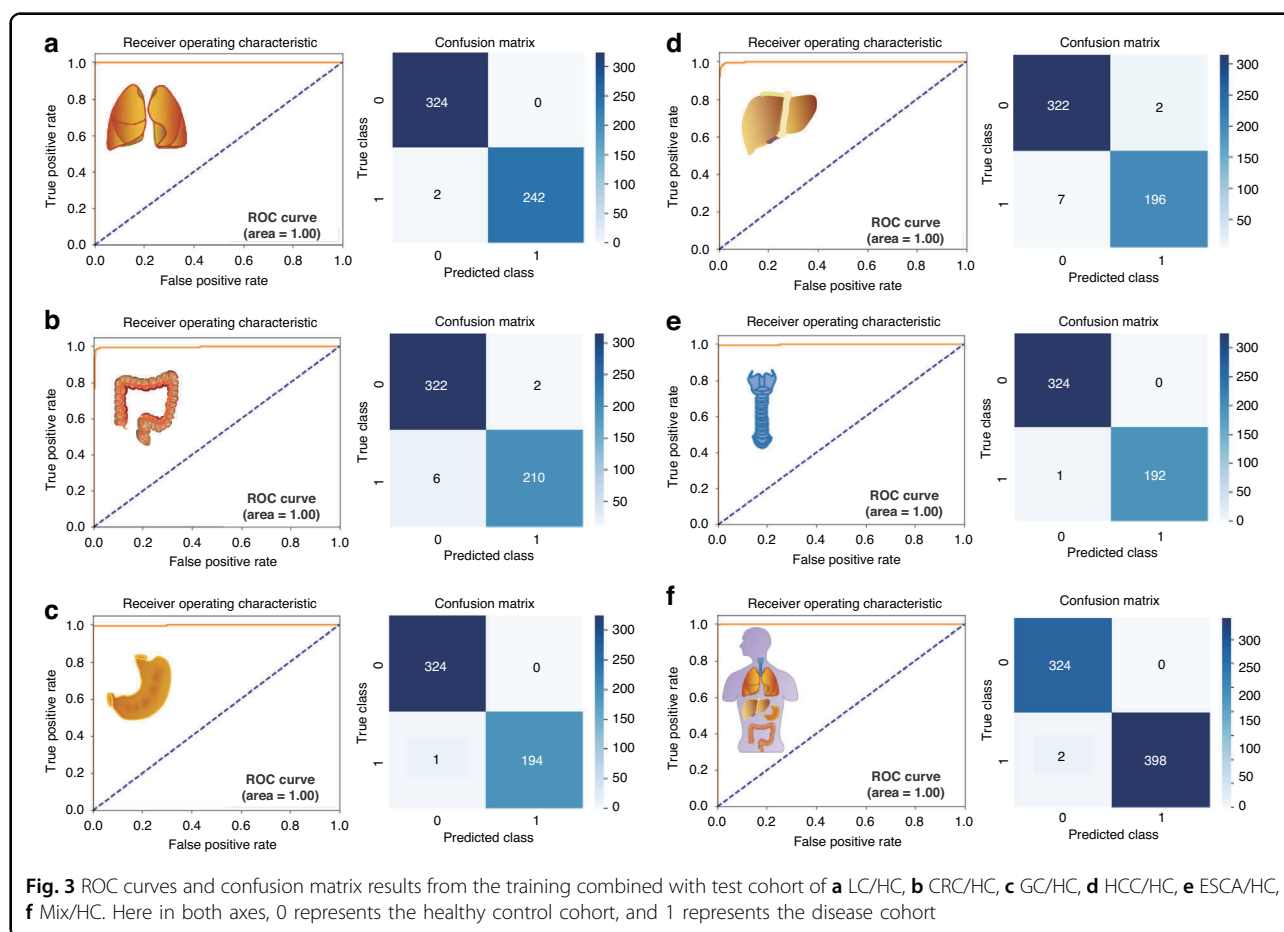


internal or external cohorts, which resulted from the data transfer from a former team member to his successors. The small adjustments are as follows: (1) for CRC, the sample sizes of the internal training group and test group have been adjusted to 173 and 43, respectively (previously reported as 172 and 44); (2) for GC, the sample size of the external group has been updated to 53 (previously stated as 52); (3) for HCC, the sample sizes of the internal training group and test group have been updated to 162 and 41, respectively (previously stated as 163 and 40); (4) for ESCA, the sample sizes of the internal training group and test group should be 154 and 39, respectively (previously reported as 155 and 38). We will use the revised numbers for the training and test groups in the following calculations.

To provide a clearer breakdown of our data processing, we randomly re-selected training and test sets in an 8:2 ratio from our total internal cohorts. We then recalculated the ROC curves and confusion matrices for the test cohort alone (Fig. 2) and the combined training and test cohort (Fig. 3) for all five cancer types separately. Additionally, to facilitate better comparison, we generated bar charts displaying accuracy, sensitivity, and specificity for

both the test cohort and the combined training and test cohort for each cancer type (Fig. 4). For the LC/Hc group, the test cohort exhibited an accuracy of 98.25% and a sensitivity of 95.92% at 100% specificity, which are lower than or equal to the combined training and test cohort values of 99.65% accuracy and 99.18% sensitivity at 100% specificity (Fig. 4a). Other cancer types also exhibited similar trends (Fig. 4b–e), suggesting that the combined cohort results may reflect overfitting as the commenters emphasized. Furthermore, when compared to these re-evaluated data, our previous data of Fig. 3g–i of the original paper showed slightly lower prediction values (Fig. 4). This comparison highlights our intent not to cherry-pick better results but to demonstrate the reliability of cancer prediction using our well-established algorithm. In summary, all the results indicate that we indeed used only the test cohort (described as “internal”) for the performance evaluation of our SERS-AICS method, excluding the training cohort to avoid biased results in the original paper. This suggests that our model for early cancer prediction is both reliable and applicable.

