Duration of post-operative antibiotic treatment in acute complicated appendicitis: systematic review and meta-analysis

Running head (Short Title):
Duration of post-operative antibiotic treatment in acute complicated appendicitis

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Abstract

Purpose:

Appendicitis is the most frequent aetiology of acute abdominal pain requiring surgical treatment, with an estimated lifetime risk between 7-8%. Antibiotics play a substantial role in treatment, there is considerable debate regarding duration of antibiotics in treating appendicitis.

Methodology:

We searched multiple databases from inception until June 2019 for peer reviewed studies which compared different durations of antibiotic treatment after appendicectomy for acute complicated appendicitis in adults. We dichotomised reported data into short and extended term antibiotic use and controlled for different definitional thresholds in the meta-analysis. We generated risk ratios using restricted maximum likelihood methods and mixed effects modelling for each outcome of interest.

Results:

Four observational studies involving 847 participants were included in the meta-analysis. For the primary outcomes of intraabdominal infection, we did not find a statistically significant difference between extended and short-term antibiotic strategies for intraabdominal infection (RR 0.92 [95% CI 0.49-1.74). Three RCTs involving 291 participants were included in a separate meta-analysis. We found that extended antibiotic usage was
not associated with a statistically significant reduced risk for intrabdominal infection (RR 0.52 [95% CI 0.21 to 1.29] or surgical site skin infection (RR 1.44 [95% CI 0.43 to 4.81]

Conclusion:

This systematic review found and meta-analysis found that extended postoperative antibiotic treatment may not be associated with a reduced risk of intraabdominal infection; however meta-analysis was significantly limited by heterogeneity between studies and underpowered trials. Further large randomised controlled trials are needed to confirm these findings.
Keywords:

General surgery, antibiotics, appendicitis, intraabdominal infection, appendicectomy, postoperative
Introduction

Appendicitis is the most frequent aetiology of acute abdominal pain requiring surgical treatment, with an estimated lifetime risk between 7-8% (1). Despite controversy surrounding the primary definitive treatment of appendicitis, appendectomy remains the gold standard (2). Nevertheless, antibiotics play a substantial role in treatment, whether they be the definitive treatment of choice or as an adjunct to appendicectomy in both the pre- and post-operative roles. There is substantial debate regarding the type, route of administration and duration of antibiotics in treating appendicitis. Compounding the debate further, there are escalating concerns regarding antibiotic resistant bowel organisms (3). Extended spectrum beta-lactamase (ESBL) resistance has been documented following short courses of antimicrobials, with significant implications on cost and increased mortality (4). Given the connection between antibiotic use and antibiotic-resistance, judicious use of antibiotics has become increasingly paramount. The use of preoperative prophylactic antibiotics is less controversial with meta-analysis of randomised trials comparing preoperative antimicrobials to placebo showing a significant reduction in wound infection rates (4). Antibiotic regimens for this purpose require broad coverage of gram-negative microorganisms, and metronidazole is often given alone or in combination with other agents (5). There is substantially less consensus regarding the optimal antibiotic therapy postoperatively. The use of postoperative antibiotics is generally stratified according to disease severity with guidelines recommending the avoidance of antibiotics after surgery for simple appendicitis (6). The optimal duration of postoperative antibiotics in treating complicated appendicitis is poorly understood. Whilst there is no consensus definition for the duration of short course antibiotics, in previous studies, between 3-5 days has been a common cut-off. (7)
durations of antibiotics may be equally as efficacious in paediatric populations when considered alongside clinical parameters (8). Differences in appendicitis pathophysiology between adult and children manifest in the differing epidemiology, clinical presentation, complications and management between these two groups. Small children have fewer symptoms and may often present as complicated appendicitis (9). The anatomical variation and pathophysiological differences between adult and paediatric populations warrant segregation of these groups in trials (10). The optimal duration of postoperative antibiotic therapy in adults is unclear. We therefore conducted this systematic review and meta-analysis to compare short term and extended duration postoperative antibiotic treatment in adults with acute complicated appendicitis.

Methods

Study design and registration

This systematic review and meta-analysis of study-level data was conducted following guidelines provided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and designed according to latest methodologic guidance (11). There were no protocol deviations.

