fortune Journals

Research Article

FORTUNE JOURNAL OF HEALTH SCIENCES

ISSN: 2644-2906

Efficacy, Tolerability and Cost Effectiveness of Cytosponge in Patients with Barrett Esophagus. A Systemic Review and Meta Analysis

Bheesham[1], Fizza Hanif[2], Anitha Sangem[3], Aderinsola Wale-Oyedele[4], FNU Geeta[5], Sona Kumari[2], Muneeb Khalid[6], Hira Riaz[7*]

Abstract

Background: Barrett's esophagus (BE) is a premalignant condition associated with an increased risk of esophageal adenocarcinoma. Early detection remains challenging because conventional endoscopic screening is invasive, resource-intensive, and unsuitable for large-scale implementation. The Cytosponge–trefoil factor 3 (TFF3) test is a minimally invasive, non-endoscopic alternative designed to improve accessibility to BE detection. This meta-analysis evaluates its diagnostic accuracy and cost-effectiveness.

Methods: A systematic search of PubMed and Web of Science was conducted for studies published through January 2026. Eligible studies assessed the diagnostic performance of Cytosponge–TFF3 compared with endoscopy and histology. Two reviewers independently performed study selection, data extraction, and quality assessment using QUADAS-2. A bivariate random-effects model generated pooled sensitivity, specificity, diagnostic odds ratios (DOR), and summary receiver operating characteristic (SROC) curves.

Results: Ten studies comprising 4,005 participants were included. For BE with circumferential length ≥1 cm (C1), pooled sensitivity and specificity were 0.75 (95% CI: 0.70–0.79) and 0.88 (95% CI: 0.76–0.94), Results: Ten studies comprising 4,005 participants were included. For BE with circumferential length ≥1 cm (C1), pooled sensitivity and specificity were 0.75 (95% CI: 0.70–0.79) and 0.88 (95% CI: 0.76–0.94), with an AUROC of 0.80. For BE of any circumferential length, sensitivity increased to 0.81 (95% CI: 0.76–0.85) and specificity to 0.89 (95% CI: 0.82–0.93), with an AUROC of 0.90, indicating excellent overall performance. Across economic analyses, Cytosponge-based strategies demonstrated favorable incremental cost-effectiveness ratios compared with both no screening and endoscopy, while reducing endoscopic utilization.

Conclusions: Cytosponge–TFF3 demonstrates good diagnostic accuracy for detecting BE and represents an effective and cost-efficient alternative to conventional endoscopic screening, particularly for population-based and primary care implementation.

Keywords: Barrett's esophagus; Cytosponge; Trefoil Factor 3; TFF3; Non-invasive screening; Diagnostic accuracy; Esophageal adenocarcinoma; Sensitivity; Specificity; Meta-analysis.

Novel Findings of this Work

- This is the first meta-analysis to comprehensively evaluate the diagnostic accuracy of the Cytosponge-TFF3 technique across different circumferential lengths of Barrett's esophagus.

Affiliation:

[1]Isra University, Hyderabad, Pakistan

[2]Jinnah Sindh Medical University, Karachi, Pakistan

[3]Mamata Medical College, Khammam, Telangana, India

[4]Obafemi Awolowo University, Ile-Ife, Nigeria

[5]Peoples University of Medical and Health Sciences for Women, Nawabshah, Pakistan

[6]Akhtar Saeed Medical and Dental College, Lahore, Pakistan

[7]Kabul Medical University, Kabul, Afghanistan

***Corresponding author:**
Hira Riaz, Kabul Medical University, Kabul, Afghanistan.

Citation: Bheesham, Fizza Hanif, Anitha Sangem, Aderinsola Wale-Oyedele, FNU Geeta, Sona Kumari, Muneeb Khalid, Hira Riaz. Efficacy, Tolerability and Cost Effectiveness of Cytosponge in Patients with Barrett Esophagus. A Systemic Review and Meta Analysis. Fortune Journal of Health Sciences. 9 (2026): 429-439.

Received: July 04, 2026
Accepted: July 17, 2026
Published: August 12, 2026

- The study demonstrates that the Cytosponge-TFF3 test has higher diagnostic performance for detecting any length of metaplasia compared to >1 cm segments, with pooled sensitivity of 0.81 and specificity of 0.89.
- A pooled AUROC of 0.90 for any circumferential length indicates excellent overall diagnostic accuracy.
- The meta-analysis identifies variability in study design and patient characteristics as potential contributors to heterogeneity, offering insights for future diagnostic research.
- The work provides a comparative context between Cytosponge and other non-invasive alternatives, such as EsophaCap, underscoring the relative strengths of the Cytosponge-TFF3 approach.
- Clinical implications of this work:
- The Cytosponge-TFF3 test can serve as an effective, non-invasive screening tool for Barrett's esophagus in primary care settings, reducing dependence on upper endoscopy.
- Its high sensitivity, specificity, and cost-effectiveness support its use in large-scale screening programs for early detection of esophageal adenocarcinoma.
- The test's simplicity and minimal patient discomfort promote higher screening uptake among individuals with chronic gastroesophageal reflux symptoms.
- Integration of the Cytosponge into standard clinical practice may enable earlier diagnosis of Barrett's esophagus, contributing to reduced cancer progression and improved patient outcomes.
- The findings support policy changes favoring the adoption of non-endoscopic screening techniques in both community and specialized care settings.

Key Learning Points

- Cytosponge–TFF3 demonstrates good-to-excellent diagnostic accuracy for Barrett's esophagus, with pooled AUROC up to 0.90.
- Non-endoscopic screening significantly reduces endoscopy utilization while maintaining clinical effectiveness.
- Economic analyses consistently show Cytosponge-based strategies are cost-effective compared with both no screening and routine endoscopy.

