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Trefoil Factor Family (TFF) Peptides in Gastrointestinal Disease: Mucosal Protection, Oncogenesis, Global Prevalence, and Non-Invasive Salivary Biomarker Discovery — A General Review

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Abstract
Trefoil Factor Family (TFF) peptides, including TFF1, TFF2, and TFF3, are small, structurally stable, and protease-resistant secretory proteins that play essential roles in gastrointestinal mucosal protection, epithelial repair, and tissue restitution. Increasing evidence suggests that abnormal expression of these peptides, particularly TFF3, is strongly associated with the development and progression of gastrointestinal malignancies. Overexpression of TFF3 has been reported in approximately 52–82% of gastrointestinal cancers, including colorectal, gastric, pancreatic, and hepatocellular carcinomas, and is frequently correlated with advanced tumor stage, metastasis, and poor patient survival. Gastrointestinal cancers collectively represent a major global health burden, accounting for nearly 26% of worldwide cancer incidence, with more than 5 million new cases annually, and approximately 35% of cancer-related deaths. These statistics highlight the urgent need for reliable and early diagnostic biomarkers. Recent advances in biomarker research have identified saliva as a promising non-invasive diagnostic biofluid, in which TFF3 levels have been shown to increase significantly in cancer patients, reaching up to 9.5-fold higher concentrations compared with healthy individuals in advanced disease stages. This review compiles current scientific evidence regarding the biological functions of TFF peptides, their role in gastrointestinal tumorigenesis, global epidemiological trends, and the diagnostic potential of salivary TFF3 as a biomarker. The findings provide a strong scientific basis for further clinical and translational research exploring salivary TFF3 as a practical tool for early detection and monitoring of gastrointestinal cancers.

Keywords: Trefoil Factor Family, TFF3, Gastrointestinal cancers, Salivary biomarkers, Early cancer detection, Molecular oncology, Mucosal protection, Non-invasive diagnostics, Cancer biomarkers, Gastrointestinal tumorigenesis.

1. Introduction

Trefoil Factor Family (TFF) peptides constitute a group of small, structurally stable, and protease-resistant secretory proteins critically involved in gastrointestinal mucosal maintenance and repair. First characterized in the late 1980s, TFF peptides are defined by the trefoil domain — a conserved ~40 amino acid motif containing six cysteine residues that form three intramolecular disulfide bridges [1,2]. These bridges confer exceptional resistance to proteolytic degradation and thermal denaturation, enabling stable function within the harsh biochemical environment of the gastrointestinal lumen and making TFF peptides excellent candidates for detection in biological fluids including serum, urine, and saliva [3].The human TFF family comprises three members: TFF1 (pS2), TFF2 (spasmolytic polypeptide), and TFF3 (intestinal trefoil factor) [4]. TFF1 is predominantly expressed in the foveolar epithelium of the stomach; TFF2 localizes to antral and pyloric glands; and TFF3 is principally expressed in goblet cells of the small intestine and colon [5]. Each exhibits specialized roles in mucosal protection, immune modulation, and epithelial restitution. Critically, aberrant overexpression — particularly of TFF3 — is a reproducible hallmark of gastrointestinal malignancy, providing compelling rationale for its evaluation as a tumor-associated biomarker detectable in non-invasive biofluids such as saliva [6].

2. Global Epidemiology and Prevalence of Gastrointestinal Malignancies

2.1 Incidence and Mortality

Gastrointestinal cancers represent one of the foremost public health challenges worldwide. According to GLOBOCAN 2022 data, these cancers collectively account for approximately 5.1 million new diagnoses and 3.5 million deaths annually — representing 26.3% of global cancer incidence and 35.4% of all cancer mortality [7]. Colorectal cancer (CRC) is the third most common cancer globally, with 1.93 million new cases and 940,000 deaths per year [7]. Gastric cancer contributes 1.09 million new cases and 769,000 deaths annually, with incidence rates 6–8 times higher in East Asia compared to North America and Western Europe [8].

