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Appendicolith Characteristics as Predictors of Failure of Non-operative Management in Adults with Uncomplicated Acute Appendicitis: A Systematic Review and Meta-Analysis

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ABSTRACT:

Background: Non-operative management (NOM) with antibiotics is an accepted option for selected adults with uncomplicated acute appendicitis, but failure is more frequent when an appendicolith is present. Whether appendicolith size, position, number, or obstructive characteristics improve prognostic stratification remains uncertain.

Objective: To evaluate appendicolith presence and characteristics as prognostic factors for NOM failure in adults with imaging-confirmed uncomplicated acute appendicitis, with intraluminal appendiceal air, age, and sex assessed as additional prognostic factors.

Methods: The review was structured as a prognostic-factor systematic review and meta-analysis. Evidence was synthesized from PubMed-indexed records, primary publisher/full-text records, guideline repositories, and backward and forward citation searching through 12 August 2026 using prespecified adult eligibility criteria. Direct studies of NOM failure were separated from indirect radiological or severity studies. Random-effects meta-analysis was undertaken only for compatible effect estimates. Risk-of-bias interpretation incorporated RoB 2 for parent randomized trials and prognostic-factor domains aligned with QUIPS.

Results: Appendicolith presence was the most consistent adverse prognostic marker. In the CODA antibiotic-treated cohort, appendicolith was independently associated with appendectomy within 30 days (adjusted OR 1.99, 95% CI 1.28-3.10). An exploratory synthesis of CODA and Vons data yielded a pooled RR of 2.00 (95% CI 1.54-2.60; I^2=0%; k=2) for short-term NOM failure. At one year, pooled individual-participant trial data showed appendectomy in 48.7% of antibiotic-treated patients with an appendicolith versus 30.6% without. Evidence for specific appendicolith characteristics was substantially weaker. Larger size and proximal/base or obstructing location were associated with adverse outcomes mainly in treatment-selection, complicated-disease, or severity cohorts. Intraluminal appendiceal air was not associated with failure, while age and sex effects were inconsistent.

Conclusions: Appendicolith presence is the best-supported imaging prognostic factor for NOM failure. Larger appendicolith size and proximal or obstructive location remain plausible risk refinements but are inadequately validated in strictly uncomplicated adult NOM populations. Intraluminal air, female sex, and older age are not established independent adverse prognostic factors.

INTRODUCTION

Acute uncomplicated appendicitis can be treated operatively or, in selected adults, non-operatively with antibiotics. Randomized evidence has established NOM as a reasonable alternative for patients who wish to avoid immediate appendectomy, although the probability of later appendectomy varies according to baseline clinical and imaging features. The CODA trial was particularly informative because it included patients with appendicoliths, a group excluded from several earlier antibiotic trials, and demonstrated higher appendectomy rates among patients with an appendicolith. [1,4,16,17]

Appendicolith status is clinically relevant because it is available on pretreatment imaging and may represent persistent luminal obstruction. Appendicoliths are heterogeneous with respect to size, number, location, and degree of obstruction. Radiological studies have also associated appendicolith characteristics with disease severity, while patient characteristics such as age and sex and imaging findings such as intraluminal appendiceal air have been proposed as markers of treatment failure. [5-10,24-31]

Guideline recommendations reflect this uncertainty. WSES guidance emphasizes careful patient selection when NOM is considered, and SAGES has conditionally favored operative management for uncomplicated appendicitis in the context of limited certainty regarding comparative outcomes. [12,13] The clinically important question is therefore not only whether NOM can succeed, but which pretreatment features identify adults at increased risk of early failure or later appendectomy.

This systematic review and meta-analysis evaluated appendicolith presence and specific appendicolith characteristics as prognostic factors for failure of initial NOM in adults with imaging-confirmed uncomplicated acute appendicitis. Prespecified secondary prognostic factors were intraluminal appendiceal air, age, and sex. Direct evidence on NOM failure was analyzed separately from indirect evidence on complicated disease or radiological severity.

