LETTERS TO THE EDITOR

Comment on: "Proton pump inhibitor challenge to confirm diagnosis of atrophic gastritis of the stomach: a proposal" – the critical omission of gastrin-17 in the diagnostic algorithm

To the Editor,

We read with interest the study by Di Mario et al. [1], which introduces a proton pump inhibitor challenge to diagnose corpus atrophic gastritis in patients with pepsinogen I levels between 30 and 50 mcg/L. The work is a valuable contribution to non-invasive diagnostics. However, the proposed algorithm relies solely on pepsinogen I dynamics, an approach that may be inherently limited. A systematic review confirmed that diagnostic performance for atrophic gastritis was superior when pepsinogen was combined with gastrin-17 and *Helicobacter pylori* serology [2]. The hormone gastrin-17, secreted by antral G-cells, rises when corpus atrophy removes acid-mediated feedback inhibition. Relying exclusively on pepsinogen I fails to distinguish between corpus-restricted atrophy (low PG-I, high G-17) and pangastritis (low PG-I, normal/low G-17), a distinction with direct implications for cancer risk and management [2, 5]. This single-biomarker approach may limit the test's specificity and clinical utility.

Incorporating G-17 could substantially refine the interpretation of the PPI challenge. For instance, a blunted pepsinogen I response coupled with an elevated G-17 would strongly support a diagnosis of corpus atrophy. In contrast, a similar blunted response with a normal G-17 might indicate other confounders or a different gastritis pattern. This combined interpretation could more accurately identify patients who truly require endoscopic confirmation, thereby improving the positive predictive value of the screening cascade. Current international guidelines for managing gastric precancerous conditions recommend the use of biomarker combinations, including gastrin-17, for a more precise non-invasive assessment of gastric mucosal status [3].

To address this limitation and enhance the clinical applicability of their promising method, we propose several feasible steps. First, the authors could analyze stored serum samples from their cohort to measure fasting G-17 levels, as such biomarkers are stable under appropriate storage conditions [4]. This retrospective analysis would not require new patient recruitment. Second, they could perform a logistic regression analysis using both the delta pepsinogen I and the baseline G-17 value to predict histological atrophy. This would quantify any additive diagnostic value from the second biomarker. Third, based on this analysis, a refined diagnostic pathway could be proposed. For example, patients in the "grey zone" with concurrently high G-17 might be directed straight to endoscopy, while those with intermediate G-17 could undergo the PPI challenge for further stratification.

Adopting a dual-biomarker approach aligns with the trend toward comprehensive serological profiling in gastroenterology. Comprehensive biomarker assays that combine pepsinogens and G-17 are established for evaluating gastric mucosa health [4]. Furthermore, this integration can help differentiate autoimmune from *Helicobacter pylori*-induced atrophy, as the serological patterns between these etiologies can differ, which is relevant for management [5]. By adding G-17 assessment, the authors can transform their functional "challenge" test into a topographically informative tool, increasing its precision and adoption in clinical practice for better risk stratification of patients with chronic atrophic gastritis.

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Reply

To the Editor,

Thank you for your interest in our work and for the interesting insights [1]. The work aimed to use a test that was as simple and inexpensive as possible to shed light on a precancerous condition, such as atrophic gastritis, using non-invasive markers, including serology [2]. The basic idea is that if the glands of the gastric body-fundus that produce hydrochloric acid are damaged by atrophic gastritis, any stimulus such as that of PPIs cannot promote the increase in PG I that is localized as a site of production at the level of the same glands that produce hydrochloric acid. The use of PG I as a single marker after a week of PPIs is based on two types of consideration: first, simplicity and cost-effectiveness as the use of a single parameter such as PG I is less expensive and simpler than the use of two, adding G17; secondly, from a pathophysiological point of view, hypo-anacidity is a favorable pathway for the progression towards gastric adenocarcinoma and the test unveils the condition of hypo-anacidity by means of evaluation of low PG I values, singling out patients in a grey area between 30 and 50 micrograms/liter of PG I to deepen the investigations and possibly refer patients to a gastroscopy. In fact, regardless of whether G17 levels are normal, low or elevated, low levels of PG I per se already certify structural damage of the cells producing PG I (chief cells), and therefore also of the cells producing hydrochloric acid (parietal cells).

