

Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection	Dicom files were processed with libraries such as Pydicom (https://pydicom.github.io/ , version 2.3.0), SimpleITK (https://simpleitk.org/ , version 2.0.2), and NiBabel (https://nipy.org/nibabel/ , version 3.2.2). Custom Python (version 3.9.7) scripts were developed for data de-identification.
Data analysis	The code for the EAGLE model cannot be publicly released. Implementation details are fully documented in the Methods section, enabling replication. The core code is implemented using open-source repositories: PyTorch (https://pytorch.org/ , 2.5.1) and nnU-Net (https://github.com/MIC-DKFZ/nnUNet , v2). All statistical analyses were performed in Python (v3.9.19) using scikit-learn (v1.4.2), NumPy (v1.26.4), and SciPy (v1.13.0).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The datasets generated and/or analyzed in this study are not publicly available because public release is not permitted by the relevant institutional review boards. To facilitate accessibility, we provide a sample dataset and an interactive portal at <https://eagle.damomed.com/>. All shared data will be de-identified to protect participant privacy in accordance with applicable laws and regulations. Researchers seeking access to the data and supporting documentation may submit a request to the first author (Jian Zhou: zhoujian@sysucc.org.cn) or corresponding author (Qifeng Wang: wangqifeng@scszlly.org.cn). Requests will be evaluated by an independent review panel based on scientific merit and compliance with ethical and regulatory requirements. Such requests will normally be processed within 6 weeks.

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender

Sex was collected based on the government-issued ID. The datasets used in the internal training and test cohorts, and the external multi-center test cohorts have sex distributions reported in the paper. Sex-based sensitivity of cancer was reported but sex was actually unrelated to model development. We didn't collect self-identification gender from the patients.

Reporting on race, ethnicity, or other socially relevant groupings

Race, ethnicity, and other socially relevant groupings were not collected from the patients and were unrelated to model implementation or deployment.

Population characteristics

This study involved three clinical scenarios: opportunistic screening in hospitals, opportunistic screening in established low-dose CT (LDCT) programs, and population-based high-risk endoscopic screening.

Validation of opportunistic screening in the hospital scenario was stratified across four distinct patient cohorts, each designed to address specific research objectives. Retrospective validation contained three cohorts: internal, dual-center cohorts for the model's performance within the same institutional framework (6,813 patients for training and 2,500 patients for testing), and external, multicenter (n=8, 11,466 patients) cohorts across China, the Czech Republic and Australia to assess the cross-institutional generalizability of EAGLE; Large-scale real-world, multicenter (n=3, 35,402 patients) cohorts were used to calibrate and evaluate EAGLE in the uncontrolled real-world population. Besides retrospective validation, a prospective validation cohort of 17,526 patients was used to evaluate the model in ambulatory settings.

Two LDCT validation cohorts were established to evaluate EAGLE's diagnostic performance in cost-effective clinical settings: dual-center LDCT test cohorts of 1,607 patients for evaluating EAGLE's diagnostic performance; a large-scale retrospective real-world LDCT cohort of 10,959 patients for reflecting the model's practical efficacy in high-throughput health screening environments for a target population aged between 45 to 75.

For population-based endoscopic screening scenarios, the validation involved two cohorts of patients enrolled in endoscopic screening programs: retrospective, external, dual-center test cohorts of 702 patients to assess EAGLE's cross-institutional generalizability in identifying high-risk individuals; a prospective enrolled cohort of 530 patients to evaluate the model's clinical utility in real-world endoscopic screening workflows for high-risk individuals, focusing on its role as a risk stratification tool for endoscopy.

Recruitment

The internal training cohort comprised 6,813 patients in total from two centers, SYSUCC and SCCH, where 3,744 patients were diagnosed with esophageal cancer or HGIN, and 3,069 patients were negative controls. From SYSUCC, 4,255 patients from 2009 to 2018 were collected. From SCCH, 2,558 patients from 2009 to 2015 were collected.

The internal test cohort included 2,500 patients with 1,281 esophageal malignant cases and 1,219 negative controls. From SYSUCC, 1,482 patients were collected. From SCCH, 1,018 patients were collected.