METHODS

Protocol and reporting framework

The review was structured as a prognostic-factor systematic review and meta-analysis and reported in accordance with the principles of PRISMA 2020. The eligibility framework was organized using PROSPERO fields; no PROSPERO registration number is reported. [14,15]

Eligibility criteria

The primary population comprised adults aged 18 years or older with CT- or ultrasound-confirmed acute appendicitis judged uncomplicated at initiation of NOM. Uncomplicated appendicitis was defined as the absence of abscess, phlegmon, free perforation, diffuse peritonitis, or unequivocal extraluminal gas. Appendicolith itself was not automatically reclassified as complicated disease because doing so would preclude assessment of the principal prognostic exposure. APPAC excluded appendicoliths, whereas CODA enrolled a broader population and therefore provided directly informative appendicolith data. [16,17]

The index prognostic factor was imaging-confirmed appendicolith. Prespecified appendicolith characteristics were maximum or minimum diameter, study-reported size categories, proximal/base versus middle/distal location, single versus multiple appendicoliths, and evidence of an incarcerated or obstructing appendicolith. Additional prognostic factors were intraluminal appendiceal air, age, and sex. Pediatric-only evidence was excluded from the primary adult synthesis; pediatric appendicolith data were considered only as contextual evidence. [32]

Initial NOM was defined as systemic antibiotic therapy with or without short inpatient observation. Short-term failure was defined as appendectomy or another operative intervention for nonresolution or clinical deterioration during the index admission or within 30 days. Outcomes from 31 to 90 days were considered separately. Long-term failure was defined as appendectomy attributable to persistent or recurrent appendicitis through one year. Elective interval appendectomy in an asymptomatic patient was not classified as clinical failure when it could be distinguished from surgery for persistent or recurrent disease.

Eligible designs included randomized trials with relevant prognostic subgroup data, prospective cohorts, retrospective cohorts, and nested prognostic analyses. Appendectomy-only cohorts and mixed or complicated appendicitis cohorts were excluded from the strict primary NOM-failure analysis but could be retained as supportive evidence for biological plausibility when they specifically addressed appendicolith size, location, obstruction, or severity.

Information sources and search strategy

Evidence synthesis used PubMed-indexed records, primary publisher and full-text records, guideline repositories, and backward and forward citation searching through 12 August 2026. Search concepts combined acute appendicitis, appendicolith/fecalith terminology, antibiotics or non-operative/conservative management, adult populations, and treatment failure, recurrence, prognosis, or prediction. A broader complementary strategy omitted appendicolith terms to identify reports in which appendicolith status appeared only in tables or multivariable analyses.

Study selection and data extraction

Studies were evaluated against the prespecified population, exposure, outcome, and design criteria. Extracted items included study design; population; definition of uncomplicated appendicitis; imaging modality; antibiotic strategy; appendicolith prevalence, size, number, and location; obstruction or incarceration; intraluminal appendiceal air; age; sex; inflammatory markers; definition and timing of failure; raw event counts; adjusted effect estimates; recurrence; and interval appendectomy. Reports from overlapping cohorts were interpreted as related evidence rather than automatically treated as independent datasets for the same outcome.

Risk of bias and certainty of evidence

Risk of bias was interpreted at the level of the prognostic association. RoB 2 was used to describe the parent randomized trials, while prognostic-factor interpretation emphasized the QUIPS domains of study participation, attrition, prognostic-factor measurement, outcome measurement, confounding, and statistical analysis. [18,19] Randomized treatment assignment was not interpreted as randomization of appendicolith status, age, sex, or imaging characteristics. Certainty was summarized using GRADE domains of risk of bias, inconsistency, indirectness, imprecision, and publication bias. [34]