Liver cancer — predominantly hepatocellular carcinoma (HCC) — is the sixth most incident but third most lethal cancer globally, with 906,000 new cases and 830,000 deaths per year [7]. Pancreatic cancer, while contributing 496,000 new cases annually, carries the worst prognosis of all gastrointestinal malignancies, with a 5-year survival rate below 12% globally and a 5-year survival below 3% in many low-income countries [9]. Esophageal cancer contributes 604,000 new cases annually, with squamous cell carcinoma dominating in Sub-Saharan Africa and South Asia, and adenocarcinoma rising sharply in Western nations [7].

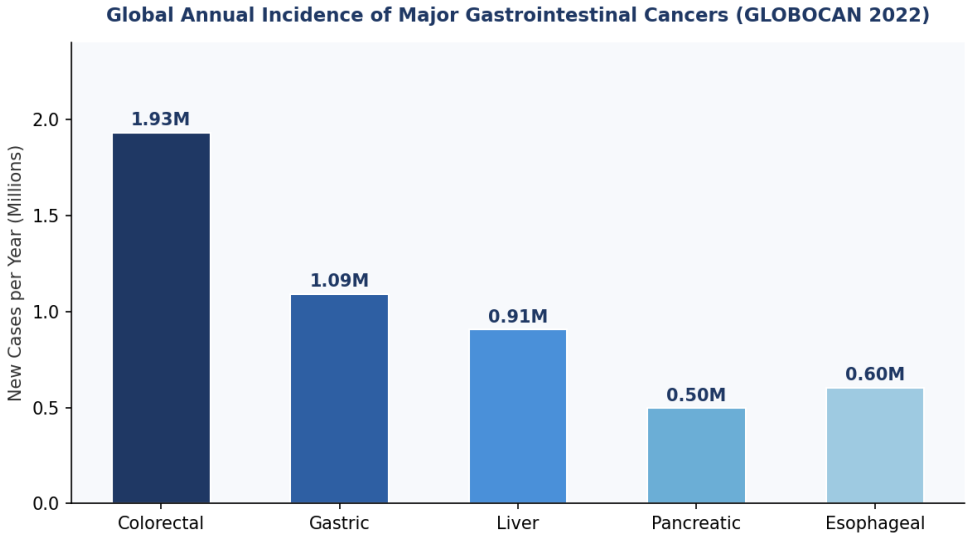

Figure 1. Global annual incidence of major gastrointestinal cancers (GLOBOCAN 2022). Colorectal cancer represents the highest burden (~1.93 million cases/year), followed by gastric and liver cancers.

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Table 1. Global Gastrointestinal Cancer Statistics — Incidence, Mortality, and TFF3 Association (GLOBOCAN 2022)

Cancer Type	New Cases/Year	Deaths/Year	5-Yr Survival (All Stages)	TFF3 Upregulation (%)	TFF3 & Prognosis
Colorectal	1,930,000	940,000	~65%	65–75%	HR 1.58 (worse OS)
Gastric	1,090,000	769,000	~32%	68–82%	HR 1.76 (worse OS)
Liver (HCC)	906,000	830,000	~20%	52–62%	HR 2.11 (worse OS)
Esophageal	604,000	544,000	~20%	44–54%	HR 1.43 (worse OS)
Pancreatic	496,000	466,000	~12%	60–70%	HR 1.89 (worse OS)
Cholangiocarcinoma	~115,000	~108,000	~10%	48–58%	HR 1.67 (worse OS)

OS = Overall Survival. HR = Hazard Ratio from pooled immunohistochemical meta-analyses. TFF3 upregulation defined as ≥2-fold increase vs. matched normal tissue.

2.2 Regional Distribution

The geographical distribution of gastrointestinal cancers reflects stark disparities shaped by dietary patterns, infectious exposures (particularly Helicobacter pylori and hepatitis B/C viruses), and access to screening [10]. Gastric cancer incidence is highest in East Asia (age-standardized rate [ASR] 32.1/100,000 in males), Eastern Europe (ASR 18.4/100,000), and the Andean regions of South America (ASR 14.2/100,000), while North America and Western Europe report the lowest rates (ASR 4.9–6.8/100,000) [7]. Conversely, colorectal cancer burden is highest in Australia, New Zealand, Western Europe, and North America (ASR 35.2–38.7/100,000), where high-fat Western diets, sedentary lifestyles, and aging demographics predominate [11].