Secondly, Bratchenko et al. also pointed out that only one split of the dataset into training and test sets was



shown in our original paper, which could mask the variability and reliability of the model's performance. They emphasized the importance of demonstrating the resulting accuracy over multiple data splits, represented as mean $\pm$ deviation/confidence interval, for a more accurate depiction of model performance.

Actually, our analysis is already unbiased, based on the random selection of a test cohort with a 20% portion from the large dataset comprising approximately 200 independent individuals for each cancer patient group. To better address the commenters' questions regarding repetitions, we performed multiple random data splits for both the internal cohort and the early cancer/common disease cohort. This was done on an 8:2 basis, and the process was repeated a total of four times. The specific data resulting from these operations are presented in detail in Tables 1 and 2 below. In addition, the corresponding "Mean $\pm$ SD" values have been visually presented in graphs, which can be found in Figs. 5–6 for internal cohorts and Figs. 7–8 for early screening cohorts, respectively. Based on the data displayed, it is evident that the pan-cancer recognition strategy mentioned in our original paper continues to demonstrate significant

recognition advantages and stability. In our manuscript, using random data segmentation only once is not the optimal data segmentation type selected to achieve the best classification results, so it can more accurately reflect the model's ability to identify diseases. And similar practices are also reflected in some relevant literature references, including Zhang, H. et al.'s work on "Multiplexed Nanomaterial-Assisted Laser Desorption/Ionization for Pan-Cancer Diagnosis and Classification"⁹, Huang, L. et al.'s work on "Rapid, label-free histopathological diagnosis of liver cancer based on Raman spectroscopy and deep learning"¹⁰ and Wang, R. et al.'s work on "Bio-Inspired In-Sensor Compression and Computing Based on Phototransistors"¹¹. Therefore, we did not include standard deviation data with multiple splits of the same cohort in the original manuscript.

In addition to the internal cohorts, we have also re-executed the algorithm while implementing optimized processing techniques for the external cohorts. Upon comparing the original data with the revised data, it is evident that, with the exception of the sensitivity values for LC, GC, HCC, and ESCA, which experienced slight reductions in the revised external dataset, the majority of