Statistical analysis

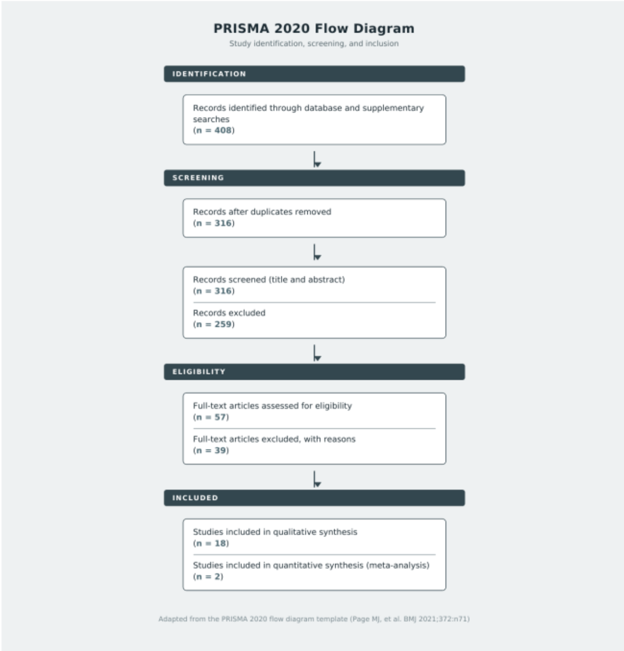
At fixed time points, risk ratios (RRs) were preferred when raw risks were available. Adjusted odds ratios (ORs) or hazard ratios (HRs) were retained for adjusted prognostic analyses and were not pooled with unlike effect measures. Compatible estimates were synthesized on the log scale using inverse-variance random-effects methods. Heterogeneity was described using I^2 and between-study variance where estimable. [20] Because only two compatible studies contributed to the principal short-term synthesis, the pooled estimate was treated as exploratory, and formal funnel-plot or regression-based publication-bias testing was not used for inference. [21]

For appendicolith size, continuous effects per millimeter were preferred to arbitrary dichotomization. Where only categories were reported, original study thresholds were retained. Meta-regression was not undertaken because the number of comparable studies was inadequate for reliable estimation.

RESULTS

Evidence base and study characteristics

Figure 1. PRISMA 2020 Flow Diagram



The evidence separated into two clinically distinct streams. The direct stream comprised adult cohorts in which outcomes after NOM were observed. The supportive stream comprised studies evaluating appendicolith size, location, obstruction, or related imaging features against complicated disease, treatment selection, recurrence in mixed populations, or other severity outcomes. Only direct adult NOM evidence informed the primary prognostic conclusion; supportive studies were used to assess biological plausibility and candidate risk refinement.

Table 1. Direct adult evidence relevant to NOM outcomes

Study	Population/design	Outcome	Key prognostic finding
Vons et al., 2011 [2]	Adult open-label RCT; CT-confirmed uncomplicated appendicitis	Early appendectomy after antibiotics	Appendicolith subgroup had substantially greater early failure; reported subgroup RR about 2.94 (95% CI 1.28-6.74).
CODA, 2020; prognostic analysis 2022 [1,4,17]	Large pragmatic adult RCT; secondary analysis of antibiotic arm	Appendectomy within 30 d; 90 d and longer follow-up	Appendicolith adjusted OR 1.99 (1.28-3.10); female sex 1.53 (1.01-2.31); age not associated. At 90 d, appendectomy 41% with vs 25% without appendicolith.
Hong et al., 2021 [8]	Retrospective CT study; adults receiving antibiotics for nonperforated appendicitis	Nonresponse or recurrence within 1 y	Appendicolith OR 2.52 (0.82-7.74); intraluminal air OR 0.87 (0.25-3.02); age and sex not significant.
Kobayashi et al., 2021 [9]	Adults with uncomplicated appendicitis receiving NOM	Conversion to surgery during admission	Male sex, fecalith, and appendix diameter >=15 mm independently predicted failure.
Loftus et al., 2018 [22]	Retrospective cohort receiving NOM for uncomplicated appendicitis	Resolution without recurrence within 180 d	Appendicolith was a candidate predictor; smaller appendix diameter and lower clinical severity measures were associated with success.

Shindoh et al., 2010 [23]	Initial NOM for suspected appendicitis; older diagnostic context	Negative outcome/conversion	Appendicolith and CRP >4 mg/dL were adverse predictors; applicability to modern CT-defined uncomplicated disease is limited.
Richards et al., 2022 [10]	Adults with CT-confirmed appendicitis managed non-operatively	Recurrence	Age and sex were not significantly associated with recurrence.

