

ULTRASOUND VERSUS COMPUTED TOMOGRAPHY IN THE DIAGNOSIS OF ACUTE APPENDICITIS: A COMPARATIVE REVIEW OF DIAGNOSTIC ACCURACY, IMAGING STRATEGY, AND CLINICAL OUTCOMES

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Abstract:

Background: Acute appendicitis is the most common surgical emergency of the abdomen, yet its clinical diagnosis remains imprecise. Ultrasonography (US) and computed tomography (CT) are the two dominant cross-sectional imaging modalities used to confirm the diagnosis, but institutions differ markedly in how, and in what sequence, they deploy them.

Objective: To synthesize contemporary comparative evidence on the diagnostic accuracy, operational efficiency, and safety of US versus CT — used alone, in combination, or as staged (conditional) strategies — for the diagnosis of acute appendicitis in adolescents and adults.

Methods: Five comparative studies published between 2010 and 2025 (one prospective multicenter diagnostic-accuracy study, one prospective single-center cohort, one international two-center retrospective comparison, and two single-center cross-sectional/retrospective analyses; pooled N = 1,772 patients) were identified and analyzed. Data on sensitivity, specificity, positive and negative predictive values, false-positive/negative-appendectomy rates, imaging turnaround time, and CT-utilization were extracted and tabulated for comparison; findings were synthesized narratively and illustrated graphically.

Results: CT consistently outperformed US in sensitivity (88-100% vs. 68-91%) and specificity (71-100% vs. 50-98%) across all five studies. A conditional (US-first, CT-only-if-inconclusive) strategy reduced CT utilization by roughly half to five-sixths (17.9-47.2% of imaged patients vs. 100% under an immediate-CT policy) while achieving a sensitivity for appendicitis (95-96%) statistically indistinguishable from an immediate-CT policy, at the cost of a modestly higher false-positive rate (14% vs. 8% in the largest series). US was markedly faster to obtain (median 20-38 minutes) than CT (median 184-194 minutes) and shortened emergency-department length of stay by roughly 90-150 minutes per patient, without ionizing radiation or contrast exposure.

Conclusion: A staged, US-first diagnostic pathway with selective (conditional) use of CT for negative or inconclusive ultrasound examinations offers a favorable balance of diagnostic accuracy, radiation stewardship, resource use, and patient throughput, and should be considered the preferred default strategy for suspected acute appendicitis in adults where institutional expertise in appendicular ultrasound is available. CT alone or as a first-line test remains appropriate where US expertise or accessibility is limited, or when a rapid, highly specific diagnosis is clinically imperative.

Keywords — acute appendicitis; ultrasonography; computed tomography; diagnostic imaging; conditional CT; negative appendectomy; emergency department; diagnostic accuracy.

1. Introduction

Acute appendicitis remains the most frequent cause of emergency abdominal surgery worldwide, with a lifetime incidence of approximately 7-9%.^[1,4] Despite its ubiquity, the clinical diagnosis of appendicitis continues to challenge emergency physicians and surgeons: classic signs such as right-lower-quadrant tenderness, migration of pain, and rebound tenderness lack sufficient discriminative power when used in isolation, and clinical scoring systems such as the Alvarado score, while useful for risk stratification, are not by themselves adequate to confirm or exclude the diagnosis.^[4,23]

Cross-sectional imaging — principally ultrasonography (US) and computed tomography (CT) — has therefore become central to the modern diagnostic pathway. Multiple meta-analyses have shown CT to be more sensitive and specific than graded-compression US for the detection of appendicitis,^[7,8,12] and its widespread adoption in North America has been associated with

substantial reductions in the negative (“white”) appendectomy rate. ^[2,27] However, CT carries non-trivial disadvantages: it exposes patients to ionizing radiation with an associated lifetime radiation-induced cancer risk, ^[9] requires intravenous, oral, or rectal contrast agents that carry their own risks of nephrotoxicity or allergic reaction, is comparatively costly, and — particularly outside large academic centers — may not be rapidly available. ^[2,21] Ultrasonography, by contrast, is radiation-free, inexpensive, rapid, and repeatable at the bedside, but its diagnostic performance is more operator-dependent and its sensitivity for appendicitis is consistently reported as inferior to that of CT. ^[2,7,12,13]

