Background and importance A greater benefit was suggested with early treatment with remdesivir against COVID-19.

Aim and objectives To develop a systematic review and methodological interpretation of subgroup analyses according to timing of use of remdesivir in COVID-19.

Material and methods A bibliographic review in MEDLINE was conducted up to 10 October 2020. The ‘Clinical Queries/ Narrow’ tool was used with the search strategy: ((Therapy/Narrow[filter]) AND (remdesivir AND COVID)). Randomised clinical trials (RCTs) with subset analysis about early and late use of remdesivir (≤10 vs >10 days from symptom onset, or ≤9 vs >9 days) were selected. The rest of the studies were excluded. All endpoints with subgroup analysis regarding timing of remdesivir use were assessed. Two methodologies were applied. The first considered statistical interaction among subsets, prespecification, biological plausibility and consistency of the subgroup analyses of similar RCTs. The second methodology was a validated tool with preliminary questions to discard subset analysis without minimal relevance, and a checklist. This checklist assigned a score related to a recommendation for applicability of subgroup analysis in clinical practice.

Results 20 results were found after review; 16 studies were excluded because they were not RCTs and 1 study had no efficacy evaluation of remdesivir. Therefore, three RCTs were selected. Endpoints considered were: time to clinical improvement, and clinical status at day 15 of an RCT. Biological plausibility was established in time to clinical improvement, and clinical status was consistent. The PC-pembrolizumab combination was considered as the reference (treatment with the greatest magnitude of effect). HR for OS were: 1.4 (95% CI 0.89 to 2.3) versus carboplatin–gemcitabine; 1.6 (1.2 to 2.1) versus PC; 1.5 (1.1 to 2.1) versus nab–PC-atezolizumab; 1.8 (1.3 to 2.5) versus PC-figitumumab; 1.4 (0.96 to 2.0) versus PC-motesanib; 1.3 (0.66 to 2.5) versus PC-necitumumab; 2.1 (0.86 to 5.0) versus PC-olaratumab; 2.9 (1.7 to 4.8) versus PC-sorafenib and 1.2 (0.82 to 1.7) versus pembrolizumab monotherapy. Carboplatin–gemcitabine, PC-motesanib, PC-necitumumab, PC-olaratumab and pembrolizumab did not present statistically significant differences between direct and indirect evidence and therefore NMA was consistent. The PC-pembrolizumab combination was considered as the reference treatment (with the greatest magnitude of effect). HR for OS were: 1.4 (95% CI 0.89 to 2.3) versus pembrolizumab; 1.6 (1.2 to 2.1) versus PC; 1.5 (1.1 to 2.1) versus nab–PC-atezolizumab; 1.8 (1.3 to 2.5) versus PC-figitumumab; 1.4 (0.96 to 2.0) versus PC-motesanib; 1.3 (0.66 to 2.5) versus PC-necitumumab; 2.1 (0.86 to 5.0) versus PC-olaratumab; 2.9 (1.7 to 4.8) versus PC-sorafenib and 1.2 (0.82 to 1.7) versus pembrolizumab monotherapy. Carboplatin–gemcitabine, PC-motesanib, PC-necitumumab, PC-olaratumab and pembrolizumab did not present statistically significant differences between direct and indirect evidence and therefore NMA was consistent. The PC-pembrolizumab combination was considered as the reference treatment (with the greatest magnitude of effect).