Table 2. Supportive evidence for appendicolith characteristics (not pooled with the strict primary analysis)

Study	Context	Finding	Reason for indirectness
Ando et al., 2021 [7]	Adults undergoing NOM for complicated appendicitis	Proximal fecalith independently predicted failure.	Complicated appendicitis population.
Kubota et al., 2022 [5]	Appendicitis with appendicolith; treatment selected clinically	Stones <=5 mm with low CRP favored nonsurgical completion; >10 mm associated with perforation.	Confounding by indication and mixed severity.
Kohga et al., 2021 [24]	NOM cohort with broader acute appendicitis severity	Appendicolith presence alone was not predictive; incarcerated appendicolith was strongly associated with failure.	Population not restricted to strict uncomplicated disease.
Lie et al., 2023 [25]	Prospective NOM cohort including mixed disease severity	Appendicolith associated with recurrent appendicitis within 6 months.	Mixed complicated/uncomplicated population.
Ramadan et al., 2024 [26]	Conservatively treated cohort	Appendicolith not associated with recurrence; appendix diameter >10 mm and abscess were adverse factors.	Mixed severity and recurrence endpoint.
Sula et al., 2024 [6]	Large CT severity cohort	Larger appendicolith diameter (approximately OR 1.15 per mm) and base location associated with complicated appendicitis.	Outcome was disease severity, not NOM failure.
Kaewlai et al., 2024 [28]	Adult CT cohort	Larger appendicolith dimensions associated with complicated disease; proposed dimension thresholds were not treatment-failure cutoffs.	Outcome was complicated versus uncomplicated appendicitis.

Study	Context	Finding	Reason for indirectness
Kupietzky et al., 2025 [27]	Long-term NOM recurrence cohort	Stone size and location did not significantly influence recurrence; appendicolith was associated with earlier recurrence timing.	Recurrence endpoint; applicability to strict adult uncomplicated NOM requires caution.
Shay et al., 2022 [29]	Selected uncomplicated NOM cohort	Low failure rates when appendicolith and other adverse features were excluded.	Exposed group designed out; cannot estimate appendicolith effect.
Khan et al., 2019; Ishiyama et al., 2013 [30,31]	Imaging/severity studies of appendicolith characteristics	Size and location associated with appendicitis severity in imaging-based analyses.	Not direct antibiotic-failure cohorts.

Overall short-term and one-year outcomes

CODA provides the clearest modern pragmatic estimate. Among adults randomized to antibiotics, appendectomy occurred in approximately one fifth by 30 days and remained more frequent among patients with an appendicolith. At 90 days, appendectomy occurred in 41% of patients with an appendicolith compared with 25% without. [1,17] In the individual-participant-data meta-analysis of six adult randomized trials, appendectomy within one year occurred in 94 of 193 patients with an appendicolith (48.7%) and 262 of 857 without an appendicolith (30.6%), corresponding to an approximate RR of 1.59 and an absolute difference of about 18 percentage points. [3]

Appendicolith presence

For the short-term quantitative synthesis, the CODA 30-day data yielded a crude RR of approximately 1.91, while Vons et al. reported RR 2.94 (95% CI 1.28-6.74) for early appendicolith-associated failure. [1,2] Random-effects inverse-variance synthesis produced a pooled RR of 2.00 (95% CI 1.54-2.60; I^2=0%; k=2). Because only two compatible datasets contributed, the pooled estimate is exploratory and the I^2 value should not be interpreted as evidence that clinically important heterogeneity is absent.