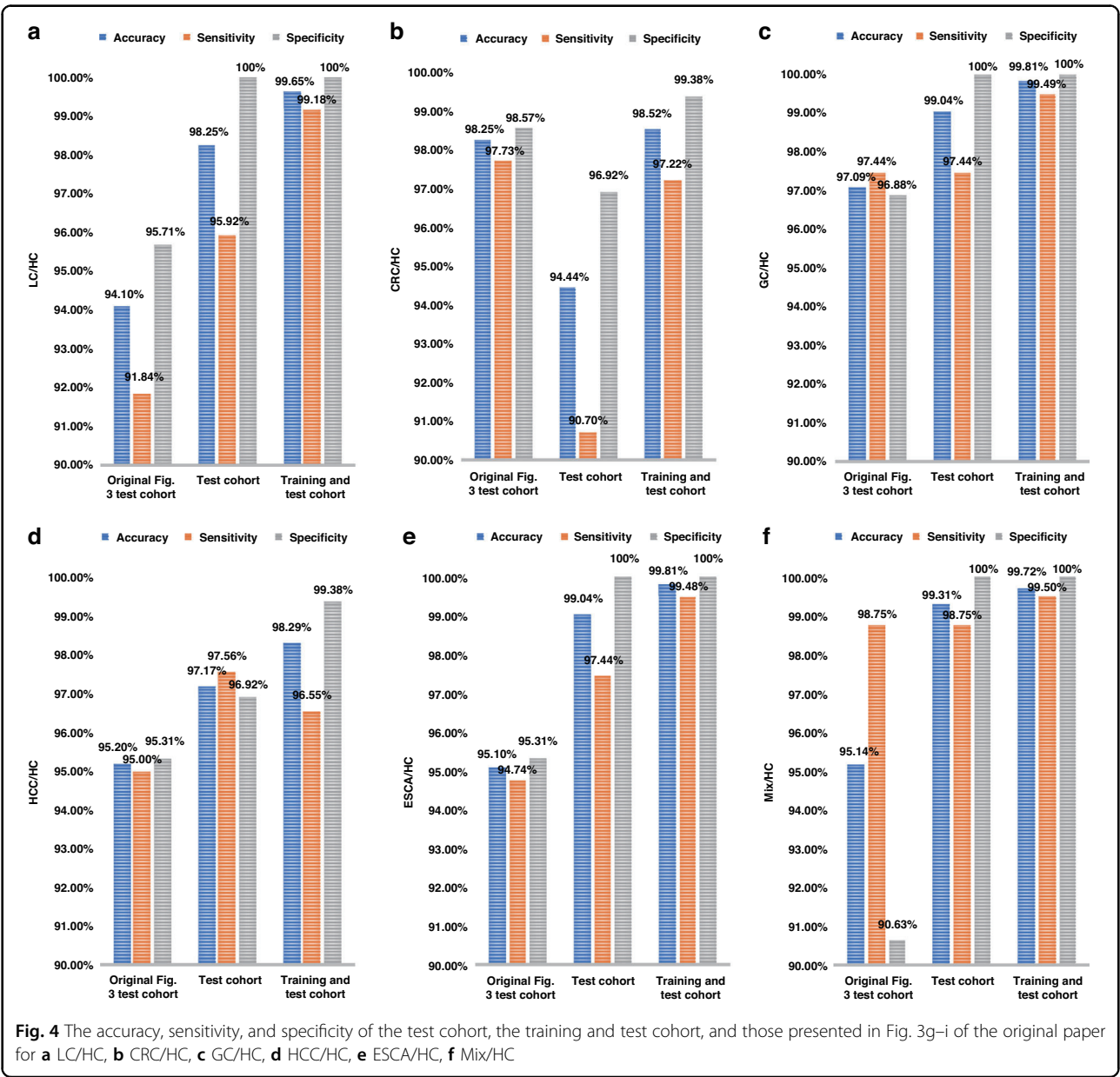


Table 1 Summary of accuracy, sensitivity, specificity, and AUC values with four repetitions from test and training sets separately within internal cohorts

Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal test sets of LC/Hc	Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal training sets of LC/Hc
1	97.37%	95.92%	98.46%	1.00		1	97.80%	95.90%	99.23%	0.99	
2	97.37%	93.88%	100.00%	0.99		2	97.36%	94.87%	99.23%	0.99	
3	95.61%	91.84%	98.46%	0.98		3	96.92%	94.36%	98.84%	0.99	
4	94.74%	89.80%	98.46%	1.00		4	97.36%	94.87%	99.23%	0.99	
Mean	96.27%	92.86%	98.85%	0.99		Mean	97.36%	95.00%	99.13%	0.99	
SD	1.10%	2.04%	0.58%	0.01		SD	0.22%	0.45%	0.15%	0.00	



Table 1 continued

Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal test sets of CRC/HC	Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal training sets of CRC/HC
1	95.37%	90.70%	98.46%	0.98		1	95.83%	93.06%	97.68%	0.99	
2	99.07%	97.67%	100.00%	1.00		2	95.83%	90.75%	99.23%	0.99	
3	92.59%	83.72%	98.46%	0.96		3	96.53%	92.49%	99.23%	0.99	
4	95.37%	88.37%	100.00%	0.99		4	96.06%	91.33%	99.23%	0.99	
Mean	95.60%	90.12%	99.23%	0.98		Mean	96.06%	91.91%	98.84%	0.99	
SD	1.74%	4.07%	0.77%	0.01		SD	0.23%	0.87%	0.58%	0.00	
Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal test sets of GC/HC	Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal training sets of GC/HC
1	99.04%	97.44%	100.00%	0.99		1	100.00%	100.00%	100.00%	1.00	
2	99.04%	97.44%	100.00%	1.00		2	99.76%	99.36%	100.00%	1.00	
3	98.08%	94.87%	100.00%	0.99		3	100.00%	100.00%	100.00%	1.00	
4	100.00%	100.00%	100.00%	1.00		4	99.76%	99.36%	100.00%	1.00	
Mean	99.04%	97.44%	100.00%	1.00		Mean	99.88%	99.68%	100.00%	1.00	
SD	0.48%	1.28%	0.00%	0.01		SD	0.12%	0.32%	0.00%	0.00	
Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal test sets of HCC/HC	Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal training sets of HCC/HC
1	99.06%	97.56%	100.00%	1.00		1	100.00%	100.00%	100.00%	1.00	
2	100.00%	100.00%	100.00%	1.00		2	99.76%	99.38%	100.00%	1.00	
3	95.28%	90.24%	98.46%	1.00		3	99.76%	99.38%	100.00%	1.00	
4	100.00%	100.00%	100.00%	1.00		4	99.76%	99.38%	100.00%	1.00	
Mean	98.59%	96.95%	99.62%	1.00		Mean	99.82%	99.54%	100.00%	1.00	
SD	1.65%	3.36%	0.58%	0.00		SD	0.09%	0.23%	0.00%	0.00	
Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal test sets of ESCA/HC	Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal training sets of ESCA/HC
1	99.04%	97.44%	100.00%	1.00		1	100.00%	100.00%	100.00%	1.00	
2	100.00%	100.00%	100.00%	1.00		2	99.76%	99.35%	100.00%	1.00	
3	99.04%	97.44%	100.00%	1.00		3	100.00%	100.00%	100.00%	1.00	
4	100.00%	100.00%	100.00%	1.00		4	99.76%	99.35%	100.00%	1.00	
Mean	99.52%	98.72%	100.00%	1.00		Mean	99.88%	99.68%	100.00%	1.00	
SD	0.48%	1.28%	0.00%	0.00		SD	0.12%	0.32%	0.00%	0.00	
Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal test sets of Mix/HC	Repeat	Accuracy	Sensitivity	Specificity	AUC	Internal training sets of Mix/HC
1	96.55%	95.00%	98.46%	0.99		1	99.31%	98.75%	100.00%	1.00	
2	99.31%	98.75%	100.00%	1.00		2	98.79%	98.12%	99.61%	1.00	
3	97.24%	98.75%	95.38%	1.00		3	98.96%	98.12%	100.00%	1.00	
4	97.24%	95.00%	100.00%	1.00		4	99.14%	98.44%	100.00%	1.00	
Mean	97.59%	96.88%	98.46%	1.00		Mean	99.05%	98.36%	99.90%	1.00	
SD	0.86%	1.88%	1.54%	0.00		SD	0.17%	0.24%	0.15%	0.00	

values demonstrated significant improvements in cancer prediction when utilizing our AICS algorithm. This comparative analysis is presented in Table 3 and Fig. 9.