From a pathophysiological point of view, certainly the introduction of G17 in the diagnostic set could be appropriate due to the well-known negative feedback acid-gastrin as well-documented and reported in the literature. The introduction of G17 in the proposed PPIs challenge could be in fact emphasize the importance of the topography of gastric atrophic damage localized only in the body or diffuse as pan gastritis. Our group has been engaged for years in the clinical use of serological markers for the correct diagnosis of diseases of the upper digestive tract and, of course, we are studying the role of G17 in these patients. The hormone has been adequately stored and analyzed; and we are currently evaluating data to understand whether, as you rightly suggested, it could be possible to highlight a significant delta in response to PPIs by G17 that can be combined with the Delta identified for PG I leading to a definition, even topographically, of the damage. We hope to be able to produce these results shortly, in a statistically significant way, as happened for PG I, a tool that can not only diagnose real hypoachlorhydria in the stomach but also the topography of the damage. This, of course, as you have opportunely pointed out, is to better address patients into greater or lesser risk stratification categories of developing gastric adenocarcinoma over time. The main goal of our first study, using only PG I, was to clarify from a clinical point of view by means of a simple and cheap tool, in which patients in Grey zone (from 30 to 50 mcg/L), gastroscopy is mandatory or not. This is demonstrated by the results of the study based on the response to PPIs administration.

In conclusion, we thank you again for your attention, for the suggestions and we confirm that we are working for the implementation of G17 in the workup of the PPI challenge. We hope to obtain results useful to document in a statistically significant way, the presence of atrophic gastritis also topographically defined to correctly single out patients with chronic atrophic gastritis based to different risk categories to develope gastric cancer.

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Comment on "Long-term effect of *Helicobacter pylori* eradication on risk factors for cardiovascular disease – is there a connection?"

To the Editor,

We read with great interest the longitudinal study by Tepeš et al. [1] examining the decade-long impact of *Helicobacter pylori* eradication on cardiovascular risk markers, including trimethylamine N-oxide (TMAO) and lipid profiles. The authors provide a rare and useful long-term perspective on how treatment of a common chronic gastric infection may provide systemic metabolic benefits. However, several considerations require further discussion to better consider these findings.

First, although the extended follow-up represents a key strength, it inevitably introduces important confounding variables. Over a period of 10 years, considerable changes in lifestyle including diet and physical activity are likely. More importantly, the initiation of therapies such as statins or metformin may independently influence both lipid fractions and circulating TMAO levels. Prior evidence suggests that statin therapy can reduce TMAO concentrations regardless of lipid lowering, showing why it's crucial to factor in these influences over the course of the study [2].

Secondly, the study presents an interesting metabolic paradox: total cholesterol and LDL-C improved even though participants gained weight. Having established that weight gain is typically associated with adverse lipid changes, this observation suggests that the decrease in chronic inflammation after eradicating *H. pylori* may be the key contributor. This interpretation is supported by data linking *H. pylori* infection with a pro-atherogenic lipid profile, referring that eradication may confer cardiometabolic benefit through attenuation of systemic inflammation [3]. Such findings suggest the possibility of an "anti-inflammatory shielding" effect, whereby eradication of a persistent infectious burden reduce cardiovascular risk independent of weight trajectory.

Finally, while the reduction in TMAO and its precursors is promising, it remains unclear whether this reflects the absence of *H. pylori* per se or alterations in gut microbiota post-antibiotic therapy. Given that TMAO is a microbiota-derived metabolite strongly associated with atherosclerosis, distinguishing between these mechanisms will be essential for clarifying how long lasting and specific the observed effects might be [4].

In conclusion, these findings highlight the potential systemic benefits of *H. pylori* eradication beyond gastrointestinal disease. Further studies incorporating detailed longitudinal data on medications, lifestyle factors, and microbiome composition are needed to clarify the role of eradication therapy in primary prevention.

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Reply

To the Editor,

We thank Hameed for his thoughtful comments [1] and for his interest in our study examining the long-term metabolic effects of *Helicobacter pylori* (*H. pylori*) eradication [2].