Introduction

Barrett's esophagus (BE) is a premalignant condition characterized by the replacement of the normal squamous epithelium of the esophagus with metaplastic columnar epithelium. This condition significantly increases the risk of developing esophageal adenocarcinoma (EAC), a cancer type with survival rates if detected later [1, 2]. Early diagnosis and surveillance of BE are crucial to mitigate the growing incidence of esophageal cancer [3].

Traditional methods for diagnosing BE, such as upper endoscopy with biopsy, are invasive, resource-intensive, and not feasible for widespread screening [2]. To address this, the Cytosponge, a minimally invasive device, has been developed. It collects esophageal cells, which are analyzed for Trefoil Factor 3 (TFF3), a biomarker specific for intestinal metaplasia [1, 4]. The Cytosponge offers a cost-effective alternative to traditional endoscopy for the detection of Barrett's esophagus. According to the National Institute for Health and Care Excellence (NICE) Medtech Innovation Briefing (MIB240), the technology cost of the Cytosponge is £280 (excluding VAT), compared with £407 for standard endoscopy based on the NHS tariff. In the United States, early research models and manufacturer estimates (Medtronic) suggest a base cost of approximately $182 per device, with broader clinical simulation models estimating the cost per participant in a screening program at around $240 [26, 27]. The Cytosponge-TFF3 technique offers a potential alternative to endoscopy for detecting BE [3].

Several studies have evaluated the diagnostic performance of the Cytosponge-TFF3 technique. However, the reported sensitivity and specificity vary across studies, necessitating a comprehensive meta-analysis to provide pooled estimates of diagnostic accuracy. This study aims to synthesize the available evidence to assess the sensitivity, specificity, and overall diagnostic performance of the Cytosponge-TFF3 for detecting BE [5, 6].

Materials and Methods

Search Strategy

A systematic literature search was conducted in PubMed and Web of Science databases to identify studies evaluating the diagnostic accuracy of the Cytosponge-TFF3 for Barrett's esophagus. The search included articles published up to January 2026, using keywords such as "Cytosponge," "Capsule Sponge TFF3," "Barrett's esophagus," "Trefoil Factor 3," "diagnostic accuracy," and "meta-analysis." The search strategy adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [7]. Detailed search strategy is given in Table S3.

This meta analysis has been registered in the OSF (Open Science Forum) Registry with the following DOI: https://doi.org/10.17605/OSF.IO/U2M8P

Mir Hasan R, et al., Fortune J Health Sci 2026
DOI:10.26502/fjhs.435

Inclusion and Exclusion Criteria

Inclusion Criteria

The inclusion criteria for the meta-analysis will focus on studies that evaluate the efficacy, safety, and patient experience of the Cytosponge-TFF3 test for diagnosing Barrett's oesophagus in primary care settings. Specifically, randomized controlled trials (RCTs), cohort studies, and case-control studies that compare the Cytosponge-TFF3 test with usual care or endoscopic methods will be included. Studies must report on primary outcomes such as the detection rate of Barrett's oesophagus, diagnostic accuracy (sensitivity and specificity), or secondary outcomes including patient acceptability, adverse events, and cost-effectiveness. Only studies involving adult participants (aged 50 years or older) with chronic gastro-oesophageal reflux symptoms or long-term use of acid-suppressant medications were considered. Additionally, studies must provide sufficient methodological detail, including sample size, follow-up duration, and statistical analyses, to ensure quality assessment and data extraction.

Exclusion Criteria

The exclusion criteria eliminated studies that do not meet the predefined scope or quality standards. Non-primary research articles, such as reviews, editorials, and case reports, were excluded. Studies lacking a control group or comparator (e.g., usual care or endoscopy) were also omitted. Furthermore, studies with insufficient data on outcomes of interest, those involving pediatric populations, or those not published in English were not included. Studies that focus solely on technical aspects of the Cytosponge device without clinical outcomes or patient-related measures were also excluded. This ensures the meta-analysis remains focused on clinically relevant and methodologically robust evidence.

Study Selection

Two independent reviewers screened titles and abstracts to identify eligible studies. Full-text articles were assessed for inclusion based on the following criteria:

Studies evaluating the Cytosponge-TFF3 technique for detecting BE. Reporting sensitivity, specificity, or data that allowed their calculation. Original research articles (excluding reviews, editorials, or conference abstracts). Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Data Extraction

Data were extracted independently by two reviewers using a standardized form. Extracted data included study characteristics (author, year, location, and sample size), patient characteristics (age, sex, and risk factors for BE), and diagnostic accuracy measures (sensitivity, specificity, and diagnostic odds ratios).

Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool (8), which is specifically designed for evaluating diagnostic accuracy studies. This tool examines four domains: patient selection, index test, reference standard, and flow and timing. Each domain was evaluated for risk of bias, and the first three were also assessed for concerns regarding applicability. Studies were rated as having low, high, or unclear risk of bias within each domain. Two reviewers independently performed the quality assessment, and disagreements were resolved through discussion or consultation with a third reviewer. The results were summarized narratively and graphically, providing a structured appraisal of study quality and its potential impact on the overall findings of the meta-analysis. Details are shown in Figure S1 and S2.

Statistical Analysis

Pooled sensitivity, specificity, and diagnostic odds ratios (DORs) were calculated using a bivariate random-effects model. Summary receiver operating characteristic (SROC) curves were constructed to evaluate the overall diagnostic performance. The area under the curve (AUROC) was calculated to summarize the accuracy of the test. Heterogeneity was assessed using the I^2 statistic, and potential sources of heterogeneity were explored through subgroup analyses.

To assess the diagnostic performance of the Cytosponge for detecting Barrett's esophagus with different circumferential segment lengths, we extracted sensitivity values along with their 95% confidence intervals from each included study. Forest plots were constructed to visually represent the variation in sensitivity estimates across the studies (Figure S4-S9). The horizontal lines indicate the confidence intervals for each study's sensitivity, and the black dots represent the point estimates. This graphical summary facilitates an intuitive comparison of the individual study results and provides insight into the consistency of sensitivity values across different study populations and designs.