These trade-offs have given rise to divergent international practice patterns. In the United States, CT has traditionally been used as the first-line (or sole) imaging test for suspected appendicitis in adults, whereas in several European and Middle Eastern health systems — including the Netherlands and Israel — ultrasound is used as the primary investigation, with CT reserved for patients in whom the ultrasound examination is negative or inconclusive (a so-called “conditional” or “staged” strategy). ^[2,6,10] Which of these approaches — immediate CT for all, US alone, or a conditional US-first pathway — offers the best balance of diagnostic accuracy, safety, speed, and resource utilization remains a subject of ongoing debate.

This review synthesizes the evidence from five comparative studies, spanning four continents’ worth of practice settings and study designs published between 2010 and 2025, that directly compared US and CT (alone, combined, or as staged strategies) for the diagnosis of acute appendicitis. The aim is to provide clinicians, radiologists, and health-system planners with a consolidated, evidence-based overview of the comparative performance of these two modalities to inform the design of local diagnostic pathways.

2. Materials and Methods

2.1 Study identification and eligibility

This narrative comparative review is based on five peer-reviewed studies that directly compared ultrasonography and computed tomography (used alone, in combination, or as sequential/conditional strategies) for the diagnosis of acute appendicitis in adolescent or adult populations presenting with acute abdominal pain: a prospective multicenter diagnostic-accuracy study from the Netherlands, ^[3] a prospective single-center cohort study also from the Netherlands, ^[1] a retrospective two-country (United States-Israel) comparative cohort study, ^[2] a cross-sectional study from Iran, ^[4] and a retrospective single-center study from China. ^[5] Studies were required to (i) report a diagnosis of appendicitis confirmed by histopathology, intraoperative findings, or clinical follow-up as the reference standard, and (ii) provide extractable diagnostic performance data (sensitivity, specificity, and/or predictive values) for at least one of the two index modalities. Reference lists of the included studies were hand-searched to identify supporting evidence on radiation risk, cost-effectiveness, and pediatric staged-imaging protocols, which are cited to contextualize the discussion.

2.2 Data extraction and synthesis

For each study, the following data were extracted independently by the reviewing author(s): country and setting, study design, sample size, population characteristics, reference standard, and — for each imaging modality or strategy — sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false-positive rate, negative-appendectomy rate, and, where reported, process metrics such as time to imaging and emergency-department (ED) length of stay. Because of substantial clinical and methodological heterogeneity across studies (differing reference standards, differing definitions of “equivocal” results, and differing case-mix), a formal meta-analytic pooling of effect estimates was not undertaken; instead, results are presented narratively and in tabular/graphical form to allow qualitative comparison, consistent with a structured narrative review methodology.

2.3 Outcomes of interest

The primary outcomes of interest were the sensitivity and specificity of US and CT for acute appendicitis. Secondary outcomes included PPV/NPV, false-positive and negative-appendectomy rates, proportion of patients requiring CT under conditional versus immediate strategies, imaging turnaround time, ED length of stay, and safety considerations (radiation exposure, contrast-related risk).

3. Overview of Included Studies

Table 1 summarizes the design, setting, and population of the five included studies, which together report on 1,772 patients evaluated for suspected acute appendicitis. Study designs ranged from large prospective multicenter diagnostic-accuracy cohorts ^[3] to small single-center retrospective series, ^[5] and populations ranged from unselected emergency-department patients with abdominal pain ^[1] to those pre-selected by a minimum Alvarado score. ^[4]

Table 1. Characteristics of the five comparative studies included in this review. ED = emergency department; Dx = diagnosis.

