OLA strategy for ARDS: Its effect on mortality depends on achieved recruitment (PaO2/FiO2) and mechanical power. Systematic Review and Meta-analysis with Meta-Regression.

Supplementary Methods:

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1.1.- Search strategy:

Two researchers (S. F. U. and A. M. V.) conducted an independent literature search to identify potentially relevant studies. The two most recent systematic reviews of RCT´s comparing higher versus lower PEEP ventilation strategies in patients with ARDS (1, 2)[1,2] were identified and their bibliographies were manually reviewed. Then the search was updated to identify additional trials in MEDLINE, EMBASE, The Cochrane Library, the Cochrane Central Register of Controlled Trials, the ISI Web of Science, OVID, and ClinicalTrials.gov. We also searched for doctoral theses in the TESEO and Tesis Doctorals en Xarxa (website for Spanish theses) databases, for conference papers in the Conference Proceedings section of the Web of Science, and for grey literature in OpenGrey. Discrepancies between the two researchers were evaluated by a third researcher (V. M. A.).

The search combined medical subject headings (or appropriate controlled vocabulary) and keywords or Free text terms, using search terms as ''acute lung injury'', ''ALI'', ''acute respiratory distress syndrome'', ''ARDS'', ''open lung'', ''lung recruitment'', "protective ventilation", ''positive end-expiratory pressure'', ''PEEP'', "ARF", "acute respiratory failure", mortality and ICU mortality. To provide greater comprehensiveness to the review, we did not use any age filters and we did not limit the search based on study design or language of publication, including published studies from database inception until March 2020 (see search strategy in the **Appendix** of this **online supplement**).

1.2.- Study selection:

Two investigators (P.V.G. and C.C.) independently reviewed the search results to identify pertinent articles. Disagreements on eligibility were resolved by a third author (V.M.A.) through consensus. In duplicate, they also abstracted data and assessed risk of bias.

1.3.- Data extraction and study quality:

Each identified trial was assessed for evidence of bias using CASPe criteria (adequate method of randomization, allocation concealment and intention-to-treat analysis) (3)[3] and the Cochrane Collaboration risk of bias Tool (4)[4]. This instrument includes assessment for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, reporting and other bias. Judgment as ''low'', ''unclear'', or ''high'' risk of bias was provided in each of the sections for each study. Trials were considered as high risk of bias if one or more sections met criteria for high risk of bias.

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) guidelines were used for rating the quality of evidence for the group of studies included in our analysis, which includes an assessment of risk of bias, inconsistency between individual studies, precision of effect estimates, indirectness of the evidence with regards to the study question, and likelihood of publication bias (5)[5]. Imprecision was deemed to occur when either (a) 95% confidence intervals (CIs) around effect estimates crossed the threshold between recommending and not recommending a treatment (which we a priori defined as a relative risk (RR) of 1.0 for the outcome of mortality); or (b) the criteria of "optimal information size" was not met (6)[6]. Summary of findings tables were prepared using GRADE Profiler software, through a project we created in GRADEpro GDT webpage database.

1.4.- Statistical analysis:

In the GRADE evaluation, the criteria of "Optimal information size" is used to address the fragility of effect estimates and 95% CIs in the setting of small sample sizes, and is defined as the number of patients within a systematic review that would provide adequate power for a single randomized trial. Given an alpha of 0.05, 80% power, and control group mortality of 30%, the optimal information size to identify a 20% RR reduction in mortality for higher PEEP relative to lower PEEP is approximately 450 outcome events (7)[7].

In all our analyses, we established the statistical significance in p-value less than or equal to 0.05. Publication bias was assessed via visual appraisal of symmetry of the Funnel–Plot, and a statistical test for Funnel-Plot asymmetry (Egger Regression). We also estimated the number of missing studies with the Trim and Fill method.

For the Meta-analysis, we used a Random Effects Model (REM) assuming heterogeneity (tau2 = residual heterogeneity). The dependent variable was the natural log of the RR of mortality (Ln(RR)). The model was fit with a weighted least squares estimation (Max Likelihood). The weight of the ith study was W = 1 / (Variance[LN(RR)] + tau2). DerSimonian-Laird and Hartung-Knapp-Sidik-Jonkman tests were applied, and the model fit was evaluated with radial plots and QQ normality plots.

We performed all statistical analyses by using Review Manger 5.3 software (RevMan, The Cochrane Collaboration, Oxford, UK) and in R 3.6.3 with the *metafor* package (8)[8].