Eligibility criteria

Studies considered eligible for this systematic review were original research studies—randomised control trials and cohort studies—which compared different durations of antibiotic treatment after appendicectomy for acute complicated appendicitis in adults. Case reports, case series, conference abstracts, studies with incomplete data, expert opinions,
editorials, and non-human studies were excluded. Complicated appendicitis was defined as
disease that included findings of suppurative, phlegmonous, perforated and/or gangrenous
appendicitis.

Search strategy:
We searched the electronic databases Medline (Ovid), Embase (Ovid) and the Cochrane
Library from inception to May 2019. Appropriate free text and MeSH terms were used to
identify all studies relevant to complicated appendicitis (Appendix 1 – Search Strategy). No
restrictions were placed on language or publication period.

Study selection:
Two reviewers (D.M and L.A.P.) independently screened the titles and abstracts of each
search result to identify potentially relevant studies. Selected studies were independently
appraised for eligibility by both authors and any discrepancies between the two reviewers
were resolved by discussion and consensus with a third reviewer (Z.L.).

Data extraction and management:
Two reviewers (D.M. and L.A.P) used a standardised form and independently extracted data
including: study design, population characteristics, pre-interventional variables, operative
characteristics, and outcome data. In the primary comparison of observational data, we
dichotomised reported data into short and extended term antibiotic use as defined by
authors in included studies, and controlled for different definitional thresholds in the meta-
analysis. Formation of post-operative intra-abdominal abscess was the primary outcome and
surgical site infection was the secondary outcome.
**Assessment of methodological quality:**

Two reviewers (D.M and L.A.P.) independently assessed the risk of bias in included studies using the standardised Newcastle-Ottawa Scale for observational cohort studies and the Cochrane tool for controlled trials (12, 13). (Any discrepancies were resolved by a third reviewer (Z.L.)

**Statistical analysis and data synthesis**

The intention-to-treat principle was used to where possible (prospectively randomised studies), while the per-protocol figures were used in all other studies (retrospective studies). The number of patients allocated to each duration of antibiotic was identified, and the respective number of intra-abdominal collection and surgical site infections for each antibiotic duration group were obtained where available. Most studies presented the antibiotic duration into a dichotomous short duration and a long duration with an arbitrary time cut-off to distinguish the two groups. Two studies divided the antibiotic duration into more than 2 groups. In these studies, we dichotomised the cohort into a short duration group (antibiotics ≤ 5 days) and a long duration group (antibiotics > 5 days).

Meta-analysis was performed using the restricted maximum likelihood method, as implemented in the R *metafor* package.
We also performed an additional analysis, in which studies involving antibiotic durations in more than 2 groups were analysed such that only the shortest (or no antibiotic) and the longest antibiotic duration groups were included in the analysis, and all the “intermediate” antibiotic duration group(s) were excluded. In other words, only the shortest duration / no antibiotic group was compared to the longest antibiotic duration group.

**Observational studies**

Summary estimates using a general linear mixed-effects model with a restricted maximum-likelihood estimator were computed. Statistical heterogeneity was estimated with a $I^2$ statistic.

**Randomised data**

Due to the anticipated strong effects of uncontrolled confounding by indication in observational studies, we elected to analyse data from RCTs separately. We generated summary risk ratio using a restricted maximum likelihood model for each outcome of interest. Heterogeneity was again estimated using the $I^2$ statistic, and potential sources of clinical heterogeneity were examined qualitatively.

Publication bias was not formally assessed where there were fewer than 10 included studies (14).

Results

**Search results**
The electronic search returned 3,055 results, when duplicated studies between databases were excluded, there were 2230 unique results. Of the unique returned results, 7 studies were included in this review. Four of the included studies were observational cohort studies, the remaining three were randomized clinical trials. The excluded studies were twelve studies involving paediatric patients, four studies addressing simple appendicitis, two case reports and one study on animal models, and one study in which outcome and group sizes could not be deduced from presented odds ratios (Figure 1 – PRISMA Flow Chart).

