Objectives Our study aims to evaluate safety, efficacy, and the overall success of ProDisc-C versus anterior cervical discectomy and fusion (ACDF) at 48-months post-surgery in Asian patients in treating single-level symptomatic cervical disc disease (SCDD). Methods This multicentre, prospective, randomized controlled trial was conducted with patients with single-level SCDD involving C3-C7-vertebral segments. The study was initiated in January 2008 after obtaining ethical approval at nine centres in China, Hong Kong, Korea, Singapore and Taiwan. The patients were randomized into group-A treated with ProDisc-C and group-B with ACDF (treated with standalone cage with bone autograft) at 2:1 ratio. A total of 120 patients consisting of 80 patients in group-A (ProDisc-C) and 40 in group-B (ACDF) were enrolled in the study. Assessments were planned to be conducted at baseline, 6-weeks, and 3-, 6-, 12-, 18-, 24-, 36- and 48-months post-surgery and annually thereafter till 84 months. The overall success at 48-months was composed of: (1) >20% improvement in neck disability index (NDI); (2) neurological success (maintained/improved); (3) absence of secondary surgery at index level; and (4) absence of device-related adverse events. Results Of the total of 120 patients, 76-patients in group-A and 37-patients in group-B were treated as per protocol (PP). Overall success in PP last observation carried forward (LOCF) analysis was 79% in group-A and 75.7% in group-B at 48-months (p=0.0122), demonstrating non-inferiority of ProDisc to ACDF. Additionally, ProDisc-C demonstrated non-inferiority to ACDF at 18-months (81.6% vs 83.8%, p=0.0398) and at 36-months (80.3 vs 78.4, p=0.0156). The overall success in the intent to treat LOCF analysts were 78.2% in group-A (n=81) and 73.7% in group-B (n=39) at 48-months (p=0.0086). Furthermore, at 18-months (80.8% vs 81.6, p=0.0284) and 36-months (79.5% vs 76.3, p=0.0109), ProDisc-C demonstrated non-inferiority to ACDF. Both groups had similar results in (i) NDI success (97.2% in group-A vs 100% in group-B), (ii) neurological success (83.3% in group-A vs 87.5% in group-B), (iii) absence of secondary surgery at index level (97.2% in group-A vs 100% in group-B) and (iv) absence of device-related adverse events (97.2% in group-A vs 193.75% in group-B) at 48-months (pp). Both the groups had similar secondary outcomes such as VAS-pain scores and SF-36. However, the range of motion was preserved in group-A and was significantly reduced in group-B at 48-months. Conclusion The use of ProDisc-C is feasible, safe, and effective for treatment of SCDD in Asian population. ProDisc-C demonstrated non-inferiority to ACDF in overall success at 18, 36 and 48-months. Both the groups had similar secondary outcomes. Future large-scale studies focusing on Asian population are required to establish clear non-inferiority of ProDisc-C to ACDF in terms the secondary outcomes in addition to the overall success.