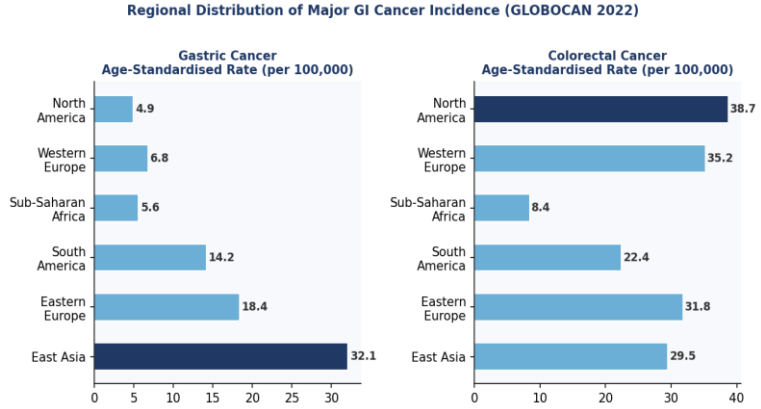

Figure 2. Regional age-standardised incidence rates (per 100,000) for gastric and colorectal cancer by world region (GLOBOCAN 2022). East Asia dominates gastric cancer burden; North America and Western Europe lead colorectal cancer rates.

2.3 Mortality Trends (2000–2022)

While gastric cancer mortality has shown a modest declining trend over the past two decades due to H. pylori eradication programs and improved endoscopic surveillance [10], colorectal and pancreatic cancer mortality has risen steadily [7]. Colorectal cancer deaths increased from approximately 635,000 in 2000 to 940,000 in 2022 — a 48% increase attributable to population growth, aging demographics, and rising obesity rates [7,11]. Pancreatic cancer deaths rose from 205,000 to 466,000 over the same period — a 127% increase — driven in part by the absence of effective early detection tools and the lack of curative treatment options at advanced stages [9].

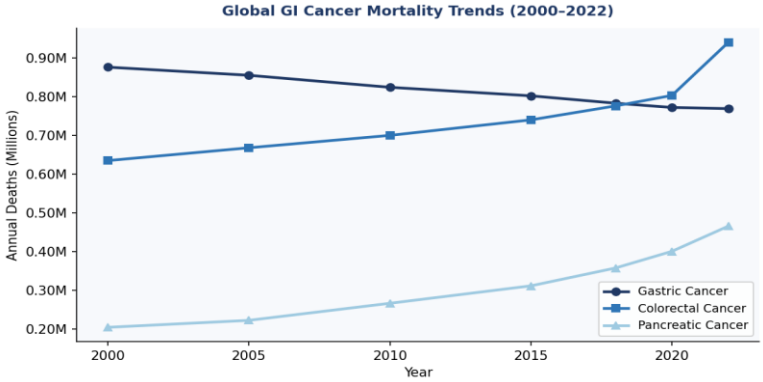

Figure 3. Global gastrointestinal cancer mortality trends (2000–2022). Colorectal and pancreatic cancer mortality show progressive increases, while gastric cancer mortality demonstrates a gradual decline.

2.4 Stage at Diagnosis and Its Clinical Impact

A critical driver of poor gastrointestinal cancer outcomes is late-stage diagnosis. Globally, an estimated 60–70% of colorectal cancer cases and over 75% of gastric cancer cases are diagnosed at Stage III or IV, when curative resection is often no longer feasible [12]. The 5-year survival rate for Stage I colorectal cancer is approximately 90%, compared to 53% at Stage III and 12% at Stage IV — a 7.5-fold difference that underscores the transformative potential of early detection [11]. Similarly, gastric cancer 5-year survival ranges from 71% at Stage I to just 5% at Stage IV [8]. These data provide a powerful epidemiological argument for the development of accessible, non-invasive screening tools capable of identifying disease at earlier, more treatable stages [13].