In summary, we addressed the commenters' concerns by (1) clarifying the accuracy of our cancer screening AI algorithm was evaluated solely based on the test cohort,

not combined with the training cohort, to avoid over-fitting; and (2) demonstrating the reliability for our cancer prediction model by presenting consistent results even across multiple data splits. All the intermediate and final data presented here provide detailed and transparent explanations of the methodologies and results, ensuring



Table 2 Summary of accuracy, sensitivity, specificity, and AUC values with four repetitions from test and training sets separately within early screening internal cohorts

Repeat	Accuracy	Sensitivity	Specificity	AUC	Common disease	Repeat	Accuracy	Sensitivity	Specificity	AUC	Common disease
1	93.75%	100.00%	88.89%	1.00	/Early LC (Test)	1	100.00%	100.00%	100.00%	1.00	/Early LC (Training)
2	100.00%	100.00%	100.00%	1.00		2	98.44%	100.00%	97.22%	1.00	
3	100.00%	100.00%	100.00%	1.00		3	98.44%	100.00%	97.22%	1.00	
4	100.00%	100.00%	100.00%	1.00		4	98.44%	100.00%	97.22%	1.00	
Mean	98.44%	100.00%	97.22%	1.00		Mean	98.83%	100.00%	97.92%	1.00	
SD	2.34%	0.00%	4.17%	0.00		SD	0.58%	0.00%	1.04%	0.00	
Repeat	Accuracy	Sensitivity	Specificity	AUC	Common disease	Repeat	Accuracy	Sensitivity	Specificity	AUC	Common disease
1	78.57%	83.33%	75.00%	0.90	/Early CRC (Test)	1	100.00%	100.00%	100.00%	1.00	/Early CRC (Training)
2	85.71%	83.33%	87.50%	0.92		2	96.67%	92.31%	100.00%	1.00	
3	100.00%	100.00%	100.00%	1.00		3	95.00%	92.31%	97.06%	1.00	
4	92.86%	100.00%	87.50%	0.94		4	100.00%	100.00%	100.00%	1.00	
Mean	89.29%	91.67%	87.50%	0.94		Mean	97.92%	96.16%	99.27%	1.00	
SD	7.15%	8.34%	6.25%	0.03		SD	2.08%	3.85%	1.10%	0.00	
Repeat	Accuracy	Sensitivity	Specificity	AUC	Common disease	Repeat	Accuracy	Sensitivity	Specificity	AUC	Common disease
1	86.67%	71.43%	100.00%	1.00	/Early GC (Test)	1	100.00%	100.00%	100.00%	1.00	/Early GC (Training)
2	100.00%	100.00%	100.00%	1.00		2	100.00%	100.00%	100.00%	1.00	
3	100.00%	100.00%	100.00%	1.00		3	100.00%	100.00%	100.00%	1.00	
4	100.00%	100.00%	100.00%	1.00		4	100.00%	100.00%	100.00%	1.00	
Mean	96.67%	92.86%	100.00%	1.00		Mean	100.00%	100.00%	100.00%	1.00	
SD	5.00%	10.71%	0.00%	0.00		SD	0.00%	0.00%	0.00%	0.00	
Repeat	Accuracy	Sensitivity	Specificity	AUC	Common disease	Repeat	Accuracy	Sensitivity	Specificity	AUC	Common disease
1	100.00%	100.00%	100.00%	1.00	/Early HCC (Test)	1	100.00%	100.00%	100.00%	1.00	/Early HCC (Training)
2	92.31%	83.33%	100.00%	1.00		2	100.00%	100.00%	100.00%	1.00	
3	100.00%	100.00%	100.00%	1.00		3	100.00%	100.00%	100.00%	1.00	
4	100.00%	100.00%	100.00%	1.00		4	100.00%	100.00%	100.00%	1.00	
Mean	98.08%	95.83%	100.00%	1.00		Mean	100.00%	100.00%	100.00%	1.00	
SD	2.88%	6.25%	0.00%	0.00		SD	0.00%	0.00%	0.00%	0.00	