A bivariate random-effects meta-analysis was performed to jointly estimate the pooled sensitivity and specificity of the Cytosponge technique, accounting for the potential correlation between them. This model also provided estimates for the diagnostic odds ratio (DOR), positive likelihood ratio (LR+), and negative likelihood ratio (LR−), which together offer a comprehensive summary of the test's diagnostic performance across studies. The random-effects structure accommodates between-study variability, providing more generalizable pooled estimates for diagnostic accuracy (Table S4, S6, S8).

Mir Hasan R, et al., Fortune J Health Sci 2026
DOI:10.26502/fjhs.435

Results

Study Selection

A systematic search across PubMed, Web of Science, identified 3944 records. After removing 117 duplicates, 3827 articles underwent screening. Titles/abstracts excluded 3733 (non-relevant, non-human, or incomplete data). Full-text review of 94 articles excluded 84 more (wrong outcome, non-compliance, or wrong study design). Ultimately, 10 studies met inclusion criteria, comprising data from 4005 participants for meta-analysis. The PRISMA flow diagram outlines the selection process (Figure S3).

Study Characteristics

The meta-analysis incorporated 10 studies published between 2007 and 2025, predominantly from the UK (Ross-Innes CS 2015 [9], Ross-Innes CS 2017 [10], Fitzgerald RC 2020 [1], Kadri SR 2010 [11], Lao-Sirieix P et al. 2007 [12]), with one conducted in the US (CASE 2 2019 [13]), Benaglia et al., 2013 , Eluri et al., 2022, Swart et al., 2021, heberle 2018. These studies utilized various designs, including case-control, multicentre cohort, multicentre randomized controlled trial, cross-sectional, prospective cohort, and comparative, with sample sizes ranging from 97 to 1,654 participants. Patient characteristics across the studies showed a mean age between 61.8 and 69.0 years, although Kadri SR (2010) reported a median age of 62 years. Gender distribution, reported in four studies, indicated a variation in the number of male (228 to 796) and female (89 to 858) participants. This variation reflects differences in study design. Case-control studies recruiting patients with known Barrett's esophagus under surveillance tended to be more male predominant, consistent with the established male predominance of Barrett's esophagus, whereas screening or proactive case-finding studies conducted in real-world settings (e.g., endoscopy waiting lists) included a higher proportion of female participants, reflecting general referral patterns rather than underlying disease prevalence alone. Body mass index (BMI) was documented in two studies (Ross-Innes CS 2015, Ross-Innes CS 2017), with mean values of 27.6 and 28.2, suggesting that participants were generally overweight. The Study and Patient characteristics are summarized in Table S1. Earlier trials (BEST1, BEST2) reported sensitivity per protocol, including incomplete swallows, whereas later studies (BEST3, CASE2, real-world implementation) offered repeat testing if no columnar cells were collected, reporting results based on successful tests. The proportion of incomplete swallows was low and repeat testing is standard practice, minimizing impact on pooled estimates.

Diagnostic Accuracy

For detecting >1cm circumferential length of metaplasia (C1), the pooled sensitivity was found to be 0.75 (95% CI: 0.70–0.79), indicating that the Cytosponge-TFF3 technique correctly identified 75% of true positive cases in this category. The pooled specificity, which reflects the ability of the test to correctly identify those without the condition, was 0.88 (95% CI: 0.76–0.94), demonstrating a high capacity for ruling out false positives. The area under the receiver operating characteristic curve (AUROC), which measures overall diagnostic accuracy, was calculated as 0.80 (95% CI: 0.77–0.84), suggesting a good level of performance for this diagnostic threshold.

For any circumferential length of metaplasia, the diagnostic accuracy improved further, with a pooled sensitivity of 0.81 (95% CI: 0.76–0.85), meaning that the test was able to correctly identify 81% of true positive cases. The pooled specificity was 0.89 (95% CI: 0.82–0.93), indicating a slightly higher accuracy in excluding individuals without the condition compared to the >1cm group. The AUROC for this category was 0.90 (95% CI: 0.87–0.92), reflecting excellent diagnostic performance overall. These findings demonstrate that the Cytosponge-TFF3 technique has greater diagnostic accuracy for detecting any circumferential length of metaplasia compared to >1cm circumferential length, highlighting its utility as a reliable and efficient diagnostic tool for Barrett's esophagus. Results are summariesed in Table S2.

The pooled diagnostic odds ratio (DOR) for the primary Cytosponge strategy (C1) was 20.49 (95% CI: 1.83–39.15), with a pooled sensitivity of 0.86 (95% CI: 0.76–0.93) and specificity of 0.77 (95% CI: 0.71–0.82) (Table S4). Positive and negative likelihood ratios were 3.71 and 0.18, respectively. Moderate heterogeneity was observed, with I^2 estimates of 0.83 for sensitivity and 0.87 for specificity (Table S5).

For alternative Cytosponge-based diagnostic thresholds (C2 and C3), pooled sensitivity ranged from 0.68 to 0.92 and specificity from 0.36 to 0.88, with wider confidence intervals reflecting greater between-study heterogeneity (Tables S6–S9). Overall, these findings indicate stable diagnostic performance across multiple analytic models.

Population-Level Budget Impact

Population-level budget impact estimates for Cytosponge-based screening were reported from United Kingdom–based analyses (Table S9). A one-round national Cytosponge rollout targeting approximately 262,941 eligible individuals with a projected uptake of 24% was associated with a total cost of £21,636,235. When annualized over an estimated 29-year horizon, this corresponded to an annual budget impact of £746,077 (Table S9).