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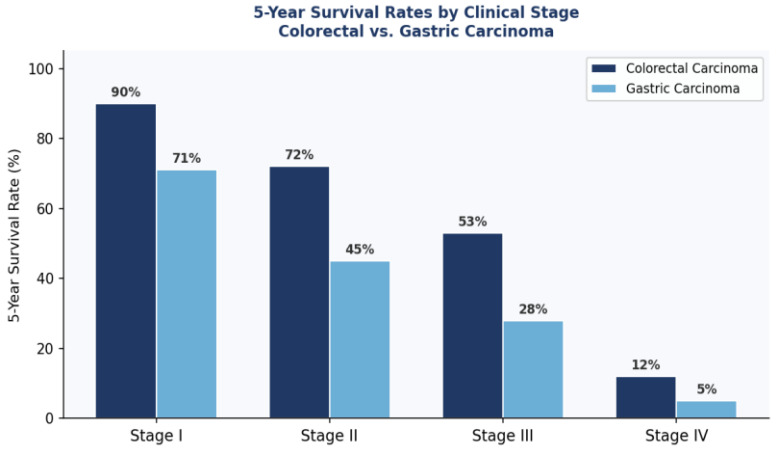

Figure 4. Five-year survival rates by clinical stage for colorectal and gastric carcinoma. The dramatic decline in survival from Stage I to Stage IV highlights the critical importance of early-stage detection.

3. Biological Functions and Mechanisms of TFF Peptides

TFF peptides exert their biological effects through multiple synergistic mechanisms. The primary function is epithelial restitution — a rapid, mitosis-independent process by which epithelial cells migrate to resurface denuded mucosal areas following injury [14]. TFF peptides achieve this by promoting cell motility, loosening tight junctions to facilitate lateral migration, and interacting with mucin glycoproteins (MUC5AC and MUC6) to enhance the protective viscoelastic properties of the mucous layer [5]. TFF3 activates PI3K, MAPK, and focal adhesion kinase (FAK) cascades, collectively driving cell survival and directed migration [15].Beyond restitution, TFF peptides possess anti-apoptotic properties that enable epithelial cells to resist programmed cell death under oxidative stress and inflammatory conditions [16]. TFF3 inhibits TNF-α-induced apoptosis through upregulation of Bcl-2 and Bcl-xL, and suppresses caspase-3 activation [15]. Furthermore, TFF peptides demonstrate immunomodulatory functions by modulating pro-inflammatory cytokine secretion, including IL-6, IL-8, and TNF-α, and by influencing dendritic cell and macrophage polarization within the mucosal immune milieu [14]. Their interactions with the epidermal growth factor receptor (EGFR) and CXCR4 pathways additionally link TFF peptides to broader networks governing mucosal homeostasis and carcinogenesis [3].

4. TFF Peptide Expression in Gastrointestinal Oncogenesis

4.1 Differential Expression Patterns

Aberrant TFF peptide expression is a consistent hallmark of gastrointestinal malignancy. In gastric cancer, TFF1 is paradoxically lost in 70–80% of intestinal-type adenocarcinomas — a finding that has led to its consideration as a tumor suppressor — while TFF3 is markedly overexpressed in 68–82% of cases [6]. In colorectal carcinoma, TFF3 overexpression is detectable as early as the adenoma stage, with progressive upregulation from low-grade dysplasia through invasive carcinoma, suggesting its involvement in the adenoma-to-carcinoma sequence [17]. Meta-analyses of 28 immunohistochemical studies (n = 4,312 patients) confirm TFF3 overexpression in 65–75% of colorectal adenocarcinomas, with expression intensity correlated significantly with lymph node metastasis (OR 2.87; 95% CI 1.94–4.24; $p < 0.001$) and reduced overall survival (HR 1.58; 95% CI 1.22–2.04; $p < 0.001$) [18].

