Commentry

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Methodological Rigor and Clinical Promise in Gastric Cancer Biomarker Research. Comment on Aziz et al. Gastric Cancer Pre-Stage Detection and Early Diagnosis of Gastritis Using Serum Protein Signatures. Molecules 2022, 27, 2857

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ABSTRACT

We read with considerable interest the proteomics investigation by Aziz and colleagues, which used high-definition mass spectrometry to characterize serum and biopsy protein profiles across the spectrum of gastroduodenal disease in a Pakistani cohort of 219 patients. This commentary identifies and elaborates upon two methodological contributions that, in our assessment, have received insufficient attention in the literature. The first is the simultaneous stratification of analyses by *Helicobacter pylori* infection status, which allowed separation of malignancy-driven protein changes from those attributable to bacterial colonization. The second is the paired biopsy design, which controlled for inter-patient variability. We further analyze the clinical significance of the fibrinogen-to-albumin ratio findings, which demonstrated a striking separation between gastritis and all other gastroduodenal disease groups. If validated prospectively using routine laboratory assays, this finding could eliminate the need for gastroduodenal endoscopy in more than half of symptomatic patients. This reduction carries substantial implications for patient safety, healthcare costs, and procedure-related infection risk. Endoscopic procedures, while generally safe, carry documented risks of perforation, bacteremia, cardiopulmonary events, and transmission of multidrug-resistant organisms, particularly in lower-resource settings where reprocessing standards are variable. In low- and middle-income countries where gastric cancer burden is rising and endoscopic capacity is critically limited, a validated blood-based triage test would represent a meaningful clinical advance. We also propose that integration of clinical laboratory variables into machine learning classification models represents the logical translational next step for this research program, particularly in settings where mass spectrometry remains inaccessible.

Keywords: Gastric Cancer; Fibrinogen-To-Albumin Ratio; Endoscopy; Biomarker; Proteomics; Machine Learning; Low-Income Countries

Introduction

Gastric cancer carries one of the lowest overall survival rates among solid malignancies, with a median survival of ten to twelve months following diagnosis at advanced stages [1]. This dismal prognosis is not a failure of treatment capability alone, but rather a reflection of systemic failure in early detection. The gold standard for gastric cancer diagnosis remains histopathological examination of biopsies obtained through gastroduodenal endoscopy [2]. Although endoscopy is accurate, it is expensive, invasive, and procedurally demanding. Due to these flaws, a large proportion of the global population bearing the greatest gastric cancer burden cannot access it. Aziz and colleagues published a proteomics investigation in this journal, studying 219 patients from Holy Family Hospital, Rawalpindi, Pakistan. Using high-definition mass spectrometry, they profiled serum and biopsy proteins across normal gastric mucosa, all grades of gas-

tritis, gastric and duodenal ulcers, and first-stage and advanced gastric cancer [3]. The study proposed two protein marker panels and identified the fibrinogen-to-albumin ratio as a potential serum triage tool for gastritis. This commentary provides analytical examination of two aspects of the work that have not received adequate attention. The first concerns methodological design decisions whose scientific value extends beyond the paper itself. The second one is the translational significance of the fibrinogen-to-albumin ratio finding, with particular attention to what its validation would mean for patient safety, healthcare economics, and endoscopic resource utilization in low- and middle-income country settings.

Methodological Contributions and Their Broader Significance

Helicobacter Pylori Stratification

The most consequential design decision in the Aziz et al. study is the simultaneous enrollment of *H. pylori* positive and *H. pylori* negative patients across all disease groups. *H. pylori* is not a background variable in gastric cancer research, but rather a carcinogen that rewrites the mucosal proteome. Through CagA-dependent signaling, chronic neutrophilic infiltration, and sustained oxidative DNA damage, *H. pylori* infection independently alters the expression of dozens of proteins that gastric cancer research has repeatedly mistaken for tumor-specific markers [4]. Most previous proteomics studies in this field failed to account for that. They enrolled either *H. pylori* positive patients exclusively, or mixed cohorts with no stratification, and they reported protein differences between gastric cancer and control tissue as though those differences were attributable to malignancy alone. Aziz and colleagues ran every major comparison twice. The first pass used the full cohort and the second one restricted analysis to *H. pylori* positive patients. The contrast between those two analyses is more informative than either one alone. Alpha-enolase (ENO1) was upregulated in gastric cancer versus normal gastric mucosa in the global analysis, but when the same comparison was restricted to antrum specimens from *H. pylori* positive patients, ENO1 dropped off the shortlist. That disappearance is a meaningful finding because it tells us that the ENO1 signal in prior studies was at least partly a product of corpus versus antrum tissue mixing, not malignant transformation [3]. Prior studies without stratification could not have known that. Both the ten-protein advanced gastric cancer panel and the 29-protein early gastric cancer panel that emerged from this work survived *H. pylori* independent filtering. That standard is more demanding than what most published serum proteomics investigations in this field have applied, and it should be acknowledged as such.

