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Letter to the Editor

# From Mucosal Lesions to Biological Aging: Can Real-Time Endoscopic AI Predict Systemic Frailty?

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**Dear Editor,**

Artificial intelligence (AI) has fundamentally transformed gastrointestinal (GI) endoscopy. Computer-aided diagnosis (CAD) platforms now enable real-time detection and characterization of mucosal polyps, active inflammation, and early dysplastic lesions.[1,2] However, recent clinical evidence has tempered initial uncritical enthusiasm. A recent systematic review and meta-analysis indicated that CAD systems across diverse clinical settings do not uniformly improve long-term clinical outcomes related to colorectal neoplasia.[3] Conversely, another meta-analysis highlighted that AI primarily excels in reducing operator-dependent variability and narrowing the performance gap between novice and expert endoscopists.[4]

When evaluated strictly through this conventional lesion-oriented paradigm, AI endoscopy may appear largely confined to mucosal boundary detection. However, we propose a broader, transformative question: Can real-time endoscopic video streams be leveraged by deep-learning architectures to capture latent phenotypic representations of systemic biological aging and frailty?

This hypothesis is substantiated by three converging conceptual pillars:

First, given the multisystem nature of biological aging, chronological age cannot fully represent it. Over the past decade, epigenetic, transcriptomic, and proteomic aging clocks have repeatedly demonstrated superior accuracy over chronological age in predicting frailty and adverse clinical outcomes.[5,6]

Second, the GI mucosa and its microvasculature constitute an accessible anatomical window into systemic vascular and cellular senescence. Endoscopic features such as mucosal atrophy, reduced capillary density, microvascular tortuosity, and aberrant vascular patterns reflect chronic, low-grade systemic inflammation (inflammaging) and systemic endothelial dysfunction. Notably, a recent prospective cohort study demonstrated that an AI system grading mucosal vascularity in ulcerative colitis robustly predicted clinical relapse, confirming that mucosal vascular architecture encodes rich, systemic prognostic signals that extend far beyond focal lesion boundaries.[7]

Third, frailty is increasingly recognized as an objectively quantifiable, multiorgan phenotype accessible through opportunistic, non-invasive imaging.[8,9] Just as routine abdominal CT scans are now repurposed to opportunistically quantify sarcopenia and visceral adiposity without additional radiation exposure, endoscopic video streams generate thousands of dynamic, high-resolution frames per examination. Crucially, these dynamic video streams capture microvascular pulsatility, mucosal perfusion, and peristaltic tone—functional physiological dynamic features absent in static cross-sectional imaging or routine serum assays.

Rather than restricting neural networks to simple classifications such as polyp versus healthy tissue, deep learning can be leveraged to deliver multi-faceted performance via an approach that outputs shared spatiotemporal latent representations. Interestingly, these representations can be used for clinical objectives extending beyond lesion classification. Examples of such applications include predicting biological age and estimating systemic frailty without requiring supplemental equipment or imposing additional effort or expense during the procedure.

However, it should be emphasized that the association between endoscopic outcomes and systemic frailty is

currently a scientific hypothesis rather than an operational reality, requiring comprehensive experimental evaluation and processing. Translating this concept from hypothesis to clinical implementation is a path characterized by substantial methodological challenges and various confounding factors. Key variables that must be systematically considered include:

1. **Patient-specific demographic and clinical variables:** These include chronological age, gender, underlying diseases such as diabetes mellitus and musculoskeletal disorders, as well as concurrent pharmacotherapy, particularly anti-inflammatory drugs and vasoactives.
2. **Procedure- and physiology-related variables:** Procedural and physiological conditions, such as the type and amount of sedative or general anesthesia, can directly alter mucosal perfusion, bowel movements, and vascular tone.
3. **Center-dependent variables:** Discrepancies in the optical characteristics of different endoscopic devices manufactured by different companies, inadequate bowel preparation, differences in operator skill and accuracy, and heterogeneous implementation protocols across clinical centers introduce significant variability.[2] Furthermore, the generalizability of procedural protocols across diverse patient populations must be systematically investigated to prevent systemic bias and performance degradation resulting from high data variability.

To our knowledge, systemic frailty screening using deep learning algorithms has not yet been investigated in any endoscopic dataset. Therefore, the following research direction is proposed to evaluate how this hypothesis can be operationalized:

1. Discovering data relationships in a retrospective manner: In this phase, models are designed that simultaneously utilize two complementary neural network architectures: convolutional networks, which are adept at extracting visual and textural patterns from endoscopic images, and recurrent neural networks that can detect and track dynamic physiological changes in images over different time sequences. Integrating these two pathways into a multi-task framework allows for the simultaneous detection of localized pathology (e.g., polyps) and more detailed clues reflective of systemic frailty from a single data source. These platforms are established using large-scale, carefully annotated endoscopic image and video databases linked to biobank resources containing biomarkers and proteomic profiles.[5,6]
2. Prospective and multicenter validation: In this phase, the generalizability of the designed platforms across diverse patient populations undergoing GI endoscopy is rigorously evaluated. This process requires carefully controlling factors such as the depth and type of sedation during endoscopy, the homogenization of bowel preparation, and the uniformity of imaging protocols.
3. Clinical and algorithmic benchmarking: In this stage, the parameters used by the AI model to estimate biological age are compared with validated systemic and phenotypic frailty measurement tools.[8,9] In addition, the discriminatory power of the model and its clinical application are quantitatively examined with indicators such as the area under the receiver operating characteristic curve (AUROC), the area under the precision-recall curve (AUPRC), the calibration slope, and decision curve analysis (DCA).
4. Domain matching between different devices: Since a major challenge of any AI model is performance degradation across different clinical centers or endoscopic devices, a federated learning approach can be used to match different models. This method allows the model to use data from multiple centers without the need for aggregation or the physical transfer of patient records. In addition, by using a domain-independent representation, the model attempts to ignore the technical differences between different devices and imaging protocols and focus solely on the biological pattern. The result is robust, uniform diagnostic performance regardless of the differences in the centers and devices used.

If prospectively validated, the tens of millions of routine endoscopies performed annually worldwide could serve as an opportunistic gateway for systemic frailty risk stratification at zero incremental hardware cost. This could enable timely comprehensive geriatric assessment and pre-procedural risk mitigation before overt functional decline occurs.

### Artificial Intelligence Use Disclosure

Artificial intelligence-assisted tools were used solely for the grammatical editing and language refinement of the manuscript.

### Authors' Contribution

Conceptualization: Reyhaneh Zahiri, Seyed Bashir Mirtajani
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### Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Data Availability Statement

Since no datasets were created or analyzed for this manuscript, data sharing is not applicable.

### Ethical Approval

Not applicable. This manuscript is a letter/perspective and does not contain any original studies with human participants or animals performed by any of the authors.

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