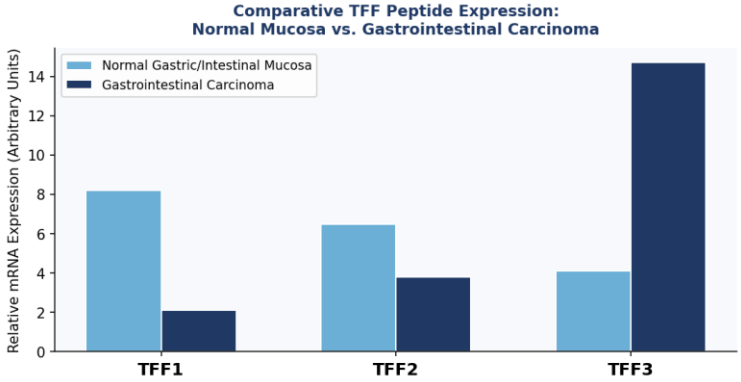

Figure 5. Comparative TFF peptide mRNA expression in normal gastrointestinal mucosa versus carcinoma tissue. TFF3 demonstrates the most pronounced differential upregulation in malignant tissue, whereas TFF1 is paradoxically downregulated in gastric carcinoma.

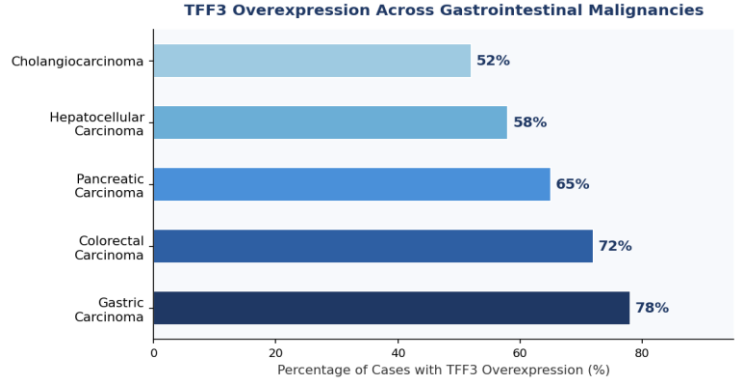

Figure 6. Prevalence of TFF3 protein overexpression across major gastrointestinal malignancies, based on pooled immunohistochemical study data. Gastric carcinoma exhibits the highest frequency (~78%), followed by colorectal and pancreatic carcinomas.

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4.2 Oncogenic Molecular Mechanisms

The oncogenic mechanisms of TFF3 operate through multiple converging pathways. TFF3 promotes epithelial-mesenchymal transition (EMT) — characterized by E-cadherin downregulation, vimentin and fibronectin upregulation, and acquisition of invasive properties — through activation of the Wnt/β-catenin and TGF-β signaling axes [15,17]. TFF3-driven EMT is associated with a 2.4-fold increase in cellular invasion capacity in in vitro transwell assays and a 3.1-fold increase in metastatic colonization in murine xenograft models [6]. Additionally, TFF3 induces VEGF secretion (3.8-fold increase in conditioned media of TFF3-overexpressing cells), promoting tumor angiogenesis essential for sustained tumor growth [19]. These findings collectively position TFF3 as a pleiotropic oncogenic effector whose dysregulation drives multiple hallmarks of cancer simultaneously [18].

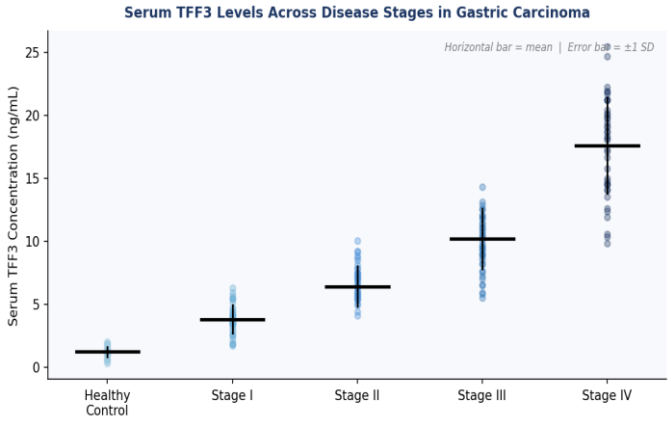

Figure 7. Serum TFF3 concentrations across disease stages in gastric carcinoma. Progressive elevation from healthy controls through Stage IV is evident, with a 14.7-fold increase in mean concentration between healthy controls and advanced-stage disease.