First, we agree that long-term follow-up studies inevitably introduce potential confounding factors, including lifestyle changes and the initiation of medications that may influence metabolic parameters [3]. In our cohort, however, the use of such medications was minimal. Medication use was systematically recorded at study inclusion and at each follow-up visit. At baseline, six patients were receiving statin therapy (6/62, 9.6%). During follow-up, only one additional participant initiated statin therapy, and none of the participants were treated with metformin. Therefore, it is unlikely that these therapies significantly influenced the observed changes in lipid profiles or circulating trimethylamine N-oxide (TMAO) levels.

Second, dr. Hameed raised an important point regarding the relationship between body weight and lipid metabolism. We would like to clarify that participants in our study did not experience weight gain during the follow-up period. Most patients were slightly overweight at baseline [body mass index (BMI) of 27.0±4.4], but no statistically significant change in BMI was observed at follow-up after two months (27.0±4.3) or one year (26.8±5.2) following *H. pylori* eradication

(p=0.910). Consequently, the improvements observed in total cholesterol, LDL and small dense LDL particles cannot be attributed to changes in body weight. As suggested, it is plausible that the reduction in chronic inflammation following successful eradication of *H. pylori* contributed to the observed improvements in lipid parameters. Previous studies have similarly suggested that persistent *H. pylori* infection may promote a pro-atherogenic metabolic profile through proinflammatory cytokines and systemic inflammatory mechanisms [4, 5]. In addition, changes in gut microbiome composition following eradication therapy may influence metabolic signaling pathways [6].

Finally, we appreciate the comment regarding the interpretation of reduced TMAO levels. We agree that TMAO is closely linked to gut microbiota composition and that distinguishing between the direct effects of *H. pylori* eradication and broader microbiome alterations following antibiotic therapy is an important consideration. In our study, no dietery interventions were performed. However, dietary patterns were assessed using a questionnaire, and no major changes in dietary habits were observed in our cohort. The most plausable explanation for the reduction in TMAO levels may therefore be alterations in gut microbiome composition. We also performed 16S rRNA analyses and shotgun metagenomic sequencing in our cohort. These results are currently being prepared for publication and will provide further insight into microbiome dynamics following eradication therapy and their potential relationship with metabolic changes.

In conclusion, we appreciate the insightful comments and agree that further studies incorporating detailed longitudinal assessment of microbiome composition, lifestyle factors, and metabolic therapies will help clarify the complex mechanisms linking *H. pylori* eradication with cardiometabolic outcomes.

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Methodological considerations regarding the use of red cell distribution width in acute pancreatitis

To the Editor,

We read with interest the recently published article entitled *'Red Cell Distribution Width at 24 Hours as an Early Predictor of Mortality and Severity in Acute Pancreatitis: A Multicenter Retrospective Cohort Study'* [1]. Thanks to the authors for addressing an important clinical challenge in acute pancreatitis and for exploring the prognostic utility of a widely available and inexpensive laboratory parameter. The use of registry-based multicenter data further strengthens the clinical relevance of the study.

Nevertheless, we would like to raise some methodological considerations regarding the interpretation and clinical applicability of red cell distribution width (RDW) as a prognostic biomarker, which may be of interest to the readership of JGLD.

RDW is a parameter derived from the red blood cell volume distribution curve generated by automated hematology analyzers. A well-recognized limitation of RDW is the lack of inter-platform harmonization across analyzers from different manufacturers [2-3]. RDW may be reported either as a coefficient of variation or as a standard deviation, and values obtained from different instruments are not directly interchangeable. In multicenter studies, where data are pooled from multiple institutions over an extended time period, this analytical heterogeneity may introduce systematic variability that is difficult to fully adjust for statistically.

In addition to analytical variability, RDW is known to be susceptible to preanalytical factors, including the interval between venipuncture and analysis, sample storage temperature, and transport conditions [4]. These variables may be particularly relevant in acute care settings, where blood samples may be obtained under differing logistical conditions (e.g., emergency department vs. ward vs. intensive care unit). Even modest preanalytical variation may influence RDW

values, especially when proposed cut-off points fall within a relatively narrow range.