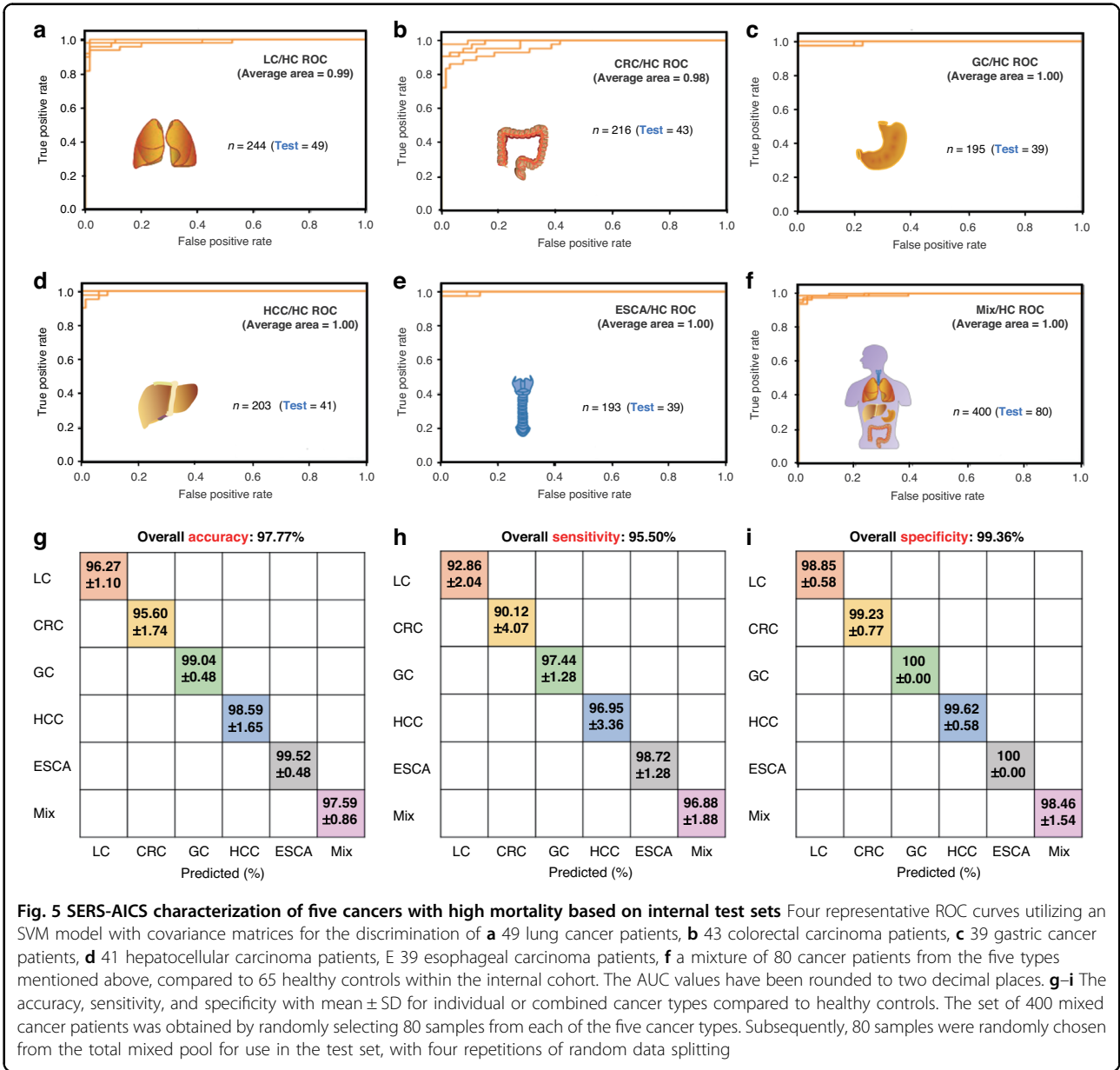
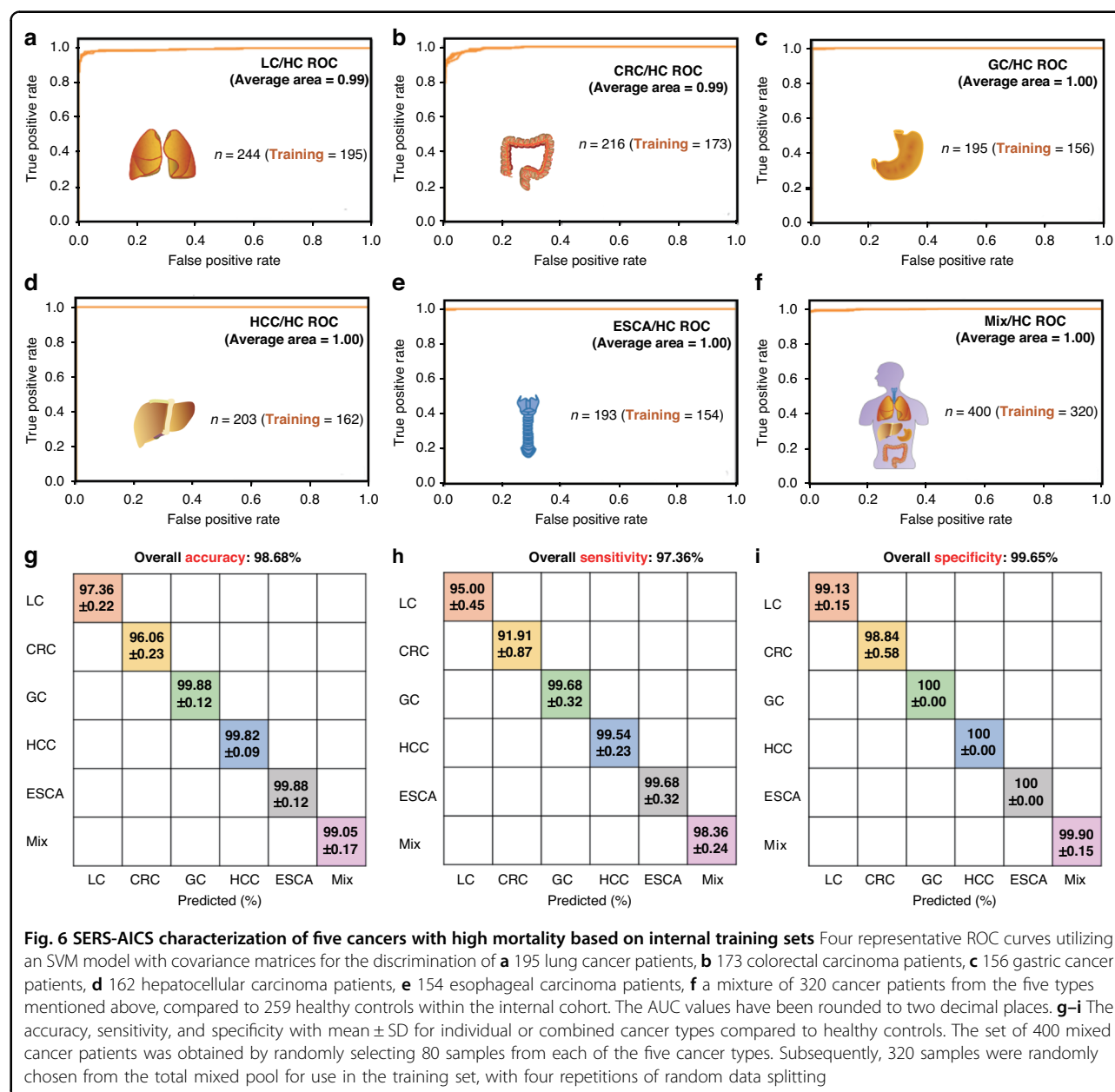