The adjusted CODA analysis supported the same direction of association: appendicolith remained independently associated with appendectomy within 30 days (adjusted OR 1.99, 95% CI 1.28-3.10). [1] Hong et al. observed a similar direction of association (OR 2.52) but with a wide confidence interval. [8]

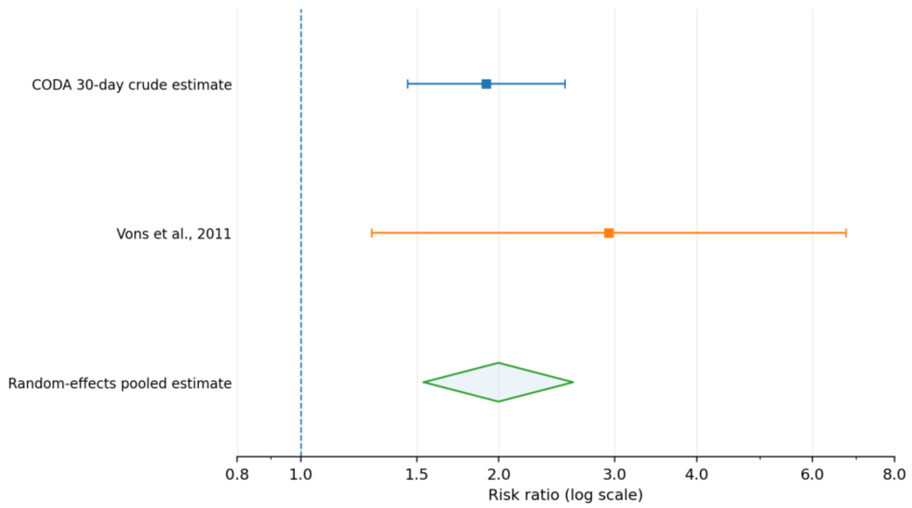


Figure 2. Exploratory random-effects meta-analysis of short-term NOM failure associated with appendicolith presence. Two compatible adult datasets contributed; the pooled estimate should be interpreted cautiously.

Appendicolith size

Direct evidence that appendicolith size independently predicts NOM failure in strictly uncomplicated adults is sparse. Kubota et al. reported that appendicoliths <=5 mm, particularly with low CRP, were more compatible with completion of nonsurgical treatment, whereas appendicoliths >10 mm were associated with perforation and unfavorable selection for conservative treatment. [5] The treatment-selection design is susceptible to confounding by indication.

Radiological severity studies support a biological gradient but assess a different endpoint. Sula et al. reported increasing odds of complicated appendicitis with increasing appendicolith diameter, and Kaewlai et al. also found larger appendicolith dimensions associated with complicated disease. [6,28] Khan et al. and Ishiyama et al. similarly linked appendicolith characteristics with disease severity. [30,31] In contrast, Kupietzky et al. found no significant association between stone size and long-term recurrence after NOM. [27] These findings do not establish a validated size cutoff for antibiotic failure.

Table 3. Appendicolith-size thresholds and interpretation

Size variable	Source/context	Interpretation
<=5 mm	Kubota et al. [5]	Potential lower-risk size in a treatment-selection cohort, especially with low CRP; not a validated universal NOM cutoff.
4.5-mm minimum / 6-mm maximum	Kaewlai et al. [28]	Radiological cutoffs proposed for complicated disease; not antibiotic-failure thresholds.
>10 mm	Kubota et al. [5]	Associated with perforation and unfavorable treatment selection; candidate high-risk category rather than a validated NOM cutoff.
Per 1-mm increase	Sula et al. [6]	Increasing appendicolith diameter associated with greater odds of complicated appendicitis; indirect for NOM failure.

Appendicolith location and functional obstruction

Evidence for proximal or base location as an independent predictor of failure in strictly uncomplicated adult NOM is very low certainty. Ando et al. found a proximal fecalith to be an independent predictor of NOM failure, but the population had complicated appendicitis. [7] Sula et al. associated base location with complicated disease, while Kupietzky et al. did not demonstrate a significant location effect on post-NOM recurrence. [6,27] Kohga et al. provided an important functional distinction: appendicolith presence alone was not predictive in their broader cohort, whereas an incarcerated appendicolith was strongly associated with NOM failure. [24]

Intraluminal appendiceal air

The directly relevant adult radiological evidence does not support intraluminal appendiceal air as an adverse prognostic factor. Hong et al. reported OR 0.87 (95% CI 0.25-3.02; P=.829) for treatment failure, nonresponse, or recurrence within one year. [8] Intraluminal air is distinct from extraluminal gas, which suggests wall disruption or perforation and conflicts with a strict uncomplicated-disease definition. No quantitative meta-analysis was undertaken because only one directly relevant extractable estimate was available.