**Characteristics of included studies**

Four studies involving 847 participants were observational retrospective cohort studies comparing various durations of post-operative antibiotic therapy following appendicectomy for acute complicated appendicitis (15-18). The size of the studies varied from 52 to 461 participants. Each of these four studies used incidence of intraabdominal abscess as the primary endpoint. Superficial surgical site infections were the most ubiquitously used secondary outcome. All studies included both male and female participants with an approximately equal distribution in Van Rossem but uneven distribution in Hughes and Kimbrell (16-18). Gender distribution was unable to be assessed in Cho due to simple and complicated appendicitis patient characteristics being pooled together (15). Mean age was similar between groups. The preoperative WBC count was a marker of inflammation that was reported in Hughes with a similar distribution across both groups (16, 19).

Three of the studies were randomised controlled trials of parallel design comparing various durations of post-operative antibiotic therapy following appendicectomy for acute complicated appendicitis (20-22). Saar compared less than or greater than 24 hours of
aminopenicillin therapy post-appendicectomy. Davoodabadi compared one group receiving ceftriaxone plus metronidazole intravenously during hospitalisation and orally 3 days after discharge with the second group receiving no antibiotics after operation. Brennan compared one group receiving rectal metronidazole 5 days post-operatively with another group receiving no antibiotics after operation. Davoodabadi was a single blinded study whilst Saar and Brennan provided no detail with regard to blinding of participants, personnel or outcome assessment. The size of the randomized trials varied from 71 to 140 participants. Each of these trials used surgical site infections as the primary endpoint. The mean age was similar between all trials. Saar had an approximately equal distribution across genders, Davoodabadi had an approximately uneven distribution and Brennan did not report on gender of participants.

The definition of complicated appendicitis was inconsistent across included studies.

Methodological quality

The overall methodological quality of the 4 included cohort studies was variable. Studies with a total score greater than 7 across all 3 subsets were considered as high-quality/low risk. All 4 cohort studies were deemed to be representative of average adults in the community, with the non-exposed arm drawn from the same community as the exposed. In all studies, exposure was ascertained from secured medical records and as such all studies were therefore deemed to be at low risk of selection bias. All four studies utilised independent
blind assessment, had adequate length of follow up with either all subjects accounted for or a small number of subjects lost to follow up. As such all studies were deemed at low risk of outcome bias. The overall risk of bias in two studies, Hughes and Kimbrell was determined high as both studies had a high risk of comparability bias due to failure to control for age, sex or any other additional risk factors. The overall risk of bias in two studies (Van Rossem and Cho) was determined as low as both studies had a low risk of comparability bias as age, sex and additional risk factors were controlled for.

Only one study reported an adjusted measure of effect size using multivariable regression. Confounding by indication, that is, that patients who received longer term antibiotics may have clinical and biochemical markers of deterioration, is therefore highly likely. (Supplementary Figure 1)

The risk of bias in the randomized controlled trials was assessed using the Cochrane risk of bias tool. A ‘high risk’ rating in any one domain resulted in an overall high risk of bias. All 3 trials were deemed at overall high risk of bias. All studies were considered to have an unclear selection bias risk except for Saar which was the only study to document the method of randomization and deemed low risk. All 3 studies were deemed an unclear risk for detection bias due to a lack of documentation regarding blinding, the exception was Davoodabi a single-blinded trial where outcome assessors were blinded resulting in a low risk of detection bias. Davoodabadi was deemed a low risk for attrition bias due to complete outcome data. Both Saar and Brennan were deemed a high risk of attrition bias due to switching of participants between cohorts and participant drop out respectfully. All 3 studies were deemed a low risk for reporting bias. No other source of bias was observed in the studies.
Meta-analyses

Observational data

Four studies involving 847 participants were included in the meta-analysis. For the primary outcomes of intraabdominal infection, we did not find a statistically significant difference between extended and short-term antibiotic strategies for intraabdominal infection (RR 0.92, 95% CI [0.49 – 1.74]) (Figure 2). Included observational studies did not report surgical site infection as an outcome.