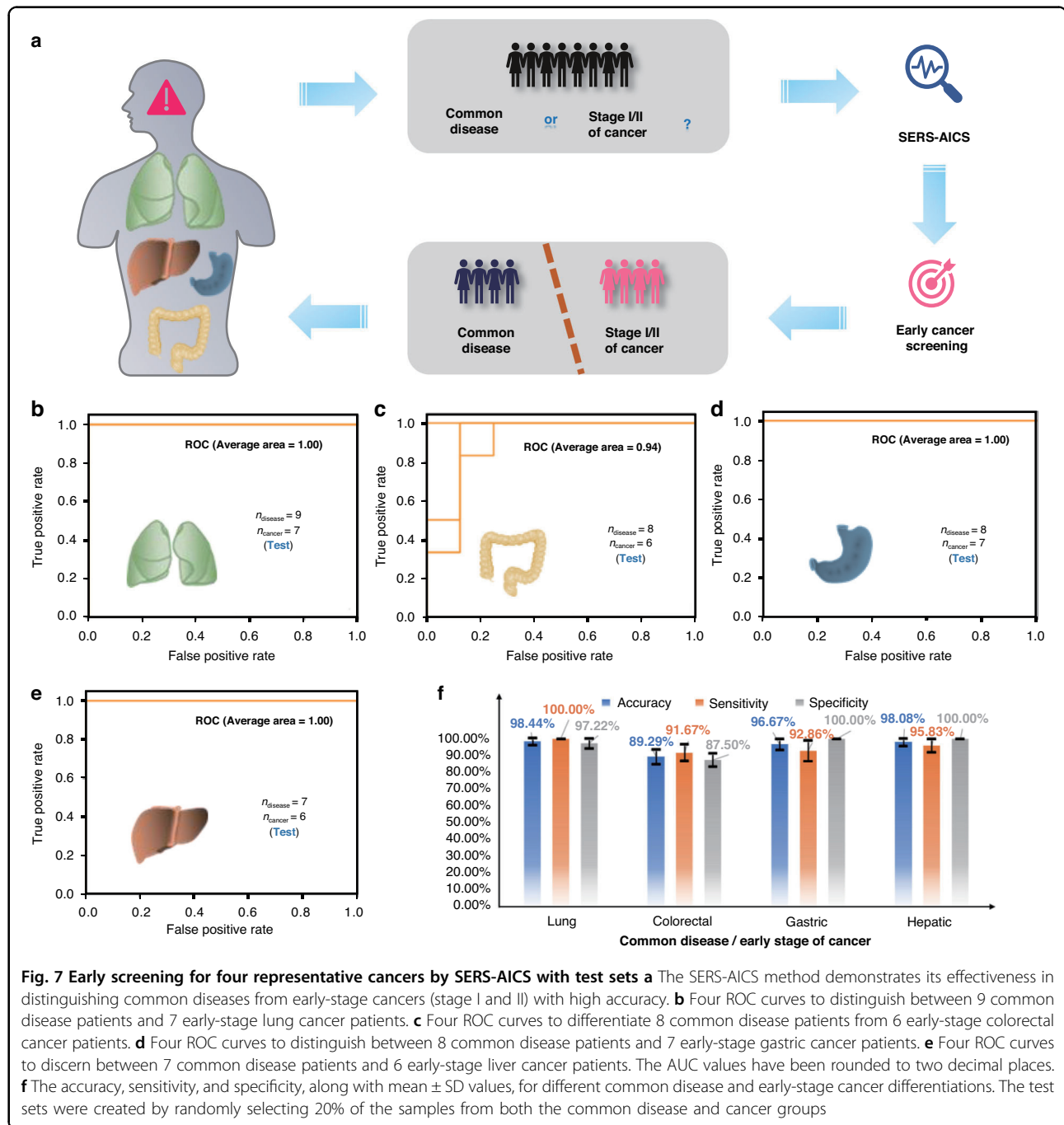