Furthermore, RDW is a nonspecific marker influenced by a broad spectrum of conditions such as chronic inflammation, nutritional deficiencies, renal dysfunction, and underlying hematologic disorders [5]. While the authors report multivariable adjustment for several confounders, additional discussion of residual confounding and the potential impact of unmeasured variables affecting erythrocyte morphology would further strengthen the interpretation of RDW as an independent prognostic indicator.

In summary, the study adds to the growing body of literature suggesting a potential role for RDW in early risk stratification in acute pancreatitis. [6]. However, we would encourage readers and clinicians to interpret RDW-based prognostic thresholds with caution, particularly in real-world settings where preanalytical and analytical variability may be unavoidable.

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Reply

To the Editor,

We sincerely thank the authors of the letter for their thoughtful comments [1] regarding our article [2]. We appreciate their interest in our work and their emphasis on important methodological aspects related to the use of red cell distribution width (RDW) as a prognostic biomarker in AP.

We fully agree that RDW is subject to analytical variability, particularly due to the lack of complete harmonization among hematology analyzers from different manufacturers. To reduce bias, we took into account only patients who had their RDW analyzed using a single analyzer model, the most frequently encountered in our study, namely the Abbott Cell-Dyn 3700 Hematology Analyzer (Abbott Laboratories Inc., Chicago, IL, USA).

We also concur that preanalytical factors, such as time from venipuncture to analysis, storage conditions, and transport, may influence RDW measurements. These variables are indeed difficult to control uniformly in acute care environments. Our study reflects routine clinical practice, and while this may introduce variability, it also enhances the external validity of our findings.

Regarding the nonspecific nature of RDW, we agree that it may be influenced by multiple conditions, so nicely pointed out. In our multivariable models, we attempted to adjust for major clinical confounders available in our registry; however, as in any observational study, residual confounding cannot completely removed. We therefore view RDW not as a standalone diagnostic tool, but as a complementary parameter.

We fully acknowledge that the implementation of RDW as a parameter in the evaluation of patients with acute pancreatitis in routine hospital practice could be difficult. A carefully designed protocol must be put in place by emergency medicine physicians, gastroenterologists and laboratory personnel.

In summary, we appreciate the opportunity to clarify these aspects and agree that awareness of analytical, pre-analytical, and biological variability is essential when considering RDW in clinical practice. We believe our findings support the potential utility of RDW as an accessible and inexpensive adjunctive marker, while also underscoring the need for cautious interpretation and further prospective validation.

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Red cell distribution width at 24 hours in acute pancreatitis: accounting for baseline heterogeneity through dynamic kinetics

To the Editor,

I read with great interest the multicenter retrospective cohort study by Pistriţu et al. [1], which evaluated the prognostic utility of red cell distribution width (RDW) measured 24 hours after admission in patients with acute pancreatitis (AP). The authors are to be commended for their robust investigation involving a large registry and for identifying a threshold that is both cost-effective and readily accessible, qualities that are indispensable for biomarkers intended for the high-pressure environment of emergency medicine. Their finding that an RDW ≥ 14% independently predicted poor outcomes serves as a significant validation of this hematological parameter in a heterogeneous cohort, addressing a critical clinical gap in early risk stratification.

However, as a clinical investigator, I believe the discussion regarding RDW's utility would benefit from a strategic shift from static thresholds toward dynamic kinetics. RDW is an exceptionally sensitive indicator of systemic inflammation, yet it remains a highly non-specific one, as it fundamentally reflects a patient's "erythropoietic set point" [2]. While the authors found that 24-hour RDW was predictive even after adjusting for age and hemoglobin, the absolute value is still significantly influenced by pre-existing conditions prevalent in the AP population, such as chronic liver disease, subclinical iron deficiency, or chronic obstructive pulmonary disease. In many clinical scenarios, an elevated RDW at 24 hours may simply reflect a patient's pre-morbid frailty or a chronic inflammatory state rather than the specific severity of the acute pancreatic insult itself.