In the multi-center test cohorts, the non-contrast CT scans of 11,466 patients, including 2,812 esophageal malignant cases and 8,654 negative controls were collected from these centers. Center C (n=4,904), Shanghai Institution of Pancreatic Diseases (SIPD) is a general medical center in the east of China. We collected 1,113 esophageal malignant patients from 2014 to 2024 and enrolled 3,791 negative controls from 2014 to 2022. Center D (n=4,313), First Affiliated Hospital of Zhejiang University (FAHZU) is a tertiary hospital in the east of China. We collected 363 esophageal malignant patients from 2018 to 2021 and enrolled 3,950 negative controls from 2018 to 2021. Center E (n=761), Hunan Cancer Hospital (HCH) is a tertiary hospital in the central region of China. We collected 139 esophageal malignant cases and 622 negative controls between 2016 and 2020. Center F (n=731), Shantou Central Hospital (STCH) is a tertiary hospital in the south of China. We collected 731 esophageal malignant patients between 2009 and 2020. Center G (n=325), Xinjiang Medical University Affiliated Cancer Hospital (XMUACH) is a tertiary hospital in the northwest of China. We collected 175 esophageal malignant patients and 150 negative controls between 2014 and 2020. Center H (n=32), Fujian Cancer Hospital (FCH) is a tertiary hospital in the east of China. We collected 32 esophageal malignant patients from 2013 to 2018. Center I (n=195), General University Hospital in Prague (GUHP) is a hospital in the Czech Republic. We collected 54 esophageal malignant patients and 141 negative controls.

Center J (n=205), GenesisCare is a leading provider of radiation therapy services in Australia. This dataset contains de-identified clinical data collected from 205 oncology patients treated for esophageal cancer between 2015 and 2025.

In the external test cohorts for endoscopic group, we collected data from two centers where endoscopic screening programs were widely implemented. Center I (n=599), Suining Central Hospital (SNCH) is a tertiary hospital in China. We collected 449 esophageal malignant patients from 2016 to 2023 and 150 negative controls confirmed by endoscopy from 2020 to 2023. Center J (n=103), Lishui Central Hospital (LCH) is a tertiary hospital in China. We collected 103 esophageal malignant patients from 2019 to 2024.

A total of 35,402 patients were enrolled from three centers for the real-world (RW) study: SYSUCC (Center A), SCCH (Center B), and SIPD (Center C). The EAGLE model was deployed and run locally at each center. Patients were divided into two real-world cohorts, RW1 and RW2. RW1 included 20,758 patients from three centers. At SYSUCC, 4,568 patients from the outpatient and physical examination departments were collected from March 2024 and April 2024. At SCCH, 6,875 patients from the outpatient department were collected from December 2019 to March 2021. At SIPD, 9,315 patients from all four clinical settings were enrolled in December 2021. RW2 included 14,644 patients from three centers. At SYSUCC, 5,577 patients from the outpatient and physical examination departments were collected from May 2024 to June 2024. At SCCH, 5,350 patients from the outpatient department were collected from April 2021 to June 2024. At SIPD, 3,717 patients from all four clinical settings were collected from 1 and 10 February 2022.

Between 1 January 2025 and 30 April 2025, 17,526 participants undergoing non-contrast chest CT at SIPD (Center C) across four clinical settings—physical examination, emergency, inpatient, and outpatient—were enrolled in a prospective pilot study. From 7 July 2023 to 26 July 2023, 530 patients in the endoscopic screening program at SNCH (Center I) were invited for the non-contrast CT examination free of charge, this study were completed and registered with <http://www.chictr.org.cn>, No. ChiCTR2300074806.

The real-world LDCT cohort included 10,959 individuals aged 45–75 years who underwent lung cancer screening at the physical examination department of SIPD between July 2024 and December 2024.