Fig. 5 SERS-AICS characterization of five cancers with high mortality based on internal test sets Four representative ROC curves utilizing an SVM model with covariance matrices for the discrimination of **a** 49 lung cancer patients, **b** 43 colorectal carcinoma patients, **c** 39 gastric cancer patients, **d** 41 hepatocellular carcinoma patients, **e** 39 esophageal carcinoma patients, **f** a mixture of 80 cancer patients from the five types mentioned above, compared to 65 healthy controls within the internal cohort. The AUC values have been rounded to two decimal places. **g–i** The accuracy, sensitivity, and specificity with mean $\pm$ SD for individual or combined cancer types compared to healthy controls. The set of 400 mixed cancer patients was obtained by randomly selecting 80 samples from each of the five cancer types. Subsequently, 80 samples were randomly chosen from the total mixed pool for use in the test set, with four repetitions of random data splitting







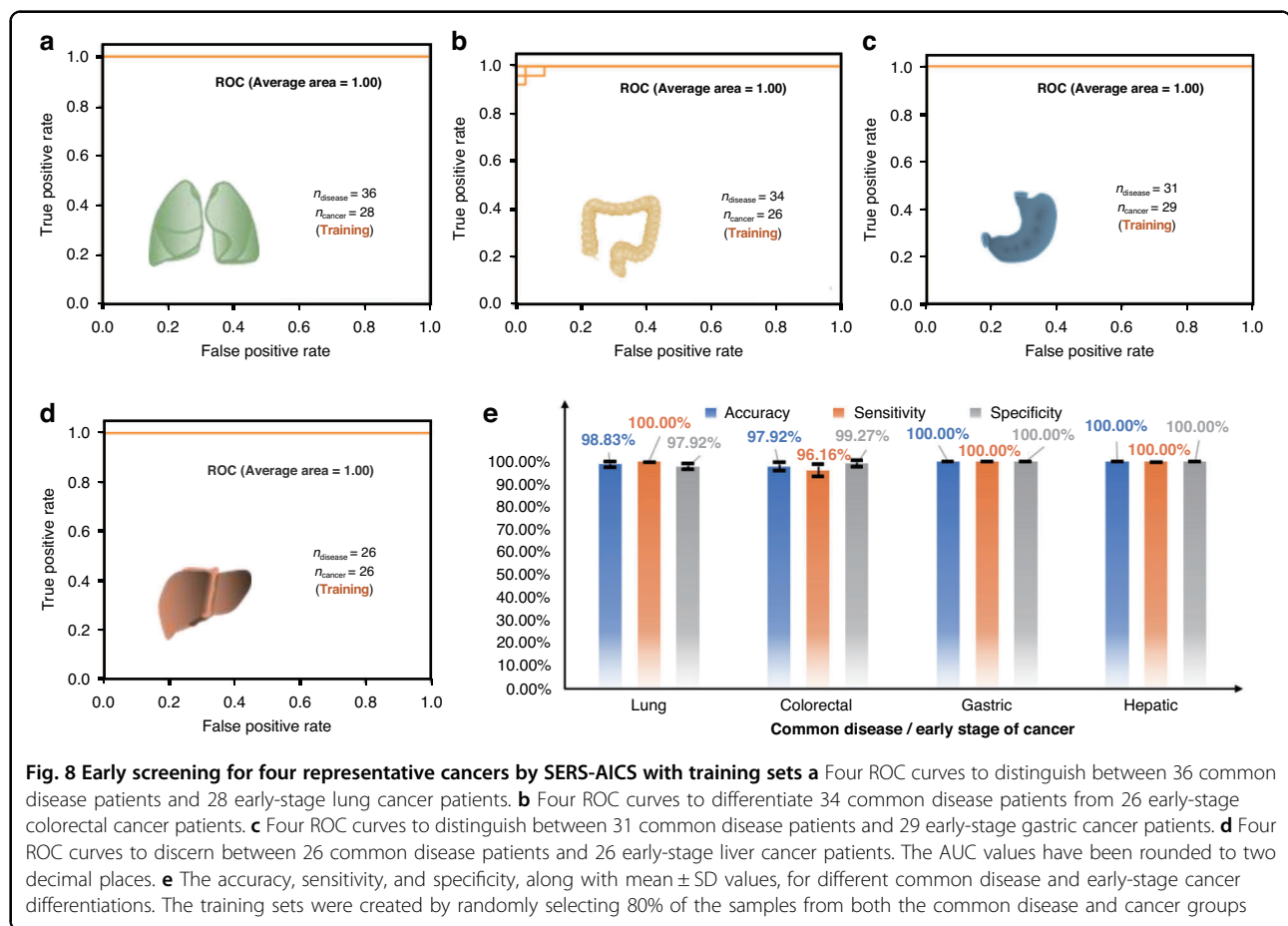
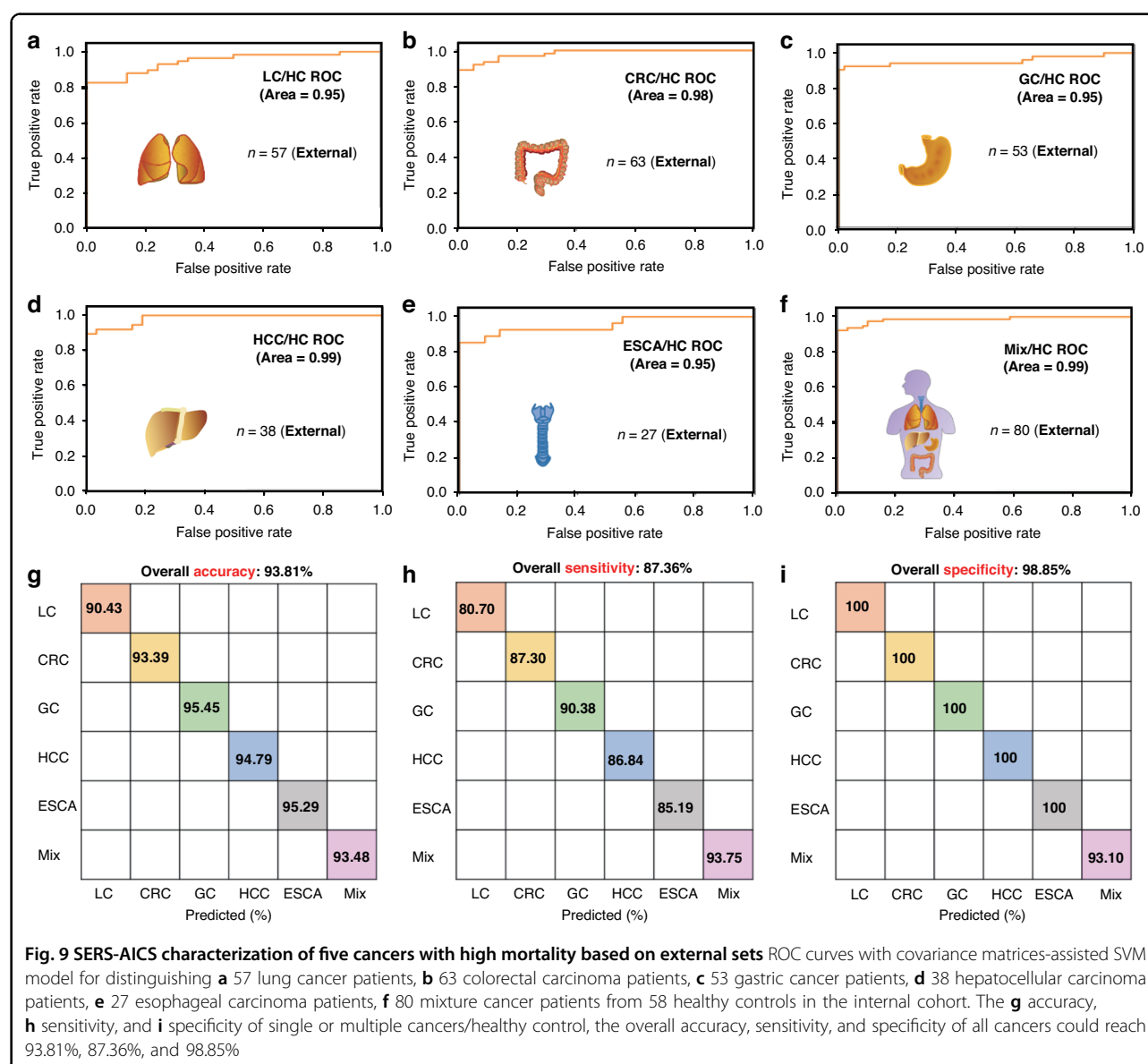