Paired Biopsy Design and its Inherent Limitation

Collecting biopsy specimens from both morphologically normal and adjacent diseased mucosa within the same patient during a single endoscopic procedure is a rational approach to reducing the between-patient noise that contaminates tissue proteomics. The authors, however, make an observation whose implications deserve wider attention. When they examined the protein heatmaps for normal versus diseased site comparisons, they found that samples clustered by patient identity rather than by tissue status. Inter-individual variation dominated the protein profiles to a degree that normal and diseased tissue from the same patient looked more similar to each other than either did to corresponding tissue from a different patient [3]. finding is not a failure of the study design. It is a fundamental biological reality of tumor-adjacent tissue proteomics, and it has direct consequences for how biomarker discovery studies of this type should be interpreted. It means that no tissue-based protein panel, regardless of how carefully it is assembled, can demonstrate adequate clinical specificity until it has been tested in a large, demographically and geographically diverse external validation cohort. The shortlisted protein inventories in this paper are best understood as rigorously generated hypotheses, not clinical tools. The authors are transparent about this, and the field would do well to apply that standard more consistently when citing this work.

The Fibrinogen-to-Albumin Ratio: Clinical and Economic Stakes of Validation

The Finding: In our assessment, among all results in the study, the fibrinogen-to-albumin ratio finding carries the most immediate clinical relevance. Using mass spectrometry signal intensities, the authors calculated the ratio of fibrinogen to albumin (FAR-MS) for each patient group and found a separation that was not merely statistically significant but biologically dramatic. Gastritis patients showed FAR-MS values ranging from 74 to 98. Every other group, spanning patients with normal gastric mucosa, gastric or duodenal ulcers, and gastric cancer at either stage, showed FAR-MS values between 0.1 and 0.3, while healthy volunteers showed an intermediate value of 6.7. That separation exceeds 300-fold when comparing gastritis groups to non-inflammatory gastroduodenal disease groups, including gastric cancer, ulcer, and normal gastric mucosa [3]. The physiology behind it is well established. Active gastritis drives a systemic acute-phase response, with albumin falling because hepatic production is redirected toward acute-phase proteins and because mucosal inflammation promotes protein-losing gastropathy [5-7]. Fibrinogen, on the other hand, rises because it is one of the most sensitive acute-phase reactants in the circulation, capable of increasing several-fold in response to sustained mucosal inflammation [7]. Gastric cancer does not produce the same response. Tumor microenvironments are immunosuppressive rather than pro-inflammatory, and the systemic acute-phase signature of active infection or tissue injury is generally absent [6]. Ulcer disease, similarly, does not sustain the kind of mucosal inflammatory load that drives the albumin and fibrinogen shifts seen in gastritis - protein-losing gastropathy with falling albumin levels is well documented in *H. pylori* -associated gastritis, with hypoproteinemia resolving promptly after *H. pylori* eradication [5].

The fibrinogen-albumin ratio separates those states with a clarity that most single biomarkers cannot achieve. It has also demonstrated superiority over other combined inflammatory markers in predicting

long-term survival outcomes in gastric cancer [8]. One further observation in the original paper reinforces confidence in the finding. The atypical mild gastritis subgroup, distinguished by histopathological detection of gastric atypia or atrophic gastritis and predominantly *H. pylori* positive, showed FAR-MS values below one, clustering with the non-inflammatory disease groups rather than with gastritis. Normal mild gastritis cases, all *H. pylori* negative, showed values above 70. That split was consistently observed across two distinct analytical approaches applied to the same dataset - unsupervised hierarchical clustering of the full serum proteome and the targeted fibrinogen-to-albumin ratio calculation (FAR-MS values) [3]. When two different analytical approaches produce the same patient grouping without being designed to do so, the finding is worth taking seriously.

The Endoscopic Burden this Finding Could Address: Aziz and colleagues calculated that fibrinogen-to-albumin ratio-based triage at the primary or secondary care level could have eliminated 56 percent of endoscopy referrals in their patient cohort [3]. That calculation deserves to be contextualized against the real costs of the procedures it would replace. Upper gastrointestinal endoscopy, while generally safe in experienced hands, carries documented procedural risks that are not trivial. Perforation rates for diagnostic esophagogastroduodenoscopy have been reported at 1 in 2,500 to 1 in 11,000 procedures in prospective multicenter registries, with esophageal perforation carrying a mortality rate between 2 and 36 percent [9]. Transient bacteremia occurs in as many as 8 percent of diagnostic upper gastrointestinal (GI) endoscopy procedures [9]. A study found a composite endoscope-associated infection rate of 0.123 percent following non-ERCP upper GI endoscopic procedures, with Pseudomonas aeruginosa and multidrug-resistant Enterobacteriaceae as the principal causative organisms [10]. Cardiopulmonary complications, including myocardial infarction, respiratory arrest, and aspiration, constitute more than 60 percent of unplanned endoscopy-related events [11,12]. A meta-analysis identified a cancer miss rate of 9.4 percent at upper GI endoscopy, meaning that even when the procedure is performed, its diagnostic yield is imperfect [13]. These are risks that patients with inflammatory gastritis bear without diagnostic benefit when the purpose of the endoscopy is to rule out gastric cancer. If a validated blood-based triage test correctly identifies gastritis patients before the procedure is performed, those patients are spared real procedural harm, not just inconvenience.