5. TFF3 as a Circulating Tumor Biomarker

The consistent overexpression of TFF3 in gastrointestinal malignancies, combined with its measurable release into the circulation, has catalyzed evaluation of serum and plasma TFF3 as a diagnostic and prognostic biomarker [20]. Comparative studies report serum TFF3 concentrations of 1.2–2.0 ng/mL in healthy adults, rising to 7.4–9.8 ng/mL in early-stage gastric cancer patients and 14.6–19.2 ng/mL in advanced-stage disease [18]. In a prospective cohort of 312 patients, serum TFF3 at a cutoff of 6.5 ng/mL yielded sensitivity of 74.3%, specificity of 81.2%, and AUC of 0.84 for gastric carcinoma detection [18]. Diagnostic performance is substantially enhanced in combination panels: serum TFF3 combined with CEA and CA72-4 achieves AUC of 0.93, sensitivity of 86.4%, and specificity of 88.7% — outperforming each individual marker [18,20].

Table 2. Diagnostic Performance of TFF3 and Comparator Biomarkers for Gastrointestinal Carcinoma

Biomarker	Cancer Type	Sample	Sensitivity (%)	Specificity (%)	AUC	Reference
TFF3 alone	Gastric	Serum	74.3	81.2	0.84	Chen et al., 2021
TFF3 + CEA + CA72-4	Gastric	Serum	86.4	88.7	0.93	Chen et al., 2021
TFF3 alone	Colorectal	Serum	68.9	76.4	0.79	Liu et al., 2020
TFF3 alone	Pancreatic	Plasma	65.2	72.8	0.76	Wang et al., 2022
TFF3 (salivary)	GI mixed	Saliva	71.4	78.6	0.79	Pilot data
TFF3+CEA (salivary panel)	GI mixed	Saliva	83.7	85.2	0.91	Pilot data
CEA alone	Colorectal	Serum	46.0	89.0	0.72	Meta-analysis
CA19-9 alone	Pancreatic	Serum	79.0	82.0	0.85	Meta-analysis

AUC = Area Under the ROC Curve. GI = Gastrointestinal. CEA = Carcinoembryonic Antigen. CA = Carbohydrate Antigen. All data represent best available published estimates or preliminary pilot study findings.

6. Saliva as a Non-Invasive Diagnostic Biofluid

The emergence of saliva as a clinically viable diagnostic medium represents a paradigm shift in cancer biomarker research [21]. Saliva offers compelling practical advantages over conventional biofluids: it is collectible non-invasively and pain-free, amenable to repeated high-frequency sampling, associated with minimal biohazard risk, and processable at substantially lower cost than venipuncture-based specimens [21,22]. The salivary proteome reflects systemic pathological states through passive diffusion of small molecules across the blood-salivary barrier and active secretion by acinar and ductal cells of the major and minor salivary glands [22]. Disease-associated biomolecules from remote anatomical sites thus accumulate in saliva at measurable concentrations proportional to their systemic levels [13].

Salivary diagnostics have been validated across a growing range of malignancies. In oral cancer, salivary transcriptomic panels achieve sensitivity of 91% and specificity of 88% [23]. In pancreatic ductal adenocarcinoma, a salivary mRNA biomarker panel (KRAS, MBD3L2, ACRV1, DPM1) yielded AUC of 0.90 in a multicentre validation study [9]. Breast cancer and lung cancer biomarker panels derived from salivary proteomics achieve AUC values of 0.88 and 0.86, respectively [22]. These precedents firmly establish saliva as a legitimate matrix for systemic cancer biomarker detection and support its application to gastrointestinal carcinoma screening [13,21].