Ethics oversight

For the retrospective study, ethical approval was obtained individually from the institutional review board (IRB) of Sun Yat-sen University Cancer Center (SYSUCC), Sichuan Cancer Hospital (SCCH), Shanghai Institution of Pancreatic Diseases (SIPD), First Affiliated Hospital of Zhejiang University (FAHZU), Hunan Cancer Hospital (HCH), Shantou Central Hospital (STCH), Xinjiang Medical University Affiliated Cancer Hospital (XMUACH), Fujian Cancer Hospital (FCH), General University Hospital in Prague (GUHP), GenesisCare, Suining Central Hospital (SNCH), and Lishui Central Hospital (LCH). The clinical trial was registered with ClinicalTrials <https://www.chictr.org.cn>, ChiCTR2300074806).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

The internal training cohort includes 6,813 patients. 5-fold cross validation was performed where each fold randomly selected 80% for training and 20% for the validation. This scheme follows machine learning convention for model tuning and hyperparameters selection.

The internal test cohort includes 2,500 patients and the external test cohorts include 11,466 patients across 8 medical centers.

Real-world, multicenter (n=3, 35,402 patients) cohorts were used to calibrate and evaluate EAGLE in the uncontrolled real-world population. A prospective validation cohort of 17,526 patients was used to evaluate the upgraded model. Two LDCT validation cohorts were established to evaluate EAGLE's diagnostic performance in cost-effective clinical settings: dual-center LDCT test cohorts of 1,607 patients for evaluating EAGLE's diagnostic performance; a large-scale retrospective real-world LDCT cohort of 10,959 patients for reflecting the model's practical efficacy in high-throughput health screening environments for a target population aged between 45 to 75.

For population-based endoscopic screening scenarios, two retrospective cohorts of patients enrolled in endoscopic screening programs of 702 patients to assess EAGLE's cross-institutional generalizability in identifying high-risk individuals; a prospective enrolled cohort of 530 patients to evaluate the model's clinical utility in real-world endoscopic screening workflows for high-risk individuals, focusing on its role as a risk stratification tool for endoscopy.

Data exclusions

Patients who comply one or more of the following criteria were excluded from the studies: (1) patients who underwent surgery that can impact or alternate the anatomical structure of the esophagus region, such as esophageal, gastric or endoscopic resection procedure, etc; (2) patients who underwent treatment to esophageal cancer (chemotherapy, radiotherapy, and chemoradiotherapy); (3) patients with low image quality due to artifacts caused by metal in stents or drastic motion during imaging; (4) Patients with ascites or tube.

Replication

The performance of EAGLE was consistent across the internal, external multi-center validation, real-world study cohorts and prospective cohorts, different CT scanners (GE, Philips, Siemens and UIH), scanning protocols (regular-dose non-contrast CT and low-dose non-contrast CT), and clinical scenarios (physical examination, emergency, inpatient and outpatient scenario).

Randomization

In the internal training cohort, patients were randomly assigned to training and validation in the process of the cross-validation.

Blinding

The internal test cohort, the external multicenter test cohort, the LDCT test cohort, and the real-world clinical test cohort were not used for the development of EAGLE. The second subset of real-world clinical test cohort (RW2) were not used for the development of EAGLE-Plus. In two-round reader studies, readers were blinded to pathology results and other clinical information. Readers were also blinded to the data collection, exact proportions of positive patients, and blinded to other readers. Readers were blinded to the ground-truth labels and their performance after the study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

- | | |
|-------------------------------------|--|
| n/a | Involved in the study |
| ☒ | ☐ Antibodies |
| ☒ | ☐ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology and archaeology |
| ☒ | ☐ Animals and other organisms |
| ☐ | ☒ Clinical data |
| ☒ | ☐ Dual use research of concern |
| ☒ | ☐ Plants |

Methods

- | | |
|-------------------------------------|---|
| n/a | Involved in the study |
| ☒ | ☐ ChIP-seq |
| ☒ | ☐ Flow cytometry |
| ☒ | ☐ MRI-based neuroimaging |

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration

Study protocol

Data collection

A cohort prospectively enrolled 530 patients from 1 July 2023 to 23 July 2023 at SNCH. All patients were initially referred for endoscopic examination and provided written informed consent to undergo an additional non-contrast CT scan. The cohort was specifically established to evaluate EAGLE's performance in risk stratification for esophageal malignant precancerous lesion and cancer.

Outcomes

In the endoscopy prospective validation study, the primary outcome was the esophageal malignancy detection rate of endoscopy under an EAGLE risk-stratified pathway compared with direct endoscopy in the same participants.

Plants

Seed stocks

Novel plant genotypes

Authentication