Cost-Effectiveness Outcomes

Incremental cost-effectiveness ratios (ICERs) for

Mir Hasan R, et al., Fortune J Health Sci 2026
DOI:10.26502/fjhs.435

Cytosponge-based strategies consistently demonstrated favorable economic performance compared with both no screening and endoscopy (Table S10). In the analysis by Benaglia et al. (2013), Cytosponge screening, compared with no screening yielded an ICER of $15,700 per quality-adjusted life year (QALY), whereas endoscopy compared with no screening resulted in a higher ICER of $22,200 per QALY. UK-based analyses from Fitzgerald et al. (2021) reported an ICER of £5,500 per QALY for Cytosponge-TFF3 versus usual care in the base-case analysis and £5,405 per QALY in probabilistic sensitivity analysis (Table S11).

In U.S.-based modeling studies, Cytosponge versus no screening was associated with ICERs ranging from $26,358 to $33,307 per QALY, remaining within commonly accepted willingness-to-pay thresholds. In contrast, endoscopy compared with Cytosponge resulted in substantially higher ICERs, ranging from $107,583 to $330,361 per QALY (Table S11).

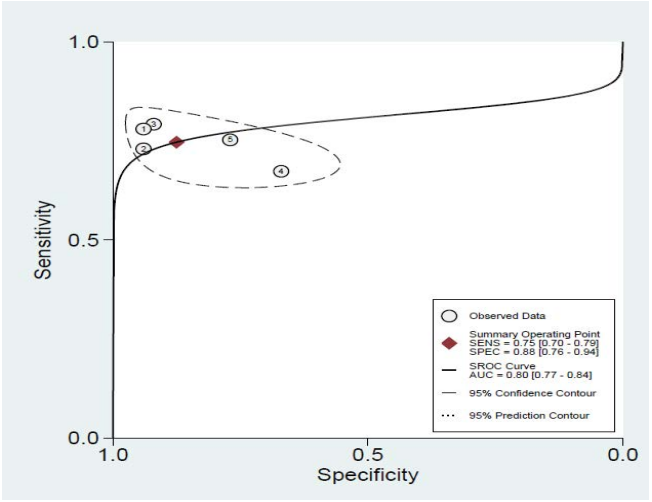

Figure 1: Sroc curve for >1cm circumferential length of metaplasia (>c1)

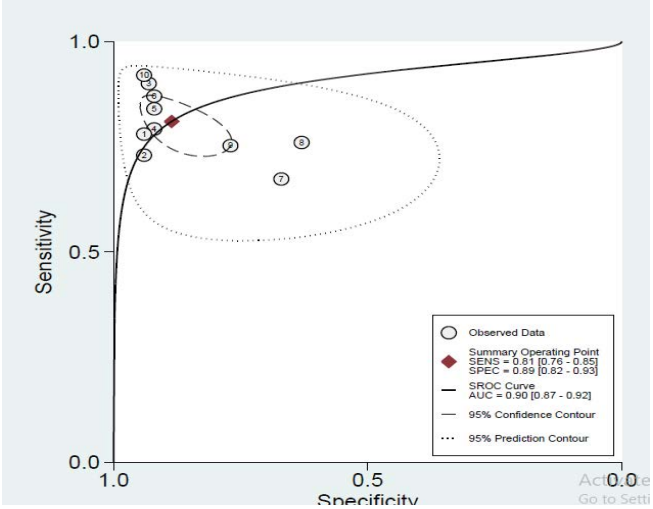

Figure 2: Sroc curve for any length

Cost Components and Resource Utilization

Detailed cost components further supported the economic efficiency of Cytosponge-based strategies (Table S12). In the Benaglia et al. model, the incremental cost per participant was $240 for Cytosponge screening compared with no screening, versus $299 for endoscopy. In the UK-based analysis, the per-patient screening cost was £77 for Cytosponge-TFF3 compared with £1.14 for usual care, reflecting opportunistic endoscopy. Treatment costs per patient were similar between strategies (£489 for Cytosponge-TFF3 vs £482 for usual care), resulting in total per-patient costs of £565 and £48, respectively (Table S12).

Additional analyses demonstrated that Cytosponge screening reduced overall screening costs by 27–29% compared with endoscopy (Table S12). In post-treatment surveillance settings, Cytosponge-based approaches reduced endoscopy utilization to less than 25% of standard surveillance protocols, serving as a proxy for substantial cost and resource savings (Table S12).

SROC Curves

The SROC curves demonstrate good diagnostic accuracy for the Cytosponge-TFF3 technique (Figures 1 and 2). The AUROC for >C1 metaplasia was 0.80, while the AUROC for any length was 0.90.

Discussion

Barrett's esophagus (BE) is characterized by the replacement of normal squamous epithelium with metaplastic columnar epithelium and is the principal precursor to esophageal adenocarcinoma (EAC), a malignancy associated with poor prognosis when diagnosed at advanced stages. Early detection of BE is therefore essential to enable surveillance and timely intervention. However, traditional diagnostic approaches have notable limitations. Upper gastrointestinal endoscopy with biopsy, although considered the gold standard, is invasive, expensive, operator-dependent, and poorly suited for population-wide screening. Reported sensitivity ranges from 80% to 90% and specificity from 70% to 80%, with diagnostic accuracy influenced by endoscopist expertise and sampling error [5]. Mucosal biopsy, despite high specificity, may miss early or patchy intestinal metaplasia, while chromoendoscopy, though useful for enhancing mucosal visualization, remains limited by variability in operator experience and inconsistent performance [5].