Randomised controlled trials

Three RCTs involving 291 participants were included in the meta-analysis. Again, we found no statistically significant difference between extended and short-term antibiotic strategies for intra-abdominal infection (RR 0.52, 95% CI [0.21 – 1.29]) (Figure 2) or surgical site infection (RR 1.44, 95% CI [0.43 - 4.81] (Figure 3).

Sensitivity to dichotomisation method

In an additional meta-analysis of all 3 RCTs and 4 observational studies involving 770 participants, we compared the longest and against the shortest antibiotic duration groups. Again, there was no statistically significant association between extended antibiotic treatment and intraabdominal infection (RR 0.69, 95% CI 0.48 - 1.01) (Supplementary Figure S1).
Investigation of heterogeneity

Meta-regression was not considered as an investigation of statistical heterogeneity due to an inadequate number of studies, 10 studies considered the required threshold. (28)(G)

Potential sources of clinical heterogeneity include: clinical severity at presentation, preoperative biochemical markers of inflammation and intra-operative determinations of severity.

Discussion

Perforated appendicitis is the most common cause of intraabdominal infections amongst participants studies in clinical trials (23). Postoperative infections, including intra-abdominal abscesses occur in a significant number of patients with appendiceal perforations (24-27). Such complications are associated with longer durations of hospital stay and increased resource use (28).

This systematic review and meta-analysis found that based on the available evidence, there may be no advantage to prolonging antibiotic course after surgery for acute complicated appendicitis for the prevention of intra-abdominal abscess, neither in the prevention of surgical site infection.

In the observational studies, there was no statistically significant difference between extended and short-term antibiotic duration in the prevention of post-operative intraabdominal abscess.
In the randomized controlled trials, there was no statistically significant difference between extended and short-term antibiotic duration in the prevention of post-operative intraabdominal abscess. Furthermore, an extended duration of antibiotic therapy was not associated with a statistically significant difference in our secondary outcome of surgical site infections.

Given the arguably arbitrary nature of dichotomisation methods, we performed an additional meta-analysis using an alternative dichotomisation method which yielded the same results that there is no statistically significant difference in intra-abdominal abscess rates between the longest and shortest antibiotic duration groups.

Methodological studies amongst observational studies was highly variable; with an equal distribution of studies categorised across the ‘high risk’ and ‘low risk’ groupings. All randomised controlled trials were considered to be at high risk of bias.

Current guidelines suggested by the Surgical Infection Society and the Infectious Diseases Society of America recommend broad spectrum antibiotic regimes effective against aerobic gram negative organisms and anaerobic organisms in the treatment of post-operative perforated or abscessed appendicitis (29). Furthermore, the guideline suggests limitation of antimicrobial therapy to between 4-7 days, unless it is difficult to obtain source control, in the treatment of patient with complicated intra-abdominal infection.

Whilst systematic review and meta-analysis has been conducted to investigate the role of post-operative antibiotics in acute non-complicated appendicitis (4). To the best of our
knowledge this is the first review to address post-appendectomy antibiotic therapy duration in an adult population.

It is important to note that the major limitation of this study was the confounding due to indication. This bias may be driven by clinical severity at presentation, intra-operative determinations of severity and post-operative antibiotic duration decisions based on clinical and investigative findings which would all impact on surgeons’ decisions (30). Two of the five observational studies attempted to overcome this by adjusting for clinical and anatomic severity, however only variables captured by each dataset could be adjusted for making such models still subject to bias as a result of confounding by indication. Given the significance of this bias, the main utility of the observational data is in corroborating the conclusions of the trial data with regard to the primary outcome.

Clinical heterogeneity was difficult to explore between extended duration and short duration groups due to poor reporting of important parameters such as: participant characteristics (e. sex, age, baseline disease, ethnicity) and intervention characteristics (such as type of antibiotic and dosing (30). Details regarding antibiotic regimen were not provided in 2 of the observational studies, with most remaining studies using various regimes of cephalosporins or metronidazole used solely or in combination. Saar and Kimbrell where the exceptions where penicillins and aminoglycosides were also included. Definitional differences in short versus long course antibiotics make comparative analysis difficult and more standardised definitions in future studies would allow for better comparison.