Study (Year)	Country	Design	N	Population / Setting	Comparison
Toorenvliet et al. [1] (2010)	Netherlands	Prospective cohort	802	All ED patients with acute abdominal pain; 164 with suspected appendicitis	Clinical Dx vs. routine US vs. limited (selective) CT
Reich et al. [2] (2011)	USA & Israel	Retrospective, 2-centre international comparison	276	Adults, ED working diagnosis of appendicitis, all taken to surgery	CT-first (USA) vs. US-first (Israel) national practice patterns
Atema et al. [3] (2015)	Netherlands	Prospective diagnostic accuracy (secondary analysis)	422	Adults with clinical suspicion of appendicitis; all had both US and CT	Conditional CT (US-first) vs. immediate CT
Bahrami et al. [4] (2023)	Iran	Cross-sectional	231	Adults 15-65y, Alvarado score ≥ 7	US vs. CT (CT performed after negative/inconclusive US)
Zhao et al. [5] (2025)	China	Retrospective, single-centre	41	Adults with suspected acute appendicitis	US vs. CT, evaluated independently and combined

4. Comparative Diagnostic Accuracy of Ultrasound and Computed Tomography

Across every study that reported modality-specific accuracy, CT outperformed US on both sensitivity and specificity (Table 2, Figure 1). In the largest single-center prospective series, US alone achieved a sensitivity of 91% and specificity of 98%, while CT alone achieved 100% sensitivity and specificity, although the CT-only subgroup was small ($n = 94$) and highly selected.^[1] In the international comparison of national practice patterns, CT in the United States cohort achieved 100% sensitivity and 100% PPV, compared with 68.4% sensitivity and 94.5% PPV for US in the Israeli cohort — the largest sensitivity gap of any study reviewed, reflecting in part the higher rate of non-diagnostic (“non-visualized”) ultrasound examinations in that series (58/197, 29%).^[2] The two more recent, smaller studies from Iran and China reported a narrower but still consistent gap: sensitivity of 74.9% (US) versus 87.9% (CT) in the Iranian cross-sectional study,^[4] and 73% (US) versus 88% (CT) in the Chinese retrospective series,^[5] with specificities of 50-63% for US versus 71-82% for CT in these two studies.

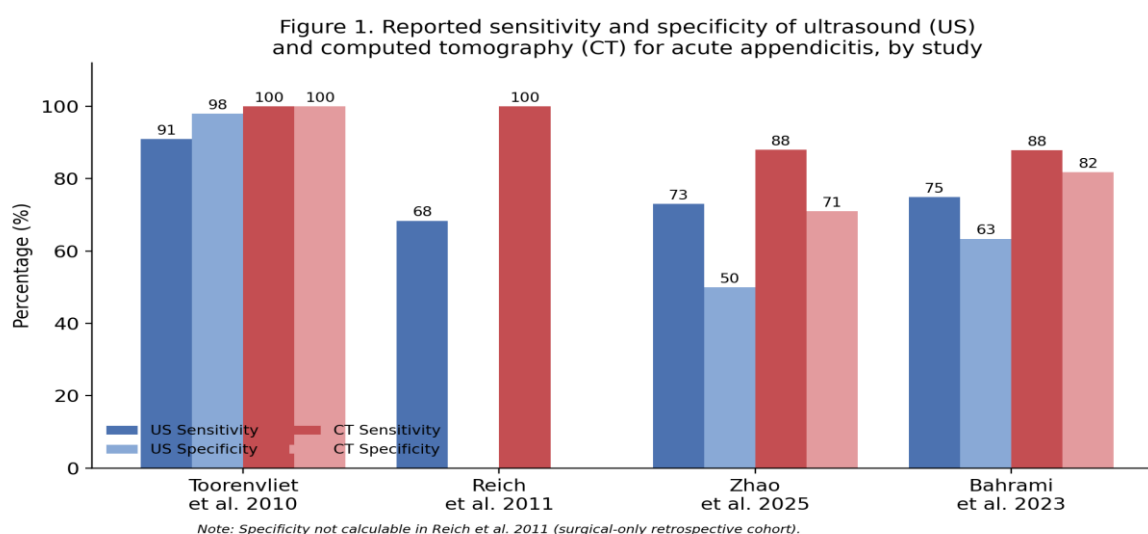


Figure 1. Reported sensitivity and specificity of ultrasound and CT for acute appendicitis across four studies reporting both metrics for each modality. Specificity could not be calculated for Reich et al. 2011 because their retrospective cohort was restricted to surgically confirmed patients.