To address these challenges, several minimally invasive and non-endoscopic diagnostic modalities have been developed to improve accessibility and patient acceptability. EsophaCap is a swallowable capsule-based device that expands in the esophagus to collect epithelial cells for cytologic analysis and has shown promising sensitivity and

Mir Hasan R, et al., Fortune J Health Sci 2026
DOI:10.26502/fjhs.435

specificity for BE detection. This techniques offer patient-friendly alternatives that may facilitate large-scale screening. Cytosponge, which utilizes a comparable cell-collection mechanism followed by TFF3 analysis, has emerged as one of the most extensively studied non-endoscopic tools for BE detection [11, 14]. While advanced imaging modalities such as chromoendoscopy, confocal laser endomicroscopy (CLE), and virtual endoscopy may provide additional diagnostic insights, their routine use is constrained by cost, availability, and technical expertise requirements [15, 16].

Among these approaches, the Cytosponge-TFF3 technique has demonstrated particularly strong clinical utility. This minimally invasive and cost-effective method involves swallowing a capsule attached to a string that expands in the stomach and collects esophageal cells during retrieval. The samples are subsequently analyzed for TFF3 expression, a hallmark of intestinal metaplasia. Multiple studies have demonstrated high sensitivity and specificity for BE detection, with diagnostic performance approaching that of endoscopy while avoiding the need for sedation or specialized procedural infrastructure [9, 17]. The favorable safety profile, minimal patient discomfort, and feasibility in outpatient or primary care settings make Cytosponge particularly attractive for large-scale screening initiatives. These characteristics position Cytosponge as a practical alternative to conventional endoscopic strategies [17].

The findings of the present meta-analysis support this growing evidence base. The pooled sensitivity and specificity estimates indicate that Cytosponge-TFF3 is a reliable diagnostic tool for BE, particularly for detecting metaplasia across a range of circumferential lengths [1, 3]. These results reinforce the role of Cytosponge as an effective non-endoscopic screening strategy capable of identifying BE with clinically meaningful accuracy.

Economic considerations are central to decisions regarding implementation of screening programs. Comparative analyses evaluating no screening, Cytosponge, and endoscopy have consistently demonstrated meaningful differences in cost and health outcomes. Cytosponge frequently emerges as a cost-effective alternative to endoscopy. In the analysis by Benaglia et al. (2013), mean survival and quality-adjusted life years (QALYs) were nearly identical between Cytosponge and endoscopic screening strategies, while Cytosponge incurred substantially lower costs ($15,724 vs. $22,167). These findings suggest that Cytosponge can deliver comparable clinical benefit at a significantly reduced financial burden, particularly when compared with no screening. Nevertheless, screening decisions must consider population characteristics such as age, disease prevalence, symptom burden, and healthcare infrastructure.

Subsequent studies further support the economic advantages of Cytosponge, particularly in high-cost healthcare settings. Eluri et al. (2021) demonstrated that Cytosponge remains economically favorable in the United States, where endoscopy-associated costs are substantially higher (28). Similarly, Heberle et al. (2018) reported consistent cost savings across diverse institutional settings, including large tertiary care centers. These findings suggest that Cytosponge offers a scalable and economically efficient option even within resource-intensive healthcare systems. However, in selected high-risk populations—such as patients with known dysplasia or alarm features—the comprehensive diagnostic capabilities of endoscopy may still justify its use.

Overall, this meta-analysis demonstrates that non-endoscopic strategies for BE screening and surveillance, particularly Cytosponge®-based approaches, are consistently cost-effective compared with traditional endoscopic pathways. Across multiple healthcare settings and modeling frameworks, Cytosponge strategies achieved lower incremental cost-effectiveness ratios (ICERs) while maintaining clinically meaningful gains in QALYs.

Early microsimulation modeling showed that Cytosponge screening incurred an incremental cost of approximately $240 per participant compared with no screening, with an ICER of $15,700 per QALY gained, outperforming endoscopic screening, which demonstrated an ICER of $22,200 per QALY [18]. These results highlight the economic advantages associated with lower test costs and improved scalability of non-endoscopic screening modalities.

Further U.S.-based analyses demonstrated that while Cytosponge reduced total screening costs by 27–29% relative to endoscopy, some models reported modestly fewer QALYs (1.8–5.5 per 1,000 patients) [21]. Despite this, ICERs for Cytosponge compared with no screening remained within accepted willingness-to-pay thresholds ($26,358–$33,307 per QALY), whereas endoscopy compared with Cytosponge often exceeded $100,000 per QALY [21]. These findings support Cytosponge as an economically efficient strategy when balancing population-level costs against health outcomes.

Evidence from the United Kingdom further reinforces these conclusions. Using data from the BEST3 randomized trial, one-off Cytosponge-TFF3 screening was associated with an incremental cost of £82 per patient and an ICER of approximately £5,500 per QALY gained compared with usual care, with a high probability of cost-effectiveness at conventional UK thresholds [20]. In surveillance settings, Cytosponge-based strategies substantially reduced the need for follow-up endoscopies, requiring less than one-quarter of procedures used in standard surveillance protocols without increasing EAC-related mortality [19].

Mir Hasan R, et al., Fortune J Health Sci 2026
DOI:10.26502/fjhs.435

In summary, the consistency of favorable diagnostic accuracy and cost-effectiveness across multiple studies and healthcare systems supports Cytosponge-based strategies as clinically effective and economically attractive options for both screening and surveillance in Barrett's esophagus care pathways.

Role of Maximal Barrett's Segment Length in Risk Stratification and Diagnostic Pathways

Several recent studies further contextualize the importance of maximal Barrett's segment length (M length) in risk stratification and non-endoscopic diagnostic pathways. These data complement the findings of the present meta-analysis by reinforcing the clinical relevance of segment length when interpreting screening and surveillance outcomes.

Chien et al. reported findings from the Scottish CytoSCOT programme, a large real-world evaluation of a non-endoscopic oesophageal cell collection device used in Barrett's surveillance. In this cohort of more than 3,700 patients, longer Barrett's segments were significantly associated with abnormal cytological biomarker profiles and higher-risk histological outcomes at confirmatory endoscopy. The study demonstrated that maximal segment length plays an important role in identifying patients at increased risk of dysplasia or early neoplasia. These results align with established evidence that longer Barrett's segments carry a greater risk of malignant progression, thereby supporting the integration of M length into triage and surveillance algorithms [29].