It is relevant to note that the major limitation of the randomised potion of this study was the relatively low number of patients, with all 3 trials yielding only 291 patients. This significantly
restricts the power of the meta-analysis. This review and meta-analysis functions as a
preliminary evaluation to induce and guide further research into the appropriate role and
effective administration of post-operative antibiotics in acute complicated appendicitis. To
detect a 5% absolute risk reduction, and with the alpha set at 0.05 and beta set at 0.80, future
RCTs would need to enrol approximately 1,126 patients to be adequately powered.

There was significant clinical heterogeneity in the studies definitions of complicated
appendicitis. This was most commonly defined by the findings of perforated appendix or the
presence of purulent peritonitis (locally or generalized). Some studies broadened the
definition of complicated appendicitis to include a necrotic or gangrenous appendix, or the
finding of a peri-appendiceal abscess. All studies definitions were very much in keeping with
those commonly accepted in the medical literature (31).

More research is needed to ascertain the optimal duration of post-operative antibiotics in
complicated appendicitis. Further randomised controlled studies are required in order to
draw strong conclusions which can be made without the bias as a result of an intention to
treat. Future studies need to be much larger than the currently published ones in order to
avoid important outcomes being underpowered.

The antibiotics used in our meta-analysis of randomised data include aminopenicillins,
cephalosporins and metronidazole. The use of rectal metronidazole in one study, whilst
relevant given its pharmacokinetic profile, is outdated and may be a source of
heterogeneity(32). Future studies will be able to investigate benefits and harms from a wider
range of antibiotics. Many other antibiotics may play a role in intra-abdominal infection and future comparative randomized trials may provide answers as to the optimal strategy.

Discontinuation of IV therapy based upon resolution of clinical parameters such as fever, CRP and WBC count likely guided the decision making for cessation of antibiotics in many of the observational studies. This likely contributed to the intention to treat bias described earlier. A study by Taylor et al. showed the discontinuation of IV antimicrobial therapy based on resolution of clinical parameters to a required minimum post-operative IV antibiotic duration is not associated with an increase in morbidity but led to less IV antibiotic usage (33). Further randomized trials are required to corroborate this finding. A trial by Erickosn et al. explored the kinetics of inflammatory biological markers such as IL-6, elastase, CRP and WBC following open appendicectomy. It is important to understand the post-operative kinetics of each marker in order to detect post-operative complications (34).

One of the major challenges of this meta-analysis involved categorising treatment regimes into short term and long term given the large variation in the threshold antibiotic duration between studies. We sought to overcome this challenge by dichotomising reported data into short and extended term antibiotic durations based upon a 120-hour cut-off where possible. We sensitised our study to different methods of dichotomising the data in this meta-analysis by comparing sub-group data including only the longest and shortest antibiotic durations reported by the studies. A standard definition of short-term vs long term treatment for future randomized controlled trial would allow more straightforward comparisons (35). One possible framework is to stratify by short term as ‘less than 24 hours’, intermediate ‘24-72 hours, and extended ‘greater than 72 hours’. Likewise, a standardized definition of complex
appendicitis is needed in order to guide post-operative antibiotic treatment and reduce meta-
analysis clinical heterogeneity.

The complications resulting from prolonged antibiotic durations in complicated appendicitis
have not been thoroughly explored, however post-operative antimicrobial therapy in non-
complicated appendicitis has been shown to result in higher rates of Clostridium difficile
infections and urinary tract infections (36).

Nevertheless, these outcomes must be balanced against the risk of surgical site infections
which are associated with pain, prolonged hospitalisation and increased treatment costs (37).

Furthermore, post-appendectomy intraabdominal abscesses, with an incidence ranging
between 1-24%, often require invasive intervention and present a significant potential source
of morbidity (38).

