**Table S3.** Bias analysis of randomized clinical trials included in the review based on the Downs and Black Quality Index1.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Studies** | Is the hypothesis/ aim/ objective of the study clearly described? | Main outcomes were clearly described in the Introduction or Methods? | Are the characteristics of the patients included in the study clearly described? | Interventions were clearly described? | Distributions of confounders in each group compared was clearly described? | Are the main findings of the study clearly described? | Provide estimates of the random variability in the data for the main outcomes? | Adverse events as consequence of the intervention were reported? | Have the characteristics of patients lost to follow-up been described? | Probability reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability is less than 0.001? |
| Andrade *et al*., 1996 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Coura *et al*., 1997 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| Sosa Estani *et al*., 1998 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 |
| Andrade *et al*., 2004 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| Sosa-Estani *et al*., 2004 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Rassi *et al*., 2007 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| Marin-Neto *et al*., 2008 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 |
| Chippaux *et al*., 2010 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| Molina *et al*., 2014 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Morillo *et al*., 2015 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 |
| Vallejo *et al*., 2016 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 |
| Morillo *et al*., 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Torrico *et al*., 2018 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Molina-Morant *et al*., 2020 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 |
| Torrico *et al*., 2021 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Partial score / items1(n)** | 13 | 13 | 15 | 15 | 13 | 14 | 08 | 14 | 14 | 11 |
| **Partial score / items (%)** | 86.6% | 86.6% | 100% | 100% | 86.6% | 93.3% | 53.3% | 93.3% | 93.3% | 73.3% |

**1**Downs SH and Black N. (1998). J. Epidemiol. Commun Health. 52(6), 377–384.

**Table S6 *(continuation)*.** Bias analysis of randomized clinical trials included in the review based on the Downs and Black Quality Index1.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Studies** | The subjects were representative of the entire population from which they were recruited? | Were the subjects prepared to participate representative of the entire population from which they were recruited? | Were the staff, places, and facilities, representative of the treatment the majority of patients receive? | Was an attempt made to blind study subjects to the intervention? | Was an attempt made to blind those measuring the main outcomes of the intervention? | Results based on “data dredging”, were clearly reported? | Do the analyses adjust for different lengths (follow-up or period between the intervention and outcome)? | Were the statistical tests used to assess the main outcomes appropriate? | Was compliance with intervention/s reliable? |
| Andrade *et al*., 1996 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 |
| Coura *et al*., 1997 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 1 |
| Estani *et al*., 1998 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Andrade *et al*., 2004 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Sosa-estani *et al*., 2004 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Rassi *et al*., 2007 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| Marin-Neto *et al*., 2008 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 |
| Chippaux *et al*., 2010 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 |
| Molina *et al*., 2014 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Morillo *et al*., 2015 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Vallejo *et al*., 2016 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 |
| Morillo *et al*., 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Torrico *et al*., 2018 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Molina-Morant *et al*., 2020 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 |
| Torrico *et al*., 2021 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Partial score / items 1 (n)** | 14 | 14 | 14 | 14 | 12 | 14 | 13 | 11 | 12 |
| **Partial score / items (%)** | 93.3% | 93.3% | 93.3% | 93.3% | 80% | 93.3% | 86.6% | 73.3% | 80% |

**1**Downs SH and Black N. (1998). J. Epidemiol. Commun Health. 52(6), 377–384.

**Table S6 *(continuation)*.** Bias analysis of randomized clinical trials included in the review based on the Downs and Black Quality Index1.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Studies** | Were the main outcome measures used accurate (valid and reliable)? | Were the patients in different groups or were the cases and controls recruited from the same population? | Were study subjects in different groups or were the cases and controls recruited over the same period of time? | Were study subjects randomized in groups? | Randomized intervention assignment concealed from patients and health care staff until recruitment was complete? | Adequate adjustment for confounding from which the main findings were drawn? | Losses of patients were considered? | **Downs and Black Quality Index1**  **N / %** |
| ***Case series*** |  |  |  |  |  |  |  |  |
| Andrade *et al*., 1996 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 24/92% |
| Coura *et al*., 1997 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 19/73% |
| Estani *et al*., 1998 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 24/92% |
| Andrade *et al*., 2004 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 25/96% |
| Sosa-estani *et al*., 2004 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 25/96% |
| Rassi *et al*., 2007 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 21/80.7% |
| Marin-Neto *et al*., 2008 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 19/73% |
| Chippaux *et al*., 2010 | 1 | 0 | 0 | 1 | 0 | 1 | 1 | 19/73% |
| Molina *et al*., 2014 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 26/100% |
| Morillo *et al*., 2015 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 23/88% |
| Vallejo *et al*., 2016 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 19/ 73% |
| Morillo *et al*., 2017 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 26/100% |
| Torrico *et al*., 2018 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 26/100% |
| Molina-Morant *et al*., 2020 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 12/46% |
| Torrico *et al*., 2021 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 26/100% |
| **Quality score / items (n)** | 11 | 13 | 13 | 15 | 13 | 14 | 13 | 13.14 |
| **Quality score / items (%)** | 73.3% | 86.6% | 86.6% | 100% | 86.6% | 93.3% | 86.6% | 85.57% |

**1**Downs SH and Black N. (1998). J. Epidemiol. Commun Health. 52(6), 377–384.