Gourgiotis et al. provided prospective real-world data from NHS England evaluating a capsule-sponge-based diagnostic pathway in patients with reflux symptoms. While the primary focus was not exclusively on segment length, the study highlighted the utility of non-endoscopic screening in prioritizing patients for endoscopy. Importantly, the findings suggest that effective biomarker-based triage may reduce unnecessary endoscopic procedures, particularly in individuals with shorter M segments where diagnostic yield and neoplastic risk are lower. This supports a length-stratified approach in which M measurement contributes to determining which patients require confirmatory endoscopic evaluation [30].

Similarly, Shaheen et al. emphasized the prognostic significance of maximal Barrett's segment length in guiding surveillance strategies. Their findings are consistent with broader guideline recommendations that incorporate segment length into clinical decision-making. Multiple analyses have demonstrated that increasing M length is associated with elevated risk of dysplasia and esophageal adenocarcinoma. This reinforces the importance of standardized reporting using the Prague C&M classification and highlights the need for consistent measurement of maximal extent in both research and routine clinical practice [31].

Angel et al. further evaluated a capsule-sponge diagnostic pathway in a large clinical cohort. Their data indicate that variations in maximal Barrett's length influence diagnostic yield and subsequent management decisions. In particular, shorter segments—especially those under 3 cm—were associated with lower neoplastic risk, although they remain clinically relevant when considered alongside biomarker findings and symptom profiles. These results underscore the nuanced relationship between segment length and clinical outcomes within contemporary non-endoscopic screening frameworks [32].

Collectively, these studies reinforce the central role of maximal segment length in Barrett's esophagus assessment across both endoscopic and non-endoscopic strategies. They provide complementary evidence that longer M segments are associated with higher diagnostic yield and greater neoplastic risk, while shorter segments may benefit from biomarker-guided triage approaches. Integration of M length into screening and surveillance pathways therefore represents a clinically meaningful strategy that enhances risk stratification and optimizes resource utilization.

Clinical Implications

The Cytosponge offers significant advantages over traditional endoscopy for diagnosing Barrett's esophagus. While most patients were satisfied with the test, some reported gagging during administration and 60% experience it during removal. A large systematic review of patient satisfaction found that the Cytosponge was less acceptable to patients than sedated esophagogastroduodenoscopy (EGD), although it was comparable to unsedated procedures; however, 80% were willing to have the procedure again or to recommend it to friends [22]. Unlike endoscopy, which requires sedation and specialized equipment, the Cytosponge can be performed in outpatient settings without the need for sedation, reducing logistical complexity and procedure time [17]. Rather than emphasizing tolerability alone, its principal advantage lies in its convenience and accessibility, as it can be administered in primary care or outpatient settings without the infrastructure required for endoscopy. This has been demonstrated in large pragmatic trials, including BEST1 and BEST3, which successfully implemented the Cytosponge in family practice and primary care settings, confirming its feasibility outside specialized centres. Importantly, the test can often be performed on the same day it is recommended during a routine clinic visit, eliminating the need for separate scheduling and thereby potentially reducing loss to follow-up. This simplicity allows it to be deployed widely and efficiently, making it a practical tool for population-level screening programs. Moreover, its ability to collect esophageal cells

Mir Hasan R, et al., Fortune J Health Sci 2026
DOI:10.26502/fjhs.435

for biomarker analysis in a non-endoscopic setting provides a potential solution to barriers often associated with traditional diagnostic methods.

Cost-Effectiveness

The Cytosponge is notably more cost-effective than traditional endoscopy, which involves higher expenses due to the need for specialized facilities, equipment, and personnel [3]. Its affordability ensures broader access and addresses financial barriers, enabling healthcare systems to implement widespread screening programs without incurring prohibitive costs. While some studies suggest that Cytosponge may be cost-effective compared to universal endoscopy, it may lead to an increased number of downstream endoscopies and Barrett's surveillance, which could contribute to overall incremental healthcare costs.

Scalability

The scalability of the Cytosponge lies in its simplicity and ease of use, which make it an excellent candidate for large-scale screening programs. Unlike endoscopic procedures, which require highly skilled operators and specialized infrastructure, the Cytosponge can be deployed in outpatient settings with minimal training and resources. This adaptability allows healthcare systems to screen large populations efficiently, particularly in regions with limited access to endoscopic facilities [1]. Its straightforward procedure also encourages higher patient participation rates, contributing to earlier detection of Barrett's esophagus and reducing the burden of esophageal adenocarcinoma. Additionally, cytostome scalability can be improved through machine learning-based automation of TFF3 slide analysis. By automatically quantifying TFF3 expression, the approach reduces reliance on time-intensive manual pathology review, enabling more standardized and high-throughput interpretation. This supports the feasibility of scaling Cytosponge as a broader screening and triage tool for Barrett's oesophagus [3, 24].

Limitations

Despite its numerous advantages, the Cytosponge has some limitations that must be considered. One major issue is heterogeneity among study populations and diagnostic thresholds, which may have introduced variability in reported outcomes. These differences could impact the generalizability of findings across different settings and populations [2]. In particular, variation in reported sensitivity and specificity for the detection of intestinal metaplasia (IM) >1 cm compared with IM of all lengths is clinically important. Since Barrett's esophagus is currently defined as metaplasia extending ≥1 cm above the gastroesophageal junction, differences in diagnostic performance depending on length thresholds have important implications for clinical interpretation. Additionally, most studies evaluating the Cytosponge included high-risk patients, raising concerns about potential selection bias and its applicability to the general population [17]. Furthermore, the Cytosponge has an inherent limitation in that it cannot measure the length of Barrett's epithelium. As a result, it may detect intestinal metaplasia <1 cm in length, which may not meet the current diagnostic criteria for Barrett's esophagus. This could potentially lead to overdiagnosis and unnecessary confirmatory endoscopies [1]. Lastly, key limitation of the current evidence is that most studies evaluating the Cytosponge have been conducted in the UK, which may limit the generalizability of findings to other healthcare systems and populations. Additional research in diverse geographic and clinical settings is needed to confirm the applicability of results internationally.