Two consistent patterns emerge from Table 2. First, the positive predictive value of US was uniformly high (94.3-94.5% in the two studies reporting it directly, and 63-100% depending on subgroup in Toorenvliet et al.), indicating that a clearly positive ultrasound examination is highly reliable and, in most cases, sufficient to proceed directly to surgery without confirmatory CT.^[1,2,4] Second, the principal weakness of US is not false-positive diagnosis but non-diagnostic (“equivocal” or “non-visualized”) examinations and false-negative results, which in the largest cohorts accounted for 29-47% of ultrasound examinations and were the dominant driver of the sensitivity gap relative to CT.^[1,2] This distinction is clinically important: it implies that the marginal diagnostic value of CT lies overwhelmingly in patients whose ultrasound was negative or inconclusive, rather than in confirming positive ultrasound findings — precisely the rationale underlying the conditional CT strategies discussed in Section 5.

*Table 2. Diagnostic performance of ultrasound and CT for acute appendicitis across the five reviewed studies. Ranges reported where available reflect 95% confidence intervals. PPV = positive predictive value; NPV = negative predictive value. *Specificity not calculable because the Reich et al. cohort included only patients who underwent surgery.*

Study	Modality	Sensitivity	Specificity	PPV	NPV
Toorenvliet 2010	US alone	91%	98%	94%	97%
Toorenvliet 2010	CT alone	100%	100%	100%	100%
Toorenvliet 2010	US and/or CT	93%	99%	95%	98%
Reich 2011	US (Israel)	68.4% (95%CI 60.9-75.0)	not calculable*	94.5%	—
Reich 2011	CT (USA)	100% (95%CI 94.2-100)	not calculable*	100%	—
Atema 2015	Conditional CT	96% (93-98)	77% (70-83)	86% (81-90)	93% (87-96)
Atema 2015	Immediate CT	95% (91-97)	87% (81-92)	92% (87-95)	92% (86-95)
Bahrami 2023	US	74.9%	63.4%	94.3%	67.6%
Bahrami 2023	CT	87.9%	81.8%	94.7%	79.3%
Zhao 2025	US	73%	50%	—	—
Zhao 2025	CT	88%	71%	—	—

5. Conditional (Staged) Versus Immediate CT Strategies

Three of the five studies directly addressed the question of imaging sequence — that is, whether CT should be used immediately in all patients with suspected appendicitis, or reserved for those with a negative or inconclusive initial ultrasound examination (Table 3, Figure 2).^[1,2,3]

In the largest and most methodologically rigorous of these, Atema et al. directly compared a conditional CT strategy (CT only after negative/inconclusive US) against an immediate CT strategy in the same cohort of 422 patients, with both US and CT performed and interpreted blind to one another.^[3] The conditional strategy correctly identified 241 of 251 appendicitis cases (96%), which was statistically indistinguishable from the 238 of 251 (95%) identified by immediate CT, while requiring CT in only 199 of 422 patients (47%) — that is, roughly halving CT utilization. The trade-off was a lower specificity (77% vs. 87%) and a higher false-positive rate (14% vs. 8%) for the conditional strategy, because a staged approach necessarily accumulates the false positives of both modalities in sequence.^[3] Encouragingly, the authors noted that this excess of imaging-defined “false positives” has not translated into correspondingly higher negative-appendectomy rates in real-world implementations of conditional pathways, likely because clinicians incorporate their level of diagnostic confidence — not merely a binary positive/negative imaging read — into the final operative decision.^[3]

Toorenvliet et al. prospectively implemented a routine-US, limited-CT pathway (CT reserved for inconclusive US or specific clinical indications such as high body-mass index or suspected mesenteric ischemia) across 802 unselected ED patients with acute abdominal pain.^[1] CT was required in only 17.9% of imaged patients (a US:CT ratio of approximately 6:1), yet the combined US-and/or-CT pathway achieved 93% sensitivity, 99% specificity, and a low overall negative-appendectomy rate of 3.3% — substantially better than the 20% historically considered acceptable under purely clinical evaluation.^[1] The missed-perforation rate was 3.4%, comparable to rates reported elsewhere in the literature and not apparently worsened by the conservative, US-first approach.^[1]