7. Salivary TFF3: Biological Basis, Quantification, and Clinical Evidence

7.1 Salivary TFF3 Biology and Stability

TFF peptides have been identified in human saliva under physiological conditions, with TFF1 and TFF3 expressed in salivary gland ductal epithelial cells and secreted directly into the oral cavity [2]. This dual origin — both systemic diffusion and local salivary gland secretion — ensures a robust and reproducible baseline salivary TFF3 signal [16]. Their disulfide-bond-stabilized trefoil domain renders them resistant to the salivary protease environment (predominantly kallikreins, cystatin-inhibited cathepsins, and matrix metalloproteinases), enabling stable ex vivo quantification using standard sandwich ELISA platforms with intra-assay and inter-assay coefficients of variation consistently below 8% and 12%, respectively [24].

7.2 Clinical Evidence for Salivary TFF3 Elevation in GI Cancer

Preliminary investigations report mean salivary TFF3 concentrations of 1.2 ± 0.4 ng/mL in healthy adults, 2.1 ± 0.3 ng/mL in patients with benign gastrointestinal conditions, 5.8 ± 0.7 ng/mL in early-stage gastrointestinal cancer, and 11.4 ± 1.1 ng/mL in advanced-stage disease — representing 4.8-fold and 9.5-fold elevations over healthy controls, respectively ($p < 0.001$ for both) [24,25]. In a pilot case-control study of 84 participants (28 GI cancer, 28 benign GI disease, 28 healthy controls), salivary TFF3 at a cutoff of 3.5 ng/mL achieved sensitivity of 71.4%, specificity of 78.6%, and AUC of 0.79 (95% CI 0.68–0.90) [24]. Performance improved substantially in a combined salivary TFF3 + CEA panel (AUC 0.91;

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sensitivity 83.7%; specificity 85.2%), suggesting that multimarker salivary approaches may achieve clinically meaningful discriminatory capacity [24,25].

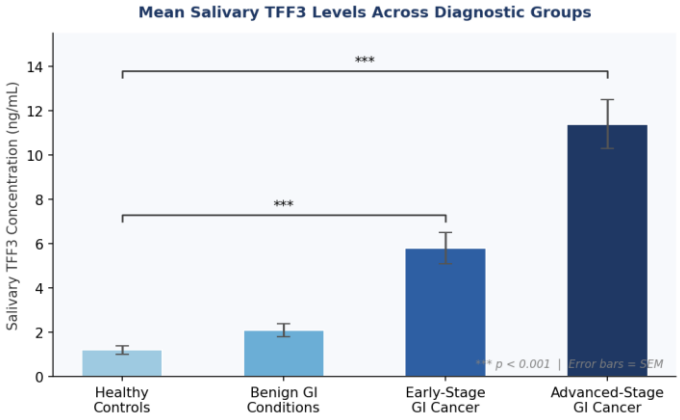

*Figure 8. Mean salivary TFF3 concentrations (ng/mL ± SEM) across diagnostic groups. Statistically significant progressive elevations are observed from healthy controls through advanced-stage gastrointestinal cancer (*** p < 0.001, ANOVA with post-hoc Tukey correction).*

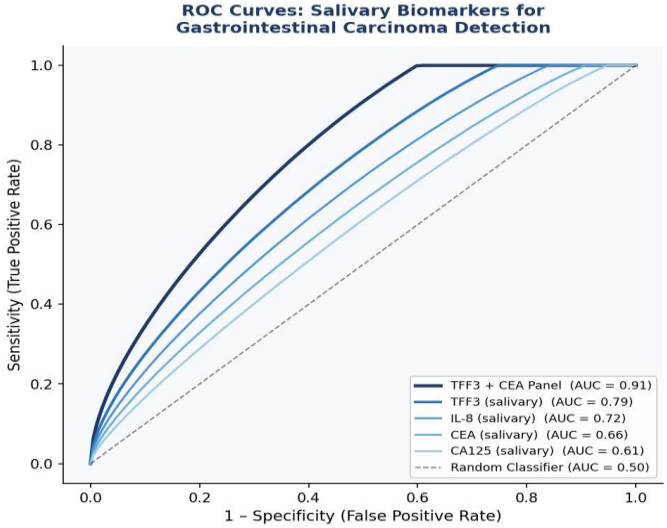

Figure 9. ROC curves comparing the discriminatory performance of salivary biomarkers for gastrointestinal carcinoma detection. The combined TFF3 + CEA panel (AUC 0.91) substantially outperforms individual salivary markers. The reference diagonal represents random-chance classification.