Future Directions

Future research should focus on validating the Cytosponge's effectiveness in broader and more diverse populations to ensure its generalizability. Expanding the demographic scope of studies would help determine its accuracy and cost-effectiveness in routine clinical practice. Additionally, investigations into the integration of the Cytosponge with other non-invasive technologies or biomarkers could enhance its diagnostic capabilities and further establish its role as a primary screening tool for Barrett's esophagus [1, 2]. There is ongoing work exploring additional biomarkers for improved risk stratification, including recent evidence reported, highlighting the evolving landscape of biomarker-driven approaches in Barrett's esophagus screening and surveillance [25]. Currently, the Cytosponge is offered clinically only in the United Kingdom and the United States, highlighting the need for international studies to evaluate feasibility and implementation in other healthcare settings. Efforts should also aim to assess the long-term outcomes of using the Cytosponge in population-level screening programs, including its potential to reduce esophageal cancer incidence and mortality rates.

Conclusion

The Cytosponge-TFF3 technique demonstrates promising diagnostic accuracy for detecting Barrett's esophagus, particularly for any circumferential length of metaplasia. It offers a minimally invasive, cost-effective alternative to traditional endoscopy, with potential for widespread use in early detection programs [1, 3]. Further studies are needed to confirm its utility in diverse populations and clinical settings, especially in primary care and high-risk patient groups [3, 5].

Declarations

Declaration of Competing Interest

The authors declare that they have no known financial or

personal relationships that could have influenced the work reported in this paper.

Financial Disclosure

The authors report no financial interests in any of the procedures, devices, or products mentioned in this manuscript. No funding or grants were received for this study.

Ethical Statement

This study is a meta-analysis of previously published diagnostic accuracy studies and did not involve direct data collection from human participants. Therefore, ethical approval and informed consent were not required. All included studies had obtained appropriate ethical approval from their respective institutional review boards.

IRB Approval

No IRB approval was required for this manuscript as no new human subjects were involved.

Data Availability Statement

All studies included in this research are publicly available through PubMed Central. Data supporting the findings of this study are provided within the article and Supplementary Material files. Additional information can be obtained from the corresponding author upon request.

Use of AI (Artificial intellegence) in Research

The authors declare that they have not used any sort of AI to produce any part of research.

Acknowledgement

Authors declare that they have no acknowledgement

List of Abbreviations

AUROC – Area Under the Receiver Operating Characteristic Curve

BE – Barrett's Esophagus

BMI – Body Mass Index

C1 – Circumferential Length ≥1 cm

CI – Confidence Interval

CLE – Confocal Laser Endomicroscopy

DOR – Diagnostic Odds Ratio

EAC – Esophageal Adenocarcinoma

EGD – Esophagogastroduodenoscopy

ICER – Incremental Cost-Effectiveness Ratio

I^2 – I-squared (Heterogeneity Statistic)

IM – Intestinal Metaplasia

IRB – Institutional Review Board

LR+ – Positive Likelihood Ratio

LR− – Negative Likelihood Ratio

M length – Maximal Barrett's Segment Length

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

OSF – Open Science Framework

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QALY – Quality-Adjusted Life Year

QUADAS-2 – Quality Assessment of Diagnostic Accuracy Studies-2

RCT – Randomized Controlled Trial

SROC – Summary Receiver Operating Characteristic

TFF3 – Trefoil Factor 3

UK – United Kingdom

US – United States

Supplementary Files:

https://cdn.fortunejournals.com/supply/efficacy-tolerability-and-cost-effectiveness-of-cytosponge-in-pat-10081-supplementary.docx

References

1. Fitzgerald RC, di Pietro M, O'Donovan M, et al. Cytosponge-trefoil factor 3 versus usual care to identify Barrett's oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial. The Lancet 396 (2020): 333-344.
2. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. American Journal of Gastroenterology 111 (2016): 30-50.
3. Benaglia T, Sharples LD, Fitzgerald RC, et al. Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus. Gastroenterology 144 (2013).
4. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, et al. Evaluation of a Minimally Invasive Cell Sampling Device Coupled with Assessment of Trefoil Factor 3 Expression for Diagnosing Barrett's Esophagus: A Multi-Center Case–Control Study. PLoS Med 12 (2015): 1-19.
5. Killcoyne S, Fitzgerald RC. Evolution and progression of Barrett's oesophagus to oesophageal cancer. Nature Reviews Cancer 21 (2021): 731-741.

6. Iqbal U, Siddique O, Ovalle A, et al. Safety and efficacy of a minimally invasive cell sampling device ('Cytosponge') in the diagnosis of esophageal pathology: A systematic review. Eur J Gastroenterol Hepatol 30 (2018): 1261-1269.

7. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. The BMJ 372 (2021).

8. Whiting PF, Rutjes AWS, Westwood ME, et al. Quadas-2: A revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 155 (2011): 529-536.

9. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, et al. Evaluation of a Minimally Invasive Cell Sampling Device Coupled with Assessment of Trefoil Factor 3 Expression for Diagnosing Barrett's Esophagus: A Multi-Center Case–Control Study. PLoS Med 12 (2015): 1-19.

10. Ross-Innes CS, Chettouh H, Achilleos A, et al. Risk stratification of Barrett's oesophagus using a non-endoscopic sampling method coupled with a biomarker panel: a cohort study. Lancet Gastroenterol Hepatol 2 (2017): 23-31.