Reich et al.’s international comparison offers a complementary, real-world perspective: because Israeli practice already uses US as the default first-line test, the authors were able to model a hypothetical “first-pass” US strategy for their United States cohort and calculate that, had 65% of their patients avoided CT after a positive ultrasound (as observed in the Israeli cohort), CT could

have been avoided in roughly two-thirds of American patients, saving an estimated 88 minutes per patient in imaging turnaround time alone. ^[2]

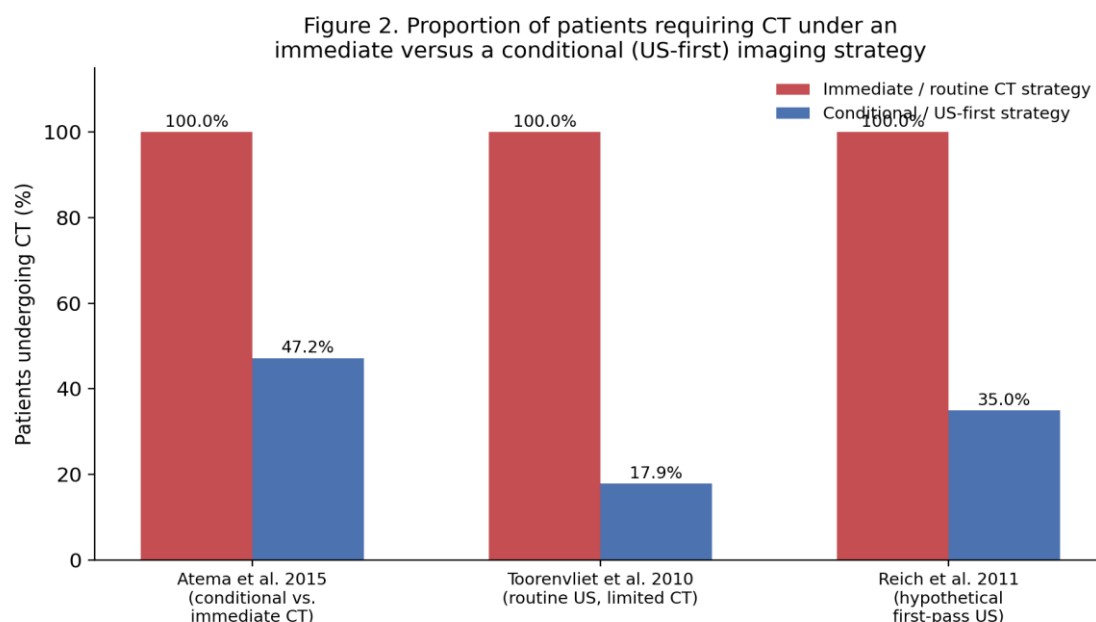


Figure 2. Proportion of imaged patients requiring CT under an immediate versus a conditional (US-first) diagnostic strategy, across three studies. A conditional strategy reduced CT utilization by roughly half to five-sixths relative to an immediate-CT-for-all policy.

Table 3. Operational and resource outcomes associated with US-based/conditional versus CT-based/immediate diagnostic pathways.