Extended postoperative antibiotic treatment may not be associated with a reduced risk of
intraabdominal infection, nor associated with reduced risk of surgical site infection, however
meta-analysis was significantly limited by heterogeneity between studies and underpowered
trials. Further large randomised controlled trials are urgently needed to confirm these
findings.
Author contributions

Dhruvesh M Ramson MBBS(Hons)
- Conceptualization
- Data Curation
- Formal Analysis
- Project administration
- Visualization
- Writing original draft
- Writing-review & editing

Hugh Gao MBBS (Hons)
- Data curation
- Formal analysis
- Writing original draft

Jahan C Penny-Dimri MBBS(Hons)
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- Formal analysis

Zhengyang Liu BBiomed
- Conceptualization
- Data curation

Jacqueline Nguyen Khong BBiomed
- Conceptualization
- Methodology

Carla B Caruana BSc
- Conceptualization
- Resources

Ryan Campbell BMedSci(Hons)
- Data curation
- Software

Sarah Jackson BBiomed
- Formal analysis
- Resources

Luke A Perry MBBS(Hons)
- Conceptualization
- Project administration
- Supervision
- Validation
- Writing-original draft
References

Figures Legends:

Figure 1: PRISMA flow chart

Figure 2: Forest plot showing results of meta-analysis of primary outcome of intra-abdominal abscess. IA+ and IA- denotes patients with and without intra-abdominal abscess, respectively. AB+ denotes long course of antibiotics. AB- denotes short course of antibiotics.

Figure 3: Forest plot showing results of meta-analysis of secondary outcome of surgical site infection. Both studies are randomised control trials. IA+ and IA- denotes patients with and without intra-abdominal abscess respectively. SSI+ and SSI- denotes patients with and without surgical site infection, respectively.
List of Supporting Information

**Figure S1** — Forest plot showing results of meta-analysis of primary outcome of intra-abdominal abscess. The dichotomisation method in this analysis differs from Figure 2. Only the longest and the shortest antibiotic duration groups were compared against each other, and all intermediate antibiotic duration groups were removed from analysis.

**Figure S2:**
Newcastle-Ottawa scale for assessment of quality of included studies- Cohort studies (each asterisk represents if individual criterion within the subsection was filled)

**Figure S3:**
Cochrane risk of bias tool

**Appendix 1:**
Search strategy

**Table S1:**
Characteristics of included studies
<table>
<thead>
<tr>
<th>Author(s), Year</th>
<th>AB+</th>
<th>IA+</th>
<th>IA-</th>
<th>Risk Ratio [95% CI]</th>
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<tbody>
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<td>AB-</td>
<td>IA+</td>
<td>IA-</td>
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<td>Randomised Control Trials</td>
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<tr>
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<td>70</td>
<td>0</td>
<td>1.00 [0.02, 49.70]</td>
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<tr>
<td>Sarr, 2019</td>
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<td>38</td>
<td>5</td>
<td>0.61 [0.17, 2.15]</td>
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<td>RE Model for Subgroup (Q = 0.31, df = 2, p = 0.85; (i^2 = 0.0))</td>
<td></td>
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<td>0.52 [0.21, 1.29]</td>
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<td>Observational studies</td>
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<td>Cho, 2016</td>
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<td>16.05 [0.78, 331.70]</td>
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<td>1.57 [0.48, 5.15]</td>
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<td>Kimbrell, 2016</td>
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<td>0.76 [0.23, 2.51]</td>
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<td>Van Rossem, 2014</td>
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<td>36</td>
<td>0.65 [0.40, 1.04]</td>
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<td>RE Model for Subgroup (Q = 5.78, df = 3, p = 0.12; (i^2 = 30.2%))</td>
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<td></td>
<td>0.92 [0.49, 1.74]</td>
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<tr>
<td>RE Model for All Studies (Q = 6.72, df = 6, p = 0.35; (i^2 = 0.0%))</td>
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<td>0.73 [0.50, 1.05]</td>
</tr>
<tr>
<td>Author(s), Year</td>
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<td>AB- SSI+SSI-</td>
<td>Risk Ratio [95% CI]</td>
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<tr>
<td>Davoodabadi, 2018</td>
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<td>0 70</td>
<td>1.00 [0.02, 49.70]</td>
<td></td>
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<tr>
<td>Sarr, 2019</td>
<td>5 36</td>
<td>3 36</td>
<td>1.50 [0.42, 5.32]</td>
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</table>

RE Model for All Studies (Q = 0.04, df = 1, p = 0.85; $I^2 = 0.0\%$) | 1.44 [0.43, 4.81] |