11. Kadri P SR, Lao-Sirieix I, O'Donovan M, et al. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: Cohort study. BMJ 341 (2010): 595.

12. Lao-Sirieix P, Rous B, O'Donovan M, et al. Non-endoscopic immunocytological screening test for Barrett's oesophagus [19]. Gut 56 (2007): 1033-1034.

13. Study Results | Cytosponge Adequacy Study Evaluation II | ClinicalTrials.gov (2025).

14. Iyer PG, Taylor WR, Johnson ML, et al. Accurate Nonendoscopic Detection of Barrett's Esophagus by Methylated DNA Markers: A Multisite Case Control Study. American Journal of Gastroenterology 115 (2020): 1201-1209.

15. Paterson AL, Gehrung M, Fitzgerald RC, et al. Role of TFF3 as an Adjunct in the Diagnosis of Barrett's Esophagus using a Minimally Invasive Esophageal Sampling Device – the CytospongeTM. Diagn Cytopathol 48 (2019): 253.

16. Katz-Summercorn AC, Jammula S, Frangou A, et al. Multi-omic cross-sectional cohort study of pre-malignant Barrett's esophagus reveals early structural variation and retrotransposon activity. Nat Commun 13 (2022).

17. di Pietro M, Modolell I, O'Donovan M, et al. Use of Cytosponge as a triaging tool to upper gastrointestinal endoscopy during the COVID-19 pandemic. Lancet Gastroenterol Hepatol 5 (2020): 805-806.

18. Benaglia T, Sharples LD, Fitzgerald RC, et al. Health benefits and cost effectiveness of endoscopic and nonendoscopic Cytosponge screening for Barrett's esophagus. Gastroenterology 144 (2013): 62-73.

19. Ross Inadomi J, Heberle CR, Omidvari AH, et al. Utility and cost-effectiveness of a nonendoscopic approach to Barrett's esophagus surveillance after endoscopic therapy. Clin Gastroenterol Hepatol 15 (2017): 1397-1404.

20. Swart N, Maroni R, Muldrew B, et al. BEST3 Consortium. Economic evaluation of Cytosponge®-trefoil factor 3 for Barrett esophagus: a cost-utility analysis of randomised controlled trial data. EclinicalMedicine 37 (2021): 100969.

21. Heberle CR, Omidvari AH, Ali A, et al. Cost effectiveness of screening patients with gastroesophageal reflux disease for Barrett's esophagus with a minimally invasive cell sampling device. Clin Gastroenterol Hepatol 15 (2017): 1397-1404.

22. Maroni R, Barnes J, Offman J, et al. Patient-reported experiences and views on the Cytosponge test: a mixed-methods analysis from the BEST3 trial. BMJ Open 12 (2022): e054258.

23. Berman AG, Tan WK, O'Donovan M, et al. Quantification of TFF3 expression from a non-endoscopic device predicts clinically relevant Barrett's oesophagus by machine learning. EbioMedicine 82 (2022): 104160.

24. Gehrung M, Crispin-Ortuzar M, Berman AG, et al. Triage-driven diagnosis of Barrett's esophagus for early detection of esophageal adenocarcinoma using deep learning. Nat Med 27 (2021): 833-841.

25. Tan WK, Ross-Innes CS, Somerset T, et al. Biomarker risk stratification with capsule sponge in the surveillance of Barrett's oesophagus: prospective evaluation of UK real-world implementation. Lancet 406 (2025): 271-282.

26. Cytosponge for detecting abnormal cells in the oesophagus Medtech innovation briefing (2020).

27. Heberle CR, Omidvari AH, Ali A, et al. Cost Effectiveness of Screening Patients With Gastroesophageal Reflux Disease for Barrett's Esophagus With a Minimally Invasive Cell Sampling Device. Clin Gastroenterol Hepatol 15 (2017): 1397-1404.

28. Eluri S, Paterson A, Lauren BN, et al. Utility and Cost-Effectiveness of a Nonendoscopic Approach to Barrett's Esophagus Surveillance After Endoscopic Therapy. Clin Gastroenterol Hepatol 20 (2022): 51-63.

29. Chien S, Glen P, Penman I, et al. Oesophageal cell

Mir Hasan R, et al., Fortune J Health Sci 2026
DOI:10.26502/fjhs.435

collection device and biomarker testing to identify high-risk Barrett's patients requiring endoscopic investigation. Br J Surg 111 (2024): znae117.

30. Gourgiotis V, Graham C, Foerster K; NHS England Pilot and NHS England Oversight Group; Fitzgerald RC, Harvey R, Morris DL. Use of a Non-Endoscopic Capsule-Sponge Triage Test for Reflux Symptoms: Results From the NHS England Prospective Real-World Evaluation. Aliment Pharmacol Ther 61 (2025): 876-885.

31. Shaheen NJ, Komanduri S, Muthusamy VR, et al. Acceptability and Adequacy of a Non-endoscopic Cell Collection Device for Diagnosis of Barrett's Esophagus: Lessons Learned. Dig Dis Sci 67 (2022): 177-186.

32. Angel D, Kumar R, Shaw K, et al. Evaluation of a novel capsule sponge triage pathway for patients routinely referred with reflux symptoms: safety, long-term outcomes and impact on endoscopy from a large volume single site cohort over 4 yearsFrontline Gastroenterology 17 (2026): 119-127.

Citation: Mir Rashedul Hasan, Md. Sohel Rana, Jebun Nahar, Muslima Swapnil, Amit Sarker, Abdullah Hill Baki. Diagnostic Utility of Serum Soluble Urokinase-Type Plasminogen Activator Receptor in Acute Kidney Injury with Sepsis. Fortune Journal of Health Sciences. 9 (2026): 429-439.