Study	Metric	US-based / Conditional pathway	CT-based / Immediate pathway
Reich 2011	Median imaging order-to-completion time	20 min (IQR 7-49)	184 min (IQR 147-228)
Reich 2011	Median total ED length of stay	387 min (IQR 259-571.5)	533 min (IQR 450-632)
Reich 2011	Negative appendectomy rate (after positive imaging)	5.5%	0.0%
Atema 2015	Proportion of patients requiring CT	47.2% (conditional)	100% (immediate)
Atema 2015	False-positive appendicitis diagnoses	39/280 (14%)	22/260 (8%)
Toorenvliet 2010	Proportion of imaged patients undergoing CT	17.9% (US:CT ≈ 6:1)	not applicable
Toorenvliet 2010	Overall negative appendectomy rate	3.3%	not applicable

6. Negative Appendectomy, False-Positive Diagnoses, and Safety

Negative (“white”) appendectomy — surgical removal of a histologically normal appendix — remains an important quality metric because it exposes patients to the morbidity, cost, and (occasionally) mortality of an unnecessary operation without therapeutic benefit. ^[2,25,26] Historically, negative-appendectomy rates of up to 20% were considered an acceptable trade-off for avoiding delayed diagnosis of perforation; contemporary imaging-supported pathways have driven this rate down substantially. ^[1,26,28] Across the studies reviewed here, the CT-based (United States) cohort in Reich et al. achieved a 0% negative-appendectomy rate after positive imaging, compared with 5.5% in the US-based (Israeli) cohort — the clearest single-study demonstration of CT’s superior positive predictive reliability. ^[2] However, the routine-US/limited-CT pathway of Toorenvliet et al., evaluated in an unselected population nearly ten-fold larger, achieved an overall negative-appendectomy rate of only 3.3%, indicating that a well-implemented staged US-first pathway with clinical re-evaluation can approach the diagnostic reliability of a CT-first strategy in practice, even though its imaging-based specificity is formally lower. ^[1] This apparent paradox

— a lower reported specificity for conditional imaging coexisting with a low real-world negative-appendectomy rate — underscores that surgeons integrate the confidence, not just the binary result, of imaging into their operative decision-making, and reinforces the value of structured clinical re-evaluation as a complement to imaging (Figure 3).^[1,3]

Figure 3. Comparative false-positive / negative-appendectomy-related rates reported across studies

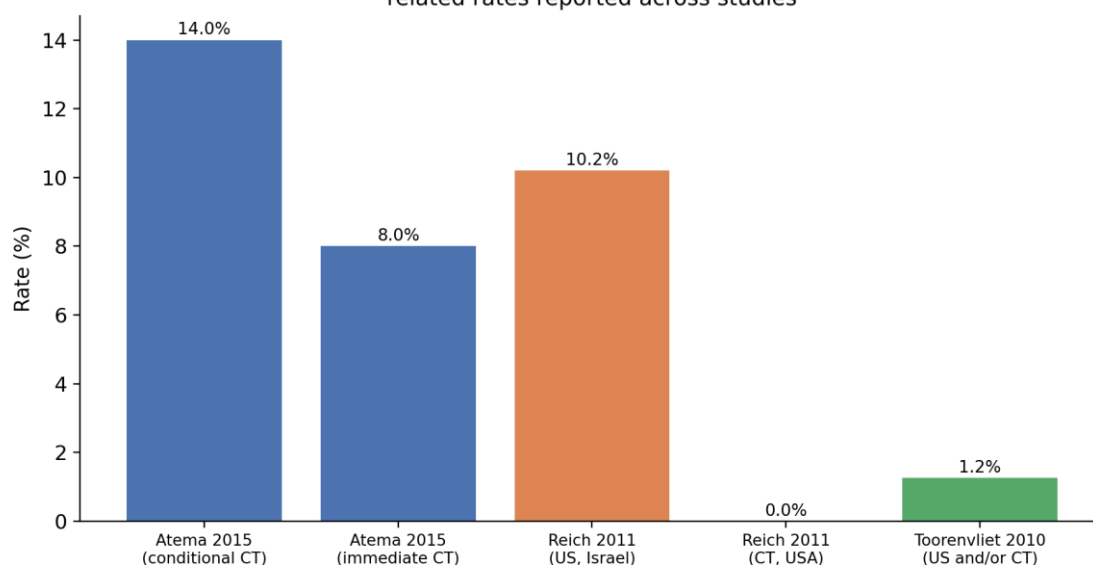


Figure 3. Comparative false-positive / negative-appendectomy-related rates reported across the reviewed studies. Values are drawn from each study's own definitions and denominators (see Sections 4-6) and are not directly poolable, but illustrate the consistently low rate achieved by CT-confirmed diagnoses and by combined US-and-CT pathways.