Age

The review was restricted to adults. Increasing age was not consistently associated with NOM failure. In CODA, age was not independently associated with 30-day appendectomy, and Hong and Richards likewise found no significant age association with treatment failure or recurrence. [1,8,10] Older age remains clinically important for diagnostic evaluation and follow-up after appendicitis, but this is conceptually distinct from evidence that age independently predicts antibiotic failure. [11]

Sex

Sex-specific findings were inconsistent. CODA reported higher adjusted odds of 30-day appendectomy in women (OR 1.53, 95% CI 1.01-2.31), while Hong did not demonstrate a significant sex association. [1,8] In contrast, Kobayashi et al. identified male sex as an independent predictor of inpatient NOM failure, and earlier recurrence work also implicated male sex. [9,33] Sex was therefore not classified as an established adverse prognostic factor in either direction.

Risk of bias and certainty of evidence

Risk of bias was driven primarily by the nonrandomized nature of prognostic exposures, selection for NOM, clinician-dependent decisions to operate, residual confounding, small numbers of failures in several cohorts, and indirectness where mixed, complicated, or operative populations were used to explore appendicolith characteristics. The origin of some observations within randomized trials strengthened treatment comparison but did not randomize appendicolith status or other prognostic factors.

Table 4. Review-level risk-of-bias assessment

Study	Assessment framework	Principal concern	Overall judgment
Vons 2011 [2]	RoB 2 (parent RCT) + prognostic domains	Open-label management; appendicolith subgroup not randomized; small exposed subgroup; clinician-dependent decision to operate.	Some concerns / moderate prognostic concern
CODA 2020 [17]	RoB 2 (parent RCT)	Pragmatic open-label design; decision to appendectomize could not be blinded; broad disease spectrum.	Some concerns
CODA prognostic analysis 2022 [1]	QUIPS-aligned prognostic domains	Prognostic exposures not randomized; residual confounding and treatment-decision bias possible despite adjustment.	Moderate concern
Hong 2021 [8]	QUIPS-aligned prognostic domains	Retrospective selection; small cohort and limited multivariable power.	Serious concern
Kobayashi 2021 [9]	QUIPS-aligned prognostic domains	Retrospective model development; limited number of failures; potential overfitting.	Moderate-to-serious concern
Loftus 2018 [22]	QUIPS-aligned prognostic domains	Small retrospective cohort; clinician selection for NOM; recurrence ascertainment.	Serious concern
Kubota 2022 [5]	QUIPS-aligned prognostic domains	Strong confounding by indication; treatment selection related to stone size/CRP; mixed severity.	Serious concern
Ando 2021 [7]	QUIPS-aligned prognostic domains	Direct treatment outcome but complicated appendicitis population.	Serious indirectness

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Table 5. Review-level certainty of evidence by prognostic factor

Prognostic factor/outcome	Summary estimate or conclusion	Certainty	Main reason
Appendicolith presence -> short-term NOM failure	Pooled RR 2.00 (95% CI 1.54-2.60), k=2	Low	Consistent sizeable effect, but only two compatible datasets and prognostic exposure not randomized.
Appendicolith presence -> appendectomy by 1 y	48.7% vs 30.6%; approximate RR 1.59	Low	Large IPD dataset and consistent direction, but varying trial eligibility and nonrandomized prognostic exposure.
Larger appendicolith size	Possible higher risk with >10 mm; severity gradient with increasing size	Very low	Direct strict-NOM evidence sparse; confounding by indication; heterogeneous outcomes and thresholds.
Base/proximal or obstructing location	Proximal/obstructing features adverse in broader cohorts	Very low	Major indirectness and inconsistent recurrence evidence.
Intraluminal air	OR 0.87 (0.25-3.02); no evidence of increased risk	Very low	Single small direct study; wide confidence interval.
Sex	Inconsistent direction across studies	Very low	Adjusted and crude results differ; studies identify opposite sex directions.
Older age	No demonstrated independent adverse association	Very low	Inconsistent thresholds and limited power for age interaction.

DISCUSSION

Principal findings

Appendicolith presence, rather than any single proposed appendicolith characteristic, was the most reproducible imaging marker of unsuccessful NOM in adults. The two compatible short-term datasets suggested approximately twice the risk of early failure, and the association persisted after multivariable adjustment in CODA. [1,2] The one-year individual-participant-data synthesis showed that the prognostic signal extended beyond immediate nonresponse, with appendectomy in nearly half of antibiotic-treated patients with an appendicolith compared with about one third of those without. [3]

The available evidence does not support an equally strong conclusion for stone size or location. Larger stones correlate with complicated appendicitis, and >10-mm stones were associated with perforation in an appendicolith-specific treatment-selection cohort. [5,6,28,30,31] Proximal or base location is biologically plausible, but the most direct location study involved complicated appendicitis and long-term recurrence evidence did not confirm a consistent location effect. [7,27] Functional obstruction may be more important than location alone, as suggested by the strong association between an incarcerated appendicolith and NOM failure in the broader Kohga cohort. [24]

Clinical interpretation

The findings support a hierarchy of prognostic information. Appendicolith presence can reasonably be incorporated into shared decision-making because its association with subsequent appendectomy is consistent and clinically meaningful. This interpretation is concordant with guideline emphasis on careful selection for NOM. [12,13] Higher failure risk does not imply inevitable failure; a substantial proportion of adults with appendicoliths in CODA avoided appendectomy during early follow-up. [1,17]

The evidence does not support treating intraluminal appendiceal air, female sex, or older age as established adverse predictors. The intraluminal-air estimate was null and imprecise, sex associations were directionally inconsistent, and age showed no reproducible independent failure signal in the principal adult datasets. [1,8-10,33]

Implications for future research

Future prognostic studies should standardize CT reporting of appendicolith maximum and minimum diameter, number, distance from the appendiceal base, and evidence of functional obstruction or incarceration. Early nonresponse should be separated from later recurrence and from elective interval appendectomy. Prospective multicenter cohorts should prespecify confounders and report both absolute risks and adjusted effect estimates. If sufficiently homogeneous data become available, continuous dose-response modeling of stone diameter and validation of a multivariable appendicolith-specific risk model would be more informative than repeated unvalidated dichotomous thresholds.

Strengths and limitations

A principal strength of this review is the deliberate separation of direct treatment-failure evidence from indirect severity evidence. This prevents associations with perforation or complicated appendicitis from being misrepresented as proof of antibiotic failure in otherwise uncomplicated disease. The review also retains negative and directionally inconsistent findings rather than forcing the proposed appendicolith characteristics into a uniformly adverse model.

Several limitations constrain certainty. Only two compatible datasets were available for the principal short-term meta-analysis, making the pooled RR exploratory and limiting interpretation of heterogeneity. Appendicolith status and other prognostic factors were not randomized, including within parent randomized trials, so residual confounding and clinician-dependent treatment decisions remain possible. Evidence for size and location frequently came from mixed-severity, complicated-disease, or radiological severity cohorts and was therefore indirect. Definitions of failure and outcome horizons varied across studies. Finally, the evidence search was centered on PubMed-indexed literature, publisher/full-text sources, and citation chaining rather than a preserved multi-database export workflow, which may have limited retrieval breadth.

CONCLUSION

Among adults undergoing initial non-operative treatment for imaging-confirmed uncomplicated acute appendicitis, appendicolith presence is the best-supported adverse prognostic marker and is associated with approximately a twofold higher risk of short-term treatment failure in the limited compatible evidence. The increased risk remains clinically relevant at one year. Larger appendicolith size and proximal or obstructing location are plausible additional risk features, but direct evidence in strictly uncomplicated adult NOM populations remains very low certainty and does not support a validated size or location cutoff. Intraluminal appendiceal air, female sex, and older age are not established independent adverse prognostic factors. Standardized prospective imaging and outcome definitions are required before an appendicolith-specific multivariable NOM risk model can be recommended.

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