Fig. 8 Early screening for four representative cancers by SERS-AICS with training sets **a** Four ROC curves to distinguish between 36 common disease patients and 28 early-stage lung cancer patients. **b** Four ROC curves to differentiate 34 common disease patients from 26 early-stage colorectal cancer patients. **c** Four ROC curves to distinguish between 31 common disease patients and 29 early-stage gastric cancer patients. **d** Four ROC curves to discern between 26 common disease patients and 26 early-stage liver cancer patients. The AUC values have been rounded to two decimal places. **e** The accuracy, sensitivity, and specificity, along with mean $\pm$ SD values, for different common disease and early-stage cancer differentiations. The training sets were created by randomly selecting 80% of the samples from both the common disease and cancer groups

Table 3 A Comparative summary of accuracy, sensitivity, and specificity values within external cohorts between the original data and the revised data

Accuracy	Original data (external)	Revised date (external)
LC	84.35%	90.43%
CRC	80.33%	93.39%
GC	83.64%	95.45%
HCC	84.38%	94.79%
ESCA	87.06%	95.29%
Sensitivity	Original data (external)	Revised date (external)
LC	93.10%	80.70%
CRC	86.21%	87.30%
GC	93.10%	90.38%
HCC	93.10%	86.84%
ESCA	96.55%	85.19%
Specificity	Original data (external)	Revised date (external)
LC	75.44%	100.00%
CRC	75.00%	100.00%
GC	73.05%	100.00%
HCC	71.05%	100.00%
ESCA	66.67%	100.00%





the accuracy and reliability of our SERS-AICS for future applications.

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Author contributions

S.D. and C.H. performed the analysis of the SERS-AICS data. S.D., J.H., and X.X. wrote the Reply with input from F.W., J.H., and X.X. Note that the author list is different from that in the original paper because we recruited the first author of the Reply whose work was not related to the subjects raised by Bratchenko et al.

Conflict of interest

The authors declare no competing interests.



Received: 26 August 2024 Revised: 3 October 2024 Accepted: 22 October 2024

Published online: 20 January 2025

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