The principal safety argument for minimizing CT use is radiation exposure. Abdominal-pelvic CT delivers an effective dose associated with a small but non-zero lifetime radiation-induced cancer risk, a concern of particular relevance in younger patients, in whom appendicitis is common, and in pregnant patients, for whom US (and, where necessary, MRI) is preferred over CT.^[9,14,15] Contrast-related risks — nephrotoxicity and allergic reaction — are an additional, CT-specific consideration largely avoided by ultrasound.^[2] These safety considerations, alongside the substantial cost and throughput advantages demonstrated in Section 5, provide the principal rationale for a conditional, US-first diagnostic strategy wherever adequate sonographic expertise exists.^[16,21]

7. Discussion

The evidence synthesized in this review consistently confirms that CT is more sensitive and more specific than US for the diagnosis of acute appendicitis when the two modalities are compared head-to-head.^[1,2,4,5] This finding is concordant with earlier systematic reviews and meta-analyses that established CT's superiority across a broader literature.^[7,8,12,13] However, the clinically relevant question is not simply "which single test is more accurate?" but "which diagnostic pathway delivers the best overall balance of accuracy, safety, speed, and resource use?" On this broader question, the evidence favours a staged, conditional approach in which US serves as the first-line test and CT is reserved for patients with negative or inconclusive sonography.^[1,3,6,10]

This conclusion rests on three converging lines of evidence identified across the reviewed studies. First, a conditional CT strategy achieves sensitivity for appendicitis statistically indistinguishable from an immediate-CT-for-all strategy, because ultrasound's positive predictive value is high enough that positive examinations can be trusted without confirmatory CT, while its negative or equivocal examinations — rather than its false positives — are reliably escalated to CT.^[3] Second, a conditional strategy reduces CT utilization by roughly half to five-sixths, translating into substantial reductions in radiation exposure, contrast-related risk, and cost across a population, even though it modestly increases the imaging-defined false-positive rate at the individual level.^[1,3,21,22] Third, ultrasound's speed advantage — a median turnaround roughly five to ten times faster than CT in the reviewed studies — offers a tangible improvement in ED throughput and length of stay, an increasingly important consideration in crowded emergency departments.^[2]

The evidence also highlights important caveats. The diagnostic performance of US is more heterogeneous across settings than that of CT, ranging from 68% to 91% sensitivity across the reviewed studies, and is explicitly acknowledged by several authors to be operator- and experience-dependent.^[2,4,5] Institutions considering a US-first pathway must therefore invest in sonographer/radiologist training and maintain a sufficiently high case volume to sustain diagnostic performance; where this

expertise is not available, an immediate-CT or CT-predominant strategy — as historically practiced in much of the United States — remains a reasonable and well-validated alternative. ^[2,29] Body habitus is a further limiting factor for US: obesity reduces sonographic image quality and is one of the clinical factors that, per Toorenvliet et al.'s protocol, appropriately triggers primary CT rather than US. ^[1]

The two smaller, more recent studies included in this review (Bahrami et al. 2023 and Zhao et al. 2025) reported somewhat lower absolute sensitivity and specificity for both modalities than the two larger, earlier European studies, and both noted persistently high rates of equivocal or indeterminate results, particularly for CT (17-33% equivocal in Zhao et al.). ^[4,5] This heterogeneity may reflect smaller sample sizes, differing scanner protocols (e.g., use versus omission of intravenous contrast), differing reference standards, and case-mix differences, and it reinforces a broader point made across the literature: reported accuracy for both US and CT is protocol- and population-dependent, and locally generated performance data should inform institutional pathway design rather than uncritical adoption of published figures. ^[4,5,34]