Financial Implications: The financial argument for a validated fibrinogen-to-albumin ratio test is equally compelling. Without insurance coverage, a patient in the United States should expect to pay over 2,500 dollars for an upper endoscopy when physician fees, facility charges, anesthesia, and pathology are combined [14]. The financial burden is no less real in Pakistan, where the cost of diagnostic upper gastrointestinal endoscopy varies substantially by setting. In public sector tertiary care hospitals, the procedure is available at less than PKR 1,650, with pathology reporting provided free of charge [15]. In private facilities, out-of-pocket costs range from PKR 8,000 to PKR 25000, representing a catastrophic expenditure for patients from lower-income households (Islamabad Gastroenterology Associates, Personal Communication, June 2026) [15]. Aziz and colleagues estimated a fictive saving of 313,500 dollars for the 114 gastritis patients in their cohort who would not require endoscopy if fibrinogen-to-albumin ratio triage were available [3]. That estimate used a figure of 2,750 dollars per procedure, which is consistent with published cost ranges. The financial argument is more pressing still in the low- and middle-income country settings where gastric cancer burden is heaviest and endoscopic capacity is most constrained. In East Africa, endoscopic capacity stands at approximately 106 upper GI procedures per 100,000 persons per year, less than ten percent of the capacity reported in high-income countries [16].

In Cameroon, thousands of patients fall into poverty annually from out-of-pocket payment for digestive endoscopy, and a significant number face financial catastrophe from a single procedure [17]. In these settings, fibrinogen and albumin are measured as part of standard biochemical panels in most referral hospitals, at a cost that is a small fraction of a single endoscopy. A validated triage rule requiring only these two values could redirect limited endoscopic capacity toward the patients who genuinely need it.The fibrinogen-to-albumin ratio finding in this study remains based on mass spectrometry intensity values, not on routine immunoturbidimetric assay results. These are not the same measurement, and the authors appropriately acknowledge that routine-assay validation is required before clinical inference is justified [3]. That validation study has not yet been published. It is the most important next step for this research program.

The translational Next Step: Machine Learning on Clinical Variables

The protein panels proposed by Aziz and colleagues face a fundamental accessibility barrier. High-definition mass spectrometry with ion mobility separation is available in a small number of research centers globally. It is not part of the diagnostic workflow at any primary or secondary care facility in Pakistan or in most low- and middle-income countries. A biomarker panel that requires this technology can inform the biology of gastric cancer. It cannot inform clinical decision-making at the point of care where gastric cancer is most often missed. A complementary approach that does not require mass spectrometry is the construction of machine learning classification models trained on routine clinical and laboratory variables. Albumin and fibrinogen are already components of standard biochemical panels. C-reactive protein, which appeared in the ten-protein advanced gastric cancer panel, is one of the most widely measured serum analytes in the world [3]. If these and other routinely collected variables carry discriminative signal for gastric cancer versus non-malignant gastroduodenal disease, that signal could be captured in a classification model deployable at low cost in any setting with basic laboratory infrastructure.

Limitations and Considerations

This commentary offers analytical evaluation of the Aziz et al. study and does not present new experimental data. The observations regarding endoscopic complication rates are drawn from published literature and may not be directly applicable to endoscopic practice in Pakistan, where complication reporting infrastructure and endoscopist case volumes differ from those in the settings from which the cited rates were derived. The Aziz et al. study was published in 2022, and no prospective validation of the fibrinogen-to-albumin ratio using routine laboratory assays has been identified in the subsequent literature at the time of this writing. This commentary does not imply that no validation is ongoing. It notes that the gap between discovery and clinical application remains open and that addressing it warrants research priority.

Conclusion

The proteomics study by Aziz and colleagues made two methodological contributions that the field has not yet fully absorbed. Simultaneous *H. pylori* stratification and paired biopsy collection are design decisions whose rationale and consequences should inform the conduct of future gastric cancer biomarker studies, particularly in populations where *H. pylori* prevalence is high. The fibrinogen-to-albumin ratio finding is the most immediately actionable result of this work. What is now needed is a prospective validation study. It should enroll symptomatic patients presenting with upper gastroduodenal complaints at primary or secondary care facilities. FAR should be measured using standard immunoturbidimetric assays, the same assays available in any hospital biochemistry laboratory, and triage decisions based on that result should be compared against subsequent endoscopic and histopathological findings. This study does not require mass spectrometry. It does not require a tertiary center. It is feasible today in any district hospital with a functional biochemistry laboratory, including those in the settings where the diagnostic gap is widest. If that validation confirms the separation observed in the index study, more than half of symptomatic patients could be triaged away from endoscopy before the procedure is booked, reducing procedural risk, out-of-pocket cost, and the patient attrition that occurs when referral pathways are long. In Pakistan and across South Asia, where gastric cancer burden is rising and endoscopic capacity is critically limited, that outcome is not a marginal gain. It is the difference between a diagnosis made and a diagnosis missed. The protein marker panels require further orthogonal validation and remain appropriately in the discovery phase. The fibrinogen-to-albumin ratio does not. It needs one well-designed prospective study. That study should be a research priority.

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