1.5.- Sensitivity analysis:

Two prespecified sensitivity analysis performed through subgroup analysis. The first one, split the trials by the modality of OLA strategy applied in the experimental group. The second, split the trials in two subgroups, depending on if VT was limited or not in the control group.

1.6.- Additional analysis of causes of heterogeneity:

Other possible causes of heterogeneity among studies were examined through meta-regression. For this analysis, a set of possible moderator variables was defined *a priori* to be included in different linear models. These moderator variables were:

- Model 1 (M1): PEEP in experimental group on day 1 (expPEEP_1st): This variable represents the amount of PEEP used on the first day of application of the OLA strategy.
- Model 2 (M2): PaO2/FiO2 ratio of control group at baseline (controlPF_0). This variable represents the severity of ARDS at the beginning of the trials.
- Model 3 (M3): PaO2/FiO2 ratio of control group on day 3 (controlPF_3rd). PaO2/FiO2 ratio after 24 hours of ventilation is a predictor of mortality in ARDS patients (9)[9]. PaO2/FiO2 estimates the amount of intrapulmonary shunt that remains due to nonaerated lung tissue (10)[10]. The PaO2/FiO2 in the control group at a delayed time point is a surrogate for the ability of conventional strategies to achieve lung recruitment. Initially PaO2/FiO2 ratios from the 1st and 3rd day were recorded. But, as recruitment is a time-dependent phenomenon (11)[11], 1st day ratio was discarded and 3rd day PaO2/FiO2 ratio was chosen because it is the most consistent data we found in all trials.
- Model 4 (M4): Difference in PaO2/FiO2 ratio between OLA and control groups on day 3 (gradPF_3rd). This variable represents the difference in lung recruitment between both groups. Since initial PaO2/FiO2 ratio is similar between intervention and control groups based on randomization of patients. Again, 3rd day ratio was chosen for consistency in the trials.
- Model M5 (M5) Relative Driving Pressure (DP) on the day 1 (RelativeDP_1st). We computed DP [DP = Plateau Pressure − Total PEEP] on the 1st day in both cohorts of any single trial. To represent every trial in the analysis we computed the ratio of DP of the OLA strategy group divided by DP of the control group. So, the value of this variable represents the balance between both groups of same trial: a value greater than one means that OLA cohort received more DP than the control group, and vice versa.
- Model 6 (M6): Relative MP on the day 1 (RelativeMP_1st). Using Gattinoni´s simplified formulae [MP (Jul/min) = 0.000098*RR*VT*(Peak − ½*DP)] (12)[12], we computed MP transmitted to the lungs of both cohorts on the 1st day in any single trial. In the few cases where the value of Peak pressure was not reported (i.e. in trials with pressure control ventilation in any of the groups), we used Plateau pressure instead. And then to represent every trial in the analysis, we computed the ratio of MP of the OLA strategy group divided by MP of the control group. Again, the value of this variable represents the balance between both groups.

Data on these variables were extracted from the published text and figures of the trials, including supplementary appendixes and files. For the meta-regression, a set of mixed-effects models (MEMs) were fitted, using in every model one of the above variables as a moderator in each model. So, every model represents a candidate source of heterogeneity. The models were adjusted by weighted least squares multivariable linear regression, assuming heterogeneity (tau^2 = residual heterogeneity), and using as the outcome variable the natural logarithm of the RR (to linearize). Weights were: Weight = 1/(Variance[LN(RR)] + tau^2). The fit of every model was tested with Residuals analysis and QQ normality plots. For model comparison, information entropy measures of predictive accuracy were used, removing the cases with missing values at the start to fit the models to exactly the same observations. This procedure reflects our interest

in the relative performance of the models, not their absolute information values. Because of n/V < 40, the Akaike's Information Criterion with the finite sample correction (AICc) was used to decide what the "best" model (of the candidates set, and in the sense of the expected Kullback-Leibler discrepancy) was. Then, for each model, the Akaike Weights (13, 14, 15)[13,14,15] and the Turing-Good Weights of Evidence (WOE) against every model relative to "best" model (16)[16] were computed.

Using every model AICc, the model with the minimum AICc was selected as the "best" one (in the expected Kullbach-Leibler discrepancy sense). For every model we computed the Likelihood of the Model (relative to the "best" one) given the data. Then, the relative model likelihoods are normalized (i.e., divided by the sum of the likelihoods of all models) to obtain Akaike weights (the probability of every model in this set to be the "best" one). And in the last step, the WOE against (in decibans), relative to the "best" one, of all models were computed.

All the additional analysis was done in R 3.6.3 with the *metafor* package (17)[17].

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