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PROTOCOL

The Prevalence of Malignancy in Appendectomy Specimens for Patients Presenting with Acute Appendicitis: A Systematic Review and Meta-Analysis Protocol

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Abstract

Background: Acute appendicitis is a common emergency, and appendectomy is often performed, yet a subset of specimens contains unsuspected primary or secondary malignancies with implications for nonoperative management strategies. **Objectives:** The review will estimate the pooled prevalence of histologically confirmed malignancy (primary appendiceal and relevant colorectal or intra abdominal cancers) in appendectomy specimens from adults with acute appendicitis and explore variation by demographics, clinical/imaging features, tumor subtype, and place/time. **Methods:** Following PRISMA P, English language observational studies (2010 onward) from the three biomedical databases will be screened by two independent reviewers, with standardized data extraction and Joanna Briggs Institute risk of bias assessment. Prevalence will be pooled using random effects meta analysis of transformed proportions, with heterogeneity, subgroup/sensitivity analyses, and, where available, meta analysis of odds ratios for risk factors; publication bias will be examined in larger evidence sets. **Ethical considerations:** This systematic review and meta analysis will use data extracted exclusively from previously published studies and will not involve direct contact with human participants, collection of identifiable personal data, or any intervention beyond secondary analysis of aggregated results. Consequently, formal approval from an institutional review board or research ethics committee is generally not required.

Keywords: Prevalence- Malignancy- Appendectomy Specimens- Acute Appendicitis

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Introduction

The appendix has historically been regarded as a vestigial organ without major physiological function in humans. However, recent studies have highlighted its important immunological role [1]. Evidence suggests that the appendix serves as a specialized reservoir for beneficial commensal microorganisms, which may contribute to the regulation of intestinal microbiota homeostasis [2]. Despite this evolving understanding of its function, the appendix is most commonly associated with appendicitis, an inflammatory condition with an etiology that remains incompletely understood. Acute appendicitis is typically linked to luminal obstruction of the appendix

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by fecaliths, lymphoid hyperplasia, inspissated stool, parasitic infections, or, more rarely, primary malignancies of the appendix or cecum [3]. Luminal obstruction is considered a critical step in the pathogenesis of appendicitis, leading to bacterial overgrowth, luminal distension, impairment of venous and lymphatic drainage, and eventually thrombosis, ischemic necrosis, and potential perforation of the appendix. Clinically, acute appendicitis may present as uncomplicated (simple) or perforated disease. Although some cases of uncomplicated acute appendicitis can be successfully managed with antibiotic therapy alone, determining which patients require appendectomy and which can be safely treated nonoperatively with antibiotics represents a key clinical decision. In contrast, if left untreated, gangrenous acute appendicitis may progress to localized leakage into the omentum with abscess formation. Free perforation of the appendix is typically associated with severe complications, including generalized peritonitis, septic thrombophlebitis of the portal vein and its branches, and pyogenic liver abscess, all of which are associated with a generally poor prognosis [4]. Appendectomy, the surgical removal of the appendix, remains the standard treatment for acute appendicitis and is the most common general emergency operation in the United States, with approximately 300,000 procedures performed annually [5]. The lifetime risk of appendicitis varies according to demographic factors such as sex, age, and race. The lifetime risk is 8.6% in men and 6.7% in women, and the incidence is approximately 1.5 times higher in White individuals compared with non-White populations [6]. Appendicitis occurs most frequently during the second and third decades of life and is relatively uncommon at more advanced ages [3].

Primary appendiceal malignancies are rare, with an estimated incidence of approximately 0.12 cases per million population per year in the United States. In recent decades, however, their reported incidence has increased, reaching approximately 0.97 cases per 100,000 persons per year [7]. These neoplasms are frequently diagnosed incidentally following appendectomy, as appendiceal tumors often present clinically as acute appendicitis and are subsequently identified on histopathological examination of the resected specimen [6]. In some patients, primary appendiceal cancers are asymptomatic and are detected during colonoscopy, cross sectional imaging, or surgery performed for other, unrelated indications [8]. The most common histologic types of primary appendiceal malignancies include adenocarcinoma, neuroendocrine carcinoma, and mixed or combined tumors. Adenocarcinoma accounts for approximately 60% of primary appendiceal cancers, yet represents less than 0.5% of all gastrointestinal malignancies [6]. Notably, several case reports have suggested that acute appendicitis may, in some instances, result from secondary inflammation due to metastatic involvement of the appendix by other primary malignancies, such as prostate cancer [9], recurrent gastric adenocarcinoma [10], and colorectal carcinoma [11].

This protocol outlines the methodology for a systematic review and meta analysis aimed at determining the prevalence of malignancy among patients undergoing appendectomy for acute appendicitis. This protocol specifies a comprehensive approach to literature search, study selection, data extraction, and risk of bias assessment, with the objective of synthesizing existing evidence on overall malignancy rates in this population. Furthermore, the review will evaluate proposed risk factors including sex, age, race, and pre existing malignancies and quantitatively assess their combined impact on the probability of detecting appendiceal or other relevant malignancies in patients managed surgically for acute appendicitis.

Objectives

Primary objective

To estimate the pooled prevalence of histologically confirmed malignancy (primary appendiceal neoplasms and relevant colorectal or intra abdominal cancers) among patients undergoing appendectomy for clinically or radiologically diagnosed acute appendicitis.

Secondary objectives

To determine how malignancy prevalence varies by age, sex, and race/ethnicity.

To evaluate associations between clinical/imaging features (e.g. complicated vs. uncomplicated appendicitis, appendiceal diameter, mass/abscess) and malignancy risk.

To describe histologic subtypes and frequencies of primary appendiceal tumors incidentally detected in appendectomy specimens.

To summarize reported cases of secondary (metastatic) involvement of the appendix presenting as acute appendicitis.

To explore temporal and geographic trends in reported malignancy rates where data allow.

Methods

Study Design

This systematic review and meta-analysis protocol adhered to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol guidelines to ensure transparency and reproducibility [12].

Search Strategy

A comprehensive search strategy will be developed to identify relevant studies from Scopus, PubMed, and Web of Science. The search will include Medical Subject Headings (MeSH) terms, keywords, and synonyms related to acute appendicitis, appendectomy specimens, and malignancy. Boolean operators ("AND," "OR") will be applied to combine search terms effectively. The search strategy will be customized for each database as follows that has been provided for PubMed.

PubMed

((“cross sectional studies”[MeSH Terms] OR “prevalence”[MeSH Terms] OR “cross sectional

study"[MeSH Terms] OR "epidemiology"[MeSH Terms] OR "incidence"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "prevalence"[Title/Abstract] OR "incidence"[Title/Abstract] OR "frequency"[Title/Abstract] OR "observational study"[Title/Abstract] OR "cohort studies"[MeSH Terms] OR "cohort study"[Title/Abstract] OR "case control study"[Title/Abstract] OR "cross sectional study"[Title/Abstract] OR "cross sectional studies"[MeSH Terms] OR "case control studies"[MeSH Terms]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[MeSH Terms] OR "malignancy"[Title/Abstract] OR "cancer"[Title/Abstract] OR "neoplasms"[MeSH Terms] OR "neoplasm"[Title/Abstract] OR "neoplasms"[MeSH Terms] OR "tumor"[Title/Abstract] OR "tumour"[Title/Abstract] OR "neoplasms"[MeSH Terms]) AND ("appendectomy"[Title/Abstract] OR "appendectomies"[Title/Abstract] OR "appendix surgery"[Title/Abstract] OR "acute appendicitis"[Title/Abstract] OR "inflamed appendix"[Title/Abstract])) AND ((english[Filter]) AND (2010:2025[pdat])).

Inclusion Criteria

- Studies that evaluate the prevalence of malignancy in appendectomy specimens from patients with acute appendicitis.
- Observational studies, including cohort, case-control, and cross-sectional designs.
- Articles published in English.
- Studies reporting sufficient data to calculate the prevalence of malignancy.

Exclusion Criteria

- Studies focusing exclusively on pediatric populations (<18 years).
- Case reports, reviews, editorials, or commentaries.
- Studies without full-text availability.
- Articles not assessing malignancy in appendectomy specimens or not reporting prevalence data.

Study Selection

Two independent reviewers will screen titles and abstracts for relevance. Full-text articles of potentially eligible studies will be retrieved and reviewed based on the inclusion and exclusion criteria. Any disagreements will be resolved through discussion or consultation with a third reviewer.

Data Extraction

Data will be extracted by two independent reviewers using a standardized data extraction form. Extracted data will include:

- Study characteristics (author, year, country, study design).
- Population demographics (age, sex).
- Prevalence of malignancy in appendectomy specimens.
- Histopathological types of malignancies (if reported).

Risk of Bias Assessment

The methodological quality of included studies will be assessed using the Joanna Briggs Institute (JBI) checklist for observational studies [13]. Two reviewers will independently evaluate each study, and discrepancies will be resolved through consensus or by involving a third reviewer.

Data Synthesis

A meta analysis will be conducted when at least three studies with sufficiently homogeneous definitions are available for a given outcome. Because prevalence data often have variance instability, proportions will be pooled using a random effects model (e.g. DerSimonian–Laird or restricted maximum likelihood) after appropriate transformation to stabilize variances, then back transformed for reporting.

Heterogeneity will be quantified using

- I^2 statistic
- Cochran's Q test with associated p values.

Planned subgroup analyses (where data permit)

- Age (e.g. <40 vs ≥40 years; study defined age strata).
- Sex.
- Race/ethnicity.
- Geographic region (continent or World Bank income group).

Planned sensitivity analyses

- Excluding studies at high risk of bias according to JBI.
- Excluding studies with extreme prevalence estimates (outliers).
- Excluding studies with unclear or atypical definitions of acute appendicitis or malignancy.

For risk factors

Where at least two studies report comparable adjusted or unadjusted ORs, random effects meta analysis of log ORs will be performed. If studies are too heterogeneous in design or measurement, results will be synthesized narratively.

Assessment of publication bias

For meta analyses including ≥10 studies, small study and publication bias will be explored using: Egger's regression tests for asymmetry, recognizing limitations when pooling proportions [14].

Ethical considerations

This systematic review and meta analysis will use data extracted exclusively from previously published studies and will not involve direct contact with human participants, collection of identifiable personal data, or any intervention beyond secondary analysis of aggregated results. Consequently, formal approval from an institutional review board or research ethics committee is generally not required.

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Statement of Transparency and Principles

• The authors declare no conflict of interest.

• The study was approved by the Research Ethics Committee of the authors' affiliated institution.

• The study data are available upon reasonable request.

• All authors contributed to the implementation of this research.

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