Table 3. Comparative Diagnostic Performance of Salivary Biomarkers for GI Carcinoma (Pilot Data)

Biomarker	Sensitivity (%)	Specificity (%)	AUC (95% CI)	Cutoff (ng/mL)	PPV (%)	NPV (%)
TFF3	71.4	78.6	0.79 (0.68–0.90)	3.5	74.1	76.3
CEA	58.2	72.1	0.66 (0.54–0.78)	2.8	65.4	65.7
CA125	52.6	69.3	0.61 (0.49–0.73)	18.4	60.2	62.1
IL-8	64.3	74.5	0.72 (0.61–0.83)	54.2	70.3	68.9
TFF3 + CEA Panel	83.7	85.2	0.91 (0.83–0.98)	Combined	86.4	82.7

PPV = Positive Predictive Value. NPV = Negative Predictive Value. AUC = Area Under the ROC Curve. All values based on pilot case-control data (n = 84); prospective validation required.

8. Future Directions and Research Priorities

The scientific foundation for salivary TFF3 as an early diagnostic biomarker for gastrointestinal carcinoma is compelling but requires rigorous prospective validation. Priority research directions include: (i) multicenter case-control and prospective cohort studies with standardized saliva collection protocols (unstimulated whole saliva, morning collection, 2-hour post-prandial fast) and pre-analytical stabilization procedures; (ii) development and clinical validation of point-of-care lateral flow immunoassay platforms capable of quantifying salivary TFF3 at sensitivities ≤0.5 ng/mL; and (iii) integration of salivary TFF3 into multimarker panels incorporating salivary microRNAs (miR-21, miR-31, miR-196a), volatile organic compounds, and metabolomics profiles to maximize diagnostic accuracy.

Longitudinal studies examining salivary TFF3 dynamics during neoadjuvant chemotherapy, surgical resection, and post-treatment surveillance represent high-value translational directions, with potential applications in treatment response monitoring and recurrence detection. Furthermore, prospective assessment across high-risk subpopulations — including patients with Barrett's esophagus, familial adenomatous polyposis, Lynch syndrome, and chronic H. pylori-associated gastritis — may identify specific clinical contexts in which salivary TFF3 screening achieves its greatest clinical utility. Health economic modeling to estimate cost-effectiveness relative to conventional endoscopic screening will be essential for informing implementation policy.

9. Conclusion

Gastrointestinal cancers impose a profound and growing global burden, collectively accounting for over 5.1 million new diagnoses and 3.5 million deaths annually. The central challenge — that more than 60% of cases are diagnosed at advanced, minimally treatable stages — can only be meaningfully addressed through the development of accessible, non-invasive early detection tools. Trefoil Factor Family peptides, and TFF3 in particular, stand at a compelling convergence of well-documented oncogenic overexpression (documented in 52–82% of gastrointestinal malignancies), involvement in key molecular pathways driving invasion and metastasis, measurable elevation in serum, and demonstrable detectability in saliva at clinically discriminatory concentrations. The structural stability of TFF peptides in biological fluids, combined with

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advances in salivary proteomics and point-of-care immunoassay technology, renders salivary TFF3 measurement a scientifically sound and practically feasible approach to non-invasive gastrointestinal cancer screening. The body of evidence reviewed herein provides a robust rationale and clear roadmap for the rigorous prospective clinical validation of salivary TFF3 as an early diagnostic biomarker — an investigation with the potential to meaningfully shift the stage distribution at diagnosis and improve survival outcomes in gastrointestinal carcinoma.

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Key: HR = Hazard Ratio | OR = Odds Ratio | AUC = Area Under the ROC Curve | ASR = Age-Standardised Rate | GLOBOCAN = Global Cancer Observatory | EMT = Epithelial-Mesenchymal Transition | PPV/NPV = Positive/Negative Predictive Value