Finally, it is worth situating US and CT within the wider, evolving diagnostic landscape for appendicitis. Low-dose CT protocols have been shown to preserve diagnostic accuracy while substantially reducing radiation dose, and may offer a future middle ground between conventional CT and US. ^[9,14] Magnetic resonance imaging has been explored, principally as a second-line test after inconclusive US in pregnant patients and children, given its lack of ionizing radiation, though its cost and limited availability restrict routine use. ^[22] Emerging endoscopic and computer-assisted diagnostic approaches, including endoscopic retrograde appendicography and machine-learning-assisted image interpretation, have shown promising early results but currently lack the comparative validation available for US and CT and require further prospective study before routine adoption. ^[5,35]

8. Limitations of the Reviewed Evidence

Several limitations of the underlying evidence base, and of this review, should be acknowledged. First, this is a narrative rather than a systematic review with a pre-registered protocol and exhaustive database search; while the five included studies span diverse settings and designs, additional relevant comparative studies may exist that were not captured. Second, substantial heterogeneity exists across studies in reference standards (histopathology versus clinical follow-up versus combined criteria), definitions of “equivocal” imaging results, CT contrast protocols (oral, rectal, intravenous, or non-contrast), and population selection (unselected ED patients versus those pre-filtered by clinical scoring), which precludes formal meta-analytic pooling and limits direct numerical comparability across studies. Third, most included studies are retrospective or single-center, with correspondingly smaller sample sizes and greater potential for selection bias; only two studies (Atema et al. and Toorenvliet et al.) employed prospective, multicenter, or unselected-population designs. Fourth, none of the included studies were randomized trials directly comparing clinical outcomes (as opposed to diagnostic accuracy) between an immediate-CT and a conditional-CT pathway; as Atema et al. themselves note, a randomized comparison of clinical management outcomes remains an important gap in the literature. ^[3] Finally, technological advances in both US and CT since the earliest included study (2005-2006 data collection in Atema et al. and Reich et al.) may have altered absolute diagnostic performance, although the relative comparison between modalities is likely to have been less affected.

9. Future Research Directions

Building on the gaps identified above, future research should prioritize: (i) prospective randomized trials directly comparing clinical outcomes — not only diagnostic accuracy — between conditional and immediate CT strategies; (ii) standardized, harmonized definitions of “equivocal” or “indeterminate” imaging results to enable meta-analytic pooling across studies; (iii) further evaluation of low-dose CT protocols as a potential means of narrowing the accuracy gap with standard-dose CT while reducing radiation exposure; ^[9,14] (iv) larger, multicenter validation of artificial-intelligence-assisted interpretation of both US and CT images, which may reduce operator-dependency, the principal Achilles' heel of ultrasound; ^[5] and (v) formal cost-effectiveness and radiation-risk modelling tailored to specific health-system contexts, extending the single-institution economic analyses already available in the literature. ^[16,21]

10. Conclusion

Across five comparative studies spanning four countries and fifteen years of practice, computed tomography consistently demonstrates higher sensitivity and specificity than ultrasonography for the diagnosis of acute appendicitis. Nonetheless, a conditional, US-first diagnostic strategy — reserving CT for patients with negative or inconclusive ultrasound findings — achieves a sensitivity for appendicitis statistically comparable to an immediate-CT-for-all policy, while roughly halving to reducing five-fold the number of CT examinations performed, shortening emergency-department length of stay, and avoiding unnecessary radiation and contrast exposure in a majority of patients. This staged approach should be regarded as the preferred default diagnostic pathway for suspected acute appendicitis in adults where adequate sonographic expertise is available, with immediate or CT-predominant strategies remaining a valid alternative where such expertise is limited or where diagnostic speed

and maximal specificity are paramount. Local validation of diagnostic performance, ongoing sonographer training, and ultimately randomized evidence on clinical (not only diagnostic) outcomes should guide the further refinement of institutional imaging pathways for this common surgical emergency.

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Ethical Approval: Not applicable — this is a review of previously published, publicly available studies; no new patient data were collected.

Author Contributions: Conceptualization, literature synthesis, and manuscript drafting were performed by the authors listed above; all authors reviewed and approved the final manuscript. [To be completed/customized by submitting authors per journal requirements, e.g., CRediT taxonomy.]

Data Availability: All data discussed in this review are derived from the previously published studies cited in the reference list.

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