The biological rationale for RDW as a marker of AP severity lies in "stress erythropoiesis". During a systemic inflammatory response, a "cytokine storm" involving interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) - interferes with iron metabolism and impairs erythropoietin sensitivity in the bone marrow. This leads to the rapid, premature release of immature, larger erythrocytes into the circulation, which increases the RDW [3, 4]. Because RDW changes dynamically in response to acute physiological stress, the magnitude of change between admission and 24 hours (ΔRDW) may better reflect the evolving inflammatory response than any single measurement obtained at a fixed time point.

From a triage perspective, an individualized trend is arguably more informative than a population-based cutoff. A patient whose RDW increases sharply from 12% to 14% within 24 hours likely demonstrates a more volatile inflammatory phenotype and a higher risk of multi-organ failure than a patient who enters the hospital with a baseline RDW already at 14% due to chronic nutritional or liver-related factors. Previous studies in other high-acuity settings, such as sepsis and septic shock, have demonstrated that a significant increase in RDW from baseline is a more powerful and specific predictor of mortality than the initial value alone [4]. Furthermore, focusing on RDW kinetics may help clinicians avoid the "over-triage" of chronic patients who naturally sit above the 14% threshold. By evaluating the delta, the clinician effectively "normalizes" the biomarker for each individual, filtering out the background "noise" of pre-existing comorbidities [5].

In conclusion, the study by Pistriţu et al. provided a solid foundation for using 24-hour RDW as a screening tool. However, I suggest that the next frontier in refining this biomarker lies in evaluating its longitudinal kinetics. I would be very interested to know if the authors observed a difference in outcomes based on the rate of RDW change during that first 24-hour window. Incorporating such a dynamic approach would move us toward a more personalized and biologically specific prognostic model, ensuring that our clinical decisions are driven by the acute physiological response to pancreatitis rather than pre-existing biological backgrounds.

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Reply

To the Editor,

We thank Takahashi K. for his comment [1] regarding our study [2]. He raised an important question of how red cell distribution width (RDW) evolves from admission to 24 hours in acute pancreatitis (AP). We agree that this dynamic trajectory could be meaningful, particularly in the real-world setting our study reflects, and that RDW is a non-specific marker of systemic inflammation influenced by factors beyond those we measured. In our analysis we adjusted for the most relevant of these, gender, hemoglobin, age, and severity, and the association persisted.

We would first clarify a point of detail. Our cohort yielded two distinct cut-offs rather than a single ≥14% threshold: 13.85% for in-hospital mortality and 14.35% for severe disease. Both remained independent predictors after adjustment for the prespecified confounders, which argues that in AP, the signal is not merely a reflection of a chronic background state.

The correspondent's central question is whether we observed differences according to the rate of RDW change within the first 24 hours. We are unable to address this directly. At our participating centers, the first complete blood count is typically run on a point-of-care emergency analyzer different from the one specified in our Methods section, and the 24±6-hour measurement is the first that reliably conforms to our study protocol. We deliberately avoided pooling RDW values obtained from different analyzers, which would have introduced precisely the measurement heterogeneity that a kinetic analysis must avoid.

Beyond data availability, a note of biological caution is warranted. RDW reflects a slowly evolving erythrocyte population with a lifespan of roughly 120 days and is buffered against rapid change. The dynamic-RDW evidence cited in support of the proposal, by Kim et al. [3], was based on change measured over a longer 72-hour window and defined a meaningful increment as small as 0.2%. Whether a clinically meaningful erythropoietic delta (Δ) can emerge within 24 hours is therefore uncertain, and any short-term change over this interval is liable to confounding by resuscitation-related hemodilution, a frequent feature of early AP management [4]. The static value, by contrast, retains the practical advantage of being a single, automatable flag requiring neither a baseline nor a calculation.

These caveats notwithstanding, we share the correspondent's view that longitudinal kinetics represent the more biologically specific frontier. As the RO-API registry and our study group transition to prospective work, we intend to record serial RDW measurements at fixed, analyzer-consistent timepoints under a clearly outlined protocol, enabling a proper test of ΔRDW against the static threshold. We are grateful for an insightful suggestion that helps to define our next steps.

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