|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Supplemental table 1**. Quality of Non-Randomized Studies Assessment (Newcastle-Ottawa Scale) | | | | |
| **Category** | **Criteria** | ***Cromartie, 1976*** 35 | ***Lyon et al., 2015*** 37 | ***Upchurch et al., 2017*** 38 |
| **Selection** | Representativeness of the exposed cohort | a\* | a\* | a\* |
| Selection of the non-exposed cohort | a\* | a\* | a\* |
| Ascertainment of exposure | a\* | a\* | a\* |
| Demonstration that outcome of interest was not present at start of study | a\* | a\* | a\* |
| **Comparability** | Comparability of cohorts on the basis of the design or analysis | NA | a\*b\* | a\*b\* |
| **Outcome** | Assessment of outcome | C | b\* | b\* |
| Was follow-up long enough for outcomes to occur | B | a\* | a\* |
|  | Adequacy of follow-up of cohorts | a\* | C | b\* |
| Total # of stars (\*) | | **6** | **8** | **9** |

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| **Supplemental table 2**. Risk of Bias in Non-Randomized Studies of Intervention (ROBINS-I) | | | |
|  | *Cromartie, 1976* 35 | *Lyon et al., 2015* 37 | *Upchurch et al., 2017* 38 |
| Confounding | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical |
| Selection | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical |
| Measurement of intervention | Low/Moderate /Serious/Critical | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical |
| Deviations from intended  intervention | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical |
| Missing data | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical |
| Measurement of outcomes | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical |
| Reported results | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical |
| **Overall** | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical | Low/Moderate/ Serious/Critical |

*Note:* ***“Low”=****comparable to a well performed randomized trial;* ***“Moderate”=****sound for an observational study;* ***“High”=****there are important problems/the study is too problematic to provide useful evidence*

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| **Supplemental table 3**. Risk of Bias in Interventional Trial | | |
|  | *Jabre et al., 2009* 36 | |
| **Risk of bias domain** | **Judgment** | **Reasoning** |
| Random sequence generation (selection bias) | Low | *“Randomization was done in blocks of four by a computerized random-number generator list provided by a statistician who was not involved in determination of patient eligibility, drug administration, or outcome assessment.”* |
|  |  |  |
| Allocation concealment (selection bias) | Low | *“The study drug was sealed in sequentially numbered, identical boxed containing the entire treatment.”* |
| Blinding of participants and personnel (performance bias) | Low | *“Emergency physician enrolling patients was aware of study group assignment. However, nurses and intensivists in the intensive care unit were masked to the treatment assigned because it was not specified on the patient’s medical record or conveyed in verbal or written reports. “* |
| Blinding of outcome assessment (detection bias) | Unclear | *Not clear whether the outcome assessors were blinded.* |
| Incomplete outcome data (attrition bias) | Low | *There seems to be no missing outcome data for included patients.* |
| Selective reporting (reporting bias) | Low | *The study protocol is available, and the results include all outcomes listed in the methods section.* |
| Other bias | Low | *There seems to be